Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Major Deficiency - Question 9

(b)(4)

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REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

ISO 10993-18 - Chemical Characterization

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OSE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

RELEASE

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STUDY PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

ISO 10993-18 - Chemical Characterization Program

TEST ARTICLE

Surgical Incise Drape with CHG (b)(4)

(b)(4)

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Dear Ms. Minagh,

Thank you for working with us hardly to address our concerns. (b)(4) (b)(4) I am wondering whether we can have a short phone call today or tomorrow.

Please let me know your thoughts. Thank you!

Best regards,
Yongqing

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Sent: Thursday, October 19, 2023 9:24 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: K230645@docs.fda.gov
Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dr Yongqing

It is a pleasure to work with you on this submission.
We have received your query and are working very hard to formulate a response that will satisfy you.
However, I fear that we do not have enough time to coordinate this to a satisfactory level.

Is it possible that we could receive an extension until Monday the 23rd of October?

Many thanks and best regards

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)
elaine.minagh@eu.averydennison.com | medical.averydennison.com

Image removed by sender.

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Tue, 17 Oct 2023 at 19:30, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Ms. Elaine Minagh,
>
> Thank you for working with us on this submission. We are reviewing the provided supplement S001 and have the following information for you to address. Please provide your response at your early convenience but not later than **the COB of this Thursday (October 19, 2023).**
>
> (b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Please contact me if you have any questions.

Best regards,
Yongqing

From: Chen, Yongqing
Sent: Tuesday, October 10, 2023 8:11 AM
To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for letting me know this contact change. Good luck for your new move!

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for you.

Best regards,
Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Tuesday, October 10, 2023 7:43 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: Re: [EXTERNAL] K230645 Update

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Dear Mr. Chen,

I hope you are well!

I am writing to inform you that I am leaving Avery Dennison at the end of this month and will therefore no longer be the point of contact for the current submission K230645.

My colleague Elaine Minagh, copied on this message, will become the point of contact for future correspondence regarding the Avery Dennison submission. I have provided Elaine's contact information below:

Elaine Minagh, Regulatory Affairs Manager
Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73, Ireland
Telephone: (b)(6)
e-mail: elaine.minagh@eu.averydennison.com

Thank you for your support on this submission.

Please let me know if you have any questions.

Best Wishes,
Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: +(b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

Image removed by sender.

Connect with Us: Twitter | LinkedIn | YouTube | News | Product Selector

On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com> wrote:

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Thank you for the update Mr Chen!

Have a great day,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: +(b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

Image removed by sender.

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On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Dr. Gallantine,
> The supplement has been received on Monday and the team review has been starting on Monday (09/25/2023).
>
> Respectfully,
> Yongqing
>
> ---
>
> **From:** Chen, Yongqing
> **Sent:** Tuesday, September 26, 2023 8:27 AM
> **To:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>
> **Subject:** RE: [EXTERNAL] K230645 Update
>
> Dear Dr. Gallantine,
> Thank you for the update. It might take one or more days for DCC to notify the appropriate Center/Office. I will let you know when the supplement has been assigned to me.
>
> Respectfully,
> Yongqing
>
> ---
>
> **From:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Sent:** Tuesday, September 26, 2023 8:16 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Good Morning Mr Chen,
>
> The USB file has now arrived in Silver Creek. Could you let us know when you have received it, please?
>
> Thank you,
>
> Lizzie
>
> **Lizzie Gallantine, Ph.D** | Project Manager Europe | Avery Dennison Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: +(b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
>
> **Error! Filename not specified.**
> Connect with Us: Twitter | LinkedIn | YouTube | News | Product Selector
>
> On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:
>
> > Dear Dr. Gallantine,
> >
> > Thank you for letting us know and look forward to working with you on this submission.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Best regards,
Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Monday, September 25, 2023 5:31 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr Chen,

We have completed our response to the hold letter for K230645. The documents on a USB file were shipped on Friday 22 September and are currently in transit (b)(4)

We have separated each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if you have any questions.

Best Wishes,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Good morning Ms. Bartakovics,
>
> Thank you for keeping us updated on your submission. I think your approach is reasonable for your purpose. We would appreciate, in your response document/letter, if you can guide us the location of your (b)(4) this will help us to quickly find them without missing any important information.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> **Sent:** Tuesday, August 29, 2023 10:16 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Good Morning Mr. Chen-
>
> I am winding down my time with Avery Dennison and therefore met with the team this morning to discuss our response to the hold letter for K230645. I just wanted to confirm that the response needs to be submitted as an e-copy that has been verified through the e-submitter tool. Since there are additional reports and documents to submit, we plan to add those documents into folders as attachments to our response. There are quite a few questions to address so it seemed as though a folder approach made the most sense for organizational purposes. If there is a better approach, please let me know so we may adopt that template.
>
> Much appreciated.
>
> Have a nice day.
>
> Regards,
>
> **Lisa Bartakovics**
> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
>
> m: (b)(6)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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7100 Lindsay Dr. Mentor, OH 44060

Error! Filename not specified.

Facebook Twitter LinkedIn

averydennison.com medical.averydennison.com

On Mon, Aug 21, 2023 at 9:02 AM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Hi Lizzie,
>
> Thank you very much for sending me your contact info. Look forward to working with you on this submission.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Sent:** Monday, August 21, 2023 9:15 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>; Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Hi Yongqing
>
> I hope you're well! My contact information is:
>
> Lizzie Gallantine, PhD., Project Manager Europe
> Avery Dennison Medical Ltd.
> IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland
> Telephone: (b)(6)
> e-mail: elizabeth.gallantine@eu.averydennison.com
>
> Thank you!
>
> Lizzie
>
> **Lizzie Gallantine, Ph.D** | Project Manager Europe | Avery Dennison Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
>
> **Error! Filename not specified.**
> Connect with Us: Twitter | LinkedIn | YouTube | News | Product Selector
>
> On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:
>
> > Dear Ms. Gallantine,
> >
> > Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our system? Thank you!
> >
> > **Error! Filename not specified.**
> > Please let me know if you have any questions.
> >
> > Best regards,
> > Yongqing
> >
> > ---
> >
> > **From:** Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> > **Sent:** Friday, August 18, 2023 4:24 PM
> > **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> > **Cc:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Elaine Minagh <elaine.minagh@eu.averydennison.com>
> > **Subject:** Re: [EXTERNAL] K230645 Update
> >
> > CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Dear Mr. Chen-

I hope you have had an enjoyable summer and this email finds you well.

I am writing to inform you that I am leaving Avery Dennison at the end of the month and will therefore no longer be the point of contact for submission K230645.

Elizabeth Gallantine, copied on this message, will serve as the point of contact for future correspondence regarding the Avery Dennison submission. She will provide updates regarding the response to the hold letter and coordinate all future correspondence.

It has been a pleasure working with you and I hope to work with you again in the future.

Please let me know if you have any questions.

Regards,
Lisa Bartakovics

On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Ms. Bartakovics,
>
> Thank you for keeping me updated and please let me know if you have any questions for us.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> **Sent:** Thursday, June 1, 2023 12:20 PM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** regulatoryaffairs regulatoryaffairs <regulatoryaffairs@eu.averydennison.com>
> **Subject:** [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Dear Mr. Chen-
>
> Thank you again for the teleconference, we greatly appreciate your time and that of the team.
>
> **(b)(4)**
>
> Therefore, Avery Dennison plans to respond to all of the points within the Hold Letter for K230645 in early September. I wanted to provide an update so that you are aware we are working on the items identified in the Hold Letter and will respond back to you as soon as (b)(4) is completed.
>
> Please let me know if you have any further questions.
>
> Thank you and have a nice day.
>
> Regards,
>
> **Lisa Bartakovics**
> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
>
> m: (b)(6)
> 7100 Lindsay Dr. Mentor, OH 44060
>
> Facebook Twitter LinkedIn
>
> averydennison.com medical.averydennison.com
>
> ---
> The information transmitted is intended only for the person or entity to which it is addressed and may contain confidential and/or privileged material. Any review, retransmission, dissemination or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is prohibited. If you received this in error, please contact the sender and delete the material from any device.
>
> For details about the personal information we process and why, please see our Privacy Notice
> ---

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

--
Lisa Bartakovics
Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical

m: (b)(6)
7100 Lindsay Dr. Mentor, OH 44060

Error! Filename not specified.

Facebook Twitter LinkedIn

averydennison.com medical.averydennison.com

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---

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For details about the personal information we process and why, please see our Privacy Notice
---

Form Approved: OMB No. 0910-0511 Expiration Date: October 31, 2024. See Instructions for OMB Statement.

Records processed under FOIA Request 2024-1745, Released by CDRH on 08-26-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

MEDICAL DEVICE USER FEE COVER SHEET

PAYMENT IDENTIFICATION NUMBER: (b)(4)
Write the Payment Identification number on your check.

A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm370879.htm

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)

AVERY DENNISON
IDA Business Park
Ballinalee Road
Longford
N39 DX73
IE

1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)
*****2269

2. CONTACT NAME
Lisa Bartakovics

2.1 E-MAIL ADDRESS
Lisa.Bartakovics@averydennison.com

2.2 TELEPHONE NUMBER (include Area code)
312-629-4608

2.3 FACSIMILE (FAX) NUMBER (Include Area code)

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm345263.htm

Select an application type:
[X] Premarket notification(510(k)); except for third party
[ ] 513(g) Request for Information
[ ] Biologics License Application (BLA)
[ ] Premarket Approval Application (PMA)
[ ] Modular PMA
[ ] Product Development Protocol (PDP)
[ ] Premarket Report (PMR)
[ ] 30-Day Notice
[ ] De Novo Request

3.1 Select a center
[X] CDRH
[ ] CBER

3.2 Select one of the types below
[X] Original Application

Supplement Types:
[ ] Efficacy (BLA)
[ ] Panel Track (PMA, PMR, PDP)
[ ] Real-Time (PMA, PMR, PDP)
[ ] 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)
[ ] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA
[X] NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number:

5. FDA WILL NOT ACCEPT YOUR SUBMISSION IF YOUR COMPANY HAS NOT PAID AN ESTABLISHMENT REGISTRATION FEE THAT IS DUE TO FDA. HAS YOUR COMPANY PAID ALL ESTABLISHMENT REGISTRATION FEES THAT ARE DUE TO FDA?
[X] YES (All of your establishments have registered and paid the fee, or this is your first device and you will register and pay the fee within 30 days after entering into an operation that requires you to register and submit device listing information.)
[ ] NO (If you currently market a medical device and your establishment is required to register and submit device listing information, FDA will not accept your submission until you have paid all fees due to FDA. See http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/ucm053165.htm for additional information)

6. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.
[ ] This application is the first PMA submitted by a qualified small business, including any affiliates
[ ] This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only
[ ] The sole purpose of the application is to support conditions of use for a pediatric population
[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

7. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).
[ ] YES
[X] NO

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PAPERWORK REDUCTION ACT STATEMENT

Public reporting burden for this collection of information is estimated to average 18 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the address below.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

[Please do NOT return this form to the above address, except as it pertains to comments on the burden estimate.]

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

(b)(4) 04-Jan-2023

Form FDA 3601 (07/22)

"Close Window" Print Cover sheet

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

From: DCCLetters@fda.hhs.gov [DCCLetters@fda.hhs.gov]
Sent: 9/25/2023 5:06:21 PM
To: regulatoryaffairs@eu.averydennison.com
CC: DCCLetters@fda.hhs.gov
Subject: K230645/S001 Acknowledgement Letter
Attachments: K230645-S001-Acknowledgement Letter.pdf

September 25, 2023

Thank you for your submission. We have attached your acknowledgement letter for your records. If you have any questions about your acknowledgement letter, please contact us at DCCmailroom@fda.hhs.gov. Please do not reply to this email.

The CDRH Portal is now available:
Instead of shipping your submissions to us, you can now upload them at our CDRH Portal.

*** This is a system-generated email notification ***

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

U.S. FOOD & DRUG ADMINISTRATION

Acknowledgement Letter

09/25/2023

Lisa Bartakovics, Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road
Longford,
Longford N39 RC80 IRELAND

Dear Lisa Bartakovics:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your submission. This submission has been assigned the unique document control number below. All future correspondence regarding this submission should be identified prominently with the number assigned and should be submitted to the Document Control Center at the address listed below. Failure to do so may result in processing delays. If you believe the information identified below is incorrect, please contact the Office of Product Evaluation and Quality (OPEQ) submission support at (301) 796-5640 or OPEQSubmissionSupport@fda.hhs.gov.

Submission Number: K230645/S001
Received: 09/25/2023
Applicant: Avery Dennison Medical Ltd.
Device: BeneHold Surgical Incise Drape with CHG antimicrobial II

We will notify you when the review of this document has been completed or if any additional information is required. If you are submitting new information about a submission for which we have already made a final decision, please note that your submission will not be re-opened. For information about CDRH review regulations and policies, please refer to http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm.

Sincerely yours,

Center for Devices and Radiological Health

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Dear Ms. Elaine Minagh,

Thank you for working with us on this submission. We are reviewing the provided supplement S001 and have the following information for you to address. Please provide your response at your early convenience but not later than **the COB of this Thursday (October 19, 2023).**

(b)(4)

Please contact me if you have any questions.

Best regards,
Yongqing

From: Chen, Yongqing
Sent: Tuesday, October 10, 2023 8:11 AM
To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for letting me know this contact change. Good luck for your new move!

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for you.

Best regards,
Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Tuesday, October 10, 2023 7:43 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen,

I hope you are well!

I am writing to inform you that I am leaving Avery Dennison at the end of this month and will therefore no longer be the point of contact for the current submission K230645.

My colleague Elaine Minagh, copied on this message, will become the point of contact for future correspondence regarding the Avery Dennison submission. I have provided Elaine's contact information below:

Elaine Minagh, Regulatory Affairs Manager
Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73, Ireland
Telephone: (b)(6)
e-mail: elaine.minagh@eu.averydennison.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Thank you for your support on this submission.

Please let me know if you have any questions.

Best Wishes,
Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: + (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

Image removed by sender.

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On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com> wrote:

> Thank you for the update Mr Chen!
>
> Have a great day,
>
> Lizzie
>
> **Lizzie Gallantine, Ph.D** | Project Manager Europe | Avery Dennison Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: + (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
>
> Image removed by sender.
>
> Connect with Us: Twitter | LinkedIn | YouTube | News | Product Selector
>
> On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:
>
> > Dear Dr. Gallantine,
> > The supplement has been received on Monday and the team review has been starting on Monday (09/25/2023).
> >
> > Respectfully,
> > Yongqing
> >
> > ---
> >
> > **From:** Chen, Yongqing
> > **Sent:** Tuesday, September 26, 2023 8:27 AM
> > **To:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> > **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>
> > **Subject:** RE: [EXTERNAL] K230645 Update
> >
> > Dear Dr. Gallantine,
> > Thank you for the update. It might take one or more days for DCC to notify the appropriate Center/Office. I will let you know when the supplement has been assigned to me.
> >
> > Respectfully,
> > Yongqing
> >
> > ---
> >
> > **From:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> > **Sent:** Tuesday, September 26, 2023 8:16 AM
> > **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> > **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>
> > **Subject:** Re: [EXTERNAL] K230645 Update
> >
> > CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
> >
> > Good Morning Mr Chen,

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

The USB file has now arrived in Silver Creek. Could you let us know when you have received it, please?

Thank you,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Dr. Gallantine,
>
> Thank you for letting us know and look forward to working with you on this submission.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Sent:** Monday, September 25, 2023 5:31 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Dear Mr Chen,
>
> We have completed our response to the hold letter for K230645. The documents on a USB file were shipped on Friday 22 September and are currently in transit (b)(4)
>
> We have separated each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if you have any questions.
>
> Best Wishes,
>
> Lizzie
>
> **Lizzie Gallantine, Ph.D** | Project Manager Europe | Avery Dennison Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
>
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>
> On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:
>
> > Good morning Ms. Bartakovics,
> >
> > Thank you for keeping us updated on your submission. I think your approach is reasonable for your purpose. We would appreciate, in your response document/letter, if you can guide us the location of your (b)(4) this will help us to quickly find them without missing any important information.
> >
> > Best regards,
> > Yongqing
> >
> > ---
> >
> > **From:** Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> > **Sent:** Tuesday, August 29, 2023 10:16 AM
> > **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> > **Cc:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> > **Subject:** Re: [EXTERNAL] K230645 Update

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good Morning Mr. Chen-

I am winding down my time with Avery Dennison and therefore met with the team this morning to discuss our response to the hold letter for K230645. I just wanted to confirm that the response needs to be submitted as an e-copy that has been verified through the e-submitter tool. Since there are additional reports and documents to submit, we plan to add those documents into folders as attachments to our response. There are quite a few questions to address so it seemed as though a folder approach made the most sense for organizational purposes. If there is a better approach, please let me know so we may adopt that template.

Much appreciated.

Have a nice day.

Regards,

Lisa Bartakovics
Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical

m: (b)(6)
7100 Lindsay Dr. Mentor, OH 44060

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averydennison.com medical.averydennison.com

On Mon, Aug 21, 2023 at 9:02 AM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Hi Lizzie,
>
> Thank you very much for sending me your contact info. Look forward to working with you on this submission.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Sent:** Monday, August 21, 2023 9:15 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>; Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Hi Yongqing
>
> I hope you're well! My contact information is:
>
> Lizzie Gallantine, PhD., Project Manager Europe
> Avery Dennison Medical Ltd.
> IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland
> Telephone: (b)(6)
> e-mail: elizabeth.gallantine@eu.averydennison.com
>
> Thank you!
>
> Lizzie
>
> **Lizzie Gallantine, Ph.D** | Project Manager Europe | Avery Dennison Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
>
> **Error! Filename not specified.**
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>
> On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Dear Ms. Gallantine,

Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our system? Thank you!

Error! Filename not specified.
Please let me know if you have any questions.

Best regards,
Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com>
Sent: Friday, August 18, 2023 4:24 PM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen-

I hope you have had an enjoyable summer and this email finds you well.

I am writing to inform you that I am leaving Avery Dennison at the end of the month and will therefore no longer be the point of contact for submission K230645.

Elizabeth Gallantine, copied on this message, will serve as the point of contact for future correspondence regarding the Avery Dennison submission. She will provide updates regarding the response to the hold letter and coordinate all future correspondence.

It has been a pleasure working with you and I hope to work with you again in the future.

Please let me know if you have any questions.

Regards,
Lisa Bartakovics

On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Ms. Bartakovics,
>
> Thank you for keeping me updated and please let me know if you have any questions for us.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> **Sent:** Thursday, June 1, 2023 12:20 PM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** regulatoryaffairs regulatoryaffairs <regulatoryaffairs@eu.averydennison.com>
> **Subject:** [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Dear Mr. Chen-
>
> Thank you again for the teleconference, we greatly appreciate your time and that of the team.
>
> **(b)(4)**
>
> Therefore, Avery Dennison plans to respond to all of the points within the Hold Letter for K230645 in early September. I wanted to provide an update so that you are aware we are working on the items identified in the Hold Letter and will respond back to you as soon as (b)(4) s completed.
>
> Please let me know if you have any further questions.
>
> Thank you and have a nice day.
>
> Regards,

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Lisa Bartakovics
Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical

m: (b)(6)
7100 Lindsay Dr. Mentor, OH 44060

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averydennison.com medical.averydennison.com

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For details about the personal information we process and why, please see our Privacy Notice
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Lisa Bartakovics
Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical

m: (b)(6)
7100 Lindsay Dr. Mentor, OH 44060

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

BIOCOMPATIBILITY REVIEW OF K230645, AVERY DENNISON MEDICAL LTD.

To:	Yongqing Chen, CDRH\OHT4\DHT4B\THT4B2
From:	Sojan Abraham, CDRH\OHT4\DHT4B\THT4B1
Through:	Clarence Murray III, Assistant Director, CDRH\OHT4\DHT4B\THT4B1
Consult Type:	Biocompatibility
Consult:	CON237401
Submission:	K230645
Device Name:	BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Sponsor:	Avery Dennison Medical Ltd.
Date:	04/24/2023

REVIEW SCOPE/BACKGROUND

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approved: OMB No. 0910-0120
Expiration Date: June 30, 2023
See PRA Statement on last page.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number *(If known)*
01/19/2023	(b)(4)	

SECTION A TYPE OF SUBMISSION

PMA & PDP
- ☐ Original
- ☐ Modular Submission
- ☐ Amendment
- ☐ Report (annual or PAS)
- ☐ Report Amendment
- ☐ Other:
  - ☐ Premarket Report (reprocessed SUD)
  - ☐ Licensing Agreement

PMA/PDP Supplement
- ☐ 180 day - PAS protocol or labeling change, location change, trade name change
- ☐ 180 day - Design or labeling change
- ☐ Special CBE
- ☐ Panel Track
- ☐ 30-day Notice
- ☐ Real-time Review
- ☐ Amendment to PMA/PDP Supplement

510(k)
- ☒ Original Submission:
  - ☒ Traditional
  - ☐ Special
  - ☐ Abbreviated
  - ☐ 3rd Party Traditional
  - ☐ 3rd Party Special
  - ☐ 3rd Party Abbreviated
  - ☐ Dual Track (Dual 510(k) and CLIA Waiver by Application)
- ☐ Amendment
- ☐ Supplement

CLIA

CLIA Categorization Record (CR)
- ☐ Original
- ☐ Amendment

CLIA Waiver by Application (CW)
- ☐ Original
- ☐ Amendment
- ☐ Supplement

Q-Submission
- ☐ Pre-Submission
- ☐ Informational Meeting
- ☐ Submission Issue Meeting
- ☐ Day 100 Meeting
- ☐ Agreement Meeting
- ☐ Determination Meeting
- ☐ Study Risk Determination
- ☐ Other *(Specify below)*

IDE
- ☐ Original IDE:
  - ☐ Amendment to Original IDE
- ☐ Supplement:
  - ☐ Amendment to Supplement
- ☐ Report:
  - ☐ Amendment to Report

HDE
- ☐ Original Submission
- ☐ Amendment to Original
- ☐ Report
- ☐ Report Amendment
- ☐ HDE Supplement:
  - ☐ 75-day Supplement
  - ☐ 30-day Notice
  - ☐ Special CBE
  - ☐ Amendment to Supplement

Class II Exemption Petition
- ☐ Original Submission
- ☐ Additional Information

Emergency Use Authorization
- ☐ Original
- ☐ Supplement
- ☐ Amendment
- ☐ Report

De Novo
- ☐ Original:
  - ☐ Direct
  - ☐ Post-NSE
- ☐ Amendment
- ☐ Supplement

Pre-Emergency Use Authorization
- ☐ Original
- ☐ Supplement
- ☐ Amendment

Other Submission
- ☐ 513(g)
- ☐ Appeal
- ☐ Other *(Briefly describe submission below)*

Expanded Access to Devices
- ☐ Compassionate Use Request **NOT associated with an IDE**
- ☐ Follow-up Report for Compassionate Use **NOT associated with an IDE**
- ☐ Emergency Use Follow-up Report **NOT associated with an IDE**

SECTION B APPLICANT / SPONSOR

Company/Institution Name		Establishment Registration Number/FEI *(If known)*
Avery Dennison Medical Ltd.		6408266P
Street Address		**City**
IDA Business Park, Ballinalee Road, Longford		Longford
State/Province	**ZIP/Postal Code**	**Country**
Longford	N39 RC80	Ireland

Contact Name	Contact Title
Lisa Bartakovics	Senior Director Global Regulatory Affairs and Quality
Division Name *(if applicable)*	**Phone Number *(including area code)***
N/A	+1(312) 206-6159
Fax Number *(including area code)*	**Contact Email Address**
	regulatoryaffairs@eu.averydennison.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION C OFFICIAL CORRESPONDENT (e.g., may be a consultant and/or 510(k) Third Party) (if different from Section B)

Company/Institution Name		Establishment Registration Number/FEI *(if known)*
Street Address		City
State/Province	ZIP/Postal Code	Country

Contact 1 Name	Contact 1 Title
Contact 1 Division Name *(if applicable)*	Contact 1 Phone Number *(including area code)*
Contact 1 Fax Number *(including area code)*	Contact 1 Email Address
Contact 2 Name	Contact 2 Title
Contact 2 Division Name *(if applicable)*	Contact 2 Phone Number *(including area code)*
Contact 2 Fax Number *(including area code)*	Contact 2 Email Address
Contact 3 Name	Contact 3 Title
Contact 3 Division Name *(if applicable)*	Contact 3 Phone Number *(including area code)*
Contact 3 Fax Number *(including area code)*	Contact 3 Email Address

To add another set of Section C items, please click on the button to the right. May be repeated as needed. Add Section C

SECTION D INTENDED USE POPULATION

Check all that apply.

- ☒ Adults Only (greater than 21 years of age)
- ☐ Adults and Pediatrics
- ☐ Neonate/Newborn (birth through 28 days)
- ☐ Infant (from 29 days to 2 years of age)
- ☐ Child (from 2 years to 12 years of age)
- ☐ Adolescent (from 12 years to 18 years of age)
- ☐ Transitional Adolescent A (18 through 21 years of age)
- ☐ Transitional Adolescent B (18 through 21 years of age)
- ☐ Other *(Specify below)*

SECTION E PRODUCT INFORMATION – APPLICABLE TO ALL SUBMISSIONS

	Trade Name
1	BeneHold™ Surgical Incise Drape with CHG antimicrobial II
2	
3	
4	
5	
	Common/Generic Name *(Include if no Trade Name)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION F PRIOR RELATED SUBMISSIONS FOR THIS DEVICE OR STUDY

FDA document numbers of all prior related submissions *(regardless of outcome)* or state no prior submission in box 1.

1 No Prior Submission	2	3
4	5	6
7	8	9
10	11	12

SECTION G PRODUCT CLASSIFICATION – APPLICABLE TO ALL SUBMISSIONS

Product Code(s) *(when applicable) (If more than one, please separate with commas.)*

KKX

C.F.R. Section *(If applicable)*	Classification Panel/Medical Specialty
878.4370	Surgical Drape and Drape Accessories

Device Class

☐ Class I ☒ Class II ☐ Class III ☐ Unclassified

SECTION H1 REASON FOR APPLICATION – PMA, PDP, OR HDE

☐ New Device
☐ STED

☐ Post-approval Study Protocol

☐ HDE Request for Annual Distribution Number (ADN)

☐ Change in Design, Component, or Specification:
- ☐ Software/Hardware
- ☐ Color Additive
- ☐ Material
- ☐ Specifications
- ☐ Other *(Specify below)*

☐ Location Change:
- ☐ Manufacturer
- ☐ Sterilizer
- ☐ Packager

☐ Report Submission:
- ☐ Annual or Periodic
- ☐ Post-approval Study

☐ Process Change:
- ☐ Manufacturing
- ☐ Packaging
- ☐ Sterilization
- ☐ Vendor/Supplier Change
- ☐ Other *(Specify below)*

☐ Labeling Change:
- ☐ Indications
- ☐ Instructions
- ☐ PAS update
- ☐ Performance Characteristics
- ☐ Shelf Life
- ☐ Trade Name
- ☐ Other *(Specify below)*

☐ Amendment:
- ☐ Withdrawal
- ☐ Change in Ownership
- ☐ Change in Correspondent
- ☐ Change of Address
- ☐ Request for Extension
- ☐ Response to FDA Correspondence
- ☐ Other *(Specify below)*

☐ Bundle Submission – *If this is selected, list in the spaces below any PMAs in the Bundle.*

1	2	3
4	5	6
7	8	9

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION H2 REASON FOR APPLICATION – IDE

☐ Original IDE

☐ Supplement:
- ☐ New Study/New Protocol
- ☐ Change in Correspondent
- ☐ Change in Manufacturer
- ☐ Change in Sponsor
- ☐ Change in Design
- ☐ Change in Informed Consent
- ☐ Change in Manufacturing
- ☐ Change in Protocol
- ☐ 5-Day Notice – Device or Manufacturing
- ☐ 5-Day Notice – Protocol
- ☐ Compassionate Use Request (under an IDE)
- ☐ Live Case Request
- ☐ Request Deviation from Protocol
- ☐ Expansion of Study (Study/Sites)
- ☐ Extension of Time to Submit Annual Report or Respond to FDA Letter

Supplement *(Continued)*
- ☐ Request for Waiver
- ☐ IRB Certification
- ☐ Request for CMS Recategorization
- ☐ Study Resumed
- ☐ Study Suspension
- ☐ Other *(Specify below)*

☐ Report:
- ☐ Adverse Effect
- ☐ Final, Study Completed
- ☐ Annual Progress
- ☐ Interim Progress
- ☐ Semiannual Investigator List
- ☐ Failure to Obtain Informed Consent
- ☐ Compassionate Use Follow-up
- ☐ Emergency Use
- ☐ Live Case Follow-up
- ☐ Completion of Patient Enrollment
- ☐ Completion of Patient Follow-up
- ☐ Other *(Specify below)*

☐ Amendment to Original IDE:
- ☐ Amendment Before Final Decision
- ☐ Response to Refuse to Accept
- ☐ Response to Disapproval
- ☐ Response to Approval with Conditions
- ☐ Withdrawal
- ☐ Other *(Specify below)*

☐ Amendment to Supplement:
- ☐ Response to Disapproval
- ☐ Response to Approval with Conditions
- ☐ Withdrawal
- ☐ Amendment Before Final Decision (additional Information)
- ☐ Other *(Specify below)*

☐ Amendment to Report:
- ☐ Response to Deficiency Letter
- ☐ Withdrawal
- ☐ Amendment Before Final Decision (additional Information)
- ☐ Other *(Specify below)*

SECTION H3 REASON FOR SUBMISSION – Q-SUBMISSION

☐ Pre-Submission:
- ☐ Request Face-to-Face Meeting
- ☐ Request Teleconference
- ☐ Request Email Response
- ☐ Submit Meeting Minutes
- ☐ Request Meeting Minutes Disagreement T-con

☐ Submission Issue Meeting:
- ☐ Request Face-to-Face Meeting
- ☐ Request Teleconference
- ☐ Request Email Response
- ☐ Submit Meeting Minutes
- ☐ Request Meeting Minutes Disagreement T-con

☐ Additional Information

☐ Change in Legal Entity:
- ☐ Change in Correspondent
- ☐ Change in Sponsors
- ☐ Change in Manufacturer
- ☐ Other *(Specify below)*

☐ Agreement Meeting:
- ☐ Request Face-to-Face Meeting
- ☐ Request Teleconference

☐ Determination Meeting:
- ☐ Request Face-to-Face Meeting
- ☐ Request Teleconference

☐ Informational Meeting:
- ☐ Request Face-to-Face Meeting
- ☐ Request Teleconference
- ☐ Submit Meeting Minutes
- ☐ Request Meeting Minutes Disagreement T-Con

☐ Other *(Specify)*:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

SECTION H4 REASON FOR SUBMISSION – 510(k)

- ☒ Original
- ☐ Withdrawal of Original
- ☐ Amendment Before Final Decision:
  - ☐ Change in Ownership
  - ☐ Change in Correspondent
  - ☐ Withdrawal
- ☐ Amendment After Final Decision
- ☐ Supplement:
  - ☐ Response to Refuse to Accept (RTA)
  - ☐ Response to Additional Information Request
  - ☐ Withdrawal
- ☐ Reprocessed SUD
- ☐ Corrective Action
- ☐ STED
- ☐ Third Party *(Complete Section C)*
- ☐ Other Reason *(Specify)*:

Information on devices to which substantial equivalence is claimed *(If known)*

	510(k) Number	*Trade Name*	*Submitter*	*Product Code*
Primary Predicate (A)	(b)(4)			
Predicate or Reference Device (B)	K202208	BeneHold™ Surgical Incise Drape with CHG antimicrobial	Avery Dennison Belgie BV	KKX

To add another Predicate or Reference Device (B) entry row, please click on the button to the right. May be repeated as needed. Add Device Information

SECTION H5 DE NOVO SUBMISSIONS

- ☐ Post NSE De Novo: Number of the 510(k) that was NSE'd in the past 30 days:
- ☐ Withdrawal

SECTION H6 REASON FOR APPLICATION – CLIA

Includes CLIA Parent Document number, CR number, or CW number.

- ☐ **CLIA Categorization Record (CR):**
  - ☐ CLIA Categorization of marketed device (include marketing submission number)
  - ☐ CLIA Categorization of device exempt from premarket review
  - ☐ Additional information regarding an open CR (include CR number)
- ☐ **CLIA Waiver by Application (CW):**
  - ☐ Request for CLIA Waiver by Application for marketed device (include marketing submission number)
  - ☐ Request for Dual 510(k) Clearance and CLIA Waiver by Application (include Pre-submission number)
  - ☐ Response to FDA correspondence
  - ☐ Additional information regarding an open CW (include CW number)
- ☐ **Other Reason** *(Specify)*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SECTION I MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION

Applicable only to IDEs

Note: Submission of this information does not affect Registration and Listing.	FDA Document Number *(if known)*

☒ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☒ Contract Sterilizer ☐ Contract Manufacturer ☐ Repackager/Relabeler

(b)(4)

☒ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☐ Contract Sterilizer ☒ Contract Manufacturer ☐ Repackager/Relabeler

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Contact 2 Name	Contact 2 Title
Contact 2 Division Name *(if applicable)*	Contact 2 Phone Number *(including area code)*
Contact 2 Fax Number *(including area code)*	Contact 2 Email Address
Contact 3 Name	Contact 3 Title
Contact 3 Division Name *(if applicable)*	Contact 3 Phone Number *(including area code)*
Contact 3 Fax Number *(including area code)*	Contact 3 Email Address

To add another set of Section I items, please click on the button to the right. May be repeated as needed. Add Section I

SECTION J UTILIZATION OF STANDARDS

Note: Please see guidance document titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices" for details on the Declaration of Conformity.

How to fill out this section:

Recognition Number: State the FDA recognition number. If the standard is not recognized, write NR.

Declaration of Conformity or General Use: Select 'Declaration of Conformity' if including a "Declaration of Conformity to a Recognized Standard" statement. For all other uses, select 'General Use' and indicate if you have made deviations from the Recognized/Non-recognized standard.

Standard: State the Standards Development Organization (SDO), the Designation Number (including year), and the Title.

Location: State the section and/or the page number(s) in the submission where the standard is applied.

Examples

	Recognition Number	Declaration of Conformity or General Use		Standards Development Organization (SDO), Designation Number-Year, and Title	Location
1 X	8-185	Declaration of Conformity	*If General Use,* Deviation?	ASTM F451-08, standard specification for acrylic bone cement.	Section 3, p. 15
2 X	3-44	General Use	*If General Use,* Deviation? Yes	AAMI ANSI BP22:1994 (R) 2011 Blood Pressure Transducers	Section 4, p. 32

Entries for Utilization of Standards

	Recognition Number	Declaration of Conformity or General Use		Standards Development Organization (SDO), Designation Number-Year, and Title	Location
1 X	6-296	Declaration of Conformity	*If General Use,* Deviation?	ANSI AAMI PB70:2012 Liquid barrier performance and classification of protective apparel and drapes intended for use in	Section 18
2 X	2-258	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-4 Biological evaluation of medical devices--Part 4: Selection of tests for interactions with blood	Section 15
3 X	2-245	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-5 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity.	Section 15
4 X	2-275	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-7 Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals [Including: Technical Corrigen	Section 14
5 X	2-296	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-10 Biological evaluation of medical devices - Part 10: Tests for skin sensitization.	Section 15
6 X	2-255	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-11 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity.	Section 15
7 X	2-237	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-17 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances	Section 15

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8 X	2-276	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-18 Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk	Section 15
9 X	2-291	Declaration of Conformity	*If General Use,* Deviation?	ISO 10993-23 Biological evaluation of medical devices - Part 23: Tests for irritation	Section 15
10 X	2-250	Declaration of Conformity	*If General Use,* Deviation?	ASTM F756-17 Standard Practice for Assessment of Hemolytic Properties of Materials	Section 15
11 X	14-529	Declaration of Conformity	*If General Use,* Deviation?	ISO 11135:2014 Sterilization Of Health Care Products - Ethylene Oxide - Requirements For Development, Validation And Routine Co	Section 14
12 X	14-502	Declaration of Conformity	*If General Use,* Deviation?	ANSI AAMI ISO 11138-1 Sterilization Of Health Care Products - Biological Indicators - Part 1: General Requirements.	Section 14
13 X	14-514	Declaration of Conformity	*If General Use,* Deviation?	ANSI AAMI ISO 11737-1:2018 Sterilization of health care products. Microbiological methods. Determination of a population of microorg	Section 14
14 X	14-540	Declaration of Conformity	*If General Use,* Deviation?	ANSI AAMI ISO 11737-2:2019 Sterilization of medical devices. Microbiological methods. Tests of sterility performed in the definitio	Section 14
15 X	5-134	Declaration of Conformity	*If General Use,* Deviation?	ISO 15223-1:2021 General requirements.Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part	Section 13
16 X	6-402	Declaration of Conformity	*If General Use,* Deviation?	ASTM F1670/F1670M-17: Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Synthetic Bl	Section 18
17 X	6-306	Declaration of Conformity	*If General Use,* Deviation?	ASTM F1671:2013 Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne	Section 18
18 X	14-497	Declaration of Conformity	*If General Use,* Deviation?	ASTM F1980:2021 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.	Section 14
19 X	14-570	Declaration of Conformity	*If General Use,* Deviation?	USP <85> Bacterial Endotoxins Test	Section 15
20 X	14-564	Declaration of Conformity	*If General Use,* Deviation?	USP <161> Medical Devices-Bacterial Endotoxin and Pyrogen Tests	Section 15

To add another row for Section J, please click on the button to the right. May be repeated as needed.
(To remove a particular row, please click on the "X" button at the beginning of the row.)

Add Row/Standard

SECTION K UTILIZATION OF CDRH GUIDANCE DOCUMENTS

How to fill out this section:

Title: Enter the title of the guidance documents used in the preparation of your premarket submission. CDRH guidance documents can be found at *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm*.

Entries for Utilization of CDRH Guidance Documents

	Title of Guidance Document
1 X	Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"
2 X	Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile
3 X	Guidance on Premarket Notification [510(k)] Submissions for Surgical Gowns and Surgical Drapes
4 X	eCopy Program for Medical Device Submissions
5 X	Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions

To add another row for Section K, please click on the button to the right. May be repeated as needed.
(To remove a particular row, please click on the "X" button at the beginning of the row.)

Add Row/Document

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average .5 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

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Major Deficiency - Question 8

(b)(4)

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(b)(4)

(b)(4)

Project Number (b)(4)
Versio (b)(4)

CONFIDENTIAL

Biological Risk Assessment

Device Name: BeneHold CHG Surgical Incise Drape (b)(4)

Prepared for:

Avery Dennison Medical
(b)(4)
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

Prepared by:

(b)(4)

(b)(4)

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AVERY DENNISON	**Operational Qualification Report** **(b)(4)** **CHG Incise coating** **(Formulation (b)(4)**	**Validation n°: (b)(4)** **(b)(4)** **Version: (b)(4)** **Date: 27-Apr-2023**

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"Classification: Avery Dennison - Confidential"

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For record.

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Tuesday, October 24, 2023 11:26 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <kelsey.kaht@averydennison.com>; Annelies Luyts <annelies.luyts@eu.averydennison.com>; Shan Perkin <shan.perkin@eu.averydennison.com>; Sarah Suy <sarah.suy@eu.averydennison.com>
Subject: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen

Please find in attachment our responses to your comments with the supporting documentation.

Thank you once again for your support with this submission. Please let us know if you have any further questions.

Kind Regards,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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Section 9 – Declaration of Conformity

I certify in my capacity as Senior Director Global Regulatory Affairs and Quality of Avery Dennison Corporation that the subject of this traditional 510(k), Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II conforms to the following FDA-recognized standards:

[Recognition number 6-296] ANSI AAMI PB70:2012 Liquid barrier performance and classification of protective apparel and drapes intended for use in health care facilities.

[Recognition number 2-258] ISO 10993-1 Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing Within a Risk Management Process.

[Recognition number 2-248] ISO 10993-4 Biological evaluation of medical devices--Part 4: Selection of tests for interactions with blood.

[Recognition number 2-245] ISO 10993-5 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity.

[Recognition number 2-275] ISO 10993-7 Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals [Including: Technical Corrigendum 1 (2009)].

[Recognition number 2-296] ISO 10993-10 Biological evaluation of medical devices - Part 10: Tests for skin sensitization.

[Recognition number 2-255] ISO 10993-11 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity.

[Recognition number 2-237] ISO 10993-17 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances.

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[Recognition number 2-276] ISO 10993-18 Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process.

[Recognition number 2-291] ISO 10993-23 Biological evaluation of medical devices - Part 23: Tests for irritation.

[Recognition number 2-250] ASTM F756-17 Standard Practice for Assessment of Hemolytic Properties of Materials.

[Recognition number 14-529] ISO 11135:2014 Sterilization of Health Care Products - Ethylene Oxide - Requirements for Development, Validation and Routine Control of A Sterilization Process for Medical Devices, [Including: Amendment 1 (2018)].

[Recognition number 14-502] ANSI AAMI ISO 11138-1 Sterilization of Health Care Products - Biological Indicators - Part 1: General Requirements.

[Recognition number 14-514] ANSI AAMI ISO 11737-1:2018 Sterilization of health care products. Microbiological methods. Determination of a population of microorganisms on products.

[Recognition number 14-540] ANSI AAMI ISO 11737-2:2019 Sterilization of medical devices. Microbiological methods. Tests of sterility performed in the definition, validation and maintenance of a sterilization process.

[Recognition number 5-134] ISO 15223-1:2021 General requirements. Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.

[Recognition number 6-402] ASTM F1670/F1670M-17: Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Synthetic Blood.

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[Recognition number 6-306] ASTM F1671:2013 Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System.

[Recognition number 14-497] ASTM F1980:2021 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

[Recognition number 14-570] USP <85> Bacterial Endotoxins Test.

[Recognition number 14-564] USP <161> Medical Devices-Bacterial Endotoxin and Pyrogen Tests.

All normative requirements were met, alternative series of tests were not performed, all requirements were applicable to the device, no deviations from the standard were applied, and there were no differences between the tested device and the device to be marketed.

All tests were performed by the following laboratories / facilities:

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• Avery Dennison België BV
Tieblokkenlaan 1,
Turnhout B2300
Belgium
medical.averydennison.com

(b)(4)

(b)(6)

Lisa Bartakovics
Senior Director Global Regulatory Affairs and Quality

February 14, 2023

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RM4620
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-9433

Premarket Notification 510(k) Review

Date: October 25, 2023

Reviewer: Yongqing Chen

510(k)# K230645/S001 Subject: Traditional

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Contact Name: Elaine Minagh	**Contact Title:** Regulatory Affairs Manager
Correspondent Firm: Avery Dennison Medical Ltd.	**Phone:** (b)(6) **Email:** elaine.minagh@eu.averydennison.com
Received Date: September 25, 2023	**Due Date:** October 25, 2023
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories

Predicate Devices:

Submission #	Pro Code	Device Trade Name	Applicant
K202208	KKX	BeneHold Surgical Incise Drape with CHG antimicrobial	Avery Dennison Belgie BVBA

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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PREMARKET NOTIFICATION
TRUTHFUL AND ACCURATE STATEMENT

[As Required by 21 CFR 807.87(k)]

I certify that, in my capacity as a Director, R&D & ATS of Avery Dennison Medical Ltd., I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

(b)(6)

Robert Schneider

3 March 2023

K_____

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RMONR
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Subject Matter Expert (SME) Review

Date: April 27, 2023

SME Reviewer: Lianji Jin

Expertise: Chemical Characterization

Submission # K230645

Applicable Review Guide (if used): Not Applicable

Is this review for a Pre-Submission, Submission Issue Request, or Expedited Program (Breakthrough/STeP) Interaction? No

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Optional Classification Information:	
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories
Rx/OTC: Rx	

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Digital Signature Concurrence Table (Doc ID: 04504.04.00)	
For each of the specific issues identified in the recommended requests to the applicant above, I have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s).	
Reviewer Sign-Off	Lianji Jin -S Digitally signed by Lianji Jin -S Date: 2023.05.07 14:57:32 -04'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Dear Ms. Callantine,

Thank you again for working with us on this submission. (b)(4)

(b)(4)

(b)(4)

Please let me know if you have other questions.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Sent: Tuesday, October 24, 2023 11:26 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <kelsey.kaht@averydennison.com>; Annelies Luyts <annelies.luyts@eu.averydennison.com>; Shan Perkin <shan.perkin@eu.averydennison.com>; Sarah Suy <sarah.suy@eu.averydennison.com>

Subject: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

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Dear Mr. Chen

Please find in attachment our responses to your comments with the supporting documentation.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Thank you once again for your support with this submission. Please let us know if you have any further questions.

Kind Regards,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: + (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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For details about the personal information we process and why, please see our Privacy Notice<https://www.averydennison.com/en/home/legal-and-privacy-notices.html>

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Dear Ms. Minagh,

Thank you for working with us hardly to address our concerns. (b)(4)

(b)(4)

Please let me know your thoughts. Thank you!

Best regards,

Yongqing

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Sent: Thursday, October 19, 2023 9:24 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: K230645@docs.fda.gov

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dr Yongqing

It is a pleasure to work with you on this submission.

We have received your query and are working very hard to formulate a response that will satisfy you.

However, I fear that we do not have enough time to coordinate this to a satisfactory level.

Is it possible that we could receive an extension until Monday the 23rd of October?

Many thanks and best regards

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)

elaine.minagh@eu.averydennison.com<mailto:firstname.lastname@eu.averydennison.com> | medical.averydennison.com<https://medical.averydennison.com/en/home.html>

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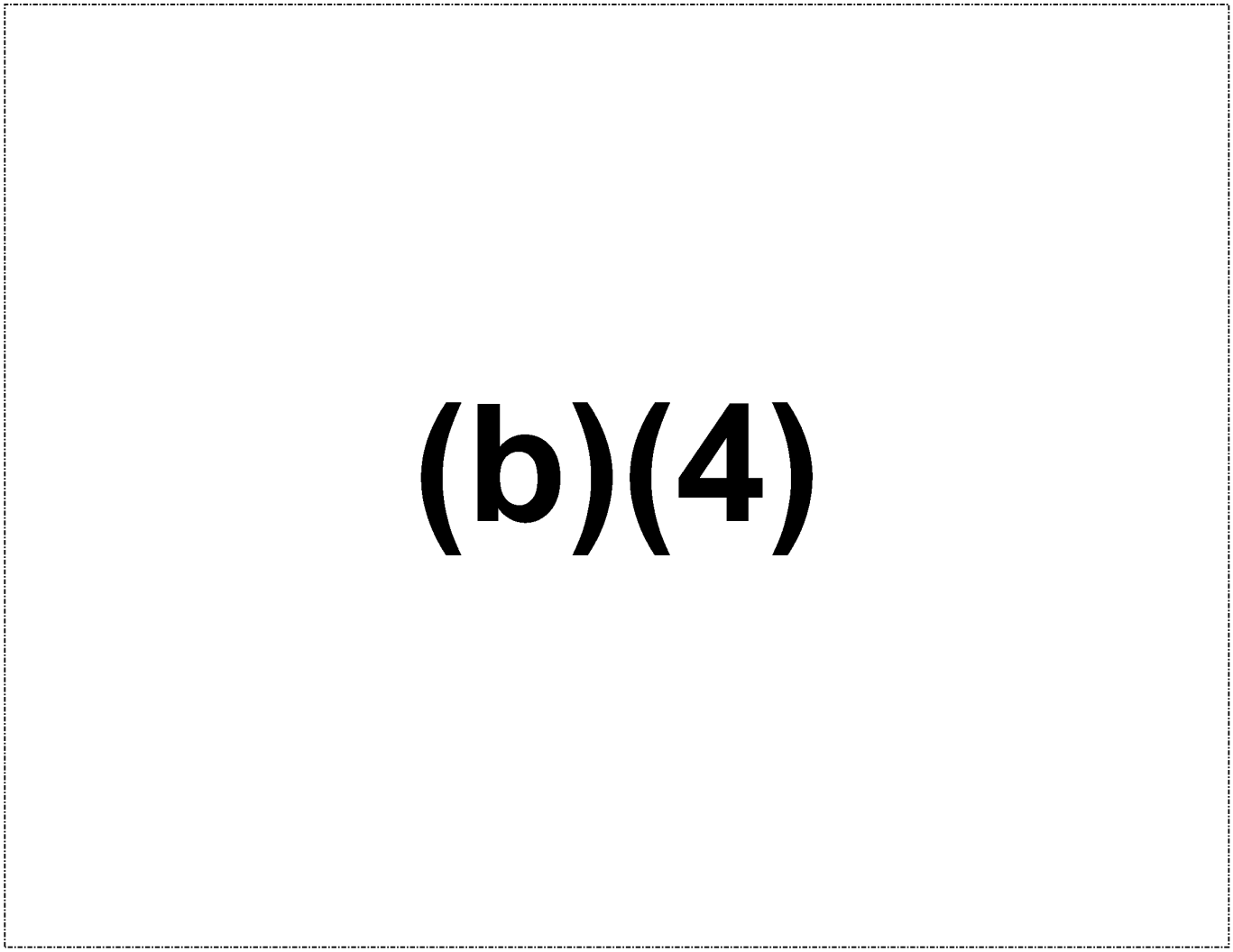
On Tue, 17 Oct 2023 at 19:30, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Elaine Minagh,

Thank you for working with us on this submission. We are reviewing the provided supplement S001 and have the following information for you to address. Please provide

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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your response at your early convenience but not later than the COB of this Thursday (October 19, 2023).



Please contact me if you have any questions.

Best regards,

Yongqing

From: Chen, Yongqing

Sent: Tuesday, October 10, 2023 8:11 AM

To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for letting me know this contact change. Good luck for your new move!

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

you.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Tuesday, October 10, 2023 7:43 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Dear Mr. Chen,

I hope you are well!

I am writing to inform you that I am leaving Avery Dennison at the end of this month and will therefore no longer be the point of contact for the current submission K230645.

My colleague Elaine Minagh, copied on this message, will become the point of contact for future correspondence regarding the Avery Dennison submission. I have provided Elaine's contact information below:

Elaine Minagh, Regulatory Affairs Manager

Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73, Ireland

Telephone: (b)(6)

e-mail: elaine.minagh@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>

Thank you for your support on this submission.

Please let me know if you have any questions.

Best Wishes,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>> wrote:

Thank you for the update Mr Chen!

Have a great day,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Dr. Gallantine,

The supplement has been received on Monday and the team review has been starting on Monday (09/25/2023).

Respectfully,

Yongqing

From: Chen, Yongqing

Sent: Tuesday, September 26, 2023 8:27 AM

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

To: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for the update. It might take one or more days for DCC to notify the appropriate Center/Office. I will let you know when the supplement has been assigned to me.

Respectfully,

Yongqing

From: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Tuesday, September 26, 2023 8:16 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good Morning Mr Chen,

The USB file has now arrived in Silver Creek. Could you let us know when you have received it, please?

Thank you,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Dr. Gallantine,

Thank you for letting us know and look forward to working with you on this submission.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Monday, September 25, 2023 5:31 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Dear Mr Chen,

We have completed our response to the hold letter for K230645. The documents on a USB file were shipped on Friday 22 September and are currently in transit (b)(4) (b)(4).

We have separated each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if you have any questions.

Best Wishes,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Good morning Ms. Bartakovics,

Thank you for keeping us updated on your submission. I think your approach is reasonable for your purpose. We would appreciate, in your response document/letter, if you can guide us the location of your **(b)(4)** this will help us to quickly find them without missing any important information.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Tuesday, August 29, 2023 10:16 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Good Morning Mr. Chen-

I am winding down my time with Avery Dennison and therefore met with the team this morning to discuss our response to the hold letter for K230645. I just wanted to confirm that the response needs to be submitted as an e-copy that has been verified through the e-submitter tool. Since there are additional reports and documents to submit, we plan to add those documents into folders as attachments to our response. There are quite a few questions to address so it seemed as though a folder approach made the most sense for organizational purposes. If there is a better approach, please let me know so we may adopt that template.

Much appreciated.

Have a nice day.

Regards,

Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: **(b)(6)**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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On Mon, Aug 21, 2023 at 9:02â€¯AM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Hi Lizzie,

Thank you very much for sending me your contact info. Look forward to working with you on this submission.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Monday, August 21, 2023 9:15 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>; Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Hi Yongqing

I hope you're well! My contact information is:

Lizzie Gallantine, PhD., Project Manager Europe

Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland

Telephone: (b)(6)

e-mail: elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>

Thank you!

Lizzie

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Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: + (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Gallantine,

Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our system? Thank you!

Error! Filename not specified.

Please let me know if you have any questions.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Friday, August 18, 2023 4:24 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>; Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Dear Mr. Chen-

I hope you have had an enjoyable summer and this email finds you well.

I am writing to inform you that I am leaving Avery Dennison at the end of the month and

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will therefore no longer be the point of contact for submission K230645.

Elizabeth Gallantine, copied on this message, will serve as the point of contact for future correspondence regarding the Avery Dennison submission. She will provide updates regarding the response to the hold letter and coordinate all future correspondence.

It has been a pleasure working with you and I hope to work with you again in the future.

Please let me know if you have any questions.

Regards,

Lisa Bartakovics

On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Bartakovics,

Thank you for keeping me updated and please let me know if you have any questions for us.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Thursday, June 1, 2023 12:20 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: regulatoryaffairs regulatoryaffairs <regulatoryaffairs@eu.averydennison.com<mailto:regulatoryaffairs@eu.averydennison.com>>

Subject: [EXTERNAL] K230645 Update

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Dear Mr. Chen-

Thank you again for the teleconference, we greatly appreciate your time and that of the team.

(b)(4)

Therefore, Avery Dennison plans to respond to all of the points within the Hold Letter for K230645 in early September. I wanted to provide an update so that you are aware we are working on the items identified in the Hold Letter and will respond back to you as soon as (b)(4) is completed.

Please let me know if you have any further questions.

Thank you and have a nice day.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Regards,

Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: (b)(6)

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Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

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(b)(4)

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(b)(4)

DOCUMENT Final Report

DATE September 19, 2022

PRI STUDY# (b)(4)

TITLE Microbiology Definitive Study; (b)(4)

(b)(4)

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From: DCCLetters@fda.hhs.gov [DCCLetters@fda.hhs.gov]
Sent: 3/8/2023 5:22:48 PM
To: regulatoryaffairs@eu.averydennison.com
CC: DCCLetters@fda.hhs.gov
Subject: K230645 Acknowledgement Letter
Attachments: K230645-Acknowledgement Letter.pdf

March 8, 2023

Thank you for your submission. We have attached your acknowledgement letter for your records. If you have any questions about your acknowledgement letter, please contact us at DCCmailroom@fda.hhs.gov. Please do not reply to this email.

*** This is a system-generated email notification ***

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U.S. FOOD & DRUG ADMINISTRATION

Acknowledgement Letter

03/08/2023

Lisa Bartakovics, Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road
Longford,
Longford N39 RC80 IRELAND

Dear Lisa Bartakovics:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your submission. This submission has been assigned the unique document control number below. All future correspondence regarding this submission should be identified prominently with the number assigned and should be submitted to the Document Control Center at the address listed below. Failure to do so may result in processing delays. If you believe the information identified below is incorrect, please contact the Office of Product Evaluation and Quality (OPEQ) submission support at (301) 796-5640 or OPEQSubmissionSupport@fda.hhs.gov .

Submision Number: K230645
Received: 03/08/2023
Applicant: Avery Dennison Medical Ltd.
Device: BeneHold Surgical Incise Drape with CHG antimicrobial II

We will notify you when the review of this submission document has been completed or if any additional information is required. If you are submitting new information about a submission for which we have already made a final decision, please note that your submission will not be re-opened. For information about CDRH review regulations and policies, please refer to http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm .

Sincerely yours,

Center for Devices and Radiological Health

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Section 12 – Substantial Equivalence Discussion

(b)(4)

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Attachment 12.1 MVTR Testing (BeneHold II vs Predicates) Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

MVTR Test Report for BeneHold Surgical Incise Drape with CHG Antimicrobial II (b)(4)

Approval Signatures

The following signatures will be captured electronically via MasterControl.

(b)(4)

Revision History

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 12.2 Tensile Elongation Testing (BeneHold II vs Predicates) Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

AVERY DENNISON	Document Type:	Design Verification Report
	Document Title:	Tensile and Elongation Testing Report for (b)(4) BeneHold Surgical Incise Drape with CHG
	Document Number, Revision:	(b)(4)

Tensile and Elongation Testing Report for (b)(4) BeneHold Surgical Incise Drape with CHG

Approval Signatures

The following signatures will be captured electronically in the electronic quality management system. Below is a list of required approvers and associated titles. By signing, individuals indicate their review and approval of this report.

(b)(4)

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Attachment 12.3

Antimicrobial Efficacy Report for BeneHold Surgical Incise Drape with CHG II (b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-4745; Released by CDRH on 08-26-2024

(b)(4)

July 12th, 2022

Antimicrobial Performance of Avery Dennison's CHG Incise Drape (b)(4)

(b)(4)

PART 1

FINAL REPORT

(b)(4)

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Attachment 12.4

BeneHold Surgical Incise Drape with CHG (b)(4) (b)(4) Antimicrobial Efficacy Results and Report

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Attachment 12.5

BeneHold Surgical Incise Drape with CHG (b)(4) (b)(4) Antimicrobial Efficacy Results and Report

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May 7, 2023</br></br> We have reviewed your submission. Please see attached.

If you have any questions, please contact the lead reviewer assigned to your submission, Yongqing Chen.

 *** This is a system-generated email notification ***

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RMONR
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Subject Matter Expert (SME) Review

Date: April 27, 2023

SME Reviewer: Lianji Jin

Expertise: Chemical Characterization

Submission # K230645

Applicable Review Guide (if used): Not Applicable

Is this review for a Pre-Submission, Submission Issue Request, or Expedited Program (Breakthrough/STeP) Interaction? No

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Optional Classification Information:	
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories
Rx/OTC: Rx	

(b)(5)

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AVERY DENNISON | Medical

Premarket Notification 510(k) Statement

I certify that, in my capacity as Regulatory Affairs Manager of Avery Dennison Medical Ltd, I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61.

(b)(6)

Elaine Minagh, Regulatory Affairs Manager

24 October 2023

Premarket Notification **K230645**

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Section 17 – Electromagnetic Compatibility and Electrical Safety

This section is not applicable since the Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II is not an electronic device and therefore not subjected to electromagnetic forces.

Questions? Contact FDA/CDRH/OC/DBC at CDRH-GUIDANCE@fda.hhs.gov or 301-796-8118

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DEPARTMENT OF HEALTH AND HUMAN SERVICES M E M O R A N D U M

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

OFFICE OF SURGICAL AND INFECTION CONTROL DEVICES
DIVISION OF INFECTION CONTROL AND PLASTIC SURGERY DEVICES
OFFICE OF PRODUCT EVALUATION AND QUALITY

MEDICAL OFFICER MEMORANDUM

Date: 4/20/2023

From: Michael Matsuura, MD
Medical Officer
CDRH/OHT4/DHT4A

TO: Yongqing Chen, PhD
Lead Reviewer
CDRH/OHT4/DHT4B

CC: Bifeng Quan, PhD
Assistant Director
CDRH/OHT4/DHT4B

Submission Number: K230645

Consult Number: CON237399

Applicant/Sponsor: Avery Dennison Medical

Device Trade or Propriety Name: BeneHold Surgical Incise Drape with CHG II

(b)(5)

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Major Deficiency - Question 3

(b)(4)

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Stability Report
BeneHold Surgical Incise Drape with CHG Antimicrobial II (b)(4)

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BeneHold Surgical Incise Drape with CHG (b)(4) Formulation Stability Protocol

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(b)(4)

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AVERY DENNISON	Document Type:	Verification Protocol
	Document Title:	Protocol for Transportation Simulation Shipping Study for Incise (b)(4) BeneHold Surgical Incise Drape with CHG Antimicrobial II
	Document Number:	(b)(4)

Protocol for Transportation Simulation Shipping Study for Incise (b)(4) BeneHold Surgical Incise Drape with CHG Antimicrobial II

Approval Signatures

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AVERY DENNISON	Document Type:	Verification Report
	Document Title:	Report for Transportation Simulation Shipping Study for Incise (b)(4) BeneHold Surgical Incise Drape with CHG Antimicrobial II
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Section 14 – Sterilization Validation and Shelf Life

Sterilization Summary

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II will be sold in a sterile state (via Ethylene Oxide method) and in a bulk non sterile, configuration to kit packing entities for inclusion within convenience kits. The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is a prescription device which may be sold only to medical professionals which is stated on the device packaging per FDA requirements. The sterile configuration of the drape will be sterilized via Ethylene Oxide by (b)(4) a contract sterilizer.

Table 14.1 Sterilization Overview	
Sterilization Method	Ethylene Oxide
Validation Method	ISO 11135, recognized by the FDA, number 14-529
Sterilization Assurance Level	10^{-6}

The sterilization validation of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II establishes the qualification of an Ethylene Oxide (EO) sterilization process according to the AAMI TIR28 product adoption and method "B" (Overkill Method) in accordance with ISO 11135.

Sterilization validation for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is within the same chamber as that of the BeneHold™ Surgical Incise Drape with CHG antimicrobial (K202208). Considering the similarity of material of construction and packaging configuration, a "product adoption" approach was followed as dictated by AAMI TIR28. The choice and number of cycles was based upon the sterilization evaluation report (b)(4) (Attachment 14.1), which outlines the adoption requirements set forth by AAMI TIR28. A summary of the sterilization validation cycles, following overkill approach, may be found within table 14.2 below.

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(b)(4)

Shelf Life Summary

A stability study was conducted to establish the shelf life of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II before and after ethylene oxide (EO) sterilization

(b)(4)

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II stability study was a (b)(4) as detailed within Attachment 14.5, (b)(4) Stability Report.

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Attachment 14.1

Sterilization Evaluation Report

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AVERY DENNISON	Document Type:	Sterilization Evaluation Report
	Document Title:	(b)(4) CHG Incise Drape EO Sterilization Evaluation and Specification Report
	Document Number, Revision:	(b)(4)

(b)(4) CHG Incise Drape EO Sterilization Evaluation and Specification Report

Approval Signatures

The following signatures will be captured electronically in the electronic quality management system. Below is a list of required approvers and associated titles. By signing, individuals indicate their review and approval of this report.

(b)(4)

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Attachment 14.2

Sterilization Validation Protocol

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Attachment 14.3

Sterilization Validation Report

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(b)(4)

Process Validation Report

Ethylene Oxide Sterilization Process - ISO 11135, Overkill Approach

Date: 20-Feb-2023

Customer: Avery Dennison

Report Number and Revision: (b)(4)

(b)(4)

(b)(4)

Questions? Contact FDA/OC/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 14.4

BeneHold Surgical Incise Drape with CHG antimicrobial II

Device Stability Protocol

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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BeneHold Surgical Incise Drape with CHG (b)(4) Formulation Stability Protocol

The following signatures will be captured electronically via the electronic Document Control system. Below is a list of required approvers and associated titles.

(b)(4)

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Attachment 14.5

BeneHold Surgical Incise Drape with CHG antimicrobial II

Device Stability Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Stability Report
BeneHold Surgical Incise Drape with CHG Antimicrobial II (b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 14.6

BeneHold Surgical Incise Drape with CHG antimicrobial II,

Pouch Stability Protocol

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Pouch Stability Protocol for BeneHold Surgical Incise Drape with Chlorhexidine Gluconate (CHG)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 14.7

BeneHold Surgical Incise Drape with CHG antimicrobial II,

Pouch Stability Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(Interim) Pouch Stability Report for BeneHold Surgical Incise Drape with CHG

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Major Deficiency - Question 2

(b)(4)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

(b)(4)

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*

K230645

Device Name

BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Indications for Use *(Describe)*

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is indicated for use as an incise drape with continuous antimicrobial activity (in vitro) from 30 minutes through 4 hours of use against the following organisms: S. aureus, S. epidermidis, E. coli, P. aeruginosa, E. aerogenes, and C. albicans. In vitro testing on the subject drape has also shown continuous antimicrobial activity from 30 minutes through 2.5 hours against E. faecalis and F. oxysporum. It is intended for external use only. Correlation between in vitro results and any clinical event has not been tested.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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Food and Drug Administration
Office of Chief Information Officer
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AVERY DENNISON | Medical

Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road
Longford, N39 RC80, Ireland
Phone: +353 43 33 49586
Fax: +353 43 3349566

January 20, 2023

U.S. Food and Drug Administration
Centre for Devices and Radiological Health
10903 New Hampshire Avenue
Document Control Center WO66-G609
Silver Spring, MD 20993-0002

Subject: Patent statement for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Pursuant to the requirements of FDA to provide patent and exclusivity certifications for constituent part drugs, Avery Dennison has conducted a search of the FDA databases for approved NDA applications of Chlorhexidine Gluconate (CHG). The table below lists the resulting NDA's.

NDA Number	Title
(b)(4)	

Avery Dennison Corporation is not certifying or using any data from the aforementioned NDA's or their subsequent patents for the 510(k) application of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II. Furthermore, to our knowledge, Avery Dennison Corporation does not infringe on any granted, valid, patents within the United States.

(b)(6)

Senior R&D Engineer
Avery Dennison Medical

Classification: Avery Dennison - Secret

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

Avery Dennison Medical Ltd.

BeneHold™ Surgical Incise Drape with CHG antimicrobial II

(b)(4)

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U.S. FOOD & DRUG ADMINISTRATION

eConsult Cover Sheet

Consult Number:	CON2324334
Document Number:	K230645/S001
Applicant:	Avery Dennison Medical Ltd.
Trade Name:	BeneHold Surgical Incise Drape with CHG antimicrobial II
Consult Type:	Toxicology and Chemical Risk Assessment
Requestor:	Yongqing Chen [CHENYO] yongqing.chen@fda.hhs.gov
Requestor Home:	CDRH\ OHT4\ DHT4B\ THT4B2
Requested Consultant:	Angela Burke -S (Affiliate) Digitally signed by Angela Burke -S (Affiliate) Date: 2023.10.15 16:20:53 -05'00'
Gatekeeper / Consultant:	Angela Burke [ANGELA.BURKE] angela.burke@fda.hhs.gov ; 479-579-8521
Consultant Home:	CDRH\ OPEQ
Date Requested:	September 29, 2023
Due Date:	October 16, 2023
Instructions:	Thank you so much, Angela, for willing to help us again on this submission. Please see my email sent out 09/28/2023 for more details. Best, Yongqing

For each of the specific issues identified in the recommended requests to the applicant above, I provided a statement of bases for the request(s); and cite as part of it an available, applicable, and relevant final rule, statue, final guidance, or FDA-recognized consensus standard for each.

Reviewer Sign-Off: Angela Burke -S (Affiliate)
Digitally signed by Angela Burke -S (Affiliate)
Date: 2023.10.15 16:24:47 -05'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Major Deficiency - Question 11

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This document expires upon the next approved and released revision by Avery Dennison.
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Project Number (b)(4)
Version (b)(4)

CONFIDENTIAL

Biological Risk Assessment

Device Name: BeneHold CHG Surgical Incise Drape (b)(4)

Prepared for:

Avery Dennison Medical
(b)(6)
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

Prepared by:

(b)(4)

(b)(4)

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24 October 2023

U.S. Food and Drug Administration
Centre for Devices and Radiological Health
10903 New Hampshire Avenue
Document Control Center WO66-G609
Silver Spring, MD 20993-0002

Subject: Avery Dennison Response to AINN Hold Letter for K230645, the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Dear Madam or Sir:

Please find in attachment our responses to your email from 23 October 2023 regarding the

(b)(4)

Kind regards,

(b)(6)

Elizabeth Gallantine, PhD
Project Manager Europe
Avery Dennison
Phone: + 353 43 331 1341
E-mail:elizabeth.gallantine@eu.averydennison.com

Classification: Avery Dennison - Secret

Records processed under FOIA Request 2024-2745; Released by CDRH on 08-26-2024

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Classification: Avery Dennison - Secret

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Minor Deficiency - Question 2

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Section 19 – Performance Testing – Animal

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Attachment 19.1 Antimicrobial Efficacy in Porcine Model, Validation Protocol

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

AVERY DENNISON	Document Type:	Design Validation Protocol
	Document Title:	Porcine Wound Model Design Validation Protocol of (b)(4) BeneHold Surgical Incise Drape with CHG
	Document Number, Revision:	(b)(4)

Porcine Wound Model Design Validation Protocol of (b)(4) BeneHold Surgical Incise Drape with CHG

(b)(4)

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Attachment 19.2 Antimicrobial Efficacy in Porcine Model, Validation Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

AVERY DENNISON	Document Type:	Design Validation Report
	Document Title:	Porcine Wound Model Design Validation Report for (b)(4) BeneHold Surgical Incise Drape with CHG
	Document Number, Revision:	(b)(4)

Porcine Wound Model Design Validation Report for (b)(4) BeneHold Surgical Incise Drape with CHG

(b)(4)

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Attachment 19.3

Assessing BeneHold Surgical Incise Drape with CHG and (b)(4) Protocol

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 19.4

Assessing BeneHold Surgical Incise Drape with CHG and (b)(4) Report

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U.S. FOOD & DRUG ADMINISTRATION

eConsult Cover Sheet

Consult Number:	CON2324334
Document Number:	K230645/S001
Applicant:	Avery Dennison Medical Ltd.
Trade Name:	BeneHold Surgical Incise Drape with CHG antimicrobial II
Consult Type:	Toxicology and Chemical Risk Assessment
Requestor:	Yongqing Chen [CHENYO] yongqing.chen@fda.hhs.gov
Requestor Home:	CDRH\ OHT4\ DHT4B\ THT4B2
Requested Consultant:	
Gatekeeper / Consultant:	Angela Burke [ANGELA.BURKE] angela.burke@fda.hhs.gov ; 479-579-8521
Consultant Home:	CDRH\ OPEQ
Date Requested:	September 29, 2023
Due Date:	October 16, 2023
Instructions:	Thank you so much, Angela, for willing to help us again on this submission. Please see my email sent out 09/28/2023 for more details. Best, Yongqing

For each of the specific issues identified in the recommended requests to the applicant above, I provided a statement of bases for the request(s); and cite as part of it an available, applicable, and relevant final rule, statue, final guidance, or FDA-recognized consensus standard for each.
Reviewer Sign-Off:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Section 22 – Literature Articles Referenced in Submission

Table 22.1 below contains a summary of each periodical referenced, the corresponding section where the reference was made; Section 10 (Device Description), Section 12 (Substantial Equivalence), Section 19 (Animal Studies), Section 20 (Clinical Studies) along with the justification for its use. The copies of the periodicals referenced below may be found within the attachments.

Table 22.1 Literature References and Justification for Use		
Literature References	Attachment #	Justification for use
Section 10 – Device Description		
[1] Best and Taylor's Physiological Basis of Medical Practice, 12th Edition. John B. West, Editor. Chapter 31, Regulation of Volume and Osmolality of the Body Fluids. Pg 478.	Attachment 22.1	(b)(4)
[2] Denton. 2001. Chlorhexidine, p. 321-336. In Block (ed.) Disinfection, Sterilization, and Preservation, 5th ed. Lippincott Williams and Wilkins, Philadelphia, PA.	Attachment 22.2	
[3] McDonnell and Russell. "Antiseptics and Disinfectants: Activity, Action, and Resistance" Clinical Microbiology Reviews 12(1), 147-179 (1999)	Attachment 22.3	
[4] Gomes do Amorim, Aun, and Mayer. "Susceptibility of some oral microorganisms to chlorhexidine and paramonochlorophenol" Brazilian Oral Research 18(3), 242-246 (2004)	Attachment 22.4	
[5] Semprebom et al. "Enhanced susceptibility of Candida albicans to chlorhexidine under anoxia" Brazilian Journal of Oral Sciences 8(2), 105-110 (2009)	Attachment 22.5	

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Table 22.1 Literature References and Justification for Use		
Literature References	Attachment #	Justification for use
[6] Mendes, et al. "Chlorhexidine bathing for the prevention of colonization and infection with multidrug-resistant microorganisms in a hematopoietic stem cell transplantation unit over a 9-year period: Impact on chlorhexidine susceptibility" Medicine 95:46 (2016)	Attachment 22.6	
[7] Karpinski and Szkaradkiewicz. "Chlorhexidine – pharmaco-biological activity and application" European Review for Medicinal and Pharmacological Sciences 19, 1321-1326 (2015).	Attachment 22.7	
[8] Moore and Payne. 2004. Types of antimicrobial agents, p. 8-97. In Fraise, Lambert, and Maillard (eds.) Principles and Practice of Disinfection, Preservation & Sterilization, 4th ed. Blackwell Publishing, Malden, MA	Attachment 22.8	
[9] Oliveira dos Santos, et al. "In vitro activity of chlorhexidine compared with seven antifungal agents against 98 Fusarium isolates recovered from fungal keratitis patients" Antimicrobial Agents and Chemotherapy 63(8), 1-7	Attachment 22.9	
Section 12 – Substantial Equivalence		
[1] Hsiao CR et al. Identification of medically important molds by an oligonucleotide array. J Clin Microbiol. 2005 Aug;43(8):3760-8. doi: 10.1128/JCM.43.8.3760-3768.2005. PMID: 16081907; PMCID: PMC1233923.	Attachment 22.10	(b)(4)

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Table 22.1 Literature References and Justification for Use		
Literature References	Attachment #	Justification for use
[2] Carlesse F et al. Outbreak of Fusarium oxysporum infections in children with cancer: an experience with 7 episodes of catheter-related fungemia. Antimicrob Resist Infect Control. 2017 Sep 7;6:93. doi: 10.1186/s13756-017-0247-3. PMID: 28912948; PMCID: PMC5588724.	Attachment 22.11	(b)(4)
[3] Pereiro M Jr et al. Chronic infection due to Fusarium oxysporum mimicking lupus vulgaris: case report and review of cutaneous involvement in fusariosis. Acta Derm Venereol. 2001 Jan-Feb;81(1):51-3. doi: 10.1080/000155501750208218. PMID: 11411917.	Attachment 22.12	
[4] Nucci M et al. Cutaneous infection by Fusarium species in healthy and immunocompromised hosts: implications for diagnosis and management. Clin Infect Dis. 2002 Oct 15;35(8):909-20. doi: 10.1086/342328. Epub 2002 Sep 18. PMID: 12355377.	Attachment 22.13	
[5] Best and Taylor's Physiological Basis of Medical Practice, 12th Edition. John B. West, Editor. Chapter 31, Regulation of Volume and Osmolality of the Body Fluids. Pg 478.	Attachment 22.1	
Section 19 – Animal Studies		
[1] Hidron, et.al., Infect Control Hosp Epidemiol 2008;29:996-1011.	Attachment 22.14	(b)(4)

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Table 22.1 Literature References and Justification for Use		
Literature References	Attachment #	Justification for use
		(b)(4)
Section 20 - Clinical		
[1] McNichol, et. al. "Medical Adhesives and Patient Safety: State of the Science. Consensus Statements for the Assessment, Prevention, and Treatment of Adhesive-Related Skin Injuries" Journal of Wound, Ostomy, and Continence Nursing. 2013; 40(4): 1-15.	Attachment 22.15	
[2] LeBlanc, et al., "Skin Tears: State of the Science: Consensus Statements for the Prevention, Prediction, Assessment, and Treatment of Skin Tears" Advances in Skin and Wound Care. 2011; 24(9): 2-15.	Attachment 22.16	
[3] Rayner, et al., "A review of patient and skin characteristics associated with skin tears" Journal of Wound Care 2015; 24(9): 406-414.	Attachment 22.17	
[4] White, Karam, and Cowell, "Skin Tears in Frail Elders: A Practical Approach to Prevention" Geriatric Nursing. 1994; 15(2), 95-99.	Attachment 22.18	
[5] Strazzieri-Pulido, et al., "Skin tear prevalence and associated factors: a systematic review" Journal of School of Nursing USP. 2015; 49(4):668-674.	Attachment 22.19	
[6] Cutting. "Impact of adhesive surgical tape and wound dressings on the skin, with reference to skin stripping" Journal of Wound Care 2008; 17(4): 157-162.	Attachment 22.20	

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Table 22.1 Literature References and Justification for Use		
Literature References	Attachment #	Justification for use
[7] 3 January 2018 Global guidelines for the prevention of surgical site infection, 2nd ed. (Link accessed 27 May 2022)	Attachment 22.21	(b)(4)

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BEST AND TAYLOR'S
Physiological Basis of Medical Practice

TWELFTH EDITION

EDITED BY
John B. West, M.D., Ph.D., D.Sc.

Professor of Physiology and Medicine
University of California, San Diego
School of Medicine
La Jolla, California



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Disinfection, Sterilization, and Preservation

Fifth Edition

Editor

Seymour S. Block, Ph.D.
Professor Emeritus of Bioengineering
Department of Chemical Engineering
University of Florida
Gainesville, Florida



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Attachment 22.3

McDonnell and Russell. "Antiseptics and Disinfectants: Activity, Action, and Resistance Clinical Microbiology Reviews 12(1), 147-179 (1999).

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Antiseptics and Disinfectants: Activity, Action, and Resistance

GERALD McDONNELL[1]* AND A. DENVER RUSSELL[2]

STERIS Corporation, St. Louis Operations, St. Louis, Missouri 63166,[1] and Welsh School of Pharmacy, Cardiff University, Cardiff CF1 3XF, United Kingdom[2]

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* Corresponding author. Present address: STERIS Corporation, 5960 Heisley Rd., Mentor, OH 44060. Phone: (440) 354-2600. Fax: (440) 354-7038. E-mail: gerry_mcdonnell@steris.com.

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INTRODUCTION

Antiseptics and disinfectants are used extensively in hospitals and other health care settings for a variety of topical and hard-surface applications. In particular, they are an essential part of infection control practices and aid in the prevention of nosocomial infections (277, 454). Mounting concerns over the potential for microbial contamination and infection risks in the food and general consumer markets have also led to increased use of antiseptics and disinfectants by the general public. A wide variety of active chemical agents (or "biocides") are found in these products, many of which have been used for hundreds of years for antisepsis, disinfection, and preservation (39). Despite this, less is known about the mode of action of these active agents than about antibiotics. In general, biocides have a broader spectrum of activity than antibiotics, and, while antibiotics tend to have specific intracellular targets, biocides may have multiple targets. The widespread use of antiseptic and disinfectant products has prompted some speculation on the development of microbial resistance, in particular cross-resistance to antibiotics. This review considers what is known about the mode of action of, and mechanisms of microbial resistance to, antiseptics and disinfectants and attempts, wherever possible, to relate current knowledge to the clinical environment.

A summary of the various types of biocides used in antiseptics and disinfectants, their chemical structures, and their clinical uses is shown in Table 1. It is important to note that many of these biocides may be used singly or in combination in a variety of products which vary considerably in activity against microorganisms. Antimicrobial activity can be influenced by many factors such as formulation effects, presence of an organic load, synergy, temperature, dilution, and test method. These issues are beyond the scope of this review and are discussed elsewhere (123, 425, 444, 446, 451).

DEFINITIONS

"Biocide" is a general term describing a chemical agent, usually broad spectrum, that inactivates microorganisms. Because biocides range in antimicrobial activity, other terms may be more specific, including "-static," referring to agents which inhibit growth (e.g., bacteriostatic, fungistatic, and sporistatic) and "-cidal," referring to agents which kill the target organism (e.g., sporicidal, virucidal, and bactericidal). For the purpose of this review, antibiotics are defined as naturally occurring or synthetic organic substances which inhibit or destroy selective bacteria or other microorganisms, generally at low concentrations; antiseptics are biocides or products that destroy or inhibit the growth of microorganisms in or on living tissue (e.g. health care personnel handwashes and surgical scrubs); and disinfectants are similar but generally are products or biocides that are used on inanimate objects or surfaces. Disinfectants can be sporostatic but are not necessarily sporicidal.

Sterilization refers to a physical or chemical process that completely destroys or removes all microbial life, including spores. Preservation is the prevention of multiplication of microorganisms in formulated products, including pharmaceuticals and foods. A number of biocides are also used for cleaning purposes; cleaning in these cases refers to the physical removal of foreign material from a surface (40).

MECHANISMS OF ACTION

Introduction

Considerable progress has been made in understanding the mechanisms of the antibacterial action of antiseptics and disinfectants (215, 428, 437). By contrast, studies on their modes of action against fungi (426, 436), viruses (298, 307), and protozoa (163) have been rather sparse. Furthermore, little is known about the means whereby these agents inactivate prions (503).

Whatever the type of microbial cell (or entity), it is probable that there is a common sequence of events. This can be envisaged as interaction of the antiseptic or disinfectant with the cell surface followed by penetration into the cell and action at the target site(s). The nature and composition of the surface vary from one cell type (or entity) to another but can also alter as a result of changes in the environment (57, 59). Interaction at the cell surface can produce a significant effect on viability (e.g. with glutaraldehyde) (374, 421), but most antimicrobial agents appear to be active intracellularly (428, 451). The outermost layers of microbial cells can thus have a significant effect on their susceptibility (or insusceptibility) to antiseptics and disinfectants; it is disappointing how little is known about the passage of these antimicrobial agents into different types of microorganisms. Potentiation of activity of most biocides may be achieved by the use of various additives, as shown in later parts of this review.

In this section, the mechanisms of antimicrobial action of a range of chemical agents that are used as antiseptics or disinfectants or both are discussed. Different types of microorganisms are considered, and similarities or differences in the nature of the effect are emphasized. The mechanisms of action are summarized in Table 2.

General Methodology

A battery of techniques are available for studying the mechanisms of action of antiseptics and disinfectants on microorganisms, especially bacteria (448). These include examination of uptake (215, 428, 459), lysis and leakage of intracellular constituents (122), perturbation of cell homeostasis (266, 445), effects on model membranes (170), inhibition of enzymes, electron transport, and oxidative phosphorylation (162, 272), interaction with macromolecules (448, 523), effects on macromolecular biosynthetic processes (133), and microscopic examination of biocide-exposed cells (35). Additional and useful information can be obtained by calculating concentration exponents (n values [219, 489]) and relating these to membrane activity (219). Many of these procedures are valuable for detecting and evaluating antiseptics or disinfectants used in combination (146, 147, 202, 210).

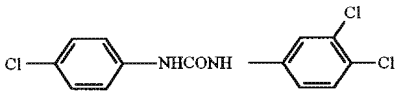
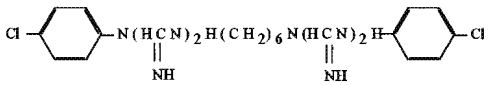
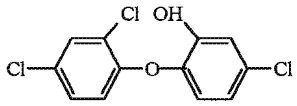
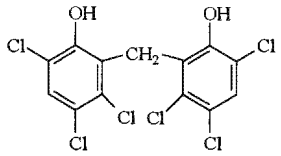
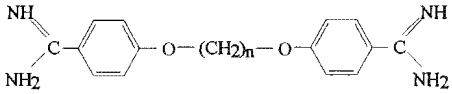
Similar techniques have been used to study the activity of antiseptics and disinfectants against fungi, in particular yeasts. Additionally, studies on cell wall porosity (117–119) may provide useful information about intracellular entry of disinfectants and antiseptics (204–208).

Mechanisms of antiprotozoal action have not been widely investigated. One reason for this is the difficulty in culturing some protozoa (e.g., *Cryptosporidium*) under laboratory conditions. However, the different life stages (trophozoites and cysts) do provide a fascinating example of the problem

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TABLE 1. Chemical structures and uses of biocides in antiseptics and disinfectants

Alcohols	Ethanol	$CH_3—CHOH$	Antisepsis
	Isopropanol	$CH_3(CH_3)CHOH$	Disinfection
			Preservation
Aldehydes	Glutaraldehyde	$OH—CCH_2CH_2CH_2C—HO$	Disinfection
	Formaldehyde	$H—C—HO$	Sterilization
			Preservation
Anilides	General structure	$C_6H_5.NH.COR$	Antisepsis
	Triclocarban		
Biguanides	Chlorhexidine		Antisepsis
			Antiplaque agents
	Alexidine, polymeric biguanides		Preservation
			Disinfection
Bisphenols	Triclosan		Antisepsis
			Antiplaque agents
	Hexachlorophene		Deodorants
			Preservation
Diamidines	Propamidine		Antisepsis
			Preservation
	Dibromopropamidine		

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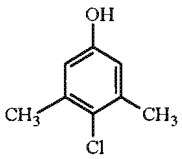
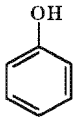
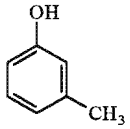
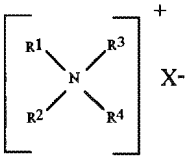
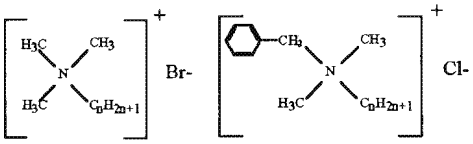
of how changes in cytology and physiology can modify responses to antiseptics and disinfectants. Khunkitti et al. (251–255) have explored this aspect by using indices of viability, leakage, uptake, and electron microscopy as experimental tools.

Some of these procedures can also be modified for studying effects on viruses and phages (e.g., uptake to whole cells and viral or phage components, effects on nucleic acids and proteins, and electron microscopy) (401). Viral targets are

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TABLE 1—*Continued*

Halogen-releasing agents	Chlorine compounds	⇨OCl-, HOCl, Cl_2	Disinfection Antisepsis
	Iodine compounds	⇨I_2	Cleaning
Halophenols	Chloroxylenol (PCMX)		Antisepsis Preservation
Heavy metal derivatives	Silver compounds	Ag	Preservation Antisepsis
	Mercury compounds	Hg	Disinfection
Peroxygens	Hydrogen peroxide	H_2O_2	Disinfection
	Ozone	O_3	Sterilization
	Peracetic acid	$CH_3.COOOH$	
Phenols and cresols	Phenol		Disinfection Preservation
	Cresol		
Quaternary ammonium compounds	General structure		Disinfection Antisepsis Preservation
	Cetrimide, benzalkonium chloride		Cleaning

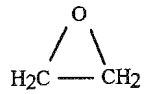
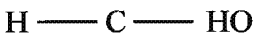
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predominantly the viral envelope (if present), derived from the host cell cytoplasmic or nuclear membrane; the capsid, which is responsible for the shape of virus particles and for the protection of viral nucleic acid; and the viral genome. Release of an intact viral nucleic acid into the environment following capsid destruction is of potential concern since some nucleic acids are infective when liberated from the capsid (317), an aspect that must be considered in viral disinfection. Important considerations in viral inactivation are dealt with by Klein and Deforest (259) and Prince et al.

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TABLE 1—*Continued*

Vapor phase	Ethylene oxide		Sterilization Disinfection
	Formaldehyde		
	Hydrogen peroxide	H_2O_2	

(384), while an earlier paper by Grossgebauer is highly recommended (189).

Alcohols

Although several alcohols have been shown to be effective antimicrobials, ethyl alcohol (ethanol, alcohol), isopropyl alcohol (isopropanol, propan-2-ol) and *n*-propanol (in particular in Europe) are the most widely used (337). Alcohols exhibit rapid broad-spectrum antimicrobial activity against vegetative bacteria (including mycobacteria), viruses, and fungi but are not sporicidal. They are, however, known to inhibit sporulation and spore germination (545), but this effect is reversible (513). Because of the lack of sporicidal activity, alcohols are not recommended for sterilization but are widely used for both hard-surface disinfection and skin antisepsis. Lower concentrations may also be used as preservatives and to potentiate the activity of other biocides. Many alcohol products include low levels of other biocides (in particular chlorhexidine), which remain on the skin following evaporation of the alcohol, or excipients (including emollients), which decrease the evaporation time of the alcohol and can significantly increase product efficacy (68). In general, isopropyl alcohol is considered slightly more efficacious against bacteria (95) and ethyl alcohol is more potent against viruses (259); however, this is dependent on the concentrations of both the active agent and the test microorganism. For example, isopropyl alcohol has greater lipophilic properties than ethyl alcohol and is less active against hydrophilic viruses (e.g., poliovirus) (259). Generally, the antimicrobial activity of alcohols is significantly lower at concentrations below 50% and is optimal in the 60 to 90% range.

Little is known about the specific mode of action of alcohols, but based on the increased efficacy in the presence of water, it is generally believed that they cause membrane damage and rapid denaturation of proteins, with subsequent interference with metabolism and cell lysis (278, 337). This is supported by specific reports of denaturation of *Escherichia coli* dehydrogenases (499) and an increased lag phase in *Enterobacter aerogenes*, speculated to be due to inhibition of metabolism required for rapid cell division (101).

Aldehydes

Glutaraldehyde. Glutaraldehyde is an important dialdehyde that has found usage as a disinfectant and sterilant, in particular for low-temperature disinfection and sterilization of endoscopes and surgical equipment and as a fixative in electron

TABLE 2. Summary of mechanisms of antibacterial action of antiseptics and disinfectants

Target	Antiseptic or disinfectant	Mechanism of action
Cell envelope (cell wall, outer membrane)	Glutaraldehyde	Cross-linking of proteins
	EDTA, other permeabilizers	Gram-negative bacteria: removal of Mg^{2+}, release of some LPS
Cytoplasmic (inner) membrane	QACs	Generalized membrane damage involving phospholipid bilayers
	Chlorhexidine	Low concentrations affect membrane integrity, high concentrations cause congealing of cytoplasm
	Diamines	Induction of leakage of amino acids
	PHMB, alexidine	Phase separation and domain formation of membrane lipids
	Phenols	Leakage; some cause uncoupling
Cross-linking of macromolecules	Formaldehyde	Cross-linking of proteins, RNA, and DNA
	Glutaraldehyde	Cross-linking of proteins in cell envelope and elsewhere in the cell
DNA intercalation	Acridines	Intercalation of an acridine molecule between two layers of base pairs in DNA
Interaction with thiol groups	Silver compounds	Membrane-bound enzymes (interaction with thiol groups)
Effects on DNA	Halogens	Inhibition of DNA synthesis
	Hydrogen peroxide, silver ions	DNA strand breakage
Oxidizing agents	Halogens	Oxidation of thiol groups to disulfides, sulfoxides, or disulfoxides
	Peroxygens	Hydrogen peroxide: activity due to from formation of free hydroxy radicals (·OH), which oxidize thiol groups in enzymes and proteins; PAA: disruption of thiol groups in proteins and enzymes

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TABLE 3. Mechanism of antimicrobial action of glutaraldehyde

Target microorganism	Glutaraldehyde action
Bacterial spores	Low concentrations inhibit germination; high concentrations are sporicidal, probably as a consequence of strong interaction with outer cell layers
Mycobacteria	Action unknown, but probably involves mycobacterial cell wall
Other nonsporulating bacteria	Strong association with outer layers of gram-positive and gram-negative bacteria; cross-linking of amino groups in protein; inhibition of transport processes into cell
Fungi	Fungal cell wall appears to be a primary target site, with postulated interaction with chitin
Viruses	Actual mechanisms unknown, but involve protein-DNA cross-links and capsid changes
Protozoa	Mechanism of action not known

icroscopy. Glutaraldehyde has a broad spectrum of activity against bacteria and their spores, fungi, and viruses, and a considerable amount of information is now available about the ways whereby these different organisms are inactivated (Tables 2 and 3). Earlier reviews of its mechanisms of action have been published (179, 182, 374, 482).

The first reports in 1964 and 1965 (182) demonstrated that glutaraldehyde possessed high antimicrobial activity. Subsequently, research was undertaken to evaluate the nature of its bactericidal (339–344, 450) and sporicidal (180, 181, 507, 508) action. These bactericidal studies demonstrated (374) a strong binding of glutaraldehyde to outer layers of organisms such as *E. coli* and *Staphylococcus aureus* (179, 212, 339–341, 343, 344), inhibition of transport in gram-negative bacteria (179), inhibition of dehydrogenase activity (343, 344) and of periplasmic enzymes (179), prevention of lysostaphin-induced lysis in *S. aureus* (453) and of sodium lauryl sulfate-induced lysis in *E. coli* (340, 344), inhibition of spheroplast and protoplast lysis in hypotonic media (340, 344), and inhibition of RNA, DNA, and protein synthesis (320). Strong interaction of glutaraldehyde with lysine and other amino acids has been demonstrated (450).

Clearly, the mechanism of action of glutaraldehyde involves a strong association with the outer layers of bacterial cells, specifically with unprotonated amines on the cell surface, possibly representing the reactive sites (65). Such an effect could explain its inhibitory action on transport and on enzyme systems, where access of substrate to enzyme is prohibited. Partial or entire removal of the cell wall in hypertonic medium, leading to the production of spheroplasts or protoplasts and the subsequent prevention of lysis by glutaraldehyde when these forms are diluted in a hypotonic environment, suggests an additional effect on the inner membrane, a finding substantiated by the fact that the dialdehyde prevents the selective release of some membrane-bound enzymes of *Micrococcus lysodeikticus* (138). Glutaraldehyde is more active at alkaline than at acidic pHs. As the external pH is altered from acidic to alkaline, more reactive sites will be formed at the cell surface, leading to a more rapid bactericidal effect. The cross-links thus obtained mean that the cell is then unable to undertake most, if not all, of its essential functions. Glutaraldehyde is also mycobactericidal. Unfortunately, no critical studies have as yet been undertaken to evaluate the nature of this action (419).

The bacterial spore presents several sites at which interaction with glutaraldehyde is possible, although interaction with a particular site does not necessarily mean that this is associated with spore inactivation. *E. coli*, *S. aureus*, and vegetative cells of *Bacillus subtilis* bind more glutaraldehyde than do resting spores of *B. subtilis* (377, 378); uptake of glutaraldehyde is greater during germination and outgrowth than with mature spores but still lower than with vegetative cells. Low concentrations of the dialdehyde (0.1%) inhibit germination, whereas much higher concentrations (2%) are sporicidal. The aldehyde, at both acidic and alkaline pHs, interacts strongly with the outer spore layers (508, 509); this interaction reduces the release of dipicolinic acid (DPA) from heated spores and the lysis induced by mercaptoethanol (or thioglycolate)-peroxide combinations. Low concentrations of both acidic and alkaline glutaraldehyde increase the surface hydrophobicity of spores, again indicating an effect at the outermost regions of the cell. It has been observed by various authors (182, 374, 376, 380) that the greater sporicidal activity of glutaraldehyde at alkaline pH is not reflected by differences in uptake; however, uptake per se reflects binding and not necessarily penetration into the spore. It is conceivable that acidic glutaraldehyde interacts with and remains at the cell surface whereas alkaline glutaraldehyde penetrates more deeply into the spore. This contention is at odds with the hypothesis of Bruch (65), who envisaged the acidic form penetrating the coat and reacting with the cortex while the alkaline form attacked the coat, thereby destroying the ability of the spore to function solely as a result of this surface phenomenon. There is, as yet, no evidence to support this theory. Novel glutaraldehyde formulations based on acidic rather than alkaline glutaraldehyde, which benefit from the greater inherent stability of the aldehyde at lower pH, have been produced. The improved sporicidal activity claimed for these products may be obtained by agents that potentiate the activity of the dialdehyde (414, 421).

During sporulation, the cell eventually becomes less susceptible to glutaraldehyde (see "Intrinsic resistance of bacterial spores"). By contrast, germinating and outgrowing cells reacquire sensitivity. Germination may be defined as an irreversible process in which there is a change of an activated spore from a dormant to a metabolically active state within a short period. Glutaraldehyde exerts an early effect on the germination process. L-Alanine is considered to act by binding to a specific receptor on the spore coat, and once spores are triggered to germinate, they are committed irreversibly to losing their dormant properties (491). Glutaraldehyde at high concentrations inhibits the uptake of L-[^{14}C]alanine by *B. subtilis* spores, albeit by an unknown mechanism (379, 414). Glutaraldehyde-treated spores retain their refractivity, having the same appearance under the phase-contrast microscope as normal, untreated spores even when the spores are subsequently incubated in germination medium. Glutaraldehyde is normally used as a 2% solution to achieve a sporicidal effect (16, 316); low concentrations (<0.1%) prevent phase darkening of spores and also prevent the decrease in optical density associated with a late event in germination. By contrast, higher concentrations (0.1 to 1%) significantly reduce the uptake of L-alanine, possibly as a result of a sealing effect of the aldehyde on the cell surface. Mechanisms involved in the revival of glutaraldehyde-treated spores are discussed below (see "Intrinsic resistance of bacterial spores").

There are no recent studies of the mechanisms of fungicidal action of glutaraldehyde. Earlier work had suggested that the fungal cell wall was a major target site (179, 182, 352), especially the major wall component, chitin, which is analogous to the peptidoglycan found in bacterial cell walls.

Glutaraldehyde is a potent virucidal agent (143, 260). It reduces the activity of hepatitis B surface antigen (HBsAg) and especially hepatitis B core antigen ([HBcAg] in hepatitis B virus [HBV]) (3) and interacts with lysine residues on the surface of hepatitis A virus (HAV) (362). Low concentrations

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(<0.1%) of alkaline glutaraldehyde are effective against purified poliovirus, whereas poliovirus RNA is highly resistant to aldehyde concentrations up to 1% at pH 7.2 and is only slowly inactivated at pH 8.3 (21). In other words, the complete poliovirus particle is much more sensitive than poliovirus RNA. In light of this, it has been inferred that glutaraldehyde-induced loss of infectivity is associated with capsid changes (21). Glutaraldehyde at the low concentrations of 0.05 and 0.005% interacts with the capsid proteins of poliovirus and echovirus, respectively; the differences in sensitivity probably reflect major structural variations in the two viruses (75).

Bacteriophages were recently studied to obtain information about mechanisms of virucidal action (298–304, 306, 307). Many glutaraldehyde-treated *P. aeruginosa* F116 phage particles had empty heads, implying that the phage genome had been ejected. The aldehyde was possibly bound to F116 double-stranded DNA but without affecting the molecule; glutaraldehyde also interacted with phage F116 proteins, which were postulated to be involved in the ejection of the nucleic acid. Concentrations of glutaraldehyde greater than 0.1 to 0.25% significantly affected the transduction of this phage; the transduction process was more sensitive to the aldehyde than was the phage itself. Glutaraldehyde and other aldehydes were tested for their ability to form protein-DNA cross-links in simian virus 40 (SV40); aldehydes (i.e., glyoxal, furfural, prionaldehyde, acetaldehyde, and benzylaldehyde) without detectable cross-linking ability had no effect on SV40 DNA synthesis, whereas acrolein, glutaraldehyde, and formaldehyde, which formed such cross-links (144, 271, 297), inhibited DNA synthesis (369).

Formaldehyde. Formaldehyde (methanal, CH_2O) is a monoaldehyde that exists as a freely water-soluble gas. Formaldehyde solution (formalin) is an aqueous solution containing *ca.* 34 to 38% (wt/wt) CH_2O with methanol to delay polymerization. Its clinical use is generally as a disinfectant and sterilant in liquid or in combination with low-temperature steam. Formaldehyde is bactericidal, sporicidal, and virucidal, but it works more slowly than glutaraldehyde (374, 482).

Formaldehyde is an extremely reactive chemical (374, 442) that interacts with protein (156, 157), DNA (155), and RNA (155) in vitro. It has long been considered to be sporicidal by virtue of its ability to penetrate into the interior of bacterial spores (500). The interaction with protein results from a combination with the primary amide as well as with the amino groups, although phenol groups bind little formaldehyde (155). It has been proposed that formaldehyde acts as a mutagenic agent (291) and as an alkylating agent by reaction with carboxyl, sulfhydryl, and hydroxyl groups (371). Formaldehyde also reacts extensively with nucleic acid (489) (e.g., the DNA of bacteriophage T2) (190). As pointed out above, it forms protein-DNA cross-links in SV40, thereby inhibiting DNA synthesis (369). Low concentrations of formaldehyde are sporostatic and inhibit germination (512). Formaldehyde alters HBsAg and HBcAg of HBV (3).

It is difficult to pinpoint accurately the mechanism(s) responsible for formaldehyde-induced microbial inactivation. Clearly, its interactive, and cross-linking properties must play a considerable role in this activity. Most of the other aldehydes (glutaraldehyde, glyoxyl, succinaldehyde, and *o*-phthalaldehyde [OPA]) that have sporicidal activity are dialdehydes (and of these, glyoxyl and succinaldehyde are weakly active). The distance between the two aldehyde groups in glutaraldehyde (and possibly in OPA) may be optimal for interaction of these-CHO groups in nucleic acids and especially in proteins and enzymes (428).

Formaldehyde-releasing agents. Several formaldehyde-releasing agents have been used in the treatment of peritonitis (226, 273). They include noxythiolin (oxymethylenethiourea), tauroline (a condensate of two molecules of the aminosulponic acid taurine with three molecules of formaldehyde), hexamine (hexamethylenetetramine, methenamine), the resins melamine and urea formaldehydes, and imidazolone derivatives such as dantoin. All of these agents are claimed to be microbicidal on account of the release of formaldehyde. However, because the antibacterial activity of taurolin is greater than that of free formaldehyde, the activity of taurolin is not entirely the result of formaldehyde action (247).

TABLE 4. Mechanisms of antimicrobial action of chlorhexidine

Type of microorganism	Chlorhexidine action
Bacterial spores	Not sporicidal but prevents development of spores; inhibits spore outgrowth but not germination
Mycobacteria	Mycobacteristatic (mechanism unknown) but not mycobactericidal
Other nonsporulating bacteria	Membrane-active agent, causing protoplast and spheroplast lysis; high concentrations cause precipitation of proteins and nucleic acids
Yeasts	Membrane-active agent, causing protoplast lysis and intracellular leakage; high concentrations cause intracellular coagulation
Viruses	Low activity against many viruses; lipid-enveloped viruses more sensitive than nonenveloped viruses; effect possibly on viral envelope, perhaps the lipid moieties
Protozoa	Recent studies against *A. castellanii* demonstrate membrane activity (leakage) toward trophozoites, less toward cysts

***o*-Phthalaldehyde.** OPA is a new type of disinfectant that is claimed to have potent bactericidal and sporicidal activity and has been suggested as a replacement for glutaraldehyde in endoscope disinfection (7). OPA is an aromatic compound with two aldehyde groups. To date, the mechanism of its antimicrobial action has been little studied, but preliminary evidence (526) suggests an action similar to that of glutaraldehyde. Further investigations are needed to corroborate this opinion.

Anilides

The anilides have been investigated primarily for use as antiseptics, but they are rarely used in the clinic. Triclocarban (TCC; 3,4,4′-triclorocarbanilide) is the most extensively studied in this series and is used mostly in consumer soaps and deodorants. TCC is particularly active against gram-positive bacteria but significantly less active against gram-negative bacteria and fungi (30) and lacks appreciable substantivity (persistency) for the skin (37). The anilides are thought to act by adsorbing to and destroying the semipermeable character of the cytoplasmic membrane, leading to cell death (194).

Biguanides

Chlorhexidine. Chlorhexidine is probably the most widely used biocide in antiseptic products, in particular in handwashing and oral products but also as a disinfectant and preservative. This is due in particular to its broad-spectrum efficacy, substantivity for the skin, and low irritation. Of note, irritability has been described and in many cases may be product specific (167, 403). Despite the advantages of chlorhexidine, its activity is pH dependent and is greatly reduced in the presence of organic matter (430). A considerable amount of research has been undertaken on the mechanism of the antimicrobial action of this important bisbiguanide (389) (Tables 2 and 4), although most of the attention has been devoted to the way in which it

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inactivates nonsporulating bacteria (215, 428, 430, 431, 451). Nevertheless, sufficient data are now available to examine its sporostatic and mycobacteriostatic action, its effects on yeasts and protozoa, and its antiviral activity.

Chlorhexidine is a bactericidal agent (120, 215). Its interaction and uptake by bacteria were studied initially by Hugo et al. (222–224), who found that the uptake of chlorhexidine by *E. coli* and *S. aureus* was very rapid and depended on the chlorhexidine concentration and pH. More recently, by using [^{14}C]chlorhexidine gluconate, the uptake by bacteria (145) and yeasts (204) was shown to be extremely rapid, with a maximum effect occurring within 20 s. Damage to the outer cell layers takes place (139) but is insufficient to induce lysis or cell death. The agent then crosses the cell wall or outer membrane, presumably by passive diffusion, and subsequently attacks the bacterial cytoplasmic or inner membrane or the yeast plasma membrane. In yeasts, chlorhexidine "partitions" into the cell wall, plasma membrane, and cytoplasm of cells (205). Damage to the delicate semipermeable membrane is followed by leakage of intracellular constituents, which can be measured by appropriate techniques. Leakage is not per se responsible for cellular inactivation but is a consequence of cell death (445). High concentrations of chlorhexidine cause coagulation of intracellular constituents. As a result, the cytoplasm becomes congealed, with a consequent reduction in leakage (222–224, 290), so that there is a biphasic effect on membrane permeability. An initial high rate of leakage rises as the concentration of chlorhexidine increases, but leakage is reduced at higher biocide concentrations because of the coagulation of the cytosol.

Chlorhexidine was claimed by Harold et al. (199) to be an inhibitor of both membrane-bound and soluble ATPase as well as of net K^+ uptake in *Enterococcus faecalis*. However, only high biguanide concentrations inhibit membrane-bound ATPase (83), which suggests that the enzyme is not a primary target for chlorhexidine action. Although chlorhexidine collapses the membrane potential, it is membrane disruption rather than ATPase inactivation that is associated with its lethal effects (24, 272).

The effects of chlorhexidine on yeast cells are probably similar to those previously described for bacteria (204–207). Chlorhexidine has a biphasic effect on protoplast lysis, with reduced lysis at higher biguanide concentrations. Furthermore, in whole cells, the yeast cell wall may have some effect in limiting the uptake of the biguanide (208). The findings presented here and elsewhere (47, 136, 137, 527) demonstrate an effect on the fungal plasma membrane but with significant actions elsewhere in the cell (47). Increasing concentrations of chlorhexidine (up to 25 μg/ml) induce progressive lysis of *Saccharomyces cerevisiae* protoplasts, but higher biguanide concentrations result in reduced lysis (205).

Work to date suggests that chlorhexidine has a similar effect on the trophozoites of *Acanthameoba castellanii*, with the cysts being less sensitive (251–255). Furr (163) reviewed the effects of chlorhexidine and other biocides on *Acanthameoba* and showed that membrane damage in these protozoa is a significant factor in their inactivation.

Mycobacteria are generally highly resistant to chlorhexidine (419). Little is known about the uptake of chlorhexidine (and other antiseptics and disinfectants) by mycobacteria and on the biochemical changes that occur in the treated cells. Since the MICs for some mycobacteria are on the order of those for chlorhexidine-sensitive, gram-positive cocci (48), the inhibitory effects of chlorhexidine on mycobacteria may not be dissimilar to those on susceptible bacteria. *Mycobacterium avium-intracellulare* is considerably more resistant than other mycobacteria (48).

Chlorhexidine is not sporicidal (discussed in "Mechanisms of resistance"). Even high concentrations of the bisbiguanide do not affect the viability of *Bacillus* spores at ambient temperatures (473, 474), although a marked sporicidal effect is achieved at elevated temperatures (475). Presumably, sufficient changes occur in the spore structure to permit an increased uptake of the biguanide, although this has yet to be shown experimentally. Little is known about the uptake of chlorhexidine by bacterial spores, although coatless forms take up more of the compound than do "normal" spores (474).

Chlorhexidine has little effect on the germination of bacterial spores (414, 422, 432, 447) but inhibits outgrowth (447). The reason for its lack of effect on the former process but its significant activity against the latter is unclear. It could, however, be reflected in the relative uptake of chlorhexidine, since germinating cells take up much less of the bisbiguanide than do outgrowing forms (474). Binding sites could thus be reduced in number or masked in germinating cells.

The antiviral activity of chlorhexidine is variable. Studies with different types of bacteriophages have shown that chlorhexidine has no effect on MS2 or K coliphages (300). High concentrations also failed to inactivate *Pseudomonas aeruginosa* phage F116 and had no effect on phage DNA within the capsid or on phage proteins (301); the transduction process was more sensitive to chlorhexidine and other biocides than was the phage itself. This substantiated an earlier finding (306) that chlorhexidine bound poorly to F116 particles. Chlorhexidine is not always considered a particularly effective antiviral agent, and its activity is restricted to the lipid-enveloped viruses (361). Chlorhexidine does not inactivate nonenveloped viruses such as rotavirus (485), HAV (315), or poliovirus (34). Its activity was found by Ranganathan (389) to be restricted to the nucleic acid core or the outer coat, although it is likely that the latter would be a more important target site.

Alexidine. Alexidine differs chemically from chlorhexidine in possessing ethylhexyl end groups. Alexidine is more rapidly bactericidal and produces a significantly faster alteration in bactericidal permeability (79, 80). Studies with mixed-lipid and pure phospholipid vesicles demonstrate that, unlike chlorhexidine, alexidine produces lipid phase separation and domain formation (Table 2). It has been proposed (80) that the nature of the ethylhexyl end group in alexidine, as opposed to the chlorophenol one in chlorhexidine, might influence the ability of a biguanide to produce lipid domains in the cytoplasmic membrane.

Polymeric biguanides. Vantocil is a heterodisperse mixture of polyhexamethylene biguanides (PHMB) with a molecular weight of approximately 3,000. Polymeric biguanides have found use as general disinfecting agents in the food industry and, very successfully, for the disinfection of swimming pools. Vantocil is active against gram-positive and gram-negative bacteria, although *P. aeruginosa* and *Proteus vulgaris* are less sensitive. Vantocil is not sporicidal. PHMB is a membrane-active agent that also impairs the integrity of the outer membrane of gram-negative bacteria, although the membrane may also act as a permeability barrier (64, 172). Activity of PHMB increases on a weight basis with increasing levels of polymerization, which has been linked to enhanced inner membrane perturbation (173, 174).

Unlike chlorhexidine but similar to alexidine (Table 2), PHMB causes domain formation of the acidic phospholipids of the cytoplasmic membrane (61–64, 172, 173, 227). Permeability changes ensue, and there is believed to be an altered function of some membrane-associated enzymes. The proposed sequence of events during its interaction with the cell envelope of *E. coli* is as follows: (i) there is rapid attraction of

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PHMB toward the negatively charged bacterial cell surface, with strong and specific adsorption to phosphate-containing compounds; (ii) the integrity of the outer membrane is impaired, and PHMB is attracted to the inner membrane; (iii) binding of PHMB to phospholipids occurs, with an increase in inner membrane permeability (K^+ loss) accompanied by bacteriostasis; and (iv) complete loss of membrane function follows, with precipitation of intracellular constituents and a bactericidal effect.

Diamidines

The diamidines are characterized chemically as described in Table 1. The isethionate salts of two compounds, propamidine (4,4-diaminodiphenoxypropane) and dibromopropamidine (2,2-dibromo-4,4-diamidinodiphenoxypropane), have been used as antibacterial agents. Their antibacterial properties and uses were reviewed by Hugo (213) and Hugo and Russell (226). Clinically, diamidines are used for the topical treatment of wounds.

The exact mechanism of action of diamidines is unknown, but they have been shown to inhibit oxygen uptake and induce leakage of amino acids (Table 2), as would be expected if they are considered as cationic surface-active agents. Damage to the cell surface of *P. aeruginosa* and *Enterobacter cloacae* has been described (400).

Halogen-Releasing Agents

Chlorine- and iodine-based compounds are the most significant microbicidal halogens used in the clinic and have been traditionally used for both antiseptic and disinfectant purposes.

Chlorine-releasing agents. Excellent reviews that deal with the chemical, physical, and microbiological properties of chlorine-releasing agents (CRAs) are available (42, 130). The most important types of CRAs are sodium hypochlorite, chlorine dioxide, and the *N*-chloro compounds such as sodium dichloroisocyanurate (NaDCC), with chloramine-T being used to some extent. Sodium hypochlorite solutions are widely used for hard-surface disinfection (household bleach) and can be used for disinfecting spillages of blood containing human immunodeficiency virus or HBV. NaDCC can also be used for this purpose and has the advantages of providing a higher concentration of available chlorine and being less susceptible to inactivation by organic matter. In water, sodium hypochlorite ionizes to produce Na^+ and the hypochlorite ion, OCl^-, which establishes an equilibrium with hypochlorous acid, HOCl (42). Between pH 4 and 7, chlorine exists predominantly as HClO, the active moiety, whereas above pH9, OCl^- predominates. Although CRAs have been predominantly used as hard-surface disinfectants, novel acidified sodium chlorite (a two-component system of sodium chlorite and mandelic acid) has been described as an effective antiseptic (248).

Surprisingly, despite being widely studied, the actual mechanism of action of CRAs is not fully known (Table 2). CRAs are highly active oxidizing agents and thereby destroy the cellular activity of proteins (42); potentiation of oxidation may occur at low pH, where the activity of CRAs is maximal, although increased penetration of outer cell layers may be achieved with CRAs in the unionized state. Hypochlorous acid has long been considered the active moiety responsible for bacterial inactivation by CRAs, the OCl^- ion having a minute effect compared to undissolved HOCl (130). This correlates with the observation that CRA activity is greatest when the percentage of undissolved HOCl is highest. This concept applies to hypochlorites, NaDCC, and chloramine-T.

Deleterious effects of CRAs on bacterial DNA that involve the formation of chlorinated derivatives of nucleotide bases have been described (115, 128, 477). Hypochlorous acid has also been found to disrupt oxidative phosphorylation (26) and other membrane-associated activity (70). In a particularly interesting paper, McKenna and Davies (321) described the inhibition of bacterial growth by hypochlorous acid. At 50 μM (2.6 ppm), HOCl completely inhibited the growth of *E. coli* within 5 min, and DNA synthesis was inhibited by 96% but protein synthesis was inhibited by only 10 to 30%. Because concentrations below 5 mM (260 ppm) did not induce bacterial membrane disruption or extensive protein degradation, it was inferred that DNA synthesis was the sensitive target. In contrast, chlorine dioxide inhibited bacterial protein synthesis (33).

CRAs at higher concentrations are sporicidal (44, 421, 431); this depends on the pH and concentration of available chlorine (408, 412). During treatment, the spores lose refractivity, the spore coat separates from the cortex, and lysis occurs (268). In addition, a number of studies have concluded that CRA-treated spores exhibit increased permeability of the spore coat (131, 268, 412).

CRAs also possess virucidal activity (34, 46, 116, 315, 394, 407, 467, 485, 486). Olivieri et al. (359) showed that chlorine inactivated naked f2 RNA at the same rate as RNA in intact phage, whereas f2 capsid proteins could still adsorb to the host. Taylor and Butler (504) found that the RNA of poliovirus type 1 was degraded into fragments by chlorine but that poliovirus inactivation preceded any severe morphological changes. By contrast, Floyd et al. (149) and O'Brien and Newman (357) demonstrated that the capsid of poliovirus type 1 was broken down. Clearly, further studies are needed to explain the antiviral action of CRAs.

Iodine and iodophors. Although less reactive than chlorine, iodine is rapidly bactericidal, fungicidal, tuberculocidal, virucidal, and sporicidal (184). Although aqueous or alcoholic (tincture) solutions of iodine have been used for 150 years as antiseptics, they are associated with irritation and excessive staining. In addition, aqueous solutions are generally unstable; in solution, at least seven iodine species are present in a complex equilibrium, with molecular iodine (I_2) being primarily responsible for antimictrobial efficacy (184). These problems were overcome by the development of iodophors ("iodine carriers" or "iodine-releasing agents"); the most widely used are povidone-iodine and poloxamer-iodine in both antiseptics and disinfectants. Iodophors are complexes of iodine and a solubilizing agent or carrier, which acts as a reservoir of the active "free" iodine (184). Although germicidal activity is maintained, iodophors are considered less active against certain fungi and spores than are tinctures (454).

Similar to chlorine, the antimicrobial action of iodine is rapid, even at low concentrations, but the exact mode of action is unknown. Iodine rapidly penetrates into microorganisms (76) and attacks key groups of proteins (in particular the free-sulfur amino acids cysteine and methionine [184, 267]), nucleotides, and fatty acids (15, 184), which culminates in cell death (184). Less is known about the antiviral action of iodine, but nonlipid viruses and parvoviruses are less sensitive than lipid enveloped viruses (384). Similarly to bacteria, it is likely that iodine attacks the surface proteins of enveloped viruses, but they may also destabilize membrane fatty acids by reacting with unsaturated carbon bonds (486).

Silver Compounds

In one form or another, silver and its compounds have long been used as antimicrobial agents (55, 443). The most important silver compound currently in use is silver sulfadiazine

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(AgSD), although silver metal, silver acetate, silver nitrate, and silver protein, all of which have antimicrobial properties, are listed in *Martindale, The Extra Pharmacopoeia* (312). In recent years, silver compounds have been used to prevent the infection of burns and some eye infections and to destroy warts.

Silver nitrate. The mechanism of the antimicrobial action of silver ions is closely related to their interaction with thiol (sulfydryl, –SH) groups (32, 49, 161, 164), although other target sites remain a possibility (397, 509). Liau et al (287) demonstrated that amino acids such as cysteine and other compounds such as sodium thioglycolate containing thiol groups neutralized the activity of silver nitrate against *P. aeruginosa*. By contrast, amino acids containing disulfide (SS) bonds, non-sulfur-containing amino acids, and sulfur-containing compounds such as cystathione, cysteic acid, L-methionine, taurine, sodium bisulfite, and sodium thiosulfate were all unable to neutralize Ag^+ activity. These and other findings imply that interaction of Ag^+ with thiol groups in enzymes and proteins plays an essential role in bacterial inactivation, although other cellular components may be involved. Hydrogen bonding, the effects of hydrogen bond-breaking agents, and the specificity of Ag^+ for thiol groups were discussed in greater detail by Russell and Hugo (443) (Table 2). Virucidal properties might also be explained by binding to –SH groups (510).

Lukens (292) proposed that silver salts and other heavy metals such as copper act by binding to key functional groups of fungal enzymes. Ag^+ causes the release of K^+ ions from microorganisms; the microbial plasma or cytoplasmic membrane, with which is associated many important enzymes, is an important target site for Ag^+ activity (161, 329, 392, 470).

In addition to its effects on enzymes, Ag^+ produces other changes in microorganisms. Silver nitrate causes marked inhibition of growth of *Cryptococcus neoformans* and is deposited in the vacuole and cell wall as granules (60). Ag^+ inhibits cell division and damages the cell envelope and contents of *P. aeruginosa* (398). Bacterial cells increase in size, and the cytoplasmic membrane, cytoplasmic contents, and outer cell layers all exhibit structural abnormalities, although without any blebs (protuberances) (398). Finally, the Ag^+ ion interacts with nucleic acids (543); it interacts preferentially with the bases in DNA rather than with the phosphate groups, although the significance of this in terms of its lethal action is unclear (231, 387, 510, 547).

Silver sulfadiazine. AgSD is essentially a combination of two antibacterial agents, Ag^+ and sulfadiazine (SD). The question whether the antibacterial effect of AgSD arises predominantly from only one of the compounds or via a synergistic interaction has been posed repeatedly. AgSD has a broad spectrum of activity and, unlike silver nitrate, produces surface and membrane blebs in susceptible (but not resistant) bacteria (96). AgSD binds to cell components, including DNA (332, 404). Based on a chemical analysis, Fox (153) proposed a polymeric structure of AgSD composed of six silver atoms bonding to six SD molecules by linkage of the silver atoms to the nitrogens of the SD pyrimidine ring. Bacterial inhibition would then presumably be achieved when silver binds to sufficient base pairs in the DNA helix, thereby inhibiting transcription. Similarly, its antiphage properties have been ascribed to the fact that AgSD binds to phage DNA (154, 388). Clearly, the precise mechanism of action of AgSD has yet to be solved.

Peroxygens

Hydrogen peroxide. Hydrogen peroxide (H_2O_2) is a widely used biocide for disinfection, sterilization, and antisepsis. It is a clear, colorless liquid that is commercially available in a variety of concentrations ranging from 3 to 90%. H_2O_2 is considered environmentally friendly, because it can rapidly degrade into the innocuous products water and oxygen. Although pure solutions are generally stable, most contain stabilizers to prevent decomposition. H_2O_2 demonstrates broad-spectrum efficacy against viruses, bacteria, yeasts, and bacterial spores (38). In general, greater activity is seen against gram-positive than gram-negative bacteria; however, the presence of catalase or other peroxidases in these organisms can increase tolerance in the presence of lower concentrations. Higher concentrations of H_2O_2 (10 to 30%) and longer contact times are required for sporicidal activity (416), although this activity is significantly increased in the gaseous phase. H_2O_2 acts as an oxidant by producing hydroxyl free radicals ($^{\bullet}OH$) which attack essential cell components, including lipids, proteins, and DNA. It has been proposed that exposed sulfhydryl groups and double bonds are particularly targeted (38).

Peracetic acid. Peracetic acid (PAA) (CH_3COOOH) is considered a more potent biocide than hydrogen peroxide, being sporicidal, bactericidal, virucidal, and fungicidal at low concentrations (<0.3%) (38). PAA also decomposes to safe by-products (acetic acid and oxygen) but has the added advantages of being free from decomposition by peroxidases, unlike H_2O_2, and remaining active in the presence of organic loads (283, 308). Its main application is as a low-temperature liquid sterilant for medical devices, flexible scopes, and hemodialyzers, but it is also used as an environmental surface sterilant (100, 308).

Similar to H_2O_2, PAA probably denatures proteins and enzymes and increases cell wall permeability by disrupting sulfhydryl (–SH) and sulfur (S–S) bonds (22, 38).

Phenols

Phenolic-type antimicrobial agents have long been used for their antiseptic, disinfectant, or preservative properties, depending on the compound. It has been known for many years (215) that, although they have often been referred to as "general protoplasmic poisons," they have membrane-active properties which also contribute to their overall activity (120) (Table 2).

Phenol induces progressive leakage of intracellular constituents, including the release of K^+, the first index of membrane damage (273), and of radioactivity from ^{14}C-labeled *E. coli* (242, 265). Pulvertaft and Lumb (386) demonstrated that low concentrations of phenols (0.032%, 320 μg/ml) and other (nonphenolic) agents lysed rapidly growing cultures of *E. coli*, staphylococci, and streptococci and concluded that autolytic enzymes were not involved. Srivastava and Thompson (487, 488) proposed that phenol acts only at the point of separation of pairs of daughter cells, with young bacterial cells being more sensitive than older cells to phenol.

Hugo and Bloomfield (216, 217) showed with the chlorinated bis-phenol fenticlor that there was a close relationship between bactericidal activity and leakage of 260-nm-absorbing material (leakage being induced only by bactericidal concentrations). Fentichlor affected the metabolic activities of *S. aureus* and *E. coli* (217) and produced a selective increase in permeability to protons with a consequent dissipation of the proton motive force (PMF) and an uncoupling of oxidative phosphorylation (41). Chlorocresol has a similar action (124). Coagulation of cytoplasmic constituents at higher phenol concentrations, which causes irreversible cellular damage, has been described by Hugo (215).

The phenolics possess antifungal and antiviral properties. Their antifungal action probably involves damage to the plas-

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ma membrane (436), resulting in leakage of intracellular constituents. Phenol does not affect the transduction of *P. aeruginosa* PAO by bacteriophage F116 (301), has no effect on phage DNA within the capsid, and has little effect on several of the phage band proteins unless treatments of 20 min or longer are used (303, 304).

Bis-Phenols

The bis-phenols are hydroxy-halogenated derivatives of two phenolic groups connected by various bridges (191, 446). In general, they exhibit broad-spectrum efficacy but have little activity against *P. aeruginosa* and molds and are sporostatic toward bacterial spores. Triclosan and hexachlorophane are the most widely used biocides in this group, especially in antiseptic soaps and hand rinses. Both compounds have been shown to have cumulative and persistent effects on the skin (313).

Triclosan. Triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether; Irgasan DP 300) exhibits particular activity against gram-positive bacteria (469, 521). Its efficacy against gram-negative bacteria and yeasts can be significantly enhanced by formulation effects. For example, triclosan in combination with EDTA caused increased permeability of the outer membrane (282). Reports have also suggested that in addition to its antibacterial properties, triclosan may have anti-inflammatory activity (25, 522). The specific mode of action of triclosan is unknown, but it has been suggested that the primary effects are on the cytoplasmic membrane. In studies with *E. coli*, triclosan at subinhibitory concentrations inhibited the uptake of essential nutrients, while higher, bactericidal concentrations resulted in the rapid release of cellular components and cell death (393). Studies with a divalent-ion-dependent *E. coli* triclosan mutant for which the triclosan MIC was 10-fold greater than that for a wild-type strain showed no significant differences in total envelope protein profiles but did show significant differences in envelope fatty acids (370). Specifically, a prominent 14:1 fatty acid was absent in the resistant strain, and there were minor differences in other fatty acid species. It was proposed that divalent ions and fatty acids may adsorb and limit the permeability of triclosan to its site of action (370). Minor changes in fatty acid profiles were recently found in both *E. coli* and *S. aureus* strains for which the triclosan MICs were elevated; however, the MBCs were not affected, suggesting, as for other phenols, that the cumulative effects on multiple targets contribute to the bactericidal activity (318, 319).

Hexachlorophene. Hexachlorophene (hexachlorophane; 2,2′-dihydroxy-3,5,6,3′,5′,6′-hexachlorodiphenylmethane) is another bis-phenol whose mode of action has been extensively studied. The primary action of hexachlorophene, based on studies with *Bacillus megatherium*, is to inhibit the membrane-bound part of the electron transport chain, and the other effects noted above are secondary ones that occur only at high concentrations (92, 158, 241, 481). It induces leakage, causes protoplast lysis, and inhibits respiration. The threshold concentration for the bactericidal activity of hexachlorphene is 10 μg/ml (dry weight), but peak leakage occurs at concentrations higher than 50 μg/ml and cytological changes occur above 30 μg/ml. Furthermore, hexachlorophene is bactericidal at 0°C despite causing little leakage at this temperature. Despite the broad-spectrum efficacy of hexachlorophene, concerns about toxicity (256), in particular in neonates, have meant that its use in antiseptic products has been limited.

Halophenols

Chloroxylenol (4-chloro-3,5-dimethylphenol; *p*-chloro-*m*-xylenol) is the key halophenol used in antiseptic or disinfectant formulations (66). Chloroxylenol is bactericidal, but *P. aeruginosa* and many molds are highly resistant (66, 432). Surprisingly, its mechanism of action has been little studied despite its widespread use over many years. Because of its phenolic nature, it would be expected to have an effect on microbial membranes.

Quaternary Ammonium Compounds

Surface-active agents (surfactants) have two regions in their molecular structures, one a hydrocarbon, water-repellent (hydrophobic) group and the other a water-attracting (hydrophilic or polar) group. Depending on the basis of the charge or absence of ionization of the hydrophilic group, surfactants are classified into cationic, anionic, nonionic, and ampholytic (amphoteric) compounds. Of these, the cationic agents, as exemplified by quaternary ammonium compounds (QACs), are the most useful antiseptics and disinfectants (160). They are sometimes known as cationic detergents. QACs have been used for a variety of clinical purposes (e.g., preoperative disinfection of unbroken skin, application to mucous membranes, and disinfection of noncritical surfaces). In addition to having antimicrobial properties, QACs are also excellent for hard-surface cleaning and deodorization.

It has been known for many years that QACs are membrane-active agents (221) (Table 2) (i.e., with a target site predominantly at the cytoplasmic (inner) membrane in bacteria or the plasma membrane in yeasts) (215). Salton (460) proposed the following sequence of events with microorganisms exposed to cationic agents: (i) adsorption and penetration of the agent into the cell wall; (ii) reaction with the cytoplasmic membrane (lipid or protein) followed by membrane disorganization; (iii) leakage of intracellular low-molecular-weight material; (iv) degradation of proteins and nucleic acids; and (v) wall lysis caused by autolytic enzymes. There is thus a loss of structural organization and integrity of the cytoplasmic membrane in bacteria, together with other damaging effects to the bacterial cell (120).

Useful information about the selectivity of membrane action can be obtained by studying the effects of biocides on protoplasts and spheroplasts suspended in various solutes. QACs cause lysis of spheroplasts and protoplasts suspended in sucrose (107, 215, 243, 428). The cationic agents react with phospholipid components in the cytoplasmic membrane (69), thereby producing membrane distortion and protoplast lysis under osmotic stress. Isolated membranes do not undergo disaggregation on exposure to QACs, because the membrane distortion is not sufficiently drastic. The non-QAC agents TCC and trichlorosalicylanide have specific effects: TCC induces protoplast lysis in ammonium chloride by increasing Cl^- permeability, whereas trichlorosalicylanide induces lysis in ammonium nitrate by increasing NO_3^- permeability (428). In contrast, QACs (and chlorhexidine) induce lysis of protoplasts or spheroplasts suspended in various solutes because they effect generalized, rather than specific, membrane damage.

The bacterial cytoplasmic membrane provides the mechanism whereby metabolism is linked to solute transport, flagellar movement, and the generation of ATP. Protons are extruded to the exterior of the bacterial cell during metabolism. The combined potential (concentration or osmotic effect of the proton and its electropositivity) is the PMF, which drives these ancillary activities (428). The QAC cetrimide was found (121) to have an effect on the PMF in *S. aureus*. At its bacteriostatic concentration, cetrimide caused the discharge of the pH component of the PMF and also produced the maximum amount of 260-nm-absorbing material.

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QACs are also believed to damage the outer membrane of gram-negative bacteria, thereby promoting their own uptake. This aspect of QACs is considered below (see "Intrinsic resistance of gram-negative bacteria").

The QAC cetylpyridium chloride (CPC) induces the leakage of K^+ and pentose material from the yeast *S. cerevisiae* and induces protoplast lysis as well as interacting with crude cell sap (205). Unlike chlorhexidine, however, no biphasic effect on protoplast lysis was observed. The initial toxic effect of QACs on yeast cells is a disorganization of the plasma membranes, with organized lipid structures in the membranes (and in lipid bilayers) being disrupted.

QACs are sporostatic; they inhibit the outgrowth of spores (the development of a vegetative cell from a germinated spore) but not the actual germination processes (development from dormancy to a metabolically active state), albeit by an unknown mechanism (414). Likewise, the QACs are not mycobactericidal but have a mycobacteriostatic action, although the actual effects on mycobacteria have been little studied (419).

The QACs have an effect on lipid, enveloped (including human immunodeficiency virus and HBV) but not nonenveloped viruses (394, 485, 486). QAC-based products induced disintegration and morphological changes of human HBV, resulting in loss of infectivity (382). In studies with different phages (298–301, 303–305, 307), CPC significantly inhibited transduction by bacteriophage F116 and inactivated the phage particles. Furthermore, CPC altered the protein bands of F116 but did not affect the phage DNA within the capsid.

Vapor-Phase Sterilants

Many heat-sensitive medical devices and surgical supplies can be effectively sterilized by liquid sterilants (in particular glutaraldehyde, PAA, and hydrogen peroxide) or by vapor-phase sterilization systems (Table 1). The most widely used active agents in these "cold" systems are ethylene oxide, formaldehyde and, more recently developed, hydrogen peroxide and PAA. Ethylene oxide and formaldehyde are both broad-spectrum alkylating agents. However, their activity is dependent on active concentration, temperature, duration of exposure, and relative humidity (87). As alkylating agents, they attack proteins, nucleic acids, and other organic compounds; both are particularly reactive with sulfhydryl and other enzyme-reactive groups. Ethylene oxide gas has the disadvantages of being mutagenic and explosive but is not generally harsh on sensitive equipment, and toxic residuals from the sterilization procedure can be routinely eliminated by correct aeration. Formaldehyde gas is similar and has the added advantage of being nonexplosive but is not widely used in health care. Vapor-phase hydrogen peroxide and PAA are considered more active (as oxidants) at lower concentrations than in the liquid form (334). Both active agents are used in combination with gas plasma in low-temperature sterilization systems (314). Their main advantages over other vapor-phase systems include low toxicity, rapid action, and activity at lower temperature; the disadvantages include limited penetrability and applications.

MECHANISMS OF RESISTANCE

Introduction

As stated above, different types of microorganisms vary in their response to antiseptics and disinfectants. This is hardly surprising in view of their different cellular structure, composition, and physiology. Traditionally, microbial susceptibility to antiseptics and disinfectants has been classified based on these differences; with recent work, this classification can be further extended (Fig. 1). Because different types of organisms react differently, it is convenient to consider bacteria, fungi, viruses, protozoa, and prions separately.

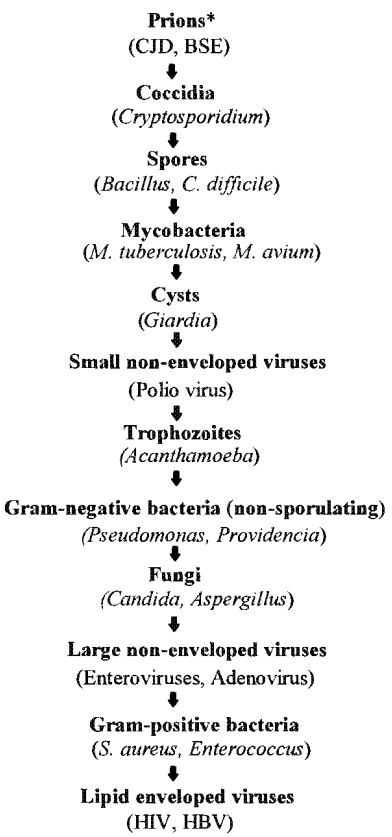


FIG. 1. Descending order of resistance to antiseptics and disinfectants. The asterisk indicates that the conclusions are not yet universally agreed upon.

Bacterial Resistance to Antiseptics and Disinfectants

In recent years, considerable progress has been made in understanding more fully the responses of different types of bacteria (mycobacteria, nonsporulating bacteria, and bacterial spores) to antibacterial agents (43, 84, 414, 415, 419, 422, 496). As a result, resistance can be either a natural property of an organism (intrinsic) or acquired by mutation or acquisition of plasmids (self-replicating, extrachromosomal DNA) or transposons (chromosomal or plasmid integrating, transmissible DNA cassettes). Intrinsic resistance is demonstrated by gram-negative bacteria, bacterial spores, mycobacteria, and, under certain conditions, staphylococci (Table 5). Acquired, plasmid-mediated resistance is most widely associated with mercury compounds and other metallic salts. In recent years, acquired resistance to certain other types of biocides has been observed, notably in staphylococci.

Intrinsic Bacterial Resistance Mechanisms

For an antiseptic or disinfectant molecule to reach its target site, the outer layers of a cell must be crossed. The nature and composition of these layers depend on the organism type and may act as a permeability barrier, in which there may be a reduced uptake (422, 428). Alternatively but less commonly, constitutively synthesized enzymes may bring about degradation of a compound (43, 214, 358). Intrinsic (innate) resistance

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TABLE 5. Intrinsic resistance mechanisms in bacteria to antiseptics and disinfectants

Type of resistance	Example(s)	Mechanism of resistance
Impermeability		
Gram-negative bacteria	QACs, triclosan, diamines	Barrier presented by outer membrane may prevent uptake of antiseptic or disinfectant; glycocalyx may also be involved
Mycobacteria	Chlorhexidine, QACs Glutaraldehyde	Waxy cell wall prevents adequate biocide entry Reason for high resistance of some strains of *M. chelonae*(?)
Bacterial spores	Chlorhexidine, QACs, phenolics	Spore coat(s) and cortex present a barrier to entry of antiseptics and disinfectants
Gram-positive bacteria	Chlorhexidine	Glycocalyx/mucoexopolysaccaride may be associated with reduced diffusion of antiseptic
Inactivation (chromosomally mediated)	Chlorohexidine	Breakdown of chlorhexidine molecule may be responsible for resistance

is thus a natural, chromosomally controlled property of a bacterial cell that enables it to circumvent the action of an antiseptic or disinfectant. Gram-negative bacteria tend to be more resistant than gram-positive organisms, such as staphylococci (Table 6).

Intrinsic resistance of bacterial spores. Bacterial spores of the genera *Bacillus* and *Clostridium* have been widely studied and are invariably the most resistant of all types of bacteria to antiseptics and disinfectants (43, 46, 150, 414, 418, 420, 422, 423, 457). Although *Bacillus* species are generally not pathogenic, their spores are widely used as indicators of efficient sterilization. *Clostridium* species are significant pathogens; for example, *C. difficile* is the most common cause of hospital-acquired diarrhea (478). Many biocides are bactericidal or bacteristatic at low concentrations for nonsporulating bacteria, including the vegetative cells of *Bacillus* and *Clostridium* species, but high concentrations may be necessary to achieve a sporicidal effect (e.g., for glutaraldehyde and CRAs). By contrast, even high concentrations of alcohol, phenolics, QACs, and chlorhexidine lack a sporicidal effect, although this may be achieved when these compounds are used at elevated temperatures (475).

A typical spore has a complex structure (29, 151). In brief, the germ cell (protoplast or core) and germ cell wall are surrounded by the cortex, outside which are the inner and outer spore coats. A thin exosporium may be present in the spores of some species but may surround just one spore coat. RNA, DNA, and DPA, as well as most of the calcium, potassium, manganese, and phosphorus, are present in the spore protoplast. Also present are large amounts of low-molecular-weight basic proteins (small acid-soluble spore proteins [SASPs]), which are rapidly degraded during germination. The cortex consists largely of peptidoglycan, including a spore-specific muramic lactam. The spore coats comprise a major portion of the spore. These structures consist largely of protein, with an alkali-soluble fraction made up of acidic polypeptides being found in the inner coat and an alkali-resistant fraction associated with the presence of disulfide-rich bonds being found in the outer coat. These aspects, especially the roles of the coat(s) and cortex, are all relevant to the mechanism(s) of resistance presented by bacterial spores to antiseptics and disinfectants.

Several techniques are available for studying mechanisms of spore resistance (428). They include removing the spore coat and cortex by using a "step-down" technique to achieve a highly synchronous sporulation (so that cellular changes can be accurately monitored), employing spore mutants that do not sporulate beyond genetically determined stages in sporulation, adding an antiseptic or disinfectant at the commencement of sporulation and determining how far the process can proceed, and examining the role of SASPs. Such procedures have helped provide a considerable amount of useful information. Sporulation itself is a process in which a vegetative cell develops into a spore and involves seven stages (designated 0 to VII). During this process, the vegetative cell (stage 0) undergoes a series of morphological changes that culminate in the release of a mature spore (stage VII). Stages IV (cortex development) to VII are the most important in the development of resistance to biocides.

Resistance to antiseptics and disinfectants develops during sporulation and may be an early, intermediate, or (very) late event (103, 375, 378, 429, 474). Useful markers for monitoring the development of resistance are toluene (resistance to which is an early event), heat (intermediate), and lysozyme (late) (236, 237). Studies with a wild-type *B. subtilis* strain, 168, and its Spo^- mutants have helped determine the stages at which resistance develops (262, 375, 474). From these studies (Fig. 2), the order of development of resistance was toluene (marker), formaldehyde, sodium lauryl sulfate, phenol, and phenylmercuric nitrate; *m*-cresol, chlorocresol, chlorhexidine gluconate, cetylpyridinium chloride, and mercuric chloride; and moist heat (marker), sodium dichloroisocyanurate, sodium hypochlorite, lysozyme (marker), and glutaraldehyde. The association of the onset of resistance to a particular antiseptic or disinfectant with a particular stage(s) in spore development is thereby demonstrated.

Spore coat-less forms, produced by treatment of spores un-

TABLE 6. MIC of some antiseptics and disinfectants against gram-positive and gram-negative bacteria[a]

Chemical agent	MIC (μg/ml) for:		
	S. aureus[b]	*E. coli*	*P. aeruginosa*
Benzalkonium chloride	0.5	50	250
Benzethonium chloride	0.5	32	250
Cetrimide	4	16	64–128
Chlorhexidine	0.5–1	1	5–60
Hexachlorophene	0.5	12.5	250
Phenol	2,000	2,000	2,000
o-Phenylphenol	100	500	1,000
Propamine isethionate	2	64	256
Dibromopropamidine isethionate	1	4	32
Triclosan	0.1	5	>300

[a] Based on references 226 and 440.
[b] MICs of cationic agents for some MRSA strains may be higher (see Table 10).

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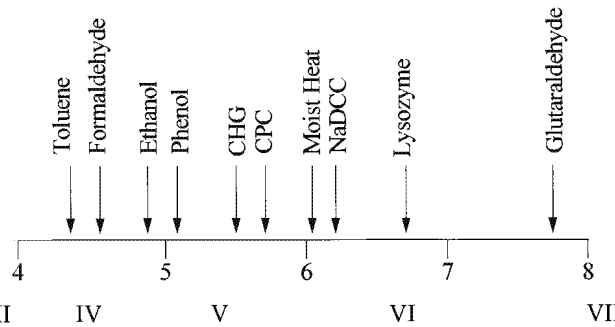


FIG. 2. Development of resistance of *Bacillus subtilis* during sporulation. Roman numerals indicate the sporulation stage from III (engulfment of the forespore) to VII (release of the mature spore). Arabic numbers indicate the time (hours) following the onset of sporulation and the approximate times at which resistance develops against biocides (262). CHG, chlorhexidine; CPC, cetylpyridinium chloride; NaDCC, sodium dichloroisocyanurate.

der alkaline conditions with urea plus dithiothreitol plus sodium lauryl sulfate (UDS), have also been of value in estimating the role of the coats in limiting the access of antiseptics and disinfectants to their target sites. However, Bloomfield and Arthur (44, 45) and Bloomfield (43) showed that this treatment also removes a certain amount of cortex and that the amount of cortex remaining can be further reduced by the subsequent use of lysozyme. These findings demonstrate that the spore coats have an undoubted role in conferring resistance but that the cortex also is an important barrier since (UDS plus lysozyme)-treated spores are much more sensitive to chlorine- and iodine-releasing agents than are UDS-exposed spores.

The initial development and maturity of the cortex are implicated in the development of resistance to phenolics. Likewise, it is now clear that cortex development is at least partially responsible for resistance to chlorhexidine and QACs; this resistance is enhanced in developing spores by the initiation of spore coat synthesis (262). The effect of various concentrations of chlorhexidine, sublethal to vegetative bacteria, on the development of spores of *B. subtilis* 168 MB_2 were investigated by Knott and Russell (261). They found that chlorhexidine affected spore development; as concentrations of the biguanide increased, spore index values (the percentage of cells forming spores) decreased and sensitivity to both heat and toluene increased. By contrast, the control (untreated) culture was highly resistant to both of these agents and had a high spore index value, indicative of high levels of mature spores. The slightly increased resistance to toluene compared to resistance to heat was not surprising, since cells must reach stages V to VI (synthesis of spore coats and maturation) to attain heat resistance but only stage III (forespore engulfment) to attain toluene resistance (Fig. 2); in other words, if sporulation is inhibited by chlorhexidine, more cells are likely to reach stage III than the later stages. While less definitive than the earlier approaches, these procedures provide further evidence of the involvement of the cortex and coats in chlorhexidine resistance.

Development of resistance during sporulation to formaldehyde was an early event but depended to some extent on the concentration (1 to 5% [vol/vol]) of formaldehyde used. This appears to be at odds with the extremely late development of resistance to the dialdehyde, glutaraldehyde. Since glutaraldehyde and the monoaldehyde, formaldehyde, contain an aldehyde group(s) and are alkylating agents, it would be plausible to assume that they would have a similar mode of sporicidal action, even though the dialdehyde is a more powerful alkylating agent. If this were true, it could also be assumed that spores would exhibit the same resistance mechanisms for these disinfectants. In aqueous solution, formaldehyde forms a glycol in equilibrium (512, 524); thus, formaldehyde could well be acting poorly as an alcohol-type disinfectant rather than as an aldehyde (327). Alkaline glutaraldehyde does not readily form glycols in aqueous solution (178). Resistance to formaldehyde may be linked to cortex maturation, and resistance to glutaraldehyde may be linked to coat formation (262).

Setlow and his coworkers (472) demonstrated that α/β-type SASPs coat the DNA in wild-type spores of *B. subtilis*, thereby protecting it from attack by enzymes and antimicrobial agents. Spores ($\alpha^-\beta^-$) lacking these α/β-type SASPs are significantly more sensitive to hydrogen peroxide (471) and hypochlorite (456). Thus, SASPs contribute to spore resistance to peroxide and hypochlorite but may not be the only factors involved, since the coats and cortex also play a role (428).

Two other aspects of spores should be considered: the revival of injured spores and the effects of antiseptics and disinfectants on germinating and outgrowing spores. Although neither aspect is truly a resistance mechanism, each can provide useful information about the site and mechanism of action of sporicidal agents and about the associated spore resistance mechanisms and might be of clinical importance.

The revival of disinfectant-treated spores has not been extensively studied. Spicher and Peters (483, 484) demonstrated that formaldehyde-exposed spores of *B. subtilis* could be revived after a subsequent heat shock process. A more recent finding with *B. stearothermophilus* casts further doubt on the efficacy of low-temperature steam with formaldehyde as a sterilizing procedure (541). The revival of spores exposed to glutaraldehyde, formaldehyde, chlorine, and iodine was examined by Russell and his colleagues (103, 376, 377, 424, 532–537). A small proportion of glutaraldehyde-treated spores of various *Bacillus* species were revived when the spores were treated with alkali after neutralization of glutaraldehyde with glycine (103, 379, 380). Experiments designed to distinguish between germination and outgrowth in the revival process have demonstrated that sodium hydroxide-induced revival increases the potential for germination. Based on other findings, the germination process is also implicated in the revival of spores exposed to other disinfectants.

Intrinsic resistance of mycobacteria. Mycobacteria are well known to possess a resistance to antiseptics and disinfectants that is roughly intermediate between those of other nonsporulating bacteria and bacterial spores (Fig. 1) (177, 345, 419). There is no evidence that enzymatic degradation of harmful molecules takes place. The most likely mechanism for the high resistance of mycobacteria is associated with their complex cell walls that provide an effective barrier to the entry of these agents. To date, plasmid- or transposon-mediated resistance to biocides has not been demonstrated in mycobacteria.

The mycobacterial cell wall is a highly hydrophobic structure with a mycoylarabinogalactan-peptidoglycan skeleton (27, 105, 106, 322, 389, 390, 461, 530). The peptidoglycan is covalently linked to the polysaccharide copolymer (arabinogalactan) made up of arabinose and galactose esterified to mycolic acids. Also present are complex lipids, lipopolysaccharides (LPSs), and proteins, including porin channels through which hydrophilic molecules can diffuse into the cell (232, 356). Similar cell wall structures exist in all the mycobacterial species examined to date (228). The cell wall composition of a particular species may be influenced by its environmental niche (27). Pathogenic bacteria such as *Mycobacterium tuberculosis* exist in a relatively nutrient-rich environment, whereas saprophytic mycobacteria living in soil or water are exposed to natural antibiotics and tend to be more intrinsically resistant to these drugs.

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Antiseptics or disinfectants that exhibit mycobacterial activity are phenol, PAA, hydrogen peroxide, alcohol, and glutaraldehyde (16, 17, 99, 419, 425, 455). By contrast, other well-known bactericidal agents, such as chlorhexidine and QACs, are mycobacteristatic even when used at high concentrations (51, 52, 419, 425, 455). However, the activity of these can be substantially increased by formulation effects. Thus, a number of QAC-based products claim to have mycobacterial activity. For example, a newer formulation (Sactimed-I-Sinald) containing a mixture of alkyl polyguanides and alkyl QACs is claimed to be mycobactericidal (211, 353). However, there is some doubt whether the antibacterial agents had been properly quenched or neutralized to prevent carryover of inhibitory concentrations into recovery media.

Many years ago, it was proposed (T. H. Shen, cited in reference 99) that the resistance of mycobacteria to QACs was related to the lipid content of the cell wall. In support of this contention, *Mycobacterium phlei*, which has a low total cell lipid content, was more sensitive than *M. tuberculosis*, which has a higher lipid content. It was also noted that the resistance of various species of mycobacteria was related to the content of waxy material in the wall. It is now known that because of the highly hydrophobic nature of the cell wall, hydrophilic biocides are generally unable to penetrate the mycobacterial cell wall in sufficiently high concentrations to produce a lethal effect. However, low concentrations of antiseptics and disinfectants such as chlorhexidine must presumably traverse this permeability barrier, because the MICs are of the same order as those concentrations inhibiting the growth of nonmycobacterial strains such as *S. aureus*, although *M. avium-intracellulare* may be particularly resistant (51, 52). The component(s) of the mycobacterial cell wall responsible for the high biocide resistance are currently unknown, although some information is available. Inhibitors of cell wall synthesis increase the susceptibility of *M. avium* to drugs (391); inhibition of myocide C, arabinogalactan, and mycolic acid biosynthesis enhances drug susceptibility. Treatment of this organism with *m*-fluoro-DL-phenylalanine (*m*-FL-phe), which inhibits mycocide C synthesis, produces significant alterations in the outer cell wall layers (106). Ethambutol, an inhibitor of arabinogalactan (391, 501) and phospholipid (461, 462) synthesis, also disorganizes these layers. In addition, ethambutol induces the formation of ghosts without the dissolution of peptidoglycan (391). Methyl-4-(2-octadecylcyclopropen-1-yl) butanoate (MOCB) is a structural analogue of a key precursor in mycolic acid synthesis. Thus, the effects of MOCB on mycolic acid synthesis and *m*-FL-phe and ethambutol on outer wall biosynthetic processes leading to changes in cell wall architecture appear to be responsible for increasing the intracellular concentration of chemotherapeutic drugs. These findings support the concept of the cell wall acting as a permeability barrier to these drugs (425). Fewer studies have been made of the mechanisms involved in the resistance of mycobacteria to antiseptics and disinfectants. However, the activity of chlorhexidine and of a QAC, cetylpyridinium chloride, against *M. avium* and *M. tuberculosis* can be potentiated in the presence of ethambutol (52). From these data, it may be inferred that arabinogalactan is one cell wall component that acts as a permeability barrier to chlorhexidine and QACs. It is not possible, at present, to comment on other components, since these have yet to be investigated. It would be useful to have information about the uptake into the cells of these antiseptic agents in the presence and absence of different cell wall synthesis inhibitors.

One species of mycobacteria currently causing concern is *M. chelonae*, since these organisms are sometimes isolated from endoscope washes and dialysis water. One such strain was not killed even after a 60-min exposure to alkaline glutaraldehyde; in contrast, a reference strain showed a 5-log-unit reduction after a contact time of 10 min (519). This glutaraldehyde-resistant *M. chelonae* strain demonstrated an increased tolerance to PAA but not to NaDCC or to a phenolic. Other workers have also observed an above-average resistance of *M. chelonae* to glutaraldehyde and formaldehyde (72) but not to PAA (187, 294). The reasons for this high glutaraldehyde resistance are unknown. However, *M. chelonae* is known to adhere strongly to smooth surfaces, which may render cells within a biofilm less susceptible to disinfectants. There is no evidence to date that uptake of glutaraldehyde by *M. chelonae* is reduced.

Intrinsic resistance of other gram-positive bacteria. The cell wall of staphylococci is composed essentially of peptidoglycan and teichoic acid. Neither of these appears to act as an effective barrier to the entry of antiseptics and disinfectants. Since high-molecular-weight substances can readily traverse the cell wall of staphylococci and vegetative *Bacillus* spp., this may explain the sensitivity of these organisms to many antibacterial agents including QACs and chlorhexidine (411, 417, 422, 428, 451).

However, the plasticity of the bacterial cell envelope is a well-known phenomenon (381). Growth rate and any growth-limiting nutrient will affect the physiological state of the cells. Under such circumstances, the thickness and degree of cross-linking of peptidoglycan are likely to be modified and hence the cellular sensitivity to antiseptics and disinfectants will be altered. For example, Gilbert and Brown (171) demonstrated that the sensitivity of *Bacillus megaterium* cells to chlorhexidine and 2-phenoxyethanol is altered when changes in growth rate and nutrient limitation are made with chemostat-grown cells. However, lysozyme-induced protoplasts of these cells remained sensitive to, and were lysed by, these membrane-active agents. Therefore, the cell wall in whole cells is responsible for their modified response.

In nature, *S. aureus* may exist as mucoid strains, with the cells surrounded by a slime layer. Nonmucoid strains are killed more rapidly than mucoid strains by chloroxylenol, cetrimide, and chlorhexidine, but there is little difference in killing by phenols or chlorinated phenols (263); removal of slime by washing rendered the cells sensitive. Therefore, the slime plays a protective role, either as a physical barrier to disinfectant penetration or as a loose layer interacting with or absorbing the biocide molecules.

There is no evidence to date that vancomycin-resistant enterococci or enterococci with high-level resistance to aminoglycoside antibiotics are more resistant to disinfectants than are antibiotic-sensitive enterococcal strains (9, 11, 48, 319). However, enterococci are generally less sensitive to biocides than are staphylococci, and differences in inhibitory and bactericidal concentrations have also been found among enterococcal species (257).

Intrinsic resistance of gram-negative bacteria. Gram-negative bacteria are generally more resistant to antiseptics and disinfectants than are nonsporulating, nonmycobacterial gram-positive bacteria (Fig. 2) (428, 440, 441). Examples of MICs against gram-positive and -negative organisms are provided in Table 6. Based on these data, there is a marked difference in the sensitivity of *S. aureus* and *E. coli* to QACs (benzalkonium, benzethonium, and cetrimide), hexachlorophene, diamidines, and triclosan but little difference in chlorhexidine susceptibility. *P. aeruginosa* is considerably more resistant to most of these agents, including chlorhexidine, and (not shown) *Proteus* spp. possess an above-average resistance to cationic agents such as chlorhexidine and QACs (311, 440).

The outer membrane of gram-negative bacteria acts as a barrier that limits the entry of many chemically unrelated types

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TABLE 7. Possible transport of some antiseptics and disinfectants into gram-negative bacteria[a]

Antiseptic/disinfectant	Passage across OM[b]	Passage across IM[b]
Chlorhexidine	Self-promoted uptake(?)	IM is a major target site; damage to IM enables biocide to enter cytosol, where further interaction occurs
QACs	Self-promoted uptake(?); also, OM might present a barrier	IM is a major target site; damage to IM enables biocide to enter cytosol, where further interaction occurs
Phenolics	Hydrophobic pathway (activity increases as hydrophobicity of phenolic increases)	IM is a major target site, but high phenolic concentrations coagulate cytoplasmic constituents

[a] Data from references 197, 433 to 435, 438, and 439.
[b] OM, outer membrane; IM, inner membrane.

of antibacterial agents (18, 169, 196, 197, 355, 366, 440, 516, 517). This conclusion is based on the relative sensitivities of staphylococci and gram-negative bacteria and also on studies with outer membrane mutants of *E. coli*, *S. typhimurium*, and *P. aeruginosa* (134, 135, 433–435, 438). Smooth, wild-type bacteria have a hydrophobic cell surface; by contrast, because of the phospholipid patches on the cell surface, deep rough (heptose-less) mutants are hydrophobic. These mutants tend to be hypersensitive to hydrophobic antibiotics and disinfectants. Low-molecular-weight (M_r <ca. 600) hydrophilic molecules readily pass via the porins into gram-negative cells, but hydrophobic molecules diffuse across the outer membrane bilayer (Table 7). In wild-type gram-negative bacteria, intact LPS molecules prevent ready access of hydrophobic molecules to phospholipid and thence to the cell interior. In deep rough strains, which lack the O-specific side chain and most of the core polysaccharide, the phospholipid patches at the cell surface have their head groups oriented toward the exterior.

In addition to these hydrophilic and hydrophobic entry pathways, a third pathway has been proposed for cationic agents such as QACs, biguanidies, and diamidines. It is claimed that these damage the outer membrane, thereby promoting their own uptake (197). Polycations disorganize the outer membrane of *E. coli* (520). It must be added, however, that the QACs and diamidines are considerably less active against wild-type strains than against deep rough strains whereas chlorhexidine has the same order of activity (MIC increase about 2 to 3 fold) against both types of *E. coli* strains (434, 435, 439). However, *S. typhimurium* mutants are more sensitive to chlorhexidine than are wild-type strains (433).

Gram-negative bacteria that show a high level of resistance to many antiseptics and disinfectants include *P. aeruginosa*, *Burkholderia cepacia*, *Proteus* spp., and *Providencia stuartii* (428, 440). The outer membrane of *P. aeruginosa* is responsible for its high resistance; in comparison with other organisms, there are differences in LPS composition and in the cation content of the outer membrane (54). The high Mg^{2+} content aids in producing strong LPS-LPS links; furthermore, because of their small size, the porins may not permit general diffusion through them. *B. cepacia* is often considerably more resistant in the hospital environment than in artificial culture media (360); the high content of phosphate-linked arabinose in its LPS decreases the affinity of the outer membrane for polymyxin antibiotics and other cationic and polycationic molecules (97, 516). *Pseudomonas stutzeri*, by contrast, is highly sensitive to many antibiotics and disinfectants (449), which implies that such agents have little difficulty in crossing the outer layers of the cells of this organism.

Members of the genus *Proteus* are invariably insensitive to chlorhexidine (311). Some strains that are highly resistant to chlorhexidine, QACs, EDTA, and diamidines have been isolated from clinical sources. The presence of a less acidic type of outer membrane LPS could be a contributing factor to this intrinsic resistance (97, 516).

A particularly troublesome member of the genus *Providencia* is *P. stuartii*. Like *Proteus* spp., *P. stuartii* strains have been isolated from urinary tract infections in paraplegic patients and are resistant to different types of antiseptics and disinfectants including chlorhexidine and QACs (492, 496). Strains of *P. stuartii* that showed low-, intermediate-, and high-level resistance to chlorhexidine formed the basis of a series of studies of the resistance mechanism(s) (86, 422, 428). Gross differences in the composition of the outer layers of these strains were not detected, and it was concluded that (i) subtle changes in the structural arrangement of the cell envelopes of these strains was associated with this resistance and (ii) the inner membrane was not implicated (230).

Few authors have considered peptidoglycan in gram-negative bacteria as being a potential barrier to the entry of inhibitory substances. The peptidoglycan content of these organisms is much lower than in staphylococci, which are inherently more sensitive to many antiseptics and disinfectants. Nevertheless, there have been instances (discussed in reference 422) where gram-negative organisms grown in subinhibitory concentrations of a penicillin have deficient permeability barriers. Furthermore, it has been known for many years (215, 409, 411) that penicillin-induced spheroplasts and lysozyme-EDTA-Tris "protoplasts" of gram-negative bacteria are rapidly lysed by membrane-active agents such as chlorhexidine. It is conceivable that the stretched nature of both the outer and inner membranes in β-lactam-treated organisms could contribute to this increased susceptibility.

The possibility exists that the cytoplasmic (inner) membrane provides one mechanism of intrinsic resistance. This membrane is composed of lipoprotein and would be expected to prevent passive diffusion of hydrophilic molecules. It is also known that changes in membrane composition affect sensitivity to ethanol (159). Lannigan and Bryan (275) proposed that decreased susceptibility of *Serratia marcescens* to chlorhexidine was linked to the inner membrane, but Ismaeel et al. (230) could find no such role with chlorhexidine-resistant *P. stuartii*. At present, there is little evidence to implicate the inner membrane in biocide resistance. In addition, chlorhexidine degradation was reported for *S. marcescens*, *P. aeruginosa*, and *Achromobacter/Alcaligenes xylosoxidans* (358).

Physiological (phenotypic) adaption as an intrinsic mechanism. The association of microorganisms with solid surfaces leads to the generation of a biofilm, defined as a consortium of organisms organized within an extensive exopolysaccharide exopolymer (93, 94). Biofilms can consist of monocultures, of several diverse species, or of mixed phenotypes of a given species (57, 73, 381). Some excellent publications that deal with the nature, formation, and content of biofilms are available (125, 178, 276, 538). Biofilms are important for several reasons,

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TABLE 8. Biofilms and microbial response to antimicrobial agents

Mechanism of resistance associated with biofilms	Comment
Exclusion or reduced access of antiseptic or disinfectant to underlying cell	Depends on (i) nature of antiseptic/disinfectant, (ii) binding capacity of glycocalyx toward antiseptic or disinfectant, and (iii) rate of growth of microcolony relative to diffusion rate of chemical inhibitor
Modulation of microenvironment	Associated with (i) nutrient limitation and (ii) growth rate
Increased production of degradative enzymes by attached cells	Mechanism unclear at present
Plasmid transfer between cells in biofilm?	Associated with enhanced tolerance to antiseptics and disinfectants?

notably biocorrosion, reduced water quality, and foci for contamination of hygienic products (10, 12–14). Colonization also occurs on implanted biomaterials and medical devices, resulting in increased infection rates and possible recurrence of infection (125).

Bacteria in different parts of a biofilm experience different nutrient environments, and their physiological properties are affected (57). Within the depths of a biofilm, for example, nutrient limitation is likely to reduce growth rates, which can affect susceptibility to antimicrobial agents (98, 142, 171, 172). Thus, the phenotypes of sessile organisms within biofilms differ considerably from the planktonic cells found in laboratory cultures (73). Slow-growing bacteria are particularly insusceptible, a point reiterated recently in another context (126).

Several reasons can account for the reduced sensitivity of bacteria within a biofilm (Table 8). There may be (i) reduced access of a disinfectant (or antibiotic) to the cells within the biofilm, (ii) chemical interaction between the disinfectant and the biofilm itself, (iii) modulation of the microenvironment, (iv) production of degradative enzymes (and neutralizing chemicals), or (v) genetic exchange between cells in a biofilm. However, bacteria removed from a biofilm and recultured in culture media are generally no more resistant than the "ordinary" planktonic cells of that species (57).

Several instances are known of the contamination of antiseptic or disinfectant solutions by bacteria. For example, Marrie and Costerton (310) described the prolonged survival of *S. marcescens* in 2% chlorhexidine solutions, which was attributed to the embedding of these organisms in a thick matrix that adhered to the walls of a storage containers. Similar conclusions were reached by Hugo et al. (225) concerning the survival of *B. cepacia* in chlorhexidine and by Anderson et al. (10, 12–14) concerning the contamination of iodophor antiseptics with *Pseudomonas*. In the studies by Anderson et al., *Pseudomonas* biofilms were found on the interior surfaces of polyvinyl chloride pipes used during the manufacture of providone-iodine antiseptics. It is to be wondered whether a similar reason could be put forward for the contamination by *S. marcescens* of a benzalkonium chloride solution implicated in meningitis (468). Recently, a novel strategy was described (540) for controlling biofilms through generation of hydrogen peroxide at the biofilm-surface interface rather than simply applying a disinfectant extrinsically. In this procedure, the colonized surface incorporated a catalyst that generated the active compound from a treatment agent.

Gram-negative pathogens can grow as biofilms in the catheterized bladder and are able to survive concentrations of chlorhexidine that are effective against organisms in noncatheterized individuals (493, 494). Interestingly, the permeability agent EDTA has only a temporary potentiating effect in the catheterized bladder, with bacterial growth subsequently recurring (495). *B. cepacia* freshly isolated from the hospital environment is often considerably more resistant to chlorhexidine than when grown in artificial culture media, and a glycocalyx may be associated with intrinsic resistance to the bisbiguanide (360). *Legionella pneumophila* is often found in hospital water distribution systems and cooling towers. Chlorination in combination with continuous heating (60°C) of incoming water is usually the most important disinfection measure; however, because of biofilm production, contaminating organisms may be less susceptible to this treatment (140). Increased resistance to chlorine has been reported for *Vibrio cholerae*, which expresses an amorphous exopolysaccharide causing cell aggregation ("rugose" morphology [336]) without any loss in pathogenicity.

One can reach certain conclusions about biofilms. The interaction of bacteria with surfaces is usually reversible and eventually irreversible. Irreversible adhesion is initiated by the binding of bacteria to the surface through exopolysaccharide glycocalyx polymers. Sister cells then arise by cell division and are bound within the glycocalyx matrix. The development of adherent microcolonies is thereby initiated, so that eventually a continuous biofilm is produced on the colonized surface. Bacteria within these biofilms reside in specific microenvironments that differ from those of cells grown under normal laboratory conditions and thus show variations in their response to antiseptics and disinfectants.

Recent nosocomial outbreaks due to *M. chelonae* (discussed under "Intrinsic resistance of mycobacteria"), *M. tuberculosis* (4, 323) and HCV (53) underscore the importance of pseudobiofilm formation in flexible fiberoptic scope contamination. These outbreaks were associated with inadequate cleaning of scopes, which compromised subsequent sterilization with glutaraldehyde. While these organisms do not form a true biofilm, the cross-linking action of glutaraldehyde can cause a buildup of insoluble residues and associated microorganisms on scopes and in automated reprocessors.

Biofilms provide the most important example of how physiological (phenotypic) adaptation can play a role in conferring intrinsic resistance (57). Other examples are also known. For example, fattened cells of *S. aureus* produced by repeated subculturing in glycerol-containing media are more resistant to alkyl phenols and benzylpenicillin than are wild-type strains (220). Subculture of these cells in routine culture media resulted in reversion to sensitivity (218). Planktonic cultures grown under conditions of nutrient limitation or reduced growth rates have cells with altered sensitivity to disinfectants, probably as a consequence of modifications in their outer membranes (56, 59, 98). In addition, many aerobic microorganisms have developed intrinsic defense systems that confer tolerance to peroxide stress (in particular H_2O_2) in vivo. The so-called oxidative-stress or SOS response has been well studied in *E. coli* and *Salmonella* and includes the production of neutralizing enzymes to prevent cellular damage (including peroxidases, catalases, glutathione reductase) and to repair DNA lesions (e.g., exonuclease III) (112, 114, 497). In both organisms, increased tolerance can be obtained by pretreatment with a subinhibitory dose of hydrogen peroxide (113, 539). Pretreatment induces a series of proteins, many of which are under the positive control of a sensor/regulator protein (OxyR), including catalase and glutathione reductase (497)

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TABLE 9. Possible mechanisms of plasmid-encoded resistance to antiseptics and disinfectants

Chemical agent	Examples	Mechanisms
Antiseptics or disinfectants	Chlorhexidine salts	(i) Inactivation: not yet found to be plasmid mediated; chromosomally mediated inactivation; (ii) efflux: some *S. aureus*, some *S. epidermidis*; (iii) Decreased uptake(?)
	QACs	(i) Efflux: some *S. aureus*, some *S. epidermidis*; (ii) Decreased uptake(?)
	Silver compounds	Decreased uptake; no inactivation (cf. mercury compounds)
	Formaldehyde	(i) Inactivation by formaldehyde dehydrogenase; (ii) Cell surface alterations (outer membrane proteins)
	Acridines[a]	Efflux: some *S. aureus*, some *S. epidermidis*
	Diamidines	Efflux: some *S. aureus*, some *S. epidermidis*
	Crystal violet[a]	Efflux: some *S. aureus*, some *S. epidermidis*
Other biocides	Mercurials[b]	Inactivation (reductases, lyases)
	Ethidium bromide	Efflux: some *S. aureus*, some *S. epidermidis*

[a] Now rarely used for antiseptic or disinfectant purposes.
[b] Organomercurials are still used as preservatives.

and further nonessential proteins that accumulate to protect the cell (338). Cross-resistance to heat, ethanol, and hypochlorous acid has also been reported (81, 128, 335). The oxidative stress response in gram-positive bacteria is less well studied, but *Bacillus* tolerance to H_2O_2 has been described to vary during the growth phase (127) and in mutant strains (67, 200). Similar inducible defense mechanisms were described for *Campylobacter jejuni* (185), *Deinococcus* (528), and *Haemophilus influenzae* (36). However, the level of increased tolerance to H_2O_2 during the oxidative stress response may not afford significant protection to concentrations used in antiseptics and disinfectants (generally >3%). For example, *B. subtilis* mutants have been described to be more resistant at ~0.5% H_2O_2 than are wild-type strains at ~0.34% H_2O_2 (200).

Acquired Bacterial Resistance Mechanisms

As with antibiotics and other chemotherapeutic drugs, acquired resistance to antiseptics and disinfectants can arise by either mutation or the acquisition of genetic material in the form of plasmids or transposons. It is important to note that "resistance" as a term can often be used loosely and in many cases must be interpreted with some prudence. This is particularly true with MIC analysis. Unlike antibiotics, "resistance," or an increase in the MIC of a biocide, does not necessarily correlate with therapeutic failure. An increase in an antibiotic MIC can may have significant consequences, often indicating that the target organism is unaffected by its antimicrobial action. Increased biocide MICs due to acquired mechanisms have also been reported and in some case misinterpreted as indicating resistance. It is important that issues including the pleiotropic action of most biocides, bactericidal activity, concentrations used in products, direct product application, formulation effects, etc., be considered in evaluating the clinical implications of these reports.

Plasmids and bacterial resistance to antiseptics and disinfectants. Chopra (82, 83) examined the role of plasmids in encoding resistance (or increased tolerance) to antiseptics and disinfectants; this topic was considered further by Russell (413). It was concluded that apart from certain specific examples such as silver, other metals, and organomercurials, plasmids were not normally responsible for the elevated levels of antiseptic or disinfectant resistance associated with certain species or strains. Since then, however, there have been numerous reports linking the presence of plasmids in bacteria with increased tolerance to chlorhexidine, QACs, and triclosan, as well as to diamidines, acridines and ethidium bromide, and the topic was reconsidered (83, 423, 427) (Table 9).

Plasmid-encoded resistance to antiseptics and disinfectants had at one time been most extensively investigated with mercurials (both inorganic and organic), silver compounds, and other cations and anions. Mercurials are no longer used as disinfectants, but phenylmercuric salts and thiomersal are still used as preservatives in some types of pharmaceutical products (226). Resistance to mercury is plasmid borne, inducible, and may be transferred by conjugation or transduction. Inorganic mercury (Hg^{2+}) and organomercury resistance is a common property of clinical isolates of *S. aureus* containing penicillinase plasmids (110). Plasmids conferring resistance to mercurials are either narrow spectrum, specifying resistance to Hg^{2+} and to some organomercurials, or broad-spectrum, with resistance to the above compounds and to additional organomercurials (331). Silver salts are still used as topical antimicrobial agents (50, 443). Plasmid-encoded resistance to silver has been found in *Pseudomonas stutzeri* (192), members of the *Enterobacteriaceae* (479, 480, 511), and *Citrobacter* spp. (511). The mechanism of resistance has yet to be elucidated fully but may be associated with silver accumulation (152, 511).

(i) Plasmid-mediated antiseptic and disinfectant resistance in gram-negative bacteria. Occasional reports have examined the possible role of plasmids in the resistance of gram-negative bacteria to antiseptics and disinfectants. Sutton and Jacoby (498) observed that plasmid RP1 did not significantly alter the resistance of *P. aeruginosa* to QACs, chlorhexidine, iodine, or chlorinated phenols, although increased resistance to hexachlorophene was observed. This compound has a much greater effect on gram-positive than gram-negative bacteria, so that it is difficult to assess the significance of this finding. Transformation of this plasmid (which encodes resistance to carbenicillin, tetracycline, and neomycin and kanamycin) into *E. coli* or *P. aeruginosa* did not increase the sensitivity of these organisms to a range of antiseptics (5).

Strains of *Providencia stuartii* may be highly tolerant to Hg^{2+}, cationic disinfectants (such as chlorhexidine and QACs), and antibiotics (496). No evidence has been presented to show that there is a plasmid-linked association between antibiotic resistance and disinfectant resistance in these organisms, pseudomonads, or *Proteus* spp. (492). High levels of disinfectant resistance have been reported in other hospital isolates (195), although no clear-cut role for plasmid-specified resistance has emerged (102, 250, 348, 373, 518). High levels of tolerance to chlorhexidine and QACs (311) may be intrinsic or may have resulted from mutation. It has been proposed (492, 496) that the extensive usage of these cationic agents could be responsible for the selection of antiseptic-disinfectant-, and antibiotic-resistant strains; however, there is little evidence to support this conclusion. All of these studies demonstrated that it was difficult to transfer chlorhexidine or QAC resistance under nor-

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TABLE 10. *qac* genes and susceptibility of *S. aureus* strains to some antiseptics and disinfectants

qac gene[a]	MIC ratios[b] of[c]:							
	Proflavine	CHG	Pt	Pi	CTAB	BZK	CPC	DC
qacA	>16	2.5	>16	>16	4	>3	>4	2
qacB	8	1	>4	2	2	>3	>2	2
qacC	1	1	ca. 1	1	6	>3	>4	1
qacD	1	1	ca. 1	1	6	>3	>4	1
MIC (μg/ml) for sensitive strain	40	0.8	<50	50[d]	1	<2	<1	4

[a] *qac* genes are otherwise known as nucleic acid binding (NAB) compound resistance genes (88).

[b] Calculated from the data in reference 289. Ratios are MICs for strains of *S. aureus* carrying various *qac* genes divided by the MIC for a strain carrying no gene (the actual MIC for the test strain is shown in the bottom row).

[c] CHG, chlorhexidine diacetate; Pt, pentamidine isethionate; Pi, propamidime isethionate; CTAB, cetyltrimethylammonium bromide; BZK, benzalkonium chloride; CPC, cetylpyridinium chloride; DC, dequalinium chloride.

[d] The MIC of propamidine isethionate for the sensitive *S. aureus* is considerably higher than the normal quoted value (ca. 2 μg/ml [Table 6]).

mal conditions and that plasmid-mediated resistance to these chemicals in gram-negative bacteria was an unlikely event. By contrast, plasmid R124 alters the OmpF outer membrane protein in *E. coli*, and cells containing this plasmid are more resistant to a QAC (cetrimide) and to other agents (406).

Bacterial resistance mechanisms to formaldehyde and industrial biocides may be plasmid encoded (71, 193). Alterations in the cell surface (outer membrane proteins [19, 246]) and formaldehyde dehydrogenase (247, 269) are considered to be responsible (202). In addition, the so-called TOM plasmid encodes enzymes for toluene and phenol degradation in *B. cepacia* (476).

(ii) Plasmid-mediated antiseptic and disinfectant resistance in staphylococci. Methicillin-resistant *S. aureus* (MRSA) strains are a major cause of sepsis in hospitals throughout the world, although not all strains have increased virulence. Many can be referred to as "epidemic" MRSA because of the ease with which they can spread (91, 295, 317). Patients at particularly high risk are those who are debilitated or immunocompromised or who have open sores.

It has been known for several years that some antiseptics and disinfectants are, on the basis of MICs, somewhat less inhibitory to *S. aureus* strains that contain a plasmid carrying genes encoding resistance to the aminoglycoside antibiotic gentamicin (Table 10). These biocidal agents include chlorhexidine, diamidines, and QACs, together with ethidium bromide and acridines (8, 238, 289, 368, 423, 427, 463). According to Mycock (346), MRSA strains showed a remarkable increase in tolerance (at least 5,000-fold) to povidone-iodine. However, there was no decrease in susceptibility of antibiotic-resistant strains to phenolics (phenol, cresol, and chlorocresol) or to the preservatives known as parabens (8).

Tennent et al. (505) proposed that increased resistances to cetyltrimethylammonium bromide (CTAB) and to propamidine isethionate were linked and that these cationic agents may be acting as a selective pressure for the retention of plasmids encoding resistance to them. The potential clinical significance of this finding remains to be determined.

Staphylococci are the only bacteria in which the genetic aspects of plasmid-mediated antiseptic and disinfectant resistant mechanisms have been described (466). In *S. aureus*, these mechanisms are encoded by at least three separate multidrug resistance determinants (Tables 10 and 11). Increased antiseptic MICs have been reported to be widespread among MRSA strains and to be specified by two gene families (*qacAB* and *qacCD*) of determinants (188, 280, 281, 288, 289, 363–365, 367, 506). The *qacAB* family of genes (Table 11) encodes proton-dependant export proteins that develop significant homology to other energy-dependent transporters such as the tetracycline transporters found in various strains of tetracycline-resistant bacteria (405). The *qacA* gene is present predominantly on the pSK1 family of multiresistance plasmids but is also likely to be present on the chromosome of clinical *S. aureus* strains as an integrated family plasmid or part thereof. The *qacB* gene is detected on large heavy-metal resistance plasmids. The *qacC* and *qacD* genes encode identical phenotypes and show restriction site homology; the *qacC* gene may have evolved from *qacD* (288).

Interesting studies by Reverdy et al. (395, 396), Dussau et al. (129) and Behr et al. (31) demonstrated a relationship between increased *S. aureus* MICs to the β-lactam oxacillin and four antiseptics (chlorhexidine, benzalkonium chloride, hexamine, and acriflavine). A gene encoding multidrug resistance was not found in susceptible strains but was present in 70% of *S. aureus* strains for which the MICs of all four of these antiseptics were increased and in 45% of the remaining strains resistant to at least one of these antiseptics (31). Genes encoding increased QAC tolerance may be widespread in food-associated staphylococcal species (203). Some 40% of isolates of coagulase-negative staphylococci (CNS) contain both *qacA* and *qacC* genes, with a possible selective advantage in possessing both as opposed to *qacA* only (281). Furthermore, there is growing evidence that *S. aureus* and CNS have a common pool of resistance determinants.

Triclosan is used in surgical scrubs, soaps, and deodorants. It is active against staphylococci and less active against most gram-negative organisms, especially *P. aeruginosa*, probably by virtue of a permeability barrier (428). Low-level transferable resistance to triclosan was reported in MRSA strains (88, 90); however, no further work on these organisms has been described. According to Sasatsu et al. (465), the MICs of triclosan against sensitive and resistant *S. aureus* strains were 100 and

TABLE 11. *qac* genes and resistance to quaternary ammonium compounds and other antiseptics and disinfectants

Multidrug resistance determinant[a]	Gene location	Resistance encoded to
qacA	pSK1 family of multiresistant plasmids, also β-lactamase and heavy-metal resistance families	QACs, chlorhexidine salts, diamidines, acridines, ethidium bromide
qacB	β-Lactamase and heavy-metal resistance plasmids	QACs, acridines, ethidium bromide
qacC[b]	Small plasmids (<3 kb) or large conjugative plasmids	Some QACs, ethidium bromide
qacD[b]	Large (50-kb) conjugative, multiresistance plasmids	Some QACs, ethidium bromide

[a] The *qacK* gene has also been described, but it is likely to be less significant than *qacAB* in terms of antiseptic or disinfectant tolerance.

[b] These genes have identical target sites and show restriction site homology.

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>6,400 μg/ml, respectively; these results were disputed because these concentrations are well in excess of the solubility of triclosan (515), which is practically insoluble in water. Sasatsu et al. (464) described a high-level resistant strain of *S. aureus* for which the MICs of chlorhexidine, CTAB, and butylparaben were the same as for a low-level resistant strain. Furthermore, the MIC quoted for methylparaben comfortably exceeds its aqueous solubility. Most of these studies with sensitive and "resistant" strains involved the use of MIC evaluations (for example, Table 6). A few investigations examined the bactericidal effects of antiseptics. Cookson et al. (89) pointed out that curing of resistance plasmids produced a fall in MICs but not a consistent decrease in the lethal activity of chlorhexidine. There is a poor correlation between MIC and the rate of bactericidal action of chlorhexidine (88, 89, 319) and triclosan (90, 319). McDonnell et al. (318, 319) have described methicillin-susceptible *S. aureus* (MSSA) and MRSA strains with increased triclosan MICs (up to 1.6 μg/ml) but showed that the MBCs for these strains were identical; these results were not surprising, considering that biocides (unlike antibiotics) have multiple cellular targets. Irizarry et al. (229) compared the susceptibility of MRSA and MSSA strains to CPC and chlorhexidine by both MIC and bactericidal testing methods. However, the conclusion of this study that MRSA strains were more resistant warrants additional comments. On the basis of rather high actual MICs, MRSA strains were some four times more resistant to chlorhexidine and five times more resistant to a QAC (CPC) than were MSSA strains. At a concentration in broth of 2 μg of CPC/ml, two MRSA strains grew normally with a threefold increase in viable numbers over a 4-h test period whereas an MSSA strain showed a 97% decrease in viability. From this, the authors concluded that it was reasonable to speculate that the residual amounts of antiseptics and disinfectants found in the hospital environment could contribute to the selection and maintenance of multiresistant MRSA strains. Irizarry et al. (229) also concluded that MRSA strains are less susceptible than MSSA strains to both chronic and acute exposures to antiseptics and disinfectants. However, their results with 4 μg of CPC/ml show no such pattern: at this higher concentration, the turbidities (and viability) of the two MRSA and one MSSA strains decreased at very similar rates (if anything, one MRSA strain appeared to be affected to a slightly greater extent that the MSSA strain). Furthermore, the authors stated that chlorhexidine gave similar results to CPC. It is therefore difficult to see how Irizarry et al. arrived at their highly selective conclusions.

Plasmid-mediated efflux pumps are particularly important mechanisms of resistance to many antibiotics (85), metals (349), and cationic disinfectants and antiseptics such as QACs, chlorhexidine, diamidines, and acridines, as well as to ethidium bromide (239, 289, 324–336, 363–368). Recombinant *S. aureus* plasmids transferred into *E. coli* are responsible for conferring increased MICs of cationic agents to the gram-negative organism (505, 544). Midgley (324, 325) demonstrated that a plasmid-borne, ethidium resistance determinant from *S. aureus* cloned in *E. coli* encodes resistance to ethidium bromide and to QACs, which are expelled from the cells. A similar efflux system is present in *Enterococcus hirae* (326).

Sasatsu et al. (463) showed that duplication of *ebr* is responsible for resistance to ethidium bromide and to some antiseptics. Later, Sasatsu et al. (466) examined the origin of *ebr* (now known to be identical to *qacCD*) in *S. aureus*; *ebr* was found in antibiotic-resistant and -sensitive strains of *S. aureus*, CNS, and enterococcal strains. The nucleotide sequences of the amplified DNA fragment from sensitive and resistant strains were identical, and it was proposed that in antiseptic-resistant cells there was an increase in the copy number of the *ebr* (*qacCD*) gene whose normal function was to remove toxic substances from normal cells of staphylococci and enterococci.

Based on DNA homology, it was proposed that *qacA* and related genes carrying resistance determinants evolved from preexisting genes responsible for normal cellular transport systems (405) and that the antiseptic resistance genes evolved before the introduction and use of topical antimicrobial products and other antiseptics and disinfectants (288, 289, 365, 367, 368, 405).

Baquero et al. (23) have pointed out that for antibiotics, the presence of a specific resistance mechanism frequently contributes to the long-term selection of resistant variants under in vivo conditions. Whether low-level resistance to cationic antiseptics, e.g., chlorhexidine, QACs, can likewise provide a selective advantage on staphylococci carrying *qac* genes remains to be elucidated. The evidence is currently contentious and inconclusive.

(iii) Plasmid-mediated antiseptic and disinfectant resistance in other gram-positive bacteria. Antibiotic-resistant coryneforms may be implicated in human infections, especially in the immunocompromised. 'Group JK' coryneforms (*Corynebacterium jeikeium*) were found to be more tolerant than other coryneforms to the cationic disinfectants ethidium bromide and hexachlorophene, but studies with plasmid-containing and plasmid-cured derivatives produced no evidence of plasmid-associated resistance (285). *Enterococcus faecium* strains showing high level resistance to vancomycin, gentamicin, or both are not more resistant to chlorhexidine or other nonantibiotic agents (9, 11, 20, 319). Furthermore, despite the extensive dental use of chlorhexidine, strains of *Streptococcus mutans* remain sensitive to it (235). To date, therefore, there is little or no evidence of plasmid-associated resistance of nonstaphylococcal gram-positive bacteria to antiseptics and disinfectants.

Mutational resistance to antiseptics and disinfectants. Chromosomal mutation to antibiotics has been recognized for decades. By contrast, fewer studies have been performed to determine whether mutation confers resistance to antiseptics and disinfectants. It was, however, demonstrated over 40 years ago (77, 78) that *S. marcescens*, normally inhibited by QACs at <100 μg/ml, could adapt to grow in 100,000 μg of a QAC per ml. The resistant and sensitive cells had different surface characteristics (electrophoretic mobilities), but resistance could be lost when the cells were grown on QAC-free media. One problem associated with QACs and chlorhexidine is the turbidity produced in liquid culture media above a certain concentration (interaction with agar also occurs), which could undoubtedly interfere with the determination of growth. This observation is reinforced by the findings presented by Nicoletti et al. (354).

Prince et al. (383) reported that resistance to chlorhexidine could be induced in some organisms but not in others. For example, *P. mirabilis* and *S. marcescens* displayed 128- and 258-fold increases, respectively, in resistance to chlorhexidine, whereas it was not possible to develop resistance to chlorhexidine in *Salmonella enteritidis*. The resistant strains did not show altered biochemical properties of changed virulence for mice, and some strains were resistant to the QAC benzalkonium chloride. Moreover, resistance to chlorhexidine was stable in *S. marcescens* but not in *P. mirabilis*. Despite extensive experimentation with a variety of procedures, Fitzgerald et al. (148) were unable to develop stable chlorhexidine resistance in *E. coli* or *S. aureus*. Similar observations were made by Cookson et al. (89), who worked with MRSA and other strains of *S. aureus*, and by McDonnell et al. (319), who worked with MRSA and enterococci. Recently, stable chlorhexidine resistance was developed in *P. stutzeri* (502); these strains showed

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various levels of increased tolerance to QACs, triclosan, and some antibiotics, probably as a result of a nonspecific alteration of the cell envelope (452). The adaptation and growth of *S. marcescens* in contact lens disinfectants containing chlorhexidine, with cross-resistance to a QAC, have been described previously (166).

Chloroxylenol-resistant strains of *P. aeruginosa* were isolated by repeated exposure in media containing gradually increasing concentrations of the phenolic, but the resistance was unstable (432). The adaptation of *P. aeruginosa* to QACs is a well-known phenomenon (1, 2, 240). Resistance to amphoteric surfactants has also been observed, and, interestingly, cross-resistance to chlorhexidine has been noted (240). This implies that the mechanism of such resistance is nonspecific and that it involves cellular changes that modify the response of organisms to unrelated biocidal agents. Outer membrane modification is an obvious factor and has indeed been found with QAC-resistant and amphoteric compound-resistant *P. aeruginosa* (240) and with chlorhexidine-resistant *S. marcescens* (166). Such changes involve fatty acid profiles and, perhaps more importantly, outer membrane proteins. It is also pertinent to note here the recent findings of Langsrud and Sundheim (274). In this study, resistance of *P. fluorescens* to QACs was reduced when EDTA was present with the QAC (although the lethal effect was mitigated after the cells were grown in medium containing QAC and EDTA); similar results have been found with laboratory-generated *E. coli* mutants for which the MICs of triclosan were increased (318). EDTA has long been known (175, 410) to produce changes in the outer membrane of gram-negative bacteria, especially pseudomonads. Thus, it appears that, again, the development of resistance is associated with changes in the cell envelope, thereby limiting uptake of antiseptics and disinfectants.

Hospital (as for other environmental) isolates of gram-negative bacteria are invariably less sensitive to disinfectants than are laboratory strains (196, 209, 279, 286, 492). Since plasmid-mediated transfer has apparently been ruled out (see above), selection and mutation could play an important role in the presence of these isolates. Subinhibitory antibiotic concentrations may cause subtle changes in the bacterial outer structure, thereby stimulating cell-to-cell contact (109); it remains to be tested if residual concentrations of antiseptics or disinfectants in clinical situations could produce the same effect.

Another insusceptibility mechanism has been put forward, in this instance to explain acridine resistance. It has been proposed (270, 351) that proflavine-sensitive and -resistant cells are equally permeable to the acridine but that resistant cells possessed the ability to expel the bound dye. This is an important point and one that has been reinforced by more recent studies that demonstrate the significance of efflux in resistance of bacteria to antibiotics (284, 330, 355). Furthermore, multidrug resistance (MDR) is a serious problem in enteric and other gram-negative bacteria. MDR is a term used to describe resistance mechanisms used by genes that form part of the normal cell genome (168). These genes are activated by induction or mutation caused by some types of stress, and because they are distributed ubiquitously, genetic transfer is not needed. Although such systems are most important in the context of antibiotic resistance, George (168) provides several examples of MDR systems in which an operon or gene is associated with changes in antiseptic or disinfectant susceptibility; e.g., (i) mutations at an *acr* locus in the Acr system render *E. coli* more sensitive to hydrophobic antibiotics, dyes, and detergents; (ii) the *robA* gene is responsible for overexpression in *E. coli* of the RobA protein that confers multiple antibiotic and heavy-metal resistance (interestingly, Ag^+ may be effluxed [350]); and (iii) the MarA protein controls a set of genes (*mar* and *soxRS* regulons) that confer resistance not only to several antibiotics but also to superoxide-generating agents. Moken et al. (333) have found that low concentrations of pine oil (used as a disinfectant) could select for *E. coli* mutants that overexpressed MarA and demonstrated low levels of cross-resistance to antibiotics. Deletion of the *mar* or *acrAB* locus (the latter encodes a PMF-dependant efflux pump) increased the susceptibility of *E. coli* to pine oil; deletion of *acrAB*, but not of *mar*, increased the susceptibility of *E. coli* to chloroxylenol and to a QAC. In addition, the *E. coli* MdfA (multidrug transporter) protein was recently identified and confers greater tolerance to both antibiotics and a QAC (benzalkonium) (132). The significance of these and other MDR systems in bacterial susceptibility to antiseptics and disinfectants, in particular the issue of cross-resistance with antibiotics, must be studied further. At present, it is difficult to translate these laboratory findings to actual clinical use, and some studies have demonstrated that antibiotic-resistant bacteria are not significantly more resistant to the lethal (or bactericidal) effects of antiseptic and disinfectants than are antibiotic-sensitive strains (11, 88, 89, 319).

TABLE 12. Possible mechanisms of fungal resistance to antiseptics and disinfectants

Type of resistance	Possible mechanism	Example(s)
Intrinsic	Exclusion	Chlorhexidine
	Enzymatic inactivation	Formaldehyde
	Phenotypic modulation	Ethanol
	Efflux	Not demonstrated to date[a]
Acquired	Mutation	Some preservative
	Inducible efflux	Some preservatives[a]
	Plasmid-mediated responses	Not demonstrated to date

[a] Efflux is now known to be one mechanism of fungal resistance to antibiotics (531).

Mechanisms of Fungal Resistance to Antiseptics and Disinfectants

In comparison with bacteria, very little is known about the ways in which fungi can circumvent the action of antiseptics and disinfectants (104, 111, 296). There are two general mechanisms of resistance (Table 12): (i) intrinsic resistance, a natural property or development of an organism (201); and (ii) acquired resistance. In one form of intrinsic resistance, the cell wall presents a barrier to reduce or exclude the entry of an antimicrobial agent. The evidence to date is somewhat patchy, but the available information links cell wall glucan, wall thickness, and relatively porosity to the susceptibility of *Saccharomyces cerevisiae* to chlorhexidine (Table 13) (204–208). Protoplasts of this organism prepared by glucuronidase in the presence of β-mercaptoethanol are lysed by chlorhexidine concentrations well below those effective against "normal" (whole) cells. Furthermore, culture age influences the response of *S. cerevisiae* to chlorhexidine; the cells walls are much less sensitive at stationary phase than at logarithmic growth phase (208), taking up much less [^{14}C]chlorhexidine gluconate (206). Gale (165) demonstrated a phenotypic increase in the resistance of *Candida albicans* to the polyenic antibiotic amphotericin B as the organisms entered the stationary growth phase, which was attributed to cell wall changes involving tighter cross-linking (74). Additionally, any factor increasing glucanase activity increased amphotericin sensitivity.

The porosity of the yeast cell wall is affected by its chemical

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TABLE 13. Parameters affecting the response of *S. cerevisiae* to chlorhexidine[a]

Parameter	Role in susceptibility of cells to chlorhexidine
Cell wall composition	
Mannan	No role found to date
Glucan	Possible significance: at concentrations below those active against whole cells, chlorhexidine lyses protoplasts
Cell wall thickness	Increases in cells of older cultures: reduced chlorhexidine uptake responsible for decreased activity(?)
Relative porosity	Decreases in cells of older cultures: reduced chlorhexidine uptake responsible for decreased activity(?)
Plasma membrane	Changes altering CHG susceptibility(?); not investigated to date

[a] Data from references 204 to 208 and 436.

composition, with the wall acting as a barrier or modulator to the entry and exit of various agents. DeNobel et al. (117–119) used the uptake of fluorescein isothiocyanurate (FITC) dextrans and the periplasmic enzyme invertase as indicators of yeast cell wall porosity. Intact *S. cerevisiae* cells were able to endocytose FITC dextrans of 70 but not of 150. A new assay for determining the relative cell wall porosity in yeast based upon polycation-induced leakage of UV-absorbing compounds was subsequently developed. Hiom et al. (206, 208) found that the relative porosity of cells decreases with increasing culture age and that there was a reduced uptake of radiolabeled chlorhexidine gluconate. As the age of an *S. cerevisiae* culture increases, there is a significant increase in the cell wall thickness, with values of 0.19, 0.25, and 0.31 μm recorded for cells from 1-, 2-, and 6-day old cultures, respectively (206).

These findings (Table 13) can provide a tentative picture of the cellular factors that modify the response of *S. cerevisiae* to chlorhexidine. Mannan mutants of *S. cerevisiae* show a similar degree of sensitivity to chlorhexidine as the parent strain (204). The glucan layer is shielded from β-glucuronidase by mannoproteins, but this effect is overcome by β-mercaptoethanol (119). The mannoprotein consists of two fractions, sodium dodecyl sulfate-soluble mannoproteins and sodium dodecyl sulfate-insoluble, glucanase-soluble ones: the latter limit cell wall porosity (119). Thus, glucan (and possibly mannoproteins) plays a key role in determining the uptake and hence the activity of chlorhexidine in *S. cerevisiae*. *C. albicans* is less sensitive and takes up less [^{14}C]chlorhexidine overall (206), but only a few studies with this organism and with molds have been performed.

Yeasts grown under different conditions have variable levels of sensitivity to ethanol (176, 402). Cells with linoleic acid-enriched plasma membranes are more resistant to ethanol than are cells with oleic acid-enriched ones, from which it has been inferred that a more fluid membrane enhances ethanol resistance (6).

There is no evidence to date of antiseptic efflux (although benzoic acid in energized cells is believed to be eliminated by flowing down the electrochemical gradient [529]) and no evidence of acquired resistance by mutation (except to some preservatives [436]) or by plasmid-mediated mechanisms (426, 436). It is disappointing that so few rigorous studies have been performed with yeasts and molds and antiseptics and disinfectants (see also Miller's [328] treatise on mechanisms for reaching the site of action). Molds are generally more resistant than yeasts (Table 14) and considerably more resistant than nonsporulating bacteria (Table 15). Mold spores, although more resistant than nonsporulating bacteria, are less resistant than bacterial spores to antiseptics and disinfectants (436). It is tempting to speculate that the cell wall composition in molds confers a high level of intrinsic resistance on these organisms.

Mechanisms of Viral Resistance to Antiseptics and Disinfectants

Early studies on the effects of disinfectants on viruses were reviewed by Grossgebauer (189). Potential viral targets are the viral envelope, which contains lipids and is a typical unit membrane; the capsid, which is principally protein in nature; and the genome. An important hypothesis was put forward in 1963 (258) and modified in 1983 (259) in which it was proposed that viral susceptibility to disinfectants could be based on whether viruses were "lipophilic" in nature, because they possessed a lipid envelope (e.g., herpes simplex virus [259]) or "hydrophilic" because they did not (e.g., poliovirus [514]). Lipid-enveloped viruses were sensitive to lipophilic-type disinfectants, such as 2-phenylphenol, cationic surfactants (QACs), chlorhexidine, and isopropanol, as well as to ether and chloroform. Klein and Deforest (259) further classified viruses into three groups (Table 16), A (lipid containing), B (nonlipid picornaviruses), and C (other nonlipid viruses larger than those in group B) and disinfectants into two groups, broad-spectrum ones that inactivated all viruses and lipophilic ones that failed to inactivate picornoviruses and parvoviruses.

Capsid proteins are predominantly protein in nature, and biocides such as glutaraldehyde, hypochlorite, ethylene oxide, and hydrogen peroxide, which react strongly with amino or sulfhydryl groups might possess virucidal activity. It must, however, be added that destruction of the viral capsid may result in the release of a potentially infectious nucleic acid and that viral inactivation would only be complete if the viral nucleic acid is also destroyed.

Unfortunately, the penetration of antiseptics and disinfectants into different types of viruses and their interaction with viral components have been little studied, although some information has been provided by investigations with bacteriophages (307). Bacteriophages are being considered as "indicator species" for assessing the virucidal activity of disinfectants (108) and could thus play an increasing important role in this context; for example, repeated exposure of *E. coli* phage f2 to chlorine was claimed to increase its resistance to disinfection (542).

Thurman and Gerber (509, 510) pointed out that conflicting results on the actions of disinfectants on different virus types were often reported, and they suggested that the structural integrity of a virus was altered by an agent that reacted with viral capsids to increase viral permeability. Thus, a "two-stage"

TABLE 14. Lethal concentrations of antiseptics and disinfectants toward some yeasts and molds[a]

Antimicrobial agent[b]	Lethal concn (μg/μl) toward:		
	Yeast (*Candida albicans*)	Molds	
		Penicillium chrysogenum	*Aspergillus niger*
QACs			
Benzalkonium chloride	10	100–200	100–200
Cetrimide/CTAB	25	100	250
Chlorhexidine	20–40	400	200

[a] Derived in part from data in reference 525.
[b] CTAB, cetyltrimethylammonium bromide.

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TABLE 15. Kinetic approach: *D*-values at 20°C of phenol and benzalkonium chloride against fungi and bacteria[a]

Antimicrobial agent	pH	Concn (%, wt/vol)	*D*-value (h)[b] against:				
			Aspergillus niger	*Candida albicans*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
Phenol	5.1	0.5	20	13.5	0.94	—[c]	0.66
	6.1	0.5	32.4	18.9	1.72	0.17	1.9
Benzalkonium chloride	5.1	0.001	—[d]	9.66	0.06	3.01	3.12
	6.1	0.002	—[d]	5.5	—[c]	0.05	0.67

[a] Abstracted from the data in references 244 and 245.
[b] *D*-values are the times to reduce the viable population by 1 log unit.
[c] Inactivation was so rapid that the *D*-values could not be measured.
[d] No inactivation: fungistatic effect only.

disinfection system could be an efficient means of viral inactivation while overcoming the possibility of multiplicity reactivation (first put forward by Luria [293]) to explain an initial reduction and then an increase in the titer of disinfectant-treated bacteriophage. Multiplicity reactivation as a mechanism of resistance was supported by the observation of Young and Sharp (546) that clumping of poliovirus following partial inactivation by hypochlorite significantly increased the phage titer. It is envisaged as consisting of random damage to the capsid protein or nucleic acid of clumped, noninfectious virions from which complementary reconstruction of an infectious particle occurs by hybridization with the gene pool of the inactivated virions (298).

Another resistance mechanism also involves viral aggregation, e.g., the persistence of infectivity of formaldehyde-treated poliovirus (458) and the resistance of Norwalk virus to chlorination (249). A typical biphasic survival curve of enterovirus and rotavirus exposed to peracetic acid is also indicative of the presence of viral aggregates (198).

Finally, there remains the possibility of viral adaptation to new environmental conditions. In this context, Bates et al. (28) described the development of poliovirus having increased resistance to chlorine inactivation. Clearly, much remains to be learned about the mechanism of viral inactivation by and viral resistance to disinfectants.

Mechanisms of Protozoal Resistance to Antiseptics and Disinfectants

Intestinal protozoa, such as *Cryptosporidium parvum*, *Entamoeba histolytica*, and *Giardia intestinalis*, are all potentially pathogenic to humans and have a resistant, transmissible cyst (or oocyst for *Cryptosporidium*) (233, 234). Of the disinfectants available currently, ozone is the most effective protozoan cysticide, followed by chlorine dioxide, iodine, and free chlorine, all of which are more effective than the chloramines (234, 264). Cyst forms are invariably the most resistant to chemical disinfectants (Fig. 1). The reasons for this are unknown, but it would be reasonable to assume that cysts, similar to spores, take up fewer disinfectant molecules from solution than do vegetative forms.

Some recent studies have compared the responses of cysts and trophozoites of *Acanthamoeba castellanii* to disinfectants used in contact lens solutions and monitored the development of resistance during encystation and the loss of resistance during excystation (251–255). The lethal effects of chlorhexidine and of a polymeric biguanide were time and concentration dependent, and mature cysts were more resistant than preencystment trophozoites or preexcystment cysts. The cyst "wall" appeared to act as a barrier to the uptake of these agents, thereby presenting a classical type of intrinsic resistance mechanism (163). Acanthamoebae are capable of forming biofilms on surfaces such as contact lenses (186). Although protozoal biofilms have yet to be studied extensively in terms of their response to disinfectants, it is apparent that they could play a significant role in modulating the effects of chemical agents.

Mechanisms of Prion Resistance to Disinfectants

The transmissible degenerative encephalopathies (TDEs) form a group of fatal neurological diseases of humans and other animals. TDEs are caused by prions, abnormal proteinaceous agents that appear to contain no agent-specific nucleic acid (385). An abnormal protease-resistant form (PrP^{res}) of a normal host protein is implicated in the pathological process.

Prions are considered highly resistant to physical and chemical agents (Fig. 1), although the fact that crude preparations are often studied means that extraneous materials could, at least to some extent, mask the true efficacy of these agents (503). According to Taylor (503), there is currently no known decontamination procedure that will guarantee the complete absence of infectivity in TDE-infected tissues processed by histopathological procedures. Prions survive acid treatment, but a synergistic effect with autoclaving plus sodium hydroxide treatment is observed. Formaldehyde, unbuffered glutaraldehyde (acidic pH), and ethylene oxide have little effect on infectivity, although chlorine-releasing agents (especially hypochlorites), sodium hydroxide, some phenols, and guanidine thiocyanate are more effective (141, 309, 503).

With the information presently available, it is difficult to explain the extremely high resistance of prions, save to comment that the protease-resistant protein is abnormally stable to degradative processes.

CONCLUSIONS

It is clear that microorganisms can adapt to a variety of environmental physical and chemical conditions, and it is therefore not surprising that resistance to extensively used antiseptics and disinfectants has been reported. Of the mechanisms that have been studied, the most significant are clearly intrinsic, in particular the ability to sporulate, adaptation of pseudomonads, and the protective effects of biofilms. In these cases, "resistance" may be incorrectly used and "tolerance," defined as developmental or protective effects that permit microorganisms to survive in the presence of an active agent, may be more correct. Many of these reports of resistance have often paralleled issues including inadequate cleaning, incorrect product use, or ineffective infection control practices, which cannot be underestimated. Some acquired mechanisms (in particular with heavy-metal resistance) have also been shown to be clinically significant, but in most cases the results have been spec-

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TABLE 16. Viral classification and response to some disinfectants[a]

Viral group	Lipid envelope[b]	Examples of viruses	Effects of disinfectants[c]	
			Lipophilic	Broad-spectrum
A	+	HSV, HIV, Newcastle disease virus, rabies virus, influenza virus	S	S
B	−	Non-lipid picornaviruses (poliovirus, Coxsackie virus, echovirus)	R	S
C	−	Other larger nonlipid viruses (adenovirus, reovirus)	R	S

[a] Data from reference 259; see also reference 444. For information on the inactivation of poliovirus, see reference 514.
[b] Present (+) or absent (−).
[c] Lipophilic disinfectants include QACs and chlorhexidine. S, sensitive; R, resistant.

ulative. Increased MICs have been confirmed, in particular for staphylococci. However, few reports have further investigated increased bactericidal concentrations or actual use dilutions of products, which in many cases contain significantly higher concentrations of biocides, or formulation attributes, which can increase product efficacy; in a number of cases, changes in the MICs have actually been shown not to be significant (9, 88, 89, 319, 428). Efflux mechanisms are known to be important in antibiotic resistance, but it is questionable if the observed increased MICs of biocides could have clinical implications for hard-surface or topical disinfection (423, 428). It has been speculated that low-level resistance may aid in the survival of microorganisms at residual levels of antiseptics and disinfectants; any possible clinical significance of this remains to be tested. With growing concerns about the development of biocide resistance and cross-resistance with antibiotics, it is clear that clinical isolates should be under continual surveillance and possible mechanisms should be investigated.

It is also clear that antiseptic and disinfectant products can vary significantly, despite containing similar levels of biocides, which underlines the need for close inspection of efficacy claims and adequate test methodology (183, 423, 428). In addition, a particular antiseptic or disinfectant product may be better selected (as part of infection control practices) based on particular circumstances or nosocomial outbreaks; for example, certain active agents are clearly more efficacious against gram-positive than gram-negative bacteria, and *C. difficile* (despite the intrinsic resistance of spores) may be effectively controlled physically by adequate cleaning with QAC-based products.

In conclusion, a great deal remains to be learned about the mode of action of antiseptics and disinfectants. Although significant progress has been made with bacterial investigations, a greater understanding of these mechanisms is clearly lacking for other infectious agents. Studies of the mechanisms of action of and microbial resistance to antiseptics and disinfectants are thus not merely of academic significance. They are associated with the more efficient use of these agents clinically and with the potential design of newer, more effective compounds and products.

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Attachment 22.4

Gomes do Amorim, Aun, and Mayer. "Susceptibility of some oral microorganisms to chlorhexidine and paramonochlorophenol" Brazilian Oral Research 18(3), 242-246 (2004).

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Susceptibility of some oral microorganisms to chlorhexidine and paramonochlorophenol

Susceptibilidade de alguns microrganismos orais frente à clorexidina e ao paramonoclorofenol

Crystiane Venditi Gomes do Amorim*
Carlos Eduardo Aun**
Marcia Pinto Alves Mayer***

ABSTRACT: Since the use of antimicrobial agents is required in endodontic therapies, this study aimed at determining the minimum inhibitory concentrations (MICs) of chlorhexidine digluconate and paramonochlorophenol (PMC) against microorganisms commonly found in endodontic infections. Both agents were tested by agar dilution tests against *Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Candida albicans, Prevotella intermedia, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella denticola* and *Prevotella melaninogenica*. The MIC of chlorhexidine ranged from 2.67 to 80.00 μg/ml, and the MIC of PMC from 46.67 to 213.33 μg/ml. The highest MIC value of PMC was detected for *E. faecalis* whereas *E. coli* was the most susceptible microorganism to this agent. The highest MIC values of chlorhexidine were observed for *P. aeruginosa* whereas *E. coli* and *P. denticola* were the most susceptible microorganisms to this agent. Since the MIC values observed are much lower than the concentrations currently used in the endodontic therapy, it is suggested that both agents are effective in reducing the microbiota in the root canal.

DESCRIPTORS: Chlorhexidine; Anti-infective agents, local; Root canal, drug effects.

RESUMO: Tendo em vista a necessidade de se utilizarem agentes antimicrobianos durante a terapia endodôntica, o presente estudo tem por objetivo determinar as concentrações inibitórias mínimas (CIMs) de digluconato de clorexidina e de paramonoclorofenol (PMC) frente a cepas de microrganismos freqüentemente isolados dos canais radiculares infectados. Ambos os agentes foram testados por meio de testes de diluição em meio sólido contra *Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Candida albicans, Prevotella intermedia, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella denticola* e *Prevotella melaninogenica*. As CIMs de clorexidina variaram de 2,67 a 80,00 μg/ml, e as CIMs de PMC variaram de 46,67 a 213,33 μg/ml. A maior CIM do paramonoclorofenol foi frente a *E. faecalis*, entretanto *E. coli* foi o microrganismo mais susceptível. A maior CIM do digluconato de clorexidina foi frente a *P. aeruginosa*, entretanto *E. coli* e *P. denticola* foram os microrganismos mais susceptíveis. Como os valores de CIM observados são bem menores do que as concentrações usadas normalmente na terapia endodôntica, sugere-se que ambos os agentes são efetivos na redução microbiana no canal radicular.

DESCRITORES: Clorexidina; Antiinfecciosos locais; Canal radicular, efeitos de drogas.

INTRODUCTION

Microorganisms and their products are involved in the etiology of pulpal and periapical diseases[26]. A reduction in the number of living bacteria in the infected root canal is achieved by a combination of measures such as mechanical cleaning, irrigation with various antimicrobial agents and use of antibacterial fillings in the canal. Root canal infections frequently lead to apical periodontitis, depending mainly on the interaction between the infective microorganism and the host's defense.

Microorganisms resident in the oral cavity such as facultative anaerobic streptococci can constitute a significant part of the microflora, mainly in the cervical portion of the exposed dental pulp. Strictly anaerobic oral bacteria, belonging mainly to the genus *Prevotella* and *Porphyromonas*, but also species of *Actinomyces*, *Peptostreptococcus*

* MS, Department of Endodontics, School of Dentistry; **PhD, Department of Endodontics, School of Dentistry; ***PhD, Department of Microbiology, Biomedical Sciences Institute – University of São Paulo.

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and *Fusobacterium nucleatum* are prevalent in endodontic infections, and may be the causative agents of periapical lesions[9,26,27]. Other species, such as *Pseudomonas aeruginosa*, can be introduced during the clinical procedures[26], increasing the risk of failure of treatment. The maintenance of highly resistant microorganisms in the root canal such as *Enterococcus faecalis* is related to persistent periapical infections[24].

Therefore, the success of the endodontic therapy is mainly dependent on the susceptibility of the infecting organism to the commonly used antimicrobial agents.

Chlorhexidine is an agent used in periodontology for more than 20 years, due to its antimicrobial properties and low cytotoxicity[5,13,14]. It can be used as an endodontic irrigant[2,4,19,28] and as an intracanal medication[1,3,6,10,11,17,21,22,23].

Paramonochlorophenol (PMC) is a phenol-derived agent that exhibits broad antiseptic activity but also high toxicity. In order to reduce its cytotoxic effect while maintaining or even increasing its antimicrobial activity, combinations of PMC with other agents and vehicles and different application methods have been proposed[3,7,12,16,22,25].

Based on the need to use antimicrobial agents during the endodontic therapy, the aim of this study was to determine the minimum inhibitory concentrations (MICs) of chlorhexidine digluconate and PMC for *Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Candida albicans, Prevotella intermedia, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella denticola* and *Prevotella melaninogenica.*

MATERIAL AND METHODS

The strains *Porphyromonas gingivalis* - ATCC 33277, *Porphyromonas endodontalis* - ATCC 35406, *Prevotella intermedia* - ATCC 33563, *Prevotella denticola* - ATCC 35308, *Prevotella melaninogenica* - ATCC 33563 were obtained from the American Type Culture Collection (Rockville, MD, USA). Clinical isolates of *Pseudomonas aeruginosa, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli* and *Candida albicans* belonging to the culture collection of the Oral Microbiology Laboratory, Biomedical Sciences Institute, University of São Paulo (SP, Brazil) were also used.

All microorganisms were maintained in frozen stocks in skim milk (Difco, Detroit, Michigan, USA) in a freezer at −80°C. Aliquots of *Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis,* and *Escherichia coli* were inoculated in brain-heart infusion agar (Biobrás Diagnósticos, Belo Horizonte, MG, Brazil) and grown overnight at 37°C; *Prevotella intermedia, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella denticola and Prevotella melaninogenica* were cultured in brucella agar (Oxoid, Basingstoke, Hampshire, England) supplemented with 5% defibrinated sheep blood, 5 μg/ml of hemin (Sigma Chemical Co., St. Louis, USA) and 1 μg/ml of menadione (Sigma) in anaerobic jars (Oxoid) for 6 days at 37°C. *Candida albicans* was cultured in Sabouraud agar tubes (Biobrás) at room temperature, for 4 days.

Minimum inhibitory concentrations (MICs) were determined by the agar dilution method. The growth resulting from the plates with *Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli* and *Candida albicans* was scraped with a platinum loop, and diluted in phosphate buffered saline solution (Sigma), pH 7.4 to an absorbance of 0.5 at 560 nm ($Å_{560}$ = 0.5).

The colonies of *Prevotella intermedia, Prevotella denticola, Prevotella melaninogenica, Porphyromonas gingivalis* and *Porphyromonas endodontalis* were scraped from the plates, and resuspended in Ringer-PRAS solution, pH 7.2 to an absorbance of 2.0 at 560 nm ($Å_{560}$ = 2.0).

Stock solutions of 20% chlorhexidine digluconate and 98% paramonochlorophenol (Oficinalis, São Paulo, SP, Brazil) were used. Samples of the bacterial suspensions were deposited on the surface of agar plates by means of a Steers replicating device (Cefar Diagnóstica, São Paulo, SP, Brazil). Mueller-Hinton (Biobrás) agar plates containing different concentrations of chlorhexidine digluconate (1.67 μg/ml to 200 μg/ml) or paramonochlorophenol (6.67 μg/ml to 244 μg/ml) were inoculated with *Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis* and *Escherichia coli*, and incubated at 37°C for 24 hours. Brucella agar plates supplemented with 5 μg/ml of hemin and 1 μg/ml of menadione added with different concentrations of chlorhexidine (1.21 μg/ml to 72.81 μg/ml) or paramonochlorophenol (4.85 μg/ml to 485.44 μg/ml) were inoculated with *Prevotella intermedia, Prevotella denticola, Prevotella melaninogenica, Porphyromonas gingivalis* or *Porphyromonas endodontalis* and incubated at 37°C in anaerobic jars using gas generating kits (Oxoid) for 6 days.

Sabouraud agar plates with different concentrations of each antimicrobial agent were inoculated by spotting 10 μl of the *Candida albicans*

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suspension using a micropipette, and incubated at room temperature, for 6 days.

Plates containing no antimicrobial agents were used as positive control. All the tests were performed in six plates and the MIC was defined as the lowest concentration of chlorhexidine or paramonochlorophenol that prevented visible bacterial growth.

RESULTS

Chlorhexidine MIC values varied from 2.67 to 80.00 μg/ml and PMC MIC varied from 46.67 to 213.33 μg/ml. The MICs of chlorhexidine and PMC for the tested microorganisms are expressed in Table 1. The highest MIC value of paramonochlorophenol observed was for *Enterococcus faecalis* and the highest MIC value of chlorhexidine digluconate observed was for *Pseudomonas aeruginosa*.

DISCUSSION

The antimicrobial effects of agents used as intracanal medications or irrigants on oral microorganisms have been extensively investigated. However, the effect of PMC on most organisms, mainly strict anaerobes, is still not elucidated, despite its extensive use in endodontic therapy. In addition, most studies on chlorhexidine discuss its effect on periodontopathogenic microorganisms only. The effectiveness of an antimicrobial agent depends, among other factors, on the susceptibility of the involved species to this agent, justifying the use of an intracanal medication of broad spectrum to complement the disinfection of the root canal[8]. In order to determine the susceptibility of the studied microorganisms to the antimicrobial agents studied, the dilution test in agar was chosen. This procedure presents several advantages over the diffusion tests usually employed, such as allowing the use of volatile agents as PMC, and providing MIC results. In addition, the dilution test in agar is not dependent on the diffusion of the agent in the culture medium, and is the method of choice for testing antimicrobials against anaerobic bacteria[18]. Blood was added to the culture medium in order to enable the appropriate growth of strict anaerobes. It is known that the presence of blood in the composition of the culture medium may alter the MIC[14]. Nevertheless, the data obtained suggest that both agents were effective against anaerobic bacteria even at high concentrations of blood. The susceptibility of the microorganism to the antimicrobial drugs varied according to the agent. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and the strict anaerobes presented intermediate susceptibility to paramonochlorophenol, whereas *Escherichia coli* was the most susceptible microorganism to this agent. *Enterococcus faecalis* exhibited the highest MIC value for PMC, approximately 4.6 times higher than the value for *Candida albicans*, which presented the lowest MIC. The average value of paramonochlorophenol MIC for the strict anaerobes (except *Prevotella denticola)* was approximately 1.4 times higher than that for *Escherichia coli.*

TABLE 1 - Minimum inhibitory concentrations (μg/ml) of chlorhexidine and paramonochlorophenol (PMC) for the tested microorganisms.

	Chlorhexidine	PMC
Pseudomonas aeruginosa	80.00	126.67
Staphylococcus aureus	4.00	126.67
Candida albicans	4.00	46.67
Porphyromonas gingivalis	3.40	194.17
Porphyromonas endodontalis	3.40	194.17
Prevotella melaninogenica	3.40	194.17
Prevotella intermedia	3.40	194.17
Enterococcus faecalis	3.33	213.33
Escherichia coli	2.67	93.33
Prevotella denticola	2.67	174.76

Pseudomonas aeruginosa was also the least susceptible organism to chlorhexidine. The increased resistance of *Pseudomonas aeruginosa* to chlorhexidine was also reported by other authors[5,13] and is also in agreement with studies showing the emergence of *P. aeruginosa* in nosocomial infections. The MIC value of chlorhexidine for *P. aeruginosa* was approximately 30 times higher than the values observed for *Prevotella denticola* and *Escherichia coli*, which presented the lowest MIC values. *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candida albicans* presented higher MIC values of chlorhexidine than Gram-negative strict anaerobes, such as *Prevotella intermedia, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella denticola* and *Prevotella melaninogenica. Pseudomonas aeruginosa* is not a resident microorganism of the oral cavity, and its growth in the root canal should be prevented with the adoption of proper biosafety procedures. Due to the persistence of *Enterococcus faecalis*

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and yeast in periapical lesions, and to the role of anaerobic organisms in endodontic infections with clinical symptoms, the MIC data reported in this study suggest that chlorhexidine be chosen as an antimicrobial agent for endodontic therapies. However, Roach *et al.*[22] (2001) reported the resistance of *Enterococcus faecalis* to chlorhexidine/methylcellulose gel penetration of a root canal model, when compared with calcium hydroxide/methylcellulose paste, camphorated parachlorophenol/calcium hydroxide paste.

Almyroudi *et al.*[1] (2002) demonstrated that all tested chlorhexidine formulations were effective in eliminating *Enterococcus faecalis* from dentinal tubules, with 1% chlorhexidine gel exhibiting slightly better results. Gomes *et al.*[11] (2003b) observed that 2% chlorhexidine gel alone was more effective against *Enterococcus faecalis* than calcium hydroxide. Evans *et al.*[6] (2003) demonstrated that the calcium hydroxide paste with 2% chlorhexidine was more effective in killing *Enterococcus faecalis* in dentinal tubules than calcium hydroxide diluted in water.

In addition, Podbielski *et al.*[21] (2003) reported that calcium hydroxide did not adversely affect the solubility and activity of chlorhexidine but rather exhibited an additive effect on some Gram-positive endodontic pathogens like *Peptostreptococcus micros* and *Streptococcus intermedius.* Even though the combination between calcium hydroxide, zinc oxide and chlorhexidine led to a faster decrease in the overall number of viable *E. faecalis* cells, no test conditions led to the complete loss of culture viability.

In the present study, the MIC of chlorhexidine for *C. albicans* was 4 μg/ml higher than that reported by Ferguson *et al.*[7] (2002). The discrepancies in antimicrobial sensitivity tests are due to variations in methodology, since a large number of factors (inoculum amount, medium composition, pH, incubation) can influence the interaction between microorganisms and antimicrobial agents, thus affecting the value obtained for MIC.

Besides its low cytotoxicity and high antimicrobial activity, chlorhexidine presents other properties that indicate its use in endodontic treatments. Chlorhexidine is able to interact with oral tissues[14,20] and to continue to be released for a longer period of time. Another advantage of chlorhexidine is its property of maintaining the disinfecting activity after contact with organic matter, unlike sodium hypochlorite[8], another irrigant agent commonly used in endodontic treatments. These characteristics lead to an increased resistance of dentine treated with chlorhexidine solutions against reinfections[15]. In addition, Lenet *et al.*[17] (2000) reported that bovine root canal models medicated with 2% chlorhexidine gel for 7 days acquire antimicrobial properties against *Enterococcus faecalis* for at least 21 days.

On the other hand, the results of this *in vitro* study showed that both chlorhexidine and paramonochlorophenol were effective in inhibiting the development of all tested microorganisms at concentrations much lower than those used in endodontic therapies. The low MIC values for chlorhexidine and PMC justify the low concentrations proposed for their use as filling materials[3,23]. Mainly in the case of PMC, the low concentration used when filling the dental canal minimizes its cytotoxic action, while keeping its antimicrobial activity[3,17].

The present data suggest that chlorhexidine digluconate can be used as an antimicrobial agent in clinical situations with persistence of signs and symptoms after the conventional endodontic procedures. Chlorhexidine should be used as the choice or alternative intracanal medication, due to its safety and antimicrobial properties.

CONCLUSIONS

These data showed that paramonochlorophenol and chlorhexidine digluconate present antimicrobial activity against several microorganisms commonly found in endodontic infections, even at low concentrations, suggesting their effectiveness when used as intracanal medication.

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Attachment 22.5

Semprebom et al. "Enhanced susceptibility of Candida albicans to chlorhexidine under anoxia" Brazilian Journal of Oral Sciences 8(2), 105-110 (2009).

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Original Article

Enhanced susceptibility of *Candida albicans* to chlorhexidine under anoxia

Andressa Marafon Semprebom[1], Ana Cláudia Azevedo Isidoro[1], Maria Ângela Naval Machado[1], Patrícia Maria Stuelp Campelo[1], José Francisco Höfling[2], Lakshman Perera Samaranayake[3], Edvaldo Antonio Ribeiro Rosa[1]

[1] Laboratory of Stomatology, Dental School, Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba (PR), Brazil
[2] Laboratory of Microbiology and Immunology, Faculdade de Odontologia de Piracicaba, Universidade Estadual de Campinas (Unicamp), Piracicaba (SP), Brazil
[3] Oral Biosciences Unity, Dental School, University of Hong Kong, Hong Kong, Hong Kong SAR.

Abstract

Aim: Periodontal pockets can be colonized not only by bacteria, but also by *Candida albicans*. However, its role in periodontitis is unknown. This study evaluated the inhibitory performance of chlorhexidine digluconate under normoxic and anoxic conditions against 16 strains of *C. albicans* from periodontal pockets and other 20 from the oral mucosa. **Methods**: Strains were grown in normoxia and anoxia to adapt themselves to the different atmospheric conditions. Microdilution-based assays were carried out to determine the minimum concentrations of chlorhexidine that may restrain the conditioned candidal strains, in normoxia (normoxic MIC) and anoxia (anoxic MIC). The Mann-Whitney U test was used to evaluate the antimicrobial effect of chlorhexidine on *C. albicans* under normoxic and anoxic conditions ($\alpha = 0.05$). **Results**: The normoxic MIC of chlorhexidine varied broadly from 150 to 1200 µg/mL, whereas its anoxic MIC varied narrower from 2.34 to 37.5 µg/mL. Regarding the origins of strains, no statistically significant differences ($p > 0.05$) were found. **Conclusions**: These results indicate that anoxic environmental conditions, compatible with periodontal pockets, tend to enhance *C. albicans* susceptibility to chlorhexidine.

Keywords: *Candida albicans*, chlorhexidine, anoxia.

Introduction

Periodontitis is a multifatorial inflammatory disease process that leads to the destruction of the periodontal tissues supporting the teeth[1]. The etiologic factor of periodontitis is the dental biofilm associated or not with calculus[2]. The progression of the disease is related to gingival crevice colonization by microorganisms such as *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, and *Treponema denticola*[1,3,4].

Although bacteria has a major role in the pathogenesis of periodontal disease, the yeast *Candida albicans* has also been isolated from periodontal pockets[2], with prevalence ranging from 14 to 19%[5]. In a previous study, yeasts were found in 19.7% of individuals with periodontal pockets > 7 mm and in 15.6% of subjects with pockets ≤ 7 mm[6]. This organism has important virulence factors such as proteolytic activity and capacity to adhere and invade the epithelium[7,8]. Although the presence of *C. albicans* in the periodontal pocket *per se* may not be

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Correspondence to:
Edvaldo Antonio Ribeiro Rosa
Faculdade de Odontologia, Pontifícia Universidade Católica do Paraná.
Rua Imaculada Conceição, 1155
CEP 80215901 – Curitiba (PR), Brazil
E-mail: edvaldo.rosa@pucpr.br

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directly associated with periodontitis, this yeast may take part in the pathogenic microbiota of some forms of periodontitis[6].

The chemotherapeutical eradication of periodontal yeasts does not follow the protocols indicated for bacteria once they are not affected by drugs commonly used in periodontics. As no antifungal therapy is routinely used, antiseptics may play an important adjuvant role. Chlorhexidine {1,1'-hexamethylene-bis[5-(p-chlorophenyl) biguanide]}, a widely used antimicrobial agent, adversely affects the microbial eukaryotic plasma membrane by nonspecific electrostatic binding[9] to negative protein and phospholipid moieties, causing alteration in the cellular membrane structure and in the cellular osmotic balance[10,11]. Normal fungal cells have a negative internal charge[12,13] that explains their susceptibility to chlorhexidine.

Based on the premise that periodontal sites are anoxic and no prior studies investigated the inhibitory effects of chlorhexidine on *C. albicans* in such environmental condition, the present study evaluated the performance of this biguanide on periodontal *C. albicans* strains under normoxic and anoxic conditions.

Material and methods

Sampling

Sixteen periodontium-related (so called "PP" strains) strains from periodontal pockets ≥ 4 mm were used. These strains were obtained from the culture collection of Faculdade de Odontologia de Piracicaba, Universidade Estadual de Campinas (Unicamp), Brazil. Twenty mucosa-related *C. albicans* isolates (so-called "OM" strains) were obtained from the culture collection of the Dental School of the Pontifícia Universidade Católica do Paraná (PUCPR), Brazil. The research project was reviewed and approved by the Ethics Committee of the second institution.

Culture media

The culture broth used throughout the study[14] contains (*per* 900 mL of distilled water) 4 g of KH_2PO_4, 3.2 g of NaH_2PO_4, 1.2 g of L-proline, and 0.7 g of $MgSO_4.7H_2O$. L-proline was replaced by 0.5 g of L-lysine and 1 g of yeast extract was added. After autoclaving, the broth received 40 mL of 20% glucose, 0.5 mL of vitamin mixture, and 0.25 mL of mineral mixture. The vitamin mixture contains (*per* 100 mL of 20% ethanol) 2 g of biotin, 20 mg of thiamine-HCl, and 20 mg of pyridoxine-HCl. The mineral mix contains (*per* 100 mL of 100 mM HCl) 0.5 g of $CuSO_4.5H_2O$, 0.5 g of $ZnSO_4.7H_2O$, 0.8 g of $MnCl_2.4H_2O$, and 0.5 g of $FeSO_4$. The vitamin and mineral mixtures were filter-sterilized with 0.22 µm pore-sized cellulose nitrate membranes (Whatman, Maidstone, UK), and stored at 4 °C. For anaerobic growth of *C. albicans*, the broth was supplemented with 200 µL of 1 mM oleic acid in 100% methanol, 200 µL of 4 mM nicotinic acid, and 1 mL of 500 mM NH_4Cl. Sterile L-cysteine was added up to 0.01%. The pH of the complete broth was 5.0. This modified broth was distributed in sterile disposable 96 wells polystyrene plates (Difco Laboratories, Detroit, MI, USA) at 100 µL *per* well and stored at -20°C.

Aerobic inoculum preparation

Both sets of strains (PP and OM strains) were inoculated in 3 mL of broth and incubated under normoxia at 37 °C for 24 h. After growth, the cells were harvested, washed three times in sterile deionized water, and suspended at 2×10^7 cells/mL. The suspensions were stored at 4°C for no more than four hours.

Anaerobic inoculum preparation

One hundred microliters of aerobic inocula were inoculated in 3 mL of modified broth and incubated in hermetically sealed jars supplied with two disposable Anaerobac® anoxia generator cartridges (Probac Co., São Paulo, SP, Brazil) at 37 °C for 48 h. One hundred milliliters of culture were transferred to 3 mL of modified broth and anaerobically incubated at 37 °C for 48 h. This procedure aimed turning the cells totally adapted to the anoxic condition. After growth, the cells were harvested, washed three times in sterile deionized water, suspended until obtaining a concentration of 2×10^7 cells/mL, and stored at 4 °C in vials whose headspaces were filled with sterile CO_2.

Susceptibility tests

The technique of broth microdilution was used for determining the minimum inhibitory concentration (MIC)[15] for chlorhexidine digluconate (Pharma Nostra Co., São Paulo, Brazil). Chlorhexidine was diluted in modified broth and transferred to microdilution plates to obtain a range of 12 wells with doubling increased concentrations ranging from 0.122 to 500 µg/mL. Each well received 10 µL of suspension of normoxic or anoxic *C. albicans*, obtaining final densities of 1×10^6 cells/mL. The microdilution plates were statically incubated at 37 °C in normoxic or anoxic atmospheres. The anoxic conditions were obtained using hermetically sealed jars supplied with two disposable Anaerobac® anoxia generator cartridges (Probac Co.) at 37°C, as stated before. The normoxic growth was monitored up to 48 h and the anoxic growth was monitored up to 72 h. The cellular growth was visually compared to the growth in wells containing only culture broth. The MIC determination assays were done in triplicate on three independent occasions.

The Mann-Whitney U test was used to evaluate the antimicrobial effect on *C. albicans* under normoxic and anoxic conditions. A p value of 0.05 was assumed as threshold for differences.

Results

During inoculum preparation, we observed that the normoxic cultures achieved an OD_{520nm} of 0.450 ± 0.030 after 24 h of incubation at 37 °C, whereas anoxic-adapted cells achieved an OD_{520nm} of 0.123 ±

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0.018 after 24 h and an OD_{520nm} of 0.420 ± 0.023 after 48 h. The predominant cell shape in normoxic cultures was budding yeast-like with some cells forming pseudo-hyphae; on the other hand, most part of cells grown in anoxia was true hyphae. By multiple Gram staining, it was estimated that less than 5% of the fungal load grew as budding yeast-like cells in anoxia.

Figures 1 and 2 indicate the variation in the susceptibility performances for consensual values after nine repetitions of PP and OM strains, respectively. For the PP strains, the results showed that chlorhexidine promoted growth restrain of all *C. albicans* strains with MIC values varying from 15.62 to 125 μg/mL (mean = 70.31 ± 50.06 μg/mL) in normoxic conditions *versus* a decreased range from 0.97 to 15.62 μg/mL (mean = 8.45 ± 6.84 μg/mL) in anoxia. For the OM strains, chlorhexidine promoted growth restrain of all *C. albicans* strains with MIC values varying from 15.62 to 125 μg/mL (mean = 70.31 ± 50.06 μg/mL) in normoxic conditions *versus* a decreased range from 0.97 to 7.81 μg/mL (mean = 5.09 ± 3.18 μg/mL) in anoxia.

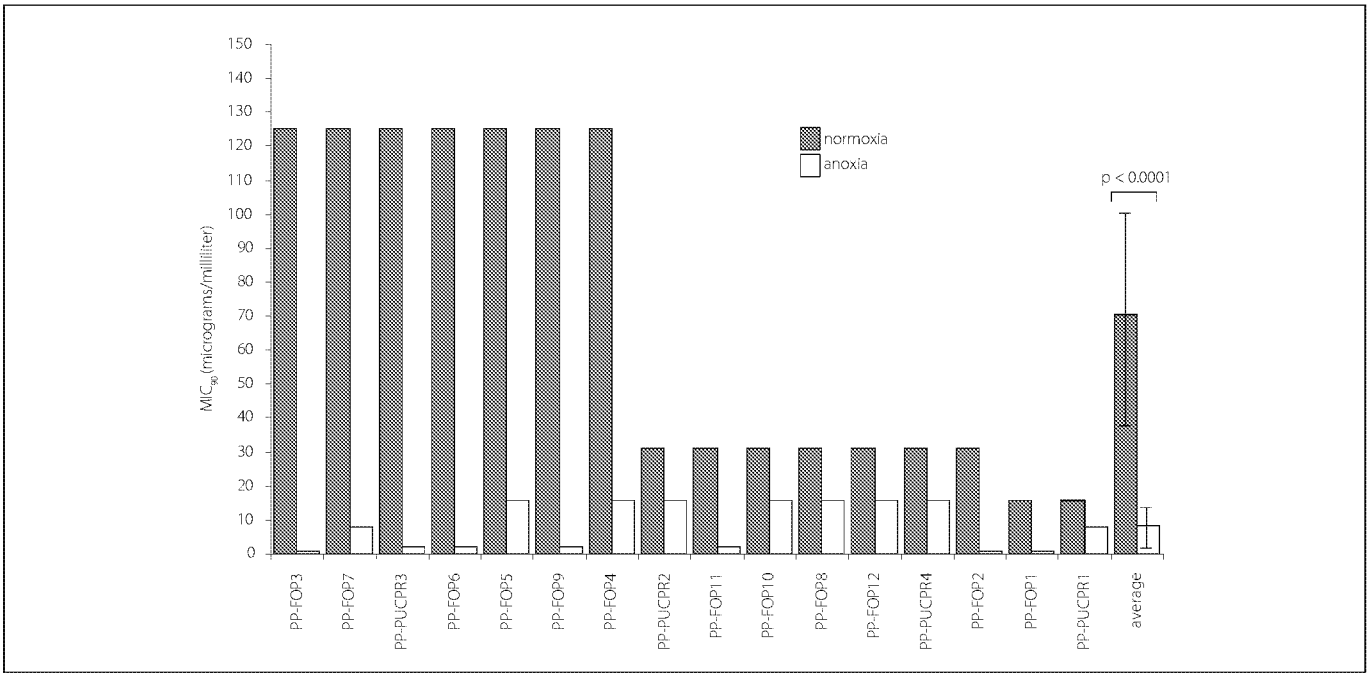


Figure 1. Minimum inhibitory concentration (MIC) of chlorhexidine digluconate for periodontium-related (PP) *Candida albicans* strains in normoxia and anoxia.

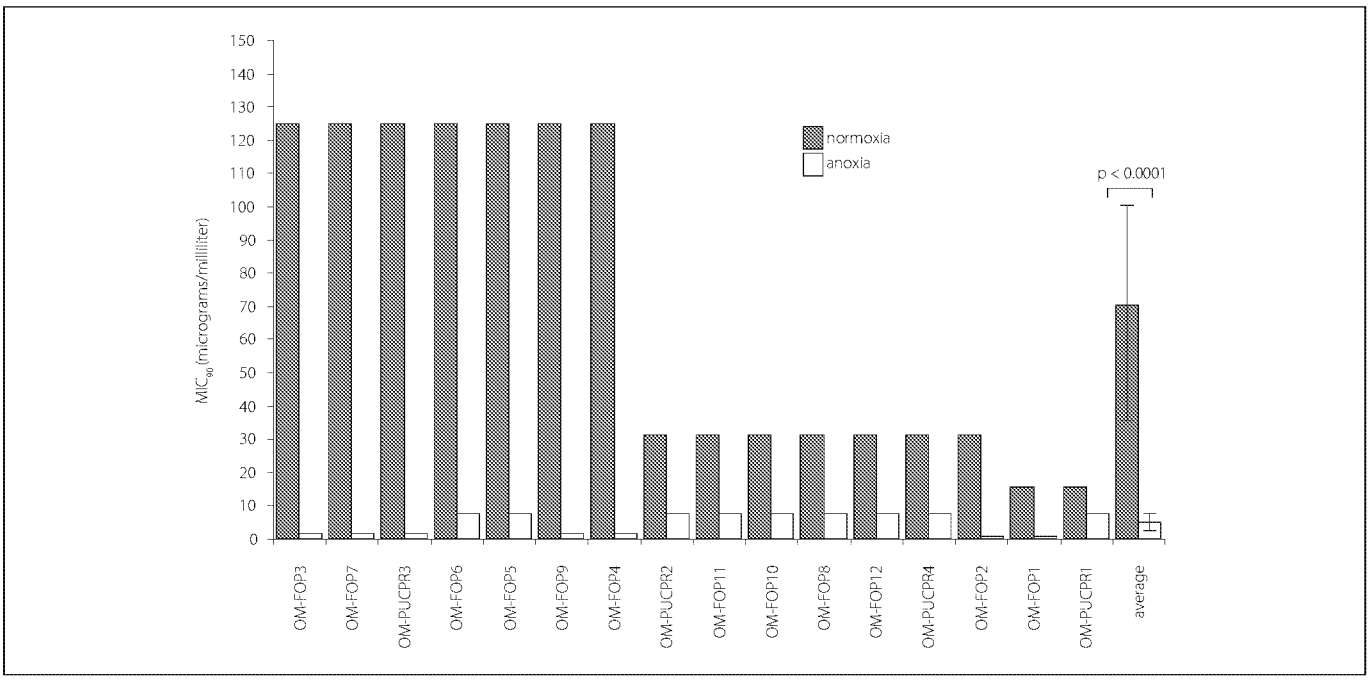


Figure 2. Minimum inhibitory concentration (MIC) of chlorhexidine digluconate for mucosa-related (OM) *Candida albicans* strains in normoxia and anoxia.

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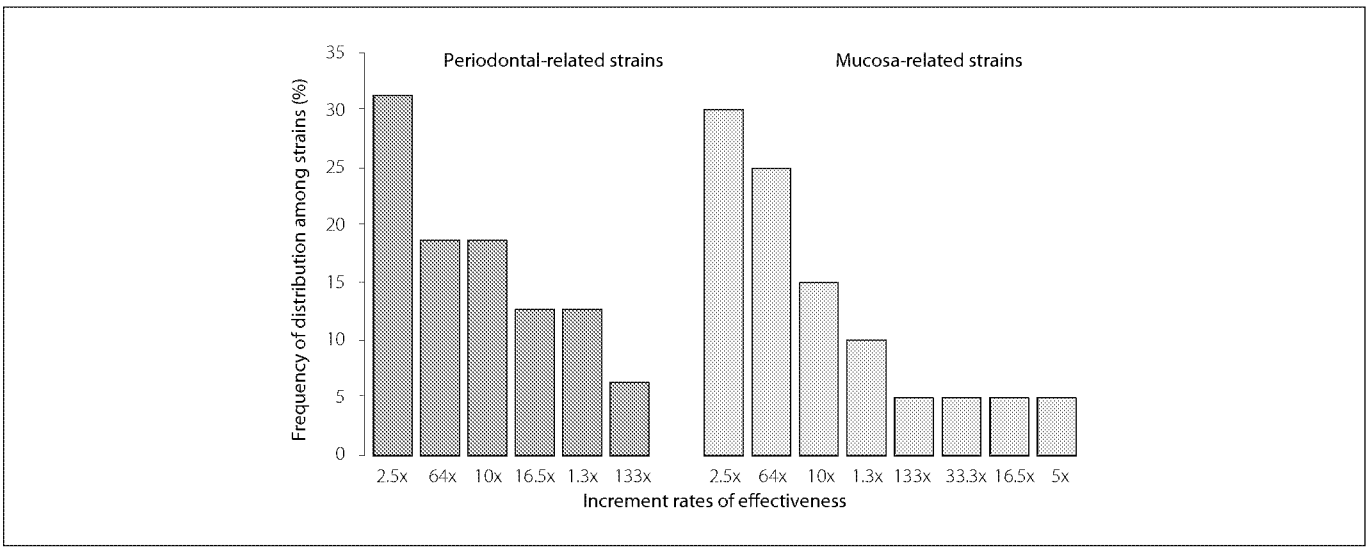


Figure 3. Increment rate of effectiveness (IRE) for minimal inhibitory concentrations (MIC) of chlorhexidine digluconate for periodontium-related (PP) and mucosa-related (OM) *Candida albicans* strains in normoxia and anoxia.

In order to determine de minimum candidacidal concentration (MCC), after the MIC determination, contents of all wells were independently recovered and transferred to tubes with 3 mL of broth without chlorhexidine. The growth in those tubes followed the same MIC assay results. Thus, it could be concluded that the MIC and MCC were the same for these strains under the experimental conditions.

In all cases, the nine values obtained (three repetitions in three independent situations) were exactly the same and no standard deviations could be noticed. The Mann-Whitney U test demonstrated a significant reduction in the resistance to chlorhexidine under anoxia. This test also showed no significant differences for MIC in relation to the anatomic origin of strains ($p = 0.9584$).

In order to evaluate the influence exerted by atmospheric oxygen on MIC performance, the increment rate of effectiveness (IRE) for each isolate was calculated through the equation: $IRE = MIC_{normoxia}/MIC_{anoxia}$. **Figure 3** shows that the IRE values for the PP strains varied from 2.0-fold to 128.8-fold, with higher frequencies of 2.0-fold (37.5%), 16-fold (18.75%), and 66.8-fold (18.75%). OM strains had their susceptibility ranging from 2.0-fold to 66.8-fold, with higher frequencies of 4.0-fold (37.5%), 66.8-fold (32.25%), and 16-fold (18.75%).

Discussion

Studies addressing the action of chlorhexidine on yeasts living in anoxia are scarce[16]. Until the present moment, no data referring to the susceptibility of PP *C. albicans* strains to antimicrobials under anoxia are available.

It has been shown that *C. albicans* cells living in anoxic environments are protected against the action of most common antimycotics[14]. This anaerobic-related resistance to antifungal probably derives from a suppression of ergosterol biosynthesis at fungal cell membrane. As the ergosterol biosynthetic pathway is the main target of azoles and such via is not used when candidal cells are under anoxia, these antimycotics completely lose their efficacy. On the other hand, as ergosterol appears not to be synthesized under anoxic conditions, polyenes do not manifest their membrane interactive behavior either. Furthermore, it has been shown that histatin-5, a potent salivary antifungal peptide, might have such effect abolished, once the mitochondrial energy level is very low when in anoxia[17,18].

In this study, the results showed that chlorhexidine had its candidacidal capacity increased in such environmental conditions. Two plausible hypotheses to explain such phenomenon are proposed.

Firstly, this increased susceptibility to chlorhexidine in an oxygen-free environment may be better discussed taking into account that oxygen is also a positively charged element[19] and has a cationic behavior. Based on this premise, we herein postulate that, in normoxia, the existing atmospheric oxygen competes with chlorhexidine for binding sites, whereas it does not occur in an anoxic environment. Plaut et al.[20] calculated the sorption enthalpy for chlorhexidine and stated that it may be mediate by electrostatic-like bonding interactions. Such interactions are weak and depend on the molecular size. Akaho and Fukumori[21] stated that an area near to 548 $Å^2$ is required for the complete absorption of chlorhexidine molecule to an amphyphylic surface in order to accommodate its ionic and hydrophobic moieties responsible for the adsorption to solid surfaces. This value is much higher than the 1.2 Å of molecular oxygen, commonly absorbed for the aerobic respiration. Additionally, the fact that the deenergization caused by the dropdown in aerobic respiration rates affects significantly the plasmatic membrane of eukaryotes leading to a reduction in the negative potentials[22-25]. Anoxic conditions cause a release of previously accumulated lipophilic cation tetraphenylphosphonium (TPP^+) into *Saccharomyces cerevisiae*[26], which is compatible with the assumption that anoxia reduces de negative feature of fungal membranes. Interestingly, the data hereby presented show that the inhibitory efficiency of chlorhexidine increases in such unfavorable environmental conditions. Our assumption that the better action of chlorhexidine in the absence of oxygen must be derived from

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a disruption in the competition rates is reinforced by the fact that some cations may reduce its adsorption and antimicrobial effectiveness by competitive ways[20,27,28].

Secondly, it has been previously reported that chlorhexidine substantially increases the cell permeability on apical and sub-apical segments of early-stage filamentous forms higher than for yeast forms[29]. This is compatible with the proposed mechanism of disruption of the membrane followed by rapid permeabilization. Therefore, it is possible that fungal cells had their susceptibility have increased by the anaerobically-induced filamentation.

Interestingly, the origin of strains did not exert any influence on the susceptibility ($p = 0.9584$). However, as strains from culture collections were used in the present study, the long-term storage or the multiple re-inoculations might have decreased their susceptibility. Although the sampling have been done six months before the study (data not shown), it was not possible to ensure whether or not it actually occurred. Further studies enrolling freshly isolated strains may possibly clarify this issue.

The extensive variation observed in the increase of effectiveness rates indicates a great heterogeneity for this characteristic. Some strains presented only an increment of mere 1.3-fold susceptibility, whereas others had increased their effectiveness rates in 133 times. It may be suggested that it is variable according to the strains and no generalizations may be done.

The results of the present study are applicable for growing planktonic cells. For *C. albicans* grown in biofilms, Lamfon et al.[30] previously reported that the resistance to chlorhexidine increases up to 8-fold the MIC in relation to planktonic counterparts grown in normoxia. Such result contrasts with those of the present study since it is widely accepted that the accessibility of oxygen to internal layers of biofilms is limited. There are two points that may clarify the differences between the results from Lamfon's et al.[30] study and those expected after assuming that anoxia increases chlorhexidine effectiveness. Firstly, those authors grew their biofilms under normoxic conditions; secondly, the extracellular matrix present in the biofilm may act as a barrier against the antiseptic diffusion.

According to the results obtained in the present study, it may be concluded that chlorhexidine is effective to restrain *C. albicans* grown in the anoxic periodontal pocket with minor concentrations than those needed to kill cells living on surfaces under normoxic conditions. The origin of strains seems not to influence the growth of *C. albicans* under neither normoxia nor anoxia. However, despite these encouraging results, our opinion is that clinicians should not indicate lower chlorhexidine doses to their patients. The main advantage of lower MIC is the maintenance of inhibition effects throughout the lixiviation of chlorhexidine.

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Attachment 22.6

Mendes, et al. "Chlorhexidine bathing for the prevention of colonization and infection with multidrug-resistant microorganisms in a hematopoietic stem cell transplantation unit over a 9-year period: Impact on chlorhexidine susceptibility" Medicine 95:46 (2016).

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Chlorhexidine bathing for the prevention of colonization and infection with multidrug-resistant microorganisms in a hematopoietic stem cell transplantation unit over a 9-year period

Impact on chlorhexidine susceptibility

Elisa Teixeira Mendes, MD[a,*], Otavio T. Ranzani, MD[b], Ana Paula Marchi, BS[c], Mariama Tomaz da Silva, MS[c], José Ulysses Amigo Filho, MD[d], Tânia Alves, NSG[d], Thais Guimarães, PhD[e], Anna S. Levin, PhD[c], Silvia Figueiredo Costa, PhD[c]

Abstract

Health care associated infections (HAIs) are currently among the major challenges to the care of hematopoietic stem cell transplantation (HSCT) patients. The objective of the present study was to evaluate the impact of 2% chlorhexidine (CHG) bathing on the incidence of colonization and infection with vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant (MDR) gram-negative pathogens, and to evaluate their CHG minimum inhibitory concentration (MIC) after the intervention.

A quasi-experimental study with duration of 9 years was conducted. VRE colonization and infection, HAI rates, and MDR gram-negative infection were evaluated by interrupted time series analysis. The antibacterial susceptibility profile and mechanism of resistance to CHG were analyzed in both periods by the agar dilution method in the presence or absence of the efflux pump inhibitor carbonyl cyanide-m-chlorophenyl hydrazone (CCCP) and presence of efflux pumps (qacA/E, qacA, qacE, cepA, AdeA, AdeB, and AdeC) by polymerase chain reaction (PCR).

The VRE colonization and infection rates were significantly reduced in the postintervention period ($P=0.001$). However, gram-negative MDR rates in the unit increased in the last years of the study. The CHG MICs for VRE increased during the period of exposure to the antiseptic. A higher MIC at baseline period was observed in MDR gram-negative strains. The emergence of a monoclonal *Pseudomonas aeruginosa* clone was observed in the second period.

Concluding, CHG bathing was efficient regarding VRE colonization and infection, whereas no similar results were found with MDR gram-negative bacteria.

Abbreviations: BMT = bone marrow transplant, BSIs = blood stream infections, CCCP = carbonyl cyanide-m-chlorophenyl hydrazone, CHG = Chlorhexidine, HAIs = health care associated infections, HSCT = hematological stem cell transplant, MDR = multidrug-resistant, VRE = vancomycin-resistant Enterococcus.

Keywords: chlorhexidine bath, hospital infection, hematopoietic stem cell transplantation infection, multidrug-resistant bacteria, transplant infection

1. Introduction

Health care associated infections (HAIs) are currently among the major challenges to the quality of hematopoietic stem cell transplantation (HSCT) patient care.[1] Multidrug-resistant (MDR) bacteria, such as vancomycin-resistant *Enterococcus* (VRE),[2] and carbapenem-resistant gram-negative bacteria,[3] constitute the leading etiologic agents of bloodstream infections (BSIs) in some bone marrow transplantation (BMT) health centers.[4,5]

Due to these conditions, daily bathing with 2% chlorhexidine (CHG) has been proposed to reduce the colonizing bacterial burden in critically ill patients[6,7] and, thus, reduce the rates of infection and cross-transmission. CHG bath impact has been evaluated, particularly in intensive care units (ICUs).[8–10] Notably, some studies report reduced colonization with MDR microorganisms and a general reduction of bacteremia, mainly due to coagulase-negative staphylococci (CNS).[8,9]

To date, clinical prospective studies that evaluate the real-life impact of prolonged CHG use on the development of bacterial resistance to antiseptics are lacking, and studies approaching HSCT population, especially non-ICU patients, remain scarce in the literature.[9,11,12]

A major concern about the introduction of CHG bath has been the potential increase in selection pressures. Indeed, cases of CHG minimum inhibitory concentration (MIC) increase have been reported mainly for *Staphylococcus aureus*[13] and *Enterococci*

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[a] Department of Infectious Diseases, [b] Pulmonary Division, Heart Institute, Hospital das Clinicas, University of São Paulo, [c] Laboratory of Bacteriology, Department of Infectious Diseases, [d] HSCT Department, Hospital das Clinicas, [e] Department of Infectious, Diseases of Hospital das Clinicas, University of São Paulo, São Paulo, Brazil.

[*] Correspondence: Elisa Teixeira Mendes, Department of Infectious, Diseases of Hospital das Clinicas, University of São Paulo, Dr. Eneas Carvalho de Aguiar 470, São Paulo 02461011, Brazil (e-mail: elisatmendes@gmail.com).

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spp.[14] isolates. Efflux-pump genes (*cepA*, *qacAE*, and *qacE*) have been identified and associated with gram-negative bacterial strains with high CHG MICs.[15,16]

The objective of the study was to evaluate the impact of CHG bathing on colonization and infection by MDR bacteria in the BMT ward of a university hospital. We also aimed to assess the CHG MICs for MDR bacteria and presence of efflux pump genes, both before and after the implementation of daily bathing with chlorhexidine.

2. Materials and methods

2.1. Study design

This is a quasi-experimental intervention study comparing a 4.5-year pre-intervention period (January 2005–July 2009), during which inpatients of the BMT ward were bathed with regular liquid soap, with an equally long intervention period (August 2009–December 2013), during which inpatients of this ward were routinely bathed with 2% chlorhexidine digluconate solution.

2.2. Setting

This study was conducted in the University of São Paulo Medical Centre (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo—HC-FMUSP) with 2200 beds, of which 1000 are located in the Central Institute, where the study was conducted. BMT unit is a ward of adult patients with occasional pediatric transplants until 2007. It performs 10 to 12 transplants a month, both autologous and allogeneic. This study was approved by the hospital's Ethics Committee for Research Projects (CAPPesq—Comissão de Ética e Análise de Projetos de Pesquisa, São Paulo, Brasil number: 08362413.9.0000.0068).

2.3. Study population

Patients of both periods were compared as to gender, age, underlying hematological diseases, types of transplants, comorbidities, and 30-day and 1-year post-HSCT mortality rates.

2.4. Procedures

The chlorhexidine bathing procedure (with 2% chlorhexidine digluconate) was standardized by the nursing team of the HSCT ward and the Hospital Infection Control Department during August 2009 and maintained during the entire intervention period. Following orientation of the nursing team at admission, patients performed their own chlorhexidine bath daily. In our hospital, 2% CHG is also used in the antisepsis of invasive procedures such as central venous catheters insertion, surgery, and biopsies.

2.5. Outcomes

Primary outcome was the incidence density (ID) of VRE colonization and infection. Secondary outcome was MDR gram-negative bacteria infection, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, resistant to carbapenems at any site.

Further endpoints included the ID of recorded HAIs by any given microorganism at any site, chlorhexidine MICs of isolates, and the characterization of mechanisms of resistance of bacteria isolated before and after the intervention.

2.6. Definitions

Monthly IDs were calculated according using the exemplary equation: ID = number of cases/1000 patient-days.

The definitions for HAIs were those used by the Centres for Disease Control and Prevention (CDC).[17]

In the BMT unit, only VRE colonization was weekly monitored with anal swabs from all inpatients in the study period. The swabs were inoculated in a 6 μg/mL vancomycin supplemented broth.[18]

All patients diagnosed as colonized or infected with MDR microorganisms were kept under cohort contact precautions until hospital discharge. International standard definitions for acquired resistance was used to MDR determination.[19] We did not to include MRSA (methicillin-resistant *Staphylococcus aureus*) in our analysis, by its low incidence in the unit only 2 infections during the study period (<2.5%).[4]

2.7. Laboratory analysis of chlorhexidine MICs

MICs for CHG were determined for 127 isolates (46 *Pseudomonas aeruginosa*; 48 VRE; 27 *Klebsiella pneumoniae*; and 6 *Acinetobacter baumannii* n: 6). Postintervention strains were compared with control strains, represented by bacteria isolated during the pre-intervention period from the unit.

The samples evaluated were those that were available at the research laboratory in the pre- and postintervention (microbiology laboratory/Institute of Tropical Medicine University of São Paulo).

There were no *K. pneumoniae* and *A baumanni* isolated in pre-intervention period at the unit, neither in surveillance or clinical cultures. These MDR gram-negatives were introduced in our BMT unit after 2010.

The MICs were determined by the agar dilution test by incorporating serial logarithmic concentrations of chlorhexidine in Mueller-Hinton agar (MHA) culture medium, which was then distributed onto individual Petri dishes as in Abuzaid et al.[15] The tested concentrations ranged from 0 to 256 mg/L, and controls, *K pneumoniae* ATCC13883 (chlorhexidine MIC of 16 μg/mL), and *Escherichia coli* ATCC25922 (chlorhexidine MIC of 2 μg/mL) were included in each experiment.

Each experiment was performed in triplicate and discarded if the ATCC strains varied by more than 1 dilution.

2.8. Evaluation of chlorhexidine MICs in the presence of the efflux pump inhibitor carbonyl cyanide-m-chlorophenyl hydrazone (CCCP) in the culture medium

The influence of the efflux pump on the antibacterial susceptibility profile of the studied strains to chlorhexidine was evaluated by assessing the MICs of chlorhexidine in the presence of the efflux pump inhibitor CCCP (Sigma-Aldrich, Saint Louis, MO, USA) in the culture medium.

Specifically, CCCP was diluted with 1 mL of distilled water and added to the MHA plates at a final concentration of 10 mg/L.[15] These plates were prepared with chlorhexidine concentrations ranging from 0 to 256 mg/mL. The influence of an efflux pump on the CHG MIC for a given bacterial strain was defined as an MIC reduction of at least 4-fold in the presence of CCCP.[15]

2.9. Evaluation of the mechanisms of resistance to chlorhexidine

The mechanisms of resistance were evaluated using polymerase chain reaction (PCR). The primers are listed in Table 1.[20–23]

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Table 1

Primers used to evaluate genes that encode resistance to antibiotics and that encode efflux pumps associated with chlorhexidine resistance.

Gene	Primers	Sequences (5′–3′)	Size, pb
blaIMP[17]	blaIMP-F	GAATAGAATGGCTTAACTCTC	188
	blaIMP-R	CCAAACCACTAGGTTATC	
blaVIM[17]	blaVIM-F	GTTTGGTCGCATATCGCAAC	382
	blaVIM-R	AATGCGCAGCACCAGGATAG	
blaSPM[17]	blaSPM-F	CTAAATCGAGAGCCCTGCTTG	798
	blaSPM-R	CCTTTTCCGCGACCTTGATC	
Oxa-23[16]	blaoxa23-F	AACGATTGCGAGCATC	501
	blaoxa23-R	GTCAACCAGCCCACTT	
Oxa-143[16]	blaoxa143-F	AGTTAACTTTCAATAATTG	149
	blaoxa143-R	TTGGAAAATTATATAATCCC	
vanA[19]	vanA-F	GCTGCGATATTCAAAGCTCA	545
	vanA-R	CAGTACAATGCGGCCGTTA	
vanB[19]	vanB-F	ATGGGAAGCCGATAGTCTC	368
	vanB-R	GTTACGCCAAAGGACGAAC	
blaKPC[20]	KPC-F	ATGTCACTGTATCGCCGTCT	893
	KPC-R	TTTTCAGAGCCTTACTGCCC	
cepA[14]	cepA-F	CAACTCCTTCGCCTATCCCG	1051
	cepA-R	TCAGGTCAGACCAAACGGCG	
*qac*AE[14]	qacAE-F	GCCCTACACAAATTGGGAGA	370
	qacAE-R	CTGCGGTACCACTGCCACAA	
qacE[14]	qacE-F	GCCCTACACAAATTGGGAGA	350
	qacE-R	TTAGTGGGCACTTGCTTTGG	
AdeA[18]	adeA-F	ATCTTCCTGCACGTGTACAT	513
	adeA-R	GGCGTTCATACTCACTAACC	
AdeB[18]	adeB-F	TTAACGATAGCGTTGTAACC	541
	adeB-R	TGAGCAGACAATGGAATAGT	
AdeC[18]	adeC-F	AGCCTGCAATTACATCTCAT	560
	adeC-R	TGGCACTTCACTATCAATAC	
QacA/B[14]	qacAB-F	GCAGAAAGTGCAGAGTTCG	350
	qacAB-R	CCAGTCCAATCATGCCTG	
cepA[14]	cepA-F	CAACTCCTTCGCCTATCCCG	1051
	cepA-R	TCAGGTCAGACCAAACGGCG	

2.10. Evaluation of clonality

The clonality of samples was characterized by pulsed-field gel electrophoresis (PFGE). The PFGE patterns were analyzed with Bionumerics version 7.1 (Applied-Maths, Sint-Martens-Latem, Belgium). DNA fragments were manually curated and normalized using the molecular weight standard from each gel. Restrictions enzymes and parameters used were SMA-I for VRE, SPE-I for *P aeruginosa*, XBA-I for *K pneumoniae*, and Apa-I for *A baumannii*.[24–28]A 1.5% band tolerance and 0.5% optimization were used. Cluster analysis was performed by the unweighted pair group method using arithmetic averages (UPGMA). Isolates were considered to be genetically related if the Dice coefficient was ≥ 80%.[24–27]

2.11. Statistical analysis

In the descriptive analysis, categorical and continuous data were presented as percentages and mean ± SD values [or medians and interquartile ranges (IQRs)], respectively. The pre- and post-intervention periods were compared. The categorical variables were compared using a Chi-square test or Fisher exact test, as appropriate. The quantitative continuous variables were compared using an unpaired *t* test and the Mann–Whitney *U* test for normally and non-normally distributed variables, respectively.

Table 2

Epidemiological and clinical characteristics of 1393 patients submitted to HSCT in Hospital das Clínicas, University of São Paulo, Brazil (2005–2013) to evaluate a daily bathing with chlorhexidine as an intervention to reduce colonization and infection by antimicrobial-resistant microorganisms.

Variable (%)	Pre-intervention	Intervention	*P*
N (1393)	870	523	
Sex M:F (%)	58.4: 41.6	53.0: 47.0	0.054
Age, y, Mean (range)	40 (1–71)	49 (15–72)	<0.001
Age >60 y (%)	47 (5.4)	126 (24.3)	<0.001
Age <15 y	60 (6.8)	0	<0.001
Acute leukemia (%)	179 (20.6)	123 (23.5)	0.09
Lymphoma (%)	310 (35.6)	159 (30.4)	0.02
Multiple myeloma (%)	205 (23.6)	157 (20.0)	0.04
Aplastic anemia (%)	64 (7.4)	36 (6.9)	0.41
Allogenic HSCT (%)	330 (37.9)	230 (44.0)	0.013
Types of transplant			
Umbilical cord (%)	9 (1)	1 (0.2)	—
Unrelated donor (%)	31 (3.6)	22 (4.2)	—
Related donor (%)	290 (33.3)	207 (39.5)	—
Autologous HSCT (%)	540 (62.1)	293 (56.0)	—
Death in 30 days (%)	93 (10.7)	65 (12.4)	0.18
Allogenic HSCT	54	38	0.52
Autologous HSCT	39	27	0.20
Deaths in 1 year (%)	204 (23.4)	115 (22.0)	0.28
Allogenic HSCT	129	80	0.16
Autologous HSCT	75	35	0.22
Incidence density of HAI (per 1000 patient-days)	151 (14.8)	242 (16.4)	0.24

HAI = health care associated infections, HSCT = hematological stem cell transplantation.

The association between the implementation of chlorhexidine bathing and the endpoints, considering time-related changes, such as general improvements in patient care and secular trends, was assessed by interrupted time series analysis (ITS).[28,29] The data were aggregated at equal time intervals (months) and we used the autoregressive integrated moving average (ARIMA) model. Therefore, we could evaluate the secular trend (coefficient Beta-1), the immediate change after intervention started (coefficient Beta-2), and the long-term effect of the intervention (coefficient Beta-3).

We checked the assumptions required for ARIMA models using Phillips–Perron, the Kwiatkowski–Phillips–Schmidt–Shin (KPSS), and Augmented Dickey–Fuller tests.[29] The autocorrelation was checked by visual inspection of autocorrelograms and partial autocorrelograms of the series and its residuals. The White neural network test was used to test for neglected nonlinearity. We also checked for seasonal or cyclical effects by decomposing our series. The Ljung–Box Q test was run to evaluate a lack of fit of the final ARIMA.[29] Because of the outbreak of *P aeruginosa* during the intervention period, we pre-specified to use a nonlinear time series for gram-negative bacteria. Therefore, we used a general additive model (GAM), allowing for autocorrelation.[28]

The database was constructed, processed, and organized with Microsoft-Excel 2010. Statistical and time series analyses were performed using Epi.Info 3.5.3 (Atlanta, GA, USA), SPSS 21.0 package for Windows (Armonk, New York, USA), and the R project (Vienna, Austria) for statistical computing.

3. Results

3.1. General Characteristics of the Studied Population

During the 9 years of the study (4.5 years pre- and 4.5 years postintervention), 1393 HSCTs were performed in the unit, with

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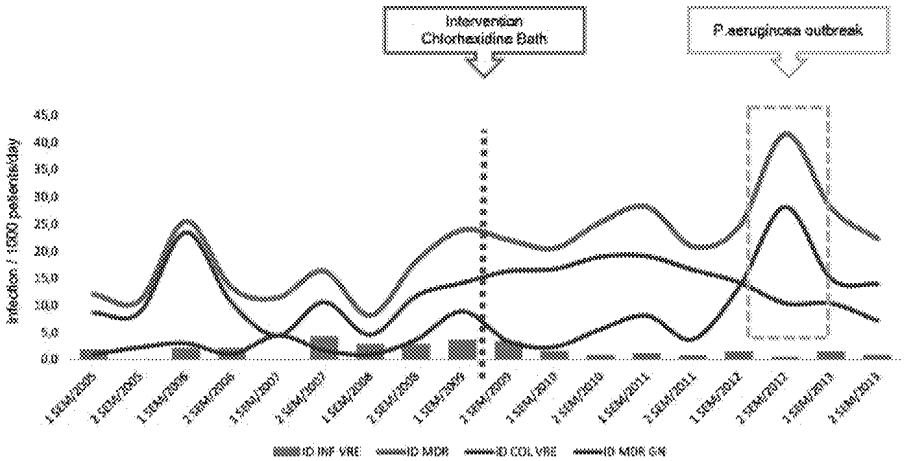
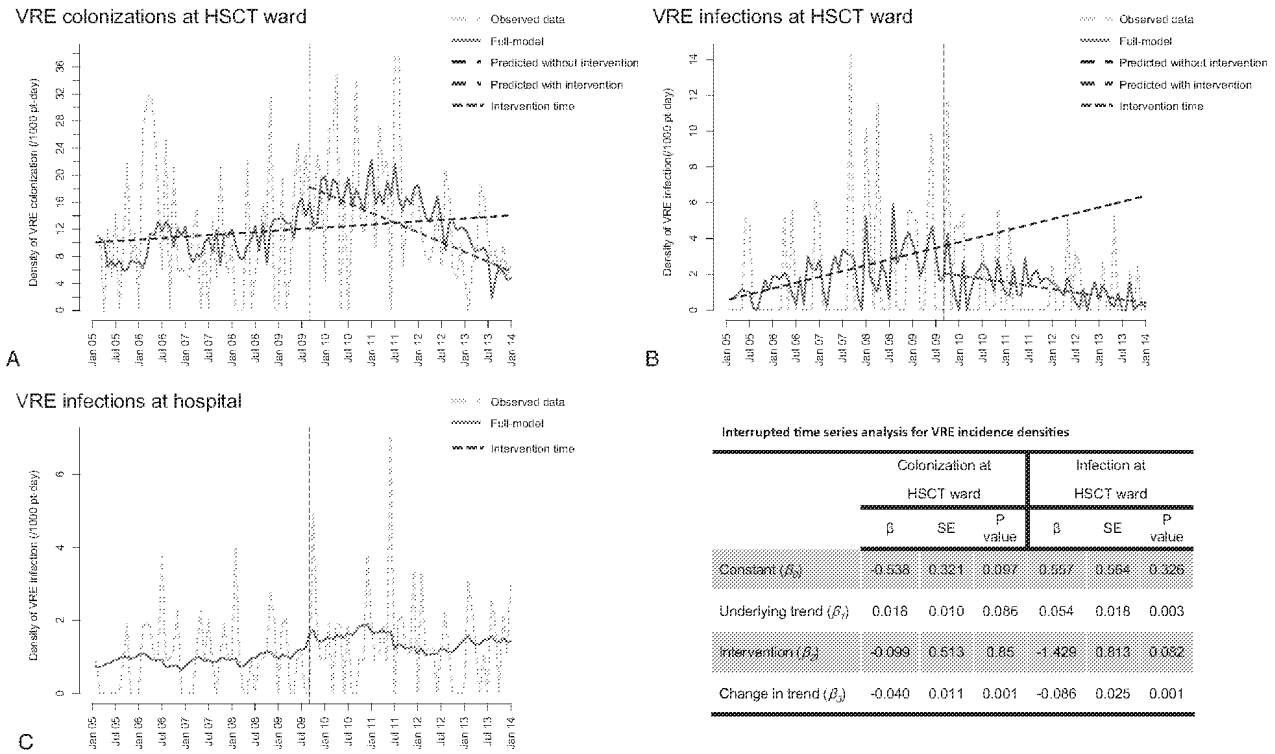


Figure 1. Bianual incidence density of MDR infection and colonization in pre- and postintervention periods, in BMT unit, HC-FMUSP, 2005–2013. Col = colonization, GN = gram-negative bacteria, ID = Incidence density, Inf = Infection, MDR = Multidrug-resistant bacteria, VRE = Vancomycin-resistent *Enterococcus*.

870 patients in the pre-intervention period and 523 patients in the intervention period. The clinical and epidemiological characteristics of the patients are listed in Table 2. Despite the higher total number of patients during pre-intervention period, we had a greater number of patient-days in the intervention period (15,600 vs 10,195 patient-days). This may mean a longer hospital stay and more severe and complex cases such as allogeneic HSCT in the intervention period.

Notwithstanding this difference, the 30-day and 1-year mortality rates did not differ between the studied periods, and the overall HAI rate was also not different, suggesting that patients of both groups exhibited similar long-term profiles of severity and prognosis, irrespective of the type of transplantation performed.

The biannual distribution of infection rates of MDR microorganisms is shown in Fig. 1. The increased infection rates of



Interrupted time series analysis for VRE incidence densities

	Colonization at HSCT ward			Infection at HSCT ward		
	β	SE	P value	β	SE	P value
Constant (β_0)	0.538	0.321	0.097	0.557	0.564	0.326
Underlying trend (β_1)	0.018	0.010	0.086	0.054	0.018	0.003
Intervention (β_2)	-0.099	0.513	0.85	-1.429	0.813	0.082
Change in trend (β_3)	-0.040	0.011	0.001	-0.086	0.025	0.001

Figure 2. Time series of VRE colonization (A), VRE infection (B) in pre- and postintervention periods, in bone marrow transplant ward, and global hospital VRE incidence (C) in HC-FMUSP, 2005–2013.

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MDR gram-negative bacteria are mainly due to an outbreak of *P aeruginosa* BSIs that occurred from December 2011 to January 2013. During this outbreak, 29 cases of *P aeruginosa* bacteraemia were recorded, especially within the first days after HSCT,[30] with 65% mortality.

3.2. Time series

Figure 2A and B show the temporal distribution of VRE colonization and infection rates in the BMT unit. There was a significant decrease in the incidence of colonization (Change in trend: Beta-3 = −0.040, $P = 0.001$) and infection (Change in trend: Beta-3 = −0.086, $P = 0.001$) during the intervention period. This reduction did not occur in the global hospital rates (Fig. 2C).

In contrast, the infection rates of MDR gram-negative bacteria increased in the last two years of the study in the BMT unit. Indeed, we observed a non-linear underlying trend for MDR gram-negative infections. Even after excluding the *P aeruginosa* outbreak, the postintervention period exhibited the highest rates ($P < 0.001$) of MDR gram-negative bacteria. The BSI ID in the HSCT unit was similar in both periods ($P = 0.31$).

3.3. Evaluation of the antibacterial susceptibility profile and mechanisms of resistance to chlorhexidine

Table 3 describes chlorhexidine MICs in the pre- and intervention periods, both in the presence and in the absence of the efflux pump inhibitor CCCP. Antimicrobial resistance genes were *SPM* in 30% of the tested *P aeruginosa*, *OXA 23* in 83% of *A baumannii*, *KPC* in 100% of *K pneumonia*, and *Van A* in 100% of *Enterococcus faecium* tested. VRE isolates exhibited a considerably lower baseline chlorhexidine MIC than gram-negative bacteria, and their MIC50 increased by 2 dilutions in the intervention period. The chlorhexidine MIC reduction with CCCP was significantly higher in intervention period for VRE isolates (90% response). MIC50 and MIC90 for *P aeruginosa* were identical in the pre- and intervention periods (32 and 64 μg/mL, respectively).

3.4. Mechanisms of resistance to chlorhexidine

We observed a positive correlation between the presence of *cep*A and the response to CCCP. Specifically, of the 25 *cep*A-positive strains, 68% exhibited a reduction of their MIC value by 4 dilutions in the presence of CCCP (Table 4).

CepA was found in 44.5% of *P aeruginosas* tested in the pre-intervention and in none tested in intervention period. CepA was also detected in 62.9% and 42.4% of *K pneumoniae* and *A aumannii*, respectively. The efflux pumps AdeB and C were detected in all *A baumannii* strains in intervention period and only one half of them tested in pre-intervention period. AdeA was only found in the pre-intervention group (51%).

The QacE efflux pump was observed in a small proportion of pre-intervention VRE isolates (10%) and its association with the MICs could not be established. QacAB and QacAE were not detected.

Regarding clonality, the VRE, *K pneumoniae*, and *A baumannii* isolates were polyclonal. With respect to the dendrogram of *P aeruginosa* strains (Fig. 3B), a cluster with >80% similarity was seen in 10 of the 22 evaluated isolates in the intervention period.

4. Discussion

Our study shows that daily chlorhexidine bathing led to a significant reduction in rates of colonization and infection by vancomycin-resistant enterococci (VRE) in a bone marrow transplant unit. We consider this an important finding for HSCT population, as, in some centers, VRE is the main bacteraemia-causing agent,[2] especially due to important vancomycin use and recurrent gastrointestinal tract injury, such as graft versus host disease (GVHD) and mucositis.[1]

CHG bathing has previously been shown to reduce the incidence of VRE in ICUs.[31,32] However, data on the use of CHG on HSCT patients are scarce and controversial.[9,11,12] A prospective multicenter study evaluating BMT inpatient unit found no impact with the use of CHG bathing.[9] In contrast, a quasi-experimental study showed a nonsignificant reduction of VRE rates.[11] In both cases, the observation periods lasted 6 months or less.

Our study is one of the few that evaluated the use of CHG bathing outside the ICU setting, using shower bath and liquid soap formula. Few studies have evaluated this method in the literature.[33]

Similar to the observations by other authors,[8–10] we found no substantial effect of CHG bathing on the incidence of infection and colonization with MDR gram-negative bacteria.

In our BMT unit, even if we exclude data on the outbreak of carbapenem-resistant *P aeruginosa*,[30] we observed an increase in infections caused by MDR enterobacteria and the appearance of carbapenemase-producing *Klebsiella pneumoniae* (KPC) in the intervention period. These MDR enterobacteria had never occurred in the hospital before 2010. The increase on gram-negative infections was observed in the entire hospital; however, the reduction of VRE incidence in BMT unit in the

Table 3

Minimal inhibitory concentrations (MIC) of chlorhexidine and effect of the efflux pump inhibitor CCCP on MIC of bacteria isolated in the pre-intervention and intervention periods in a Bone Marrow Transplant unit, Hospital das Clínicas, University of São Paulo, Brazil (2005–2013).

	Pre-intervention, μg/mL					Intervention, μg/mL				
Bacteria N = 127	N	MIC 50 (range)	MIC 90	MIC 50 CCCP (range)	CCCP response* (%)	N	CIM 50 (range)	CIM 90	CIM 50 CCCP (range)	CCCP response* (%)
P aeruginosa	18	32 (16–64)	64	4 (2–8)	1 (5)	28	32 (4–64)	64	4 (1–8)	9 (39.1)
A baumannii	NI	—	—	—	—	6	32 (8–64)	64	4 (0.5–8)	3 (42.8)
K pneumoniae	NI	—	—	—	—	27	64 (16–128)	128	2 (0.5–8)	24 (85.7)
E faecium	28	2 (1–32)	16	0.5 (0.25–4)	7 (25)	20	8 (4–32)	32	0.5 (0.125–4)	18 (90)

CCCP response = 4-fold MIC reduction compared with non-CCCP MIC, MIC50 = MIC that inhibited 50% of isolates, MIC90 = MIC that inhibited 90% of isolates, NI = not identified.
* Refers to the CCCP response.

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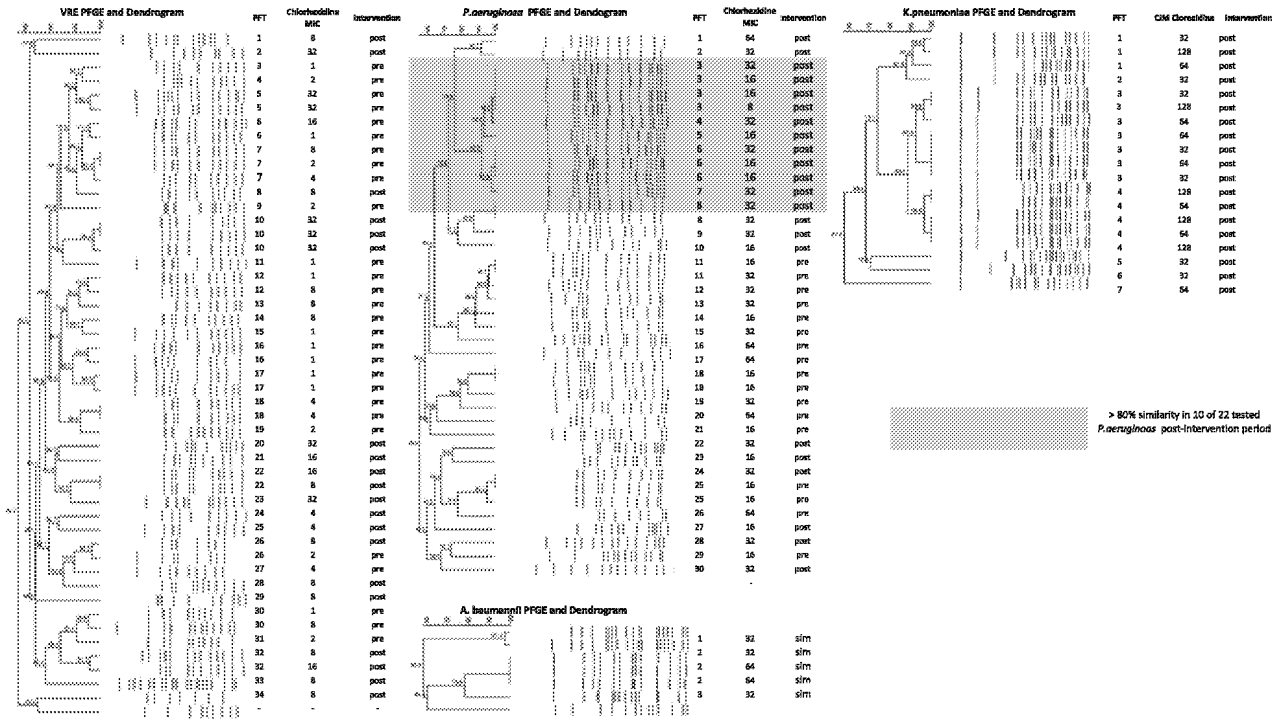


Figure 3. (A–D) PFGE and Dendrogram of VRE, *P aeruginosa*, *K pneumonia*, and *A baumannii*, respectively.

intervention period may have helped in this epidemiological change.

During both periods, isolates were polyclonal, except for the outbreak *P aeruginosa* clone in the intervention period. It is possible that the extensive use of the antiseptic in the unit may have contributed to the shift from a polyclonal *P aeruginosa* pattern seen in the pre-intervention period to a clonal pattern. This clone presented was virulent, as described in another study.[34] The success of MDR *P aeruginosa* clones has been associated with phenotypic and genetic factors.[35,36]

Chlorhexidine is a topical antiseptic that changes the bacteria osmotic equilibrium, reduces their metabolic capacity, and breaks through the bacterial cell membrane, and the presence of efflux pumps is the most important mechanism of resistance.[6] Resistance to antiseptics, in general, is poorly studied, and there are no clearly defined susceptibility break points. Thus, the increase in MICs following exposure to chlorhexidine does not necessarily imply resistance.

The evaluation of the long-term ecological impact of bathing with chlorhexidine is crucial because it is widely used in many formulations in the hospital environment. The increase in the MIC50 by 2 dilutions for VRE in the postintervention period suggests that prolonged exposure to the antiseptic might increase the MIC for these bacteria. This phenomenon has previously been described and can either imply resistance or merely indicate adaptive tolerance mechanisms that may be reversed after the interruption of exposure.[37]

In our study, gram-negative bacteria exhibited higher MIC values than gram-positive microorganisms. Studies have previously described this "intrinsic resistance" of gram-negative

Table 4

Frequency of chlorhexidine resistance genes found in bacteria isolated in the pre-intervention and intervention periods, Bone Marrow Transplant unit, Hospital das Clínicas, University of São Paulo, Brazil (2005–2013).

	P aeruginosa		*K pneumoniae*	*A baumanni*	*E faecium*	
Genes	**Pre-intervention**	**Intervention**	**Intervention**	**Intervention**	**Pre-intervention**	**Intervention**
MIC50/MIC90, μg/mL	32/64	32/64	64/128	32/64	2/16	8/32
N (%)	18 (100)	28 (100)	27 (100)	6 (100)	28 (100)	20 (100)
AdeA	----	----	----	0	----	----
AdeB	—	—	—	6 (100)	—	—
AdeC	—	—	—	6 (100)	—	—
cepA	8 (44.5)	0	17 (62.9)	0	0	0
qacAE	0	0	0	0	0	0
qacE	0	0	0	0	3 (10.7)	0
qacAB	0	0	0	0	0	0

MIC = minimal inhibitory concentration, MIC50 = MIC that inhibited 50% of isolates, MIC90 = MIC that inhibited 90% of isolates.

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bacteria[37] not only to CHG but also to other antiseptics. A possible explanation is that the outer membrane of gram-negative bacteria functions as a natural barrier against the entrance of chemical substances, including antiseptics and antimicrobials.[6] This may explain why chlorhexidine bathing was not efficient in reducing the incidence of infection with MDR gram-negative bacteria in most studies.

A significant response to CCCP in our postintervention strains suggest that efflux pump is an important resistance mechanism; however, we did not find many of the most commonly described pumps. It is possible that other efflux-pumps were responsible for this result.

We observed that the *cep*A efflux pump was associated with a response to CCCP in *K pneumoniae* isolates. This finding is consistent with the study by Abuzaid et al[15] who found reduced chlorhexidine MIC values for virtually all strains that carried the *cep*A efflux pump.

To our knowledge, our study is the first to evaluate the impact of an intervention over a long period of time, both with respect to measuring the incidence of HAI and the environmental impact of the antiseptic. All other prospective multicenter studies evaluated interventions over 4 or 6 months, a period that we considered insufficient to evaluate the impact on the microbiota of the units.[8–10] We believe that an evaluation is mainly relevant for very vulnerable units, such as those with HSCT patients.

Our study has limitations. In addition to the fact that the study was performed in only 1 center, the pre-intervention period was retrospective and it was not possible to collected important data such as chlorhexidine and antibiotics consumption. Also, the long observation period might contribute confounding factors to the analysis. In the 9-year period, outbreaks, changes in the microbiota in the hospital, and changes in hospitalization policies in the unit may have occurred, thus changing the epidemiological and patient characteristics in the ward. The increase in MDR gram-negative rates in the intervention period may have influenced the reduction in VRE incidence. However, the MDR gram-negative bacteria increased epidemically throughout the hospital and VRE rates remained stable in other units, only decreased in BMT ward.

In conclusion, chlorhexidine bathing reduced the incidence of VRE in the BMT unit, and is a promising method for the prevention of one of the most incident and difficult to control pathogens in this patient population. This effect did not occur for MDR gram-negative bacteria that became more prevalent in the unit and in the hospital.

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Attachment 22.7

Karpinski and Szkaradkiewicz. "Chlorhexidine – pharmaco-biological activity and application" European Review for Medicinal and Pharmacological Sciences 19, 1321-1326 (2015).

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European Review for Medical and Pharmacological Sciences 2015; 19: 1321-1326

Chlorhexidine – pharmaco-biological activity and application

T.M. KARPIŃSKI, A.K. SZKARADKIEWICZ[1]

Department of Medical Microbiology, University of Medical Sciences in Poznań, Poland
[1]Department of Conservative Dentistry and Periodontology, University of Medical Sciences in Poznań, Poland

Abstract. – OBJECTIVE: Chlorhexidine (CHX) is one of the most widely used antiseptic, especially in dentistry. At low concentrations CHX is bacteriostatic and at high concentrations acts bactericidal causing cell death by cytolysis. In this study, we performed a systematic review of pharmaco-biological activity and application of CHX.

MATERIALS AND METHODS: Articles for inclusion in this review were retrieved from online databases PubMed/Medline. The selected papers were included in the present manuscript according to their relevance for the topic.

RESULTS: Totally 75 papers were enrolled in this research. CHX has strong biocidal activity against Gram-positive bacteria and weaker activity against Gram-negative bacteria. It is also active against yeasts, some dermatophytes and some lipophilic viruses. The most widely application CHX has found in dentistry and antisepsis. Numerous studies have confirmed the beneficial effects of CHX in reducing of plaque accumulation, in tooth caries, gingivitis, periodontitis and in alveolar osteitis. Unfortunately, CHX exhibits cytotoxic activity on human cells, can cause colorization of teeth and fillings, and its activity depends on the pH of the environment and the presence of organic substances.

CONCLUSIONS: CHX plays a valuable role in the dentistry and antisepsis. However, it can also cause side effects, limiting its application time.

Key Words:
Chlorhexidine, Antiseptic, Biocidal activity, Cytotoxicity, Dentistry.

Introduction

Chlorhexidine (CHX) is one of the most commonly used antiseptic agents for skin and mucous membranes disinfection. In dentistry is used as mouth rinses, oral irrigations and slow release devices. CHX is helpful in gingivitis and periodontitis, is used as an adjunct to scaling and root planing procedures. Also for prevention of dental caries, oropharyngeal decontamination and in endodontal treatment[1,2]. Moreover, it is used in hand hygiene in health-care personnel, general skin cleanser, in catheter site preparation, in bladder irrigation[3,4]. CHX is active against Gram-positive and Gram-negative bacteria, yeasts and viruses[5,6]. The aim of this article was to provide a comprehensive review regarding application and biological activity of chlorhexidine.

Materials and Methods

The present study offers a review of the literature dealing with the chemical properties, antimicrobial activity, application and side effects of the chlorhexidine. To this effect, a Medline search was carried out, using the PubMed search. The identified papers were selected for inclusion in the present manuscript according to their relevance for the topic. The search was restricted to human subjects. We also reviewed the relevant references listed in the searched papers to identify potential related articles. Other articles and information were also identified in author's personal archive.

Results

Chemical Aspects

Chlorhexidine molecule is composed of two symmetrical structure with 4 chlorophenyl rings and 2 biguanide groups linked by a central hexamethylene bridge[7,8]. CHX is a cationic molecule and their biological activity owes single chlorine atoms bars on both phenolic rings. CHX is 1,1'-hexamethylene bis (5-[4-chlorophenyl] biguanide) having the chemical formula $C_{22}H_{30}Cl_2N_{10}$ (htttp://toxnet.nlm.nih.gov). It is a strong alkali practically insoluble in water. In the water soluble are the salts of chlorhexidine and

Corresponding Author: Tomasz M. Karpiński, MD; e-mail: tkarpin@interia.pl

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they have been applied in disinfectant formulations: chlorhexidine diacetate, chlorhexidine digluconate and chlorhexidine dihydrochloride[9]. CHX compound most widely used in disinfectant formulations is gluconate. Chlorhexidine gluconate is almost colorless or pale yellow liquid, and is highly soluble in water. Chlorhexidine acetate is a white microcrystalline powder. The substance is very sparingly soluble in water and soluble in 96% ethanol[7]. Chlorhexidine digluconate solution[9] is an aqueous solution which contains 1,1 -(hexane-1,6-diyl)bis[5-(4-chlorophenyl)biguanide]di-D-gluconate, with the chemical formula $C_{34}H_{54}Cl_2N_{10}O_{14}$. Chlorhexidine hydrochloride is a white to off-white crystalline powder. Substance is quite sparingly soluble in water and very difficult in 96% ethanol[8]. Aqueous solutions of chlorhexidine are relatively resistant to elevated temperatures. Heating to 100°C does not cause decay. During long-term storage under the influence of light and air chlorhexidine solution gradually darkens. Chlorhexidine activity is dependent on the pH of the environment, and the optimal range is 5.5-7.0. Activity is reduced in the presence of serum, blood, pus and other organic matter. Its activity is also reduced in the presence of soaps and other anionic compounds[7,10].

Mode of Action

The antimicrobial effect of chlorhexidine is dose-dependent. Chlorhexidine at low concentrations (0.02%-0.06%) has bacteriostatic activity, whereas at higher concentrations (> 0.12%) acts bactericidal (11). CHX is a cationic molecule and binds nonspecifically to negatively-charged membrane phospholipids of bacteria. At low concentrations CHX affects the change in the osmotic balance of the bacteria cell. This leads to the release of potassium, phosphorus and other low-weight molecules[12]. The process, taking place in an environment of sublethal concentration of chlorhexidine, leads to a loss of as much as 50% of potassium ions; it may be reversible, on condition of removing the compound[7,10]. At high concentrations CHX causes cell death by cytolysis. It leads to the release of the main intracellular components, including nucleotides, to changes of the cell's protein structure and precipitation/coagulation of cytoplasmic proteins[13].

Antimicrobial Activity

Chlorhexidine has a wide spectrum of antibacterial activity. The bactericidal action of CHX is more effective against Gram-positive bacteria and weaker against Gram-negative ones[14]. CHX is also active against fungi and viruses[5,6]. Chlorhexidine is not lethal to acid-fast organisms[15]. It is not sporicidal, however may be sporicidal at elevated temperatures[16-18]. Some bacteria, e.g. strains of *Proteus* and *Providencia*, may be highly resistant to the CHX[19-21]. Chlorhexidine as an antiseptic shows comparable activity against *Staphylococcus aureus* strains susceptible to methicillin (MSSA) and strains resistant to methicillin (MRSA)[22,23]. Also in the case of both resistant to vancomycin strains of enterococci (VRE) and sensitive to vancomycin showed a comparable sensitivity to chlorhexidine[24]. In *ex vivo* studies have been shown effectiveness of CHX solution against *Actinomyces israelii* and *Enterococcus faecalis*[25-27] in infected root canal systems. Vianna et al[28] have investigated *in vitro* the antimicrobial activity of CHX against endodontic pathogens: *Enterococcus faecalis*, *Staphylococcus aureus* and *Candida albicans*. CHX eliminated also anaerobic periopathogens: *Porphyromonas endodontalis*, *Porphyromonas gingivalis*, and *Prevotella intermedia*. Agents containing chlorhexidine gluconate are effective against *Propionibacterium*, *Selenomonas* and *Serratia marcescens*[14,29]. Bacteriostatic activity of chlorhexidine against various microbial species is presented in Table I.

Table I. Bacteriostatic activity of chlorhexidine against various microorganisms (based on ref. 30-40).

Microorganism	Minimal inhibitory concentration (MIC) of chlorhexidine (µg/mL)
Staphylococcus aureus MSSA	0.25-8
Staphylococcus aureus MRSA	2-8
Enterococcus faecalis	4-16
Streptococcus mutans	0.9-4
Lactobacillus reuteri	0.125-4
Lactobacillus fermentum	0.25-1
Lactobacillus acidophilus	0.5-2
Porphyromonas gingivalis	0.9
Fusobacterium nucleatum	1.8
Escherichia coli	2-16
Klebsiella spp.	8-16
Pseudomonas aeruginosa	16-32
Candida albicans	1-16
Candida tropicalis	75
Candida krusei	150
Aspergillus spp.	8-64

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It was observed a correlation between the sensitivity of microorganisms to antibiotics and susceptibility to chlorhexidine. Resistance of Gram-negative bacteria for such antibiotics, as ciprofloxacin, imipenem, cefotaxime, ceftazidime, aztreonam and gentamicin, was accompanied the increase in resistance to chlorhexidine[41].

Chlorhexidine has activity against dermatophytes and yeasts. Sensitivity of fungi, both on growth inhibitory concentrations, and cidal concentrations is similar (e.g. *Candida albicans*) to the sensitivity of vegetative cells of bacteria or higher (e.g. *C. tropicalis*, *C. krusei*)[5,42-44]. Studies have shown that the use of mouthwash with 0.12% CHX for up to three months (with monthly interval during treatment) has both therapeutic effect in oral fungal infection and prevent the development of infections caused by *C. albicans* in HIV-infected children[45]. It has been observed that chlorhexidine affected *C. albicans* pathogenicity – inhibited filamentation, probably as the result of some enzyme inhibition[46]. Some studies have shown that yeast adhesion to epithelial cells was reduced after pretreatment of yeast with the CHX[47,48].

Under the influence of CHX are rapidly inactivated lipophilic viruses (e.g. herpes simplex virus, HIV, influenza virus, cytomegalovirus). Chlorhexidine like other antiseptics has no significant virucidal activity against small non-enveloped viruses (enteroviruses, polio viruses, papilloma viruses)[6]. Wood and Payne demonstrated inactivating effect of CHX on the enveloped viruses herpes simplex virus type 1 and human immunodeficiency virus type 1, whilst this substance were ineffective against enveloped human coronavirus, and the non-enveloped viruses[49].

Cytotoxic Activity to Human Cells

Many reports describe cytotoxic effect of chlorhexidine to human gingival fibroblasts[50,51], human periodontal ligament cells[52], human alveolar bone cells[53], and human osteoblastic cell line[54], which is time- and dose-dependent. Solution of 0.02% CHX presents high cytotoxicity, and lower concentrations of CHX: 0.0024% and 0.004% cause slight cytopathic effects to the odontoblast-like cells MDPC-23[55]. After exposing the odontoblast-like cells MDPC-23 to the CHX solutions at concentrations of 0.06%, 0.12%, 0.2%, 1% and 2%, and times 60 s, 2 h or 60 s with a 24-h recovery period has been demonstrated decrease in cell metabolism (MTT assay) and total protein concentration. The least cytotoxic to the cells was 60-s exposure time and the most toxic was exposure to CHX for 60 s with a 24-h recovery[56]. CHX also affects the change in the level of cellular ATP. Depletion of cell ATP occurs, in a time- and concentration-dependent manner, in concentrations of CHX > 0.001%. Concentrations ≥ 0.02% produces total loss of ATP in human dermal fibroblasts. At the same time, CHX concentrations ≥ 0.005% are required to produce total cell death[12]. Giannelli et al[54] showed that chlorhexidine is able in different cell types *in vitro* to cause alterations in actin cytoskeletal assembly, alter mitochondrial membrane potential, trigger intracellular Ca^{2+} increase and cause reactive oxygen species generation, and stimulate apoptosis and autophagic/necrotic cell death.

Application of Chlorhexidine

It has been shown that CHX is very effective as surgical hand antiseptic, to destroy transient microorganisms and inhibit the growth of resident microorganisms[4,57]. Preoperative skin preparation with 0.5% chlorhexidine in methylated spirits was associated with lower rates of surgical site infections (SSIs)[58]. Rubin et al[59] indicated that the intervention of bathing with CHX can reduce the number of hospital-acquired infections (HAIs). The reduction in HAIs using CHX was found to be greater as compared to bathing with soap and water. CHX is also used in obstetrics and gynecology. There is significant evidence that topical application of chlorhexidine to umbilical cord reduces neonatal mortality[60]. Simultaneously, CHX can be used for prevention of infection following caesarean section[61].

The most widely application CHX has found in dentistry. CHX is available as oral rinses, aerosols and spray formulations (0.12-0.2%), gels (0.12-1%) and dental varnishes (1%, 10%, 40%). CHX also can be found in toothpastes, gels for cleaning teeth and dental flosses[13,62]. Using of 0.12-0.2% concentrations of CHX in mouthwashes results in significant reduction of gingival inflammation and plaque indexes[63]. The chlorhexidine as well as chlorhexidine-sodium fluoride mouthwashes have a significant effect on inhibition of plaque accumulation and gingivitis[64-67]. Also, the application of chlorhexidine varnish have beneficial effects in gingivitis, reducing plaque accumulation, bleeding levels and gingival index[68,69]. Using of 0.12% chlorhexidine rinsing pre-operatively and 7 days postop-

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eratively, have significant and clinically relevant preventive effect on alveolar osteitis (dry socket) following surgical removal of lower third molars[70]. CHX is used also in prevention of tooth caries. It has inhibitory effect on the formation of dental plaque and acts against different species of *Streptococcus*, including *S. mutans* – main etiological agent of tooth caries[71,72]. Solutions containing different concentrations of CHX have been suggested for the irrigation of infected root canals[2,8,73]. CHX can also have impact in the treatment of halitosis, especially in reducing the levels of anaerobic bacteria related with halitosis[74].

Chlorhexidine is considered to be a effective drug in dentistry[6], but used for a long time (more than 2 weeks) in dental treatment most often causes discoloration of the teeth, tongue and fillings made of composite materials and glass-ionomer. Moreover, CHX can cause mucous membrane irritation and taste disturbance, but these symptoms are transient and disappear following termination of therapy[64,66,75].

Conclusions

Chlorhexidine is a cationic antiseptic. It is characterized by a wide range of antimicrobial activity, against Gram-positive and Gram-negative bacteria, some yeasts and some viruses. This antiseptic is widely used, especially in the prevention and treatment of the oral cavity diseases. CHX has a small number of side effects *in vivo*, including teeth and fillings colorization. However, more important is cytotoxic activity to human cells *in vitro*, which can stimulate apoptosis and autophagic/necrotic cell death. Cytotoxic activity of CHX to human cells *in vivo* is recently not fully known and requires further studies.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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Attachment 22.8

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Chapter 2

Types of antimicrobial agents

Suzanne L Moore and David N Payne

(b)(4)

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Attachment 22.9

Oliveira dos Santos, et al. "In vitro activity of chlorhexidine compared with seven antifungal agents against 98 Fusarium isolates recovered from fungal keratitis patients" Antimicrobial Agents and Chemotherapy 63(8), 1-7.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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SUSCEPTIBILITY

In Vitro Activity of Chlorhexidine Compared with Seven Antifungal Agents against 98 *Fusarium* Isolates Recovered from Fungal Keratitis Patients

Claudy Oliveira dos Santos,[a,b,c] Eva Kolwijck,[a,b] Henrich A. van der Lee,[a,b] Marlou C. Tehupeiory-Kooreman,[a,b] Abdullah M. S. Al-Hatmi,[b,d,e] Einoti Matayan,[f] Matthew J. Burton,[g] Cathrien A. Eggink,[h] Paul E. Verweij[a,b]

[a]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands
[b]Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands
[c]Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[d]Westerdijk Fungal Biodiversity Institute, Utrecht, The Netherlands
[e]Directorate General of Health Services, Ministry of Health, Ibri Hospital, Ibri, Oman
[f]Department of Ophthalmology, Kilimanjaro Christian Medical Center, Moshi, Tanzania
[g]International Center for Eye Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
[h]Department of Ophthalmology, Radboud University Medical Center, Nijmegen, The Netherlands

ABSTRACT Fungal keratitis is a common but severe eye infection in tropical and subtropical areas of the world. In regions with a temperate climate, the frequency of infection is rising in patients with contact lenses and following trauma. Early and adequate therapy is important to prevent disease progression and loss of vision. The management of *Fusarium* keratitis is complex, and the optimal treatment is not well defined. We investigated the *in vitro* activity of chlorhexidine and seven antifungal agents against a well-characterized collection of *Fusarium* isolates recovered from patients with *Fusarium* keratitis. The fungus culture collection of the Center of Expertise in Mycology Radboudumc/CWZ was searched for *Fusarium* isolates that were cultured from cornea scrapings, ocular biopsy specimens, eye swabs, and contact lens fluid containers from patients with suspected keratitis. The *Fusarium* isolates that were cultured from patients with confirmed keratitis were all identified using conventional and molecular techniques. Antifungal susceptibility testing was performed according to the EUCAST broth microdilution reference method. The antifungal agents tested included amphotericin B, voriconazole, posaconazole, miconazole, natamycin, 5-fluorocytosine, and caspofungin. In addition, the activity of chlorhexidine was determined. The fungal culture collection contained 98 *Fusarium* isolates of confirmed fungal keratitis cases from 83 Dutch patients and 15 Tanzanian patients. The isolates were collected between 2007 and 2017. *Fusarium oxysporum* ($n = 24$, 24.5%) was the most frequently isolated species followed by *Fusarium solani sensu stricto* ($n = 18$, 18.4%) and *Fusarium petroliphilum* ($n = 11$, 11.2%). Amphotericin B showed the most favorable *in vitro* inhibition of *Fusarium* species followed by natamycin, voriconazole, and chlorhexidine, while 5-fluorocytosine, posaconazole, miconazole, and caspofungin showed no relevant inhibiting effect. However, chlorhexidine showed fungicidal activity against 90% of *F. oxysporum* strains and 100% of the *F. solani* strains. Our study supports the clinical efficacy of chlorhexidine and therefore warrants its further clinical evaluation for primary therapy of fungal keratitis, particularly in low and middle income countries where fungal keratitis is much more frequent and, currently, antifungal eye drops are often unavailable.

KEYWORDS *Fusarium*, antifungal susceptibility testing, keratitis, microbiology, mycology

Citation Oliveira dos Santos C, Kolwijck E, van der Lee HA, Tehupeiory-Kooreman MC, Al-Hatmi AMS, Matayan E, Burton MJ, Eggink CA, Verweij PE. 2019. *In vitro* activity of chlorhexidine compared with seven antifungal agents against 98 *Fusarium* isolates recovered from fungal keratitis patients. Antimicrob Agents Chemother 63:e02669-18. https://doi.org/10.1128/AAC.02669-18.

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Address correspondence to Claudy Oliveira dos Santos, claudy.oliveiradossantos@radboudumc.nl.

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Fungal keratitis is a common eye infection in tropical and subtropical areas of the world. In regions with a temperate climate, fungal keratitis is uncommon but mainly reported in patients with contact lenses and following trauma. Early therapy is important to prevent disease progression or dissemination. A major complication of fungal keratitis is monocular blindness, especially in tropical low and middle income countries (LMIC), where significant delay in diagnosis and simply the unavailability of antifungals are common. Most cases of fungal keratitis are caused by *Fusarium* species (1, 2), which are ubiquitous fast-growing hyalohyphomycetes that are present in soil, water, and plants. The most common route of infection is by (micro)trauma or disruptive ocular surface disease, as filamentous fungi are unable to penetrate intact cornea.

The taxonomy of the *Fusarium* order is complex and still not well defined. Molecular techniques have shown that the common medically relevant species, *Fusarium solani* and *Fusarium oxysporum*, consist of multiple (sub)species (3). Although *in vitro* antifungal susceptibility patterns of *Fusarium* species may vary greatly within each species, most species show high MICs to the currently licensed antifungals (4–7). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has not defined epidemiological cutoff (ECOFF) values and clinical breakpoints for *Fusarium* species. In 2015, Espinel-Ingroff et al. published epidemiological cutoff values (ECVs) based on the Clinical and Laboratory Standards Institute (CLSI) broth dilution method for antifungal susceptibility testing (AFST) (8). As topical antifungal therapy is important for fungal keratitis management, a meaningful classification of isolates as resistant or susceptible is challenging. These factors complicate the management of *Fusarium* keratitis (9), and the optimal treatment is not well defined.

Currently, a 0.02% chlorhexidine solution is used for the treatment of *Acanthamoeba* keratitis. A few studies have indicated that the disinfectant chlorhexidine might be an effective, affordable, and accessible treatment for fungal keratitis, which could benefit millions of people who currently have no options (10, 11). The meta-analysis in the Cochrane systematic review written by FlorCruz and Evans show that chlorhexidine has a better clinical outcome than natamycin and voriconazole (12). To our knowledge, there are no published data describing the MICs of chlorhexidine for *Fusarium* species. In this study, we investigated the *in vitro* activity of chlorhexidine and seven antifungal agents against a molecularly characterized set of *Fusarium* isolates recovered from patients with keratitis.

RESULTS

The fungal culture collection contained 98 *Fusarium* isolates from 83 patients with keratitis from the Netherlands and 15 with keratitis from Tanzania. The isolates were collected between 2007 and 2017. The first *Fusarium* isolate per patient was tested.

Molecular identification showed that *F. oxysporum* ($n = 24$, 24.5%) was the most frequently isolated species followed by *F. solani sensu stricto* ($n = 18$, 18.4%) and *Fusarium petroliphilum* ($n = 11$, 11.2%). Based on the assignment of the isolates to the according species complex, as described by Salah et al. (3), the most frequently encountered complexes were *F. solani* species complex (FSSC; $n = 43$, 43.9%), *F. oxysporum* species complex (FOSC; $n = 24$, 24.5%), *Fusarium fujikuroi* species complex (FFSC; $n = 16$, 16.3%) and *Fusarium dimerum* species complex (FDSC; $n = 12$, 12.2%). One isolate could not be assigned to any species complex or species and appears to be a new *Fusarium* species.

The MIC distributions for the various species and species complexes are shown in Tables 1 and 2. *In vitro* amphotericin B was the most active antifungal drug followed by natamycin, voriconazole, posaconazole, and miconazole. Chlorhexidine showed activity against all species at a concentration of 8 to 32 mg/liter, which corresponds with 1.56×10^{-3}% to 6.25×10^{-3}%. 5-Fluorocytosine showed no *in vitro* activity.

Statistics. The median MICs and the MIC distributions of 5-fluorocytosine and caspofungin showed no differences between any of the groups.

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TABLE 1 Molecularly identified *Fusarium* keratitis isolates and their susceptibility profiles to eight antifungal agents, including chlorhexidine and natamycin

	MIC (%) (median [range])	MIC (mg/liter) (median [range])[a]							MEC[b] mg/liter (median [range])
Fusarium species (*n*)	CHX	CHX	AMB	VCZ	5-FC	MCZ	NAT	POS	CAS[c]
Fusarium species (1)	0.003	16	0.5	2	32	16	8	16	16
F. falciforme (7)	0.006 (0.002–0.006)	32 (8–32)	2 (1–8)	16 (8–16)	>32 (>32)	16 (16)	8 (8–16)	16 (16)	16 (16)
F. keratoplasticum (7)	0.003 (0.002–0.006)	16 (8–32)	4 (2–4)	8 (4–16)	>32 (>32)	16 (16)	4 (4–8)	16 (16)	16 (0.5–16)
F. petroliphilum (11)	0.003 (0.002–0.006)	16 (8–32)	2 (0.5–4)	8 (4–16)	>32 (>32)	16 (16)	4 (4–8)	16 (16)	16 (2–16)
F. solani (18)	0.006 (0.002–0.006)	32 (8–32)	2 (0.063–16)	8 (4–16)	>32 (>32)	16 (8–16)	8 (4–16)	16 (8–16)	16 (4–32)
F. oxysporum (24)	0.002 (0.0002–0.012)	8 (1–64)	2 (0.25–16)	4 (2–16)	32 (0.063–32)	16 (16)	8 (4–8)	16 (16)	16 (0.063–32)
F. musae (1)	0.003	16	2	4	>32	8	8	1	16
F. verticillioides (3)	0.003 (0.001–0.003)	16 (4–16)	2 (1–8)	2 (1–2)	>32 (>32)	1 (0.25–8)	8 (2–8)	0.5 (0.25–1)	16 (16)
F. proliferatum (7)	0.002 (0.001–0.012)	8 (4–64)	2 (1–4)	4 (2–8)	>32 (>32)	16 (16)	8 (4–8)	4 (2–16)	16 (16)
F. ramigenum (1)	0.003	16	4	1	>32	16	4	1	16
F. sacchari (1)	0.002	8	2	1	>32	4	8	0.25	16
F. lactis (3)	0.002 (0.002–0.003)	8 (8–16)	2 (0.5–4)	4 (2–8)	>32 (>32)	16 (16)	8 (8)	16 (2–16)	16 (16)
F. equiseti (1)	NP[d]	NP	1	8	NP	NP	NP	16	32
F. dimerum (8)	0.002 (0.002–0.003)	8 (8–16)	1 (0.5–2)	8 (4–8)	>32 (>32)	16 (16)	4 (4–16)	16 (16)	16 (2–16)
F. delphinoides (4)	0.001 (0.001–0.002)	4 (4–8)	0.5 (0.125–1)	2 (2)	>32 (>32)	16 (16)	4 (2–4)	8 (1–16)	16 (2–16)
F. ambrosium (1)	0.006	32	2	16	>32	16	8	16	1

[a]CHX, chlorhexidine; AMB, amphotericin B; VCZ, voriconazole; 5FC, 5-fluorocytosine; MCZ, miconazole; NAT, natamycin; POS, posaconazole.
[b]MEC, minimal effective concentration.
[c]CAS, caspofungin.
[d]NP, susceptibility testing for this antifungal agent was not performed.

The MIC distributions of amphotericin B showed significant differences between the species complexes (Kruskal Wallis test, $P = 0.002$). FDSC differed significantly from FSSC and from FFSC.

For voriconazole, the median MICs and the MIC distributions showed significant differences between the species complexes ($P = 0.006$ and $P = 0.000$, respectively, Kruskal Wallis test). FSSC differed significantly from FOSC, from FFSC, and from FDSC.

The MIC distributions of posaconazole and miconazole showed significant differences between the species complexes ($P = 0.000$ and $P = 0.001$, respectively, Kruskal Wallis test). For posaconazole and miconazole, FFSC differed significantly from FSSC and from FOSC.

The median MICs of natamycin were not different between the species complex (SC) groups ($P = 0.747$, Kruskal-Wallis). On the other hand, the MIC distributions of natamycin differed significantly between the species complexes ($P = 0.015$, Kruskal Wallis test). FDSC differed significantly from FSSC, from FOSC, and from FFSC.

The median MICs and the MIC distributions of chlorhexidine showed significant differences between the species complexes ($P = 0.000$ and $P = 0.000$, respectively, Kruskal Wallis test). FSSC differed significantly from FOSC, from FFSC, and from FDSC.

TABLE 2 *Fusarium* keratitis isolates assigned according to the species complex and their susceptibility profile to eight antifungal agents, including chlorhexidine and natamycin

	MIC (%) (median [range])	MIC (mg/liter) (median [range])[b]							MEC[c] mg/liter (median [range])
Fusarium species complex (*n*)[a]	CHX	CHX	AMB	VCZ	5-FC	MCZ	NAT	POS	CAS[d]
Unknown (1)	0.003	16	0.5	2	32	16	8	16	16
FSSC (43)	0.003 (0.002–0.006)[e]	16 (8–32)	2 (0.063–16)	8 (4–16)[e]	>32 (>32)	16 (8–16)	8 (4–16)	16 (8–16)	16 (0.5–32)
FOSC (24)	0.002 (0.002–0.012)	8 (2–64)	2 (0.25–16)	4 (2–16)	32 (0.063–32)	16 (16)	8 (4–8)	16 (16)	16 (0.063–32)
FFSC (16)	0.002 (0.001–0.012)	8 (4–64)	2 (0.5–8)	4 (1–8)	>32 (>32)	16 (0.25–16)[e]	8 (2–8)	2 (0.25–16)[e]	16 (16)
FIESC (1)	NP[f]	NP	1	8	NP	NP	NP	16	32
FDSC (12)	0.002 (0.0008–0.003)	8 (4–16)	1 (0.125–2)[e]	8 (2–8)	>32 (>32)	16 (16)	4 (2–16)[e]	16 (1–16)	16 (2–16)
AFC (1)	0.006	32	2	16	>32	16	8	16	1

[a]FSSC, *F. solani* species complex; FOSC, *F. oxysporum* species complex; FFSC, *F. fujikuroi* species complex; FIESC, *F. incarnatum-equiseti* species complex; FD5C, *F. dimerum* species complex; AFC, Ambrosia *Fusarium* clade.
[b]CHX, chlorhexidine; AMB, amphotericin B; VCZ, voriconazole; 5FC, 5-fluorocytosine; MCZ, miconazole; NAT, natamycin; POS, posaconazole.
[c]MEC, minimal effective concentration.
[d]CAS, caspofungin.
[e]Significant difference of the median and or distribution range between the groups of species complex.
[f]NP, susceptibility testing for this antifungal agent was not performed.

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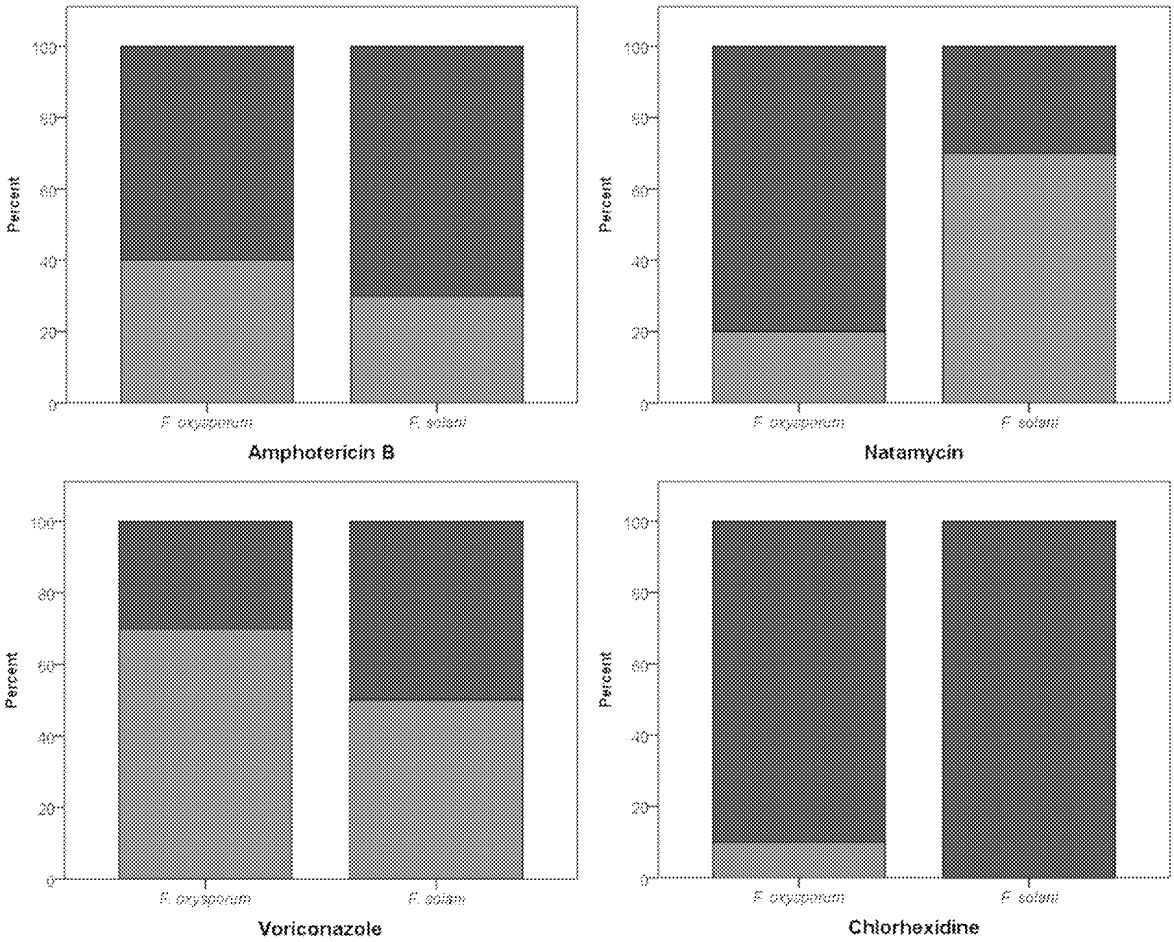


FIG 1 The proportions of fungicidal (blue) and fungistatic (green) *in vitro* effects of amphotericin B, natamycin, voriconazole, and the disinfectant chlorhexidine depicted for *Fusarium oxysporum* ($n = 10$) and *Fusarium solani* ($n = 10$), all of which were isolated from patients with fungal keratitis.

MIC values of posaconazole, miconazole, 5-fluorocytosine, and caspofungin were high, and so determining the minimal fungicidal concentration (MFC) of these agents was deemed clinically not relevant.

In vitro amphotericin B exhibited fungicidal effect on 60% of the *F. oxysporum* strains and 70% of the *F. solani* strains; the remainder of the strains showed a fungistatic effect (Fig. 1). Natamycin was fungicidal against 80% of the *F. oxysporum* strains. However, in *F. solani* strains, natamycin was mostly fungistatic; in only 30%, it acted as a fungicidal. Voriconazole was fungicidal against 30% of the *F. oxysporum* strains and 50% of the *F. solani* strains. Chlorhexidine showed fungicidal activity against 90% of *F. oxysporum* strains and 100% of the *F. solani* strains.

DISCUSSION

Chlorhexidine showed broad *in vitro* activity against all *Fusarium* species tested and, compared with the antifungal agents, showed the broadest fungicidal activity against the two species tested. Although it is likely that chlorhexidine is fungicidal in other *Fusarium* species, this was not tested. For chlorhexidine, 95% of the 20 *Fusarium* isolates were killed at concentrations far below the 0.02% and 0.2% concentrations, of which, the 0.02% concentration for eye drops is already commonly used by ophthalmologists for treatment of *Acanthamoeba* keratitis. Another important advantage of chlorhexidine gluconate solution is the broad antimicrobial spectrum, including against Gram-positive and Gram-negative bacteria, lipid-enveloped viruses, and *Acanthamoeba* (12, 13).

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A limited number of clinical trials have studied the effectiveness of chlorhexidine gluconate for the treatment of fungal keratitis. The aim of one trial was to find the most effective dose of chlorhexidine (14). In comparison to the response with natamycin, the relative efficacy in a patient without prior antifungal treatment was 1.17 with chlorhexidine 0.05%, 1.43 with chlorhexidine 0.1%, and 2.00 with chlorhexidine 0.2%. Their fungal isolates were not subjected to molecular identification and susceptibility testing. The second study by Rahman et al. (10) showed a relative efficacy of 1.85 (confidence interval [CI], 1.01 to 3.39; $P = 0.04$) with chlorhexidine 0.2% in comparison to natamycin. Of the nonsevere ulcers, 66.7% were healed at day 21 with chlorhexidine and 36.0% with natamycin. However, this trial was not double blinded due to the fact that personnel could identify the selected treatment because the solutions of chlorhexidine and natamycin were visibly different (10). The susceptibility testing was performed with a nonreference well diffusion method (0.2% chlorhexidine, 2.5% natamycin, 1% econazole). The concentration of natamycin used was 2.5%, which is half the current standard therapeutic concentration of 5%. In addition, the method of identification of the strains was also not mentioned.

In the Netherlands, the available antifungal agents which can be used as eye drops are amphotericin B 0.15% (1,500 mg/liter), voriconazole 1% (10,000 mg/liter), and the disinfectant chlorhexidine 0.02% (200 mg/liter). These formulas are not commercially available but are prepared by hospital pharmacists on request. In other countries, natamycin (5% suspension; 50,000 mg/liter) is available and frequently used in the setting of fungal keratitis (2, 10–12, 15–20). These concentrations exceed by far the *in vitro* determined MICs of the *Fusarium* isolates (Tables 1 and 2). However, effectiveness depends on many factors, including the ability of the compound to penetrate ocular tissues, local bioavailability, and drug toxicity.

The most important route of penetration of topical antifungals into ocular tissue is through the cornea, mostly by diffusion. The polyenes, amphotericin B and natamycin, are compounds with a high molecular mass (i.e., >500 Da) and, as a consequence, barely penetrate intact cornea epithelium (21). This leads to the necessity of regularly performing abrasions of the cornea during treatment with amphotericin B. In high doses, amphotericin B can be toxic to the cornea, but the 0.15% solution is well tolerated (21). Due to the viscous nature of natamycin suspension and its poor penetration, it is only suitable for treatment of superficially located keratomycosis. Furthermore, compounds that are lipophilic can penetrate across the corneal stroma, while hydrophilic agents are able to penetrate all the layers of the cornea.

There is little known about the corneal penetration of the cationic antisepticum chlorhexidine gluconate. In a small animal study, Vontobel et al. showed that the compound did not penetrate through the intact or mechanically damaged cornea into the anterior chamber (22). It appears that chlorhexidine accumulates within the cornea, explaining the need to treat deep-seated *Acanthamoeba* for a long time.

Amphotericin B showed the most favorable *in vitro* inhibition of *Fusarium* species, followed by natamycin, voriconazole, and chlorhexidine, while 5-fluorocytosine, posaconazole, miconazole, and caspofungin showed no relevant inhibiting effect. However, chlorhexidine showed fungicidal activity against 90% of *F. oxysporum* strains and 100% of the *F. solani* strains.

The differences in AFST between isolates belonging to the same species complex justifies conducting molecular identification to the species complex level. In general, the species belonging to the FDSC and the FFSC are more susceptible to chlorhexidine, amphotericin B, natamycin, voriconazole, and posaconazole (only FFSC). These differences cannot be predicted by identification based on conventional methods, because the characteristics of morphology and microscopy are not species specific.

Our study supports the clinical efficacy of chlorhexidine and therefore warrants its further clinical evaluation for primary therapy of fungal keratitis, particularly in LMIC where fungal keratitis is much more frequent and, currently, antifungal eye drops are often unavailable. Further studies should investigate the *in vitro* interaction of chlo-

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rhexidine with antifungal agents to support alternate administration and combination therapy.

MATERIALS AND METHODS

The fungus culture collection of the Center of Expertise in Mycology Radboudumc/CWZ was searched for *Fusarium* isolates that were cultured from cornea scrapings, ocular biopsy specimens, eye swabs, and contact lens fluid containers from patients with suspected keratitis. All isolates had been identified to the genus level using conventional techniques. For accurate species identification, sequencing of the *TEF1* gene was performed (3).

Antifungal susceptibility testing was performed according to the EUCAST broth microdilution reference method (23, 24). The antifungal agents tested included amphotericin B (Bristol Myers Squibb), voriconazole (Pfizer), posaconazole (Merck & Co), miconazole (Janssen Cilag), natamycin (Sigma-Aldrich), 5-fluorocytosine (Hoffman la Roche), and caspofungin (Merck & Co). In addition, the activity of chlorhexidine (Pharmaline) was determined. The test range of the antifungal agents was 0.02 to 16 mg/liter for amphotericin B, voriconazole, posaconazole, miconazole, caspofungin, and natamycin, and 0.03 to 32 mg/liter for 5-fluorocytosine. For chlorhexidine, a concentration range of 1 to 1,024 mg/liter was used, which corresponds to a range of 0.000195% to 0.2%. All antifungal agents and chlorhexidine were dissolved in RPMI 1640 supplemented with glucose to a final concentration of 2%. The MICs were determined with an inverted mirror after 48 h at 35°C as the lowest drug concentration with complete inhibition of growth visible by eye for amphotericin B, voriconazole, posaconazole, miconazole, natamycin, 5-fluorocytosine, and chlorhexidine. The endpoint for echinocandins was the minimal effective concentration (MEC). The MEC for caspofungin was determined with an inverted microscope after 48 h at 35°C as the lowest drug concentration in which abnormal, short, and branched hyphal clusters were observed in contrast to the long, unbranched, elegant hyphal elements that were visible in the growth control well. *Aspergillus fumigatus* ATCC 204305 and *Aspergillus flavus* ATCC 204304 were used as quality control strains as recommended by the EUCAST (23).

Ten *F. oxysporum* and 10 *F. solani* isolates were used to determine the minimal fungicidal concentration (MFC) for the antifungal agents and chlorhexidine. After reading the MICs at 48 h, the 96-wells plates were shaken to loosen the fungal elements. Thereafter, 20 μl from all the wells with no visible growth and 20 μl from the growth control were plated on Sabouraud agar (Oxoid). The plates were incubated for 24 and 48 h at 35°C. The MFC was determined as the lowest drug concentration which led to 99% to 99.5% growth inhibition compared to the growth control. Antifungal agents were considered fungicidal when the MIC value was no more than two dilution steps lower than the MFC (25). If the difference between MIC and MFC was >2 dilution steps, the antifungal agent was classified as fungistatic (25).

Statistical analysis was performed with IBM SPSS Statistics 24. *In vitro* susceptibility differences between *Fusarium* species and differences between species complexes were tested with a nonparametric test (one-way analysis of variance [ANOVA], Kruskal-Wallis). A P value of <0.05 was determined as significant. To correct for multitesting in the search for which groups differed from each other, the P value was adjusted according to Bonferroni's correction method (e.g., significance level [<0.05] divided by the number of tests needed). Bonferroni's correction for the species groups was a P value of <0.0011; for the species complex groups, Bonferroni's P value was <0.0083. Species and species complexes with only one isolate where not taken into account in the statistical analysis. For every antifungal or antiseptic agent, we tested for significant differences between the species complexes by comparing the median MICs or percentages of the concentration and comparing the distributions between the groups. After this comparison, the groups which were responsible for the significant difference were determined by comparing one group to another group with the Mann-Whitney U test.

The samples from Dutch participants were collected during the routine standard of care. Therefore, we did not need their informed consent in accordance with the Dutch Ethics Committee of the Radboud University Medical Center.

The collection of samples from Tanzanian participants was approved by the Ethics Committees of the National Institute for Medical Research, Tanzania, and the London School of Hygiene & Tropical Medicine, United Kingdom. Informed consent was obtained from all participants.

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C.O.D.S. performed susceptibility testing, collected the data, and drafted the manuscript. E.K. reviewed the manuscript from the microbiological point of view. H.A.V.D.L. and M.C.T.-K. performed susceptibility testing and reviewed the manuscript from the microbiological point of view. A.M.S.A.-H. performed the molecular identification of the *Fusarium* strains and reviewed the manuscript. E.M. and M.J.B. collected the *Fusarium* strains from Tanzania and reviewed the manuscript from the clinical point of view. C.A.E. reviewed the manuscript from the clinical point of view. P.E.V. reviewed the manuscript from the microbiological point of view and helped with editing the manuscript. All authors have read and approved the final and submitted manuscript.

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Attachment 22.10

Hsiao CR et al. Identification of medically important molds by an oligonucleotide array. J Clin Microbiol. 2005 Aug;43(8):3760-8. doi: 10.1128/JCM.43.8.3760-3768.2005. PMID: 16081907; PMCID: PMC1233923.

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Identification of Medically Important Molds by an Oligonucleotide Array†

Chen Ren Hsiao,[1] Liyin Huang,[1] Jean-Philippe Bouchara,[2] Richard Barton,[3] Hsin Chieh Li,[1] and Tsung Chain Chang[1]*

Department of Medical Laboratory Science and Biotechnology, School of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China[1]; Host-Parasite-Interaction Study Group (UPRES-EA 3142), Laboratory of Parasitology and Mycology, University Hospital, Angers, France[2]; and School of Biochemistry and Microbiology, University of Leeds, United Kingdom[3]

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Infections caused by fungi have increased in recent years. Accurate and rapid identification of fungal pathogens is important for appropriate treatment with antifungal agents. On the basis of the internal transcribed spacer 1 (ITS 1) and ITS 2 sequences of the rRNA genes, an oligonucleotide array was developed to identify 64 species (32 genera) of clinically important filamentous (or dimorphic) fungi. These 64 species included fungi causing superficial, cutaneous, subcutaneous, and invasive infections. The method consisted of PCR amplification of the ITS regions using a pair of universal primers, followed by hybridization of the digoxigenin-labeled PCR products to a panel of species- or group-specific oligonucleotides immobilized on a nylon membrane. Of 397 fungal strains (290 target and 107 nontarget strains) tested, the sensitivity and specificity of the array was 98.3% (285/290) and 98.1% (105/107), respectively. Misidentified strains were usually those belonging to the same genus of the target species or having partial homology with oligonucleotide probes on the membrane. The whole procedure can be finished within 24 h starting from isolated colonies; reproductive structures, which are essential for the conventional identification methods, are not needed. In conclusion, the present array is a powerful tool for identification of clinically important filamentous fungi and may have the potential to be continually extended by adding further oligonucleotides to the array without significantly increasing the cost or complexity.

The identification of molds (filamentous fungi) can be challenging, and accuracy will depend on the organism and the experience of the clinical microbiologist (20). Conventional methods for fungal identification in the clinical laboratory are based on morphological and physiological tests. These methods often require several days or even weeks and may be inaccurate (30). In the last few decades, invasive mycoses have become a major cause of infectious morbidity and mortality in patients receiving immunosuppressive chemotherapy for cancer or organ transplantation and in immunodeficient patients, such as individuals with AIDS (2, 3, 9, 14, 33). Since invasive mycoses are often associated with a poor prognosis, the early, rapid, and accurate identification of the pathogenic fungi is important for timely and appropriate management.

In recent years, numerous DNA-based methods have been developed to diagnose mycotic infections and to identify pathogenic fungi (6). PCR methods are particularly promising because of their simplicity, specificity, and sensitivity. Genes of the 18S rRNA (27, 41, 47) and 28S rRNA (15, 28, 38) have been extensively used for molecular identification. Recently, Hall et al. (20) evaluated the commercial MicroSeq D2 large-subunit rRNA gene fungal sequencing kit (Applied Biosystems, Foster City, Calif.) and drew the conclusion that the kit offers the promise of being an accurate identification system. However, they noted that 33% of clinical isolates could not be identified due to a limited sequence database in this commercial system. In addition, the MicroSeq kit requires an automatic sequencer, which is not yet standard equipment for most clinical microbiology laboratories. A number of studies have described probes, restriction fragment length polymorphism, or other methods to identify unique ribosomal DNA sequences (26, 35, 44). Although these published methods are useful for the identification of fungal species, they can identify only one or a limited number of species. The ribosomal internal transcribed spacer (ITS) regions also have been widely used as targets to detect and identify human fungal pathogens (5, 7, 10, 21, 23, 24, 31–33, 43).

DNA array (or DNA chip) technology has been found to be a useful tool to identify a variety of bacteria, especially for those bacteria that are difficult to differentiate by conventional methods or when the identification procedures may take a long time (1, 17, 45). Wu et al. (47) recently developed an array of oligonucleotide probes to detect airborne fungi. The probes were designed on the basis of the 18S rRNA gene and were used to detect 31 species belonging to 15 genera. The aim of this study was to investigate the feasibility of using a panel of oligonucleotide probes designed on the basis of the ITS regions to identify 64 mold species (32 genera) of clinical importance.

* Corresponding author. Mailing address: Department of Medical Laboratory Science and Biotechnology, School of Medicine, National Cheng Kung University, 1 University Road, Tainan 701, Taiwan, Republic of China. Phone: 886-6-2353535, ext. 5790. Fax: 886-6-2363956. E-mail: tsungcha@mail.ncku.edu.tw.

† Supplemental material for this article may be found at http://jcm.asm.org.

MATERIALS AND METHODS

Fungal strains. A total of 397 strains including 290 target (64 species) and 107 nontarget strains were used (see Table S1 in the supplemental material) (sup-

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plemental Table S1 and supplemental Fig. S2 from this study are supplied as supplemental files). Of the 290 target strains, 233 were reference strains obtained from culture collection centers and 57 were clinical isolates. Of the 107 nontarget strains, 93 were reference strains and 14 were clinical isolates. Reference strains were obtained from the American Type Culture Collection (Manassas, Va.), Bioresources Collection and Research Center (BCRC, Hsichu, Taiwan, Republic of China), and CBS (Centraalbureau voor Schimmelcultures, The Netherlands). Clinical isolates were obtained from the Mycology Reference Centre, Division of Microbiology University of Leeds, Leeds, UK (strain designated with a prefix of LM), and from the Laboratory of Parasitology and Mycology of Angers University Hospital (Angers, France) (strain designated with a prefix of LMA). Morphological identification of clinical isolates to the species level was accomplished using established procedures including microscopic and macroscopic characteristics (11, 30). All fungal strains were subcultured on Sabouraud dextrose agar (Difco, Detroit, Mich.), incubated at 30°C until there was evidence of apparent hyphal growth, and then used for DNA extraction.

DNA extraction. Mycelium (approximately 0.5 × 0.5 cm) was scraped into a 2-ml screw cap tube (Azygen Sientific, Union City, Calif.) containing 300 mg of 0.5-mm-diameter zirconium/silica beads (Biospec Products, Bartlesville, Okla.) in 1 ml of sterilized water using an inoculation loop. The mycelial suspension was shaken for 5 min at a speed of 4,200 rpm in a mechanical cell disrupter (Mini-Beadbeater, Biospec Products). An aliquot (0.1 ml) of the disrupted cell suspension was transferred to a 1.5-ml centrifuge tube and centrifuged at 8,000 × *g* for 10 min in a microcentrifuge. Fungal DNA in the supernatant was extracted by a genomic DNA extraction kit (Viogene, Taipei, Taiwan).

ITS amplification and sequencing. The ITS sequences of some species that were not available in the database of GenBank were determined in this study (see Table S1 in the supplemental material). The fungus-specific, universal primers ITS 1 (5′-TCCGTAGGTGAACCTGCGG-3′) and ITS 2 (5′-GCTGCGTT CTTCATCGATGC-3′) (46) were used to amplify a small conserved portion of the 18S ribosomal DNA, the adjacent ITS 1, and a small portion of the 5.8S ribosomal DNA. An additional pair of primers, ITS 3 (5′-GCA TCGATGAAG AACGCAGC-3′) and ITS 4 (5′-TCCTCCGCTTATTGATATGC-3′) (46), were used to amplify a conserved portion of the 5.8S ribosomal DNA, the intervening ITS 2, and a small portion of the 28S ribosomal DNA. PCR was performed with 5 μl (1 to 5 ng) of template DNA in a total reaction volume of 50 μl consisting of 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.8 mM deoxyribonucleoside triphosphates (0.2 mM each), 0.7 μM primer (each), *Taq* DNA polymerase (1.25 U), and 50 μl of a mineral oil overlay. PCR was carried out with an OmniGen thermal cycler (Hybaid Limited, Middlesex, UK) under the following conditions: initial denaturation, 94°C, 3 min; 35 cycles of denaturation (94°C, 1 min), annealing (60°C, 1 min), and extension (72°C, 1 min); and final extension, 72°C, 5 min. A negative control was performed with each test run by replacing the template DNA with sterilized water in the PCR mixture. PCR products were purified with a PCR-M CleanUp kit (Viogene, Taipei, Taiwan) and were sequenced on a model 377 sequencing system (Applied Biosystems, Taipei, Taiwan).

To amplify the ITS regions for array hybridization, the primer pair ITS 1 (5′-TCCGTAGGTGAACCTGCGG-3′) and ITS 4 (5′-TCCTCCGCTTATTGA TATG-3′) (46) was used to amplify a fragment encompassing ITS 1, the 5.8S rRNA gene, ITS 2, and partial regions of the 18S and 28S ribosomal DNA. The reverse primer ITS 4 was labeled with a digoxigenin molecule at its 5′ end and was synthesized by MDBio Inc. (Taipei, Taiwan). PCR conditions were the same as described in the previous section. DNA extracted from *Saccharomycodes ludwigii* BCRC 21378 was used as a positive control for each run of PCR and array hybridization.

Design of oligonucleotide probes. Species- or group-specific oligonucleotide probes (21- to 30-mers) used for identification of 64 fungal species are listed in Table 1. Probe design was based on sequence data from the ITS 1 or 2 regions; these sequences were either available in the GenBank database or determined in this study. Probe selection was facilitated by using visual sequence alignment employing the PrettyBox command of the Wisconsin Genetics Computer Group package (version 10.3; Accelrys Inc., San Diego, Calif.). Areas displaying sequence divergence among different species were analyzed for probe selection. A total of 58 probes, including one positive control (a probe designed on the basis of the ITS 2 region of *Saccharomycodes ludwigii* BCRC 21378), were used for fabrication of the oligonucleotide array (Table 1). The designed probes were checked for internal repeat, self-biding, secondary structure, and GC content by using Vector NTI software (Invitrogen Corporation, Carlsbad, Calif.). Seven additional bases of thymine were added to the 3′ end of each probe (4). The specificity of the prospective sequence was first analyzed with a fungal ITS database developed in our laboratory and with sequences available in the GenBank using BLAST.

Fabrication of oligonucleotide arrays. The arrays (1.1 by 0.9 cm) (Fig. 1) were made in batches of 20. The oligonucleotide probes were diluted 1:1 (final concentration 10 μM) with a tracking dye solution (30% [vol/vol] glycerol, 40% [vol/vol] dimethyl sulfoxide, 1 mM disodium EDTA, 0.15% [wt/vol] bromophenol blue, and 10 mM Tris-HCl, pH 7.5). The probe solutions were drawn into different wells of a round-bottom 96-well microtiter plate and spotted onto a positively charged nylon membrane (Roche, Mannheim, Germany) with an automatic arrayer (Wittech, Taipei, Taiwan) using a solid pin (500 μm in diameter). The array contained 80 dots, including 58 dots for identification of 64 medically relevant molds (32 genera), 1 for positive control (probe code PC), and 5 for negative controls (probe code NC; tracking dye only) (Fig. 1). In addition, 16 dots (probe code M) contained 5′-digoxigenin-labeled ITS 4 (final concentration 0.16 μM); these dots formed a cross on the array after hybridization and were used as markers to visually locate hybridized probes (see Fig. S2 in the supplemental material). Once all probes had been applied, the membrane was air-dried and exposed to shortwave UV (Stratalinker 1800; Stratagen, La Jolla, Calif.) for 30 s. Unbound oligonucleotides were removed by two washes (2 min each) at room temperature in 0.5× SSC (1× SSC is 0.15 M NaCl plus 0.015 M sodium citrate)–0.1% sodium dodecyl sulfate (SDS). The arrays were stored at room temperature for further use.

Hybridization procedures. Except where otherwise indicated, the hybridization procedures were carried out at room temperature (approximately 27°C) with a shaking speed of 60 rpm. Most reagents, except buffers, were included in the DIG Nucleic Acid Detection kit (catalog no. 1175041; Roche). Each array was prehybridized at 50°C for 2 h with 1 ml of hybridization solution (5× SSC, 1% [wt/vol] blocking reagent, 0.1% *N*-laurylsarcosine, 0.02% SDS) in an individual well of a 24-well cell culture plate. The digoxigenin-labeled PCR product amplified from an isolate was heated in a boiling water bath for 5 min and immediately cooled on an ice bath. Ten microliters of denatured PCR products of the test organism and of the positive control (*Saccharomycodes ludwigii*) were diluted with 0.3 ml of hybridization solution and added to each well. Hybridization was conducted at 55°C for 90 min. After removing the nonhybridized PCR products, the array was washed four times (5 min each) in 1 ml of 0.25× SSC–0.1% SDS, followed by incubation for 1 h with 1 ml of blocking solution (1% [wt/vol] blocking reagent dissolved in maleic acid buffer [0.1 M maleic acid, 0.15 M NaCl, pH 7.5]). After removal of the blocking solution, 0.3 ml of alkaline phosphatase-conjugated sheep antidigoxigenin antibodies (diluted 1:2,500 in blocking solution) was added to each well and incubated for 1 h. The array was washed three times (each 15 min) in 1 ml of washing solution (0.3% [vol/vol] Tween 20 in maleic acid buffer), followed by washing in 1 ml of detection buffer (0.1 M Tris-HCl, 0.15 M NaCl, pH 9.5) for 5 min. Finally, 0.3 ml of alkaline phosphatase substrate (a stock solution of nitroblue tetrazolium chloride/5-bromo-4-chloro-3-indolylphosphate diluted 1:50 in detection buffer) was added to each well and incubated at 37°C without shaking. Color development was visible between 30 min and 1 h after the start of the reaction.

Definition of sensitivity and specificity. A fungal strain was identified as one of the 64 target species when the probe (or one of several probes) designed for the species and the positive control probe (see Fig. S2 in the supplemental material) were hybridized. Sensitivity was defined as the number of target strains correctly identified (true positives) divided by total number of target strains tested (36). When a strain hybridized to its corresponding group-specific probe, the strain was considered to be correctly identified. Specificity was defined as the number of nontarget strains producing negative hybridization reactions (true negatives) divided by total number of nontarget strains tested (36). Occasionally, the PCR product of one strain hybridized to more than one species-specific probe on the array (i.e., cross-hybridization). Under these conditions, the strain was identified as the species corresponding to the probe that produced the most intense hybridization signal as judged visually. When a strain produced discrepant identification results between the conventional methods and the array, the ITS 1 and 2 regions of the isolate were amplified by PCR and sequenced for species clarification.

RESULTS

Probe development. In the beginning of this study, between one and seven probes (data not shown) were designed for identification of each species (or a group of species) and a total of 213 probes were synthesized to identify 64 fungal species listed in Table S1 in the supplemental material. Through extensive hybridization screening, many probes cross-reacted with heterologous species or produced no hybridization signals

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TABLE 1. Oligonucleotide probes used in this study

Microorganism	Probe code[a]	Sequence (5′ to 3′)[b]	Length (bp)	T_m (°C)	Location[c]	GenBank accession no.
Absidia corymbifera	Abcor3	CTGGGCTTCTAGTTGATGGCATTTAGTTGC	30	57.9	146–175 (2)	AF117938
Acremonium falciforme	Acfal1	GGAAGCCCCCTGCGGGCACAA	21	49.7	39–59 (2)	AY830120[d]
Acremonium kiliense	Ackil2	TCTGATTTTATTGTGAATCTCTGAGGGGCG	30	55.2	111–140 (1)	AJ621775
Acremonium kiliense	Ackil3	TGATTTTATTGTGAATCTCTGAGGGGCGAA	30	53.8	113–142 (1)	AJ621775
Acremonium strictum	Acstr2	CAGCCTCCCCTGCGTAGTAGCA	22	55.3	422–443 (2)	AJ621771
Alternaria alternata	Alalt3	CGCACTCTCTATCAGCAAAGGTCTAGCATC	30	57.9	461–490 (2)	AY625056
Aspergillus clavatus	Ascla3	CGACACCAACCCAATYTTTCTAAGGT	26	52.1	518–543 (2)	AY373847
Aspergillus flavus	Asfla4	CGAACGCAAATCAATCTTTTTCCAGGT	27	51.6	512–538 (2)	AY373848
Aspergillus fumigatus	Asfum2	GCCAGCCGACACCCAACTTTATTTTTCTAA	30	55.2	213–242 (2)	AY230140
Aspergillus nidulans	Asnid2	GCGTCTCCAACCTTATTTTTCTCAGGT	27	53.1	483–509 (2)	AY373888
Aspergillus niger	Asnig2	ACGTTTTCCAACCATTCTTTCCAGGT	26	51.3	517–542 (2)	AY373852
Aspergillus terreus	Aster2	CCGACGCATTTWTTGTGCAACTTGTTT	27	51.6	493–520 (2)	AJ001333
Aspergillus versicolor	Asver4	ACGTCTCCAACCATTTTCTTCAGGT	25	50.9	486–510 (2)	AY830119[d]
Aureobasidium pullulans	Aupul2	ATTTCTAACAACGCTCTTTGGGTCGGTACG	30	56.5	454–483 (2)	AF121283
Aureobasidium pullulans	Aupul3	TCAAAGGAGAGGACTTCTGCCGACTGAAAC	30	57.9	456–485 (2)	AY139395
Aureobasidium pullulans	Aupul4	GGCGTAGTAGAATTTATTCGAACGTCTGTC	30	55.2	428–457 (2)	AY139395
Beauvera bassiana	Bebas5	GGGACCTCAAACTCTTGTATTCCAGCATC	29	56.4	166–194 (1)	AJ560691
Bipolaris spicifera	Bispi	TCTTTGGCCCGCCAAAGACTCGCCTTAAA	29	64.1	395–423 (2)	AY253918
Blastomyces dermatitidis	Blder2	CCGCTAGAACTTCTGGTGAACGATTGACAT	30	56.5	163–192 (1)	AF038358
Chaetomium cochlioides/ *C. globosum*/*C. funicola*	Chcgf1[e]	GGCCTCTCTGAGTCTTCTGTACTGAATAAG	30	56.5	157–186 (1)	AJ279450
Chaetomium funicola	Chfun2	CGTAGTAGCATATCTTTGTCTCGCTCAGG	29	56.4	436–464 (2)	AJ279450
Cladophialophora bantiana	Clban5	TCTTCTCCCTCATGTGGGAAACATTGCA	28	54.8	544–571 (2)	AB091211
Cladophialophora carrionii	Clcar2	AGGCCACGGTCCTCTCCTCTAA	22	53.4	524–545 (2)	AB109180
Cokeromyces recurvatus	Corec2	TTTAGACTTTGGGGCCGCCCAAATAATACT	30	55.2	157–186 (2)	AY830118[d]
Cunninghamella bertholletiae	Cuber3	CACTCTCGGCCTAAATATAAGGCTCGAC	28	56.3	590–617 (2)	AF254930
Cunninghamella spp.	Cun4	GAGATAAATTATTACTGGTCCTGGTGATTC	30	52.4	527–556 (2)	AF254931
Epidermophyton floccosum	Epflo2	TCCATAGGTGGTTCAGTCTGAGCGTT	26	54.4	279–304 (1)	213646
Exophiala dermatitidis	Exder1	ACTCTTGAATCAAATCGTGTCCAATGTCTG	30	53.8	157–186 (1)	AF050270
Exophiala werneckii (*Hortaea werneckii*)	Hower2	GTCCGTCTCTAAGCGTTGTGAATAGCGATC	30	57.9	387–416 (2)	AY128704
Exophiala jeanselmei	Exjea	CCAAACGTGTCTTGTCTGAGTAAACGTC	28	54.8	160–187 (1)	AY163556
Fonsecaea compacta/ *F. pedrosoi*	Focp[e]	CTCACGGGAACACTTTTTTTTTTAAGGT	28	50.4	167–194 (2)	AY830117[d]
Fusarium moniliforme/ *F. oxysporum*/ *F. pallidoroseum*	Fumop[e]	AGTAGTAAAACCCTCGTTACTGGTAATCGT	30	53.8	448–477 (2)	AY462580
Fusarium moniliform	Fumon	CGAGTCAAATCGCGTTCCCCAAATTG	26	54.4	395–420 (2)	AY533376
Fusarium solani	Fusol2	AGTAGCTAACACCTCGCGACTGGAGA	26	56.0	446–471 (2)	AF129105
Geotrichum candidum	Gecan	CTCTCTTGGAATTGCWTTGCTYTTCTAAA	29	51.5	291–319 (2)	AJ279451
Geotrichum capitatum	Gecap3	GTGCAACAAGCTGTGTTGAATCTTTC	26	49.7	369–388 (2)	AF455443
Malbranchea filamentosa	Mafil4	CGGCGCTGGTCAGAACCAAATCTTTTA	27	54.6	463–489 (2)	AY177301
Microsporum audouinii/ *M. canis*/*M. ferrugineum*	Macf1[e]	TGGCCTAACGCACCATGTATTATTCAGGT	29	55.0	706–734 (2)	AJ252333
Microsporum cookei	Micok4	GCCTTGACTGGACTCCTTTGTCCGTTAAAT	30	56.5	152–181 (2)	AY830116[d]
Microsporum gallinae	Migal3	GGCCTCGTTTCAATAATTGTCGTTAGAGAAT	31	54.0	536–566 (2)	AJ000620
Microsporum gypseum	Migyp3	CCGGTTTTCTGGCCTAGTTTTAGTTAGGGAT	31	56.6	582–612 (2)	AG168128
Microsporum nanum	Minan1	AGGAACGATCAAAACACGCGAACAC	25	52.6	115–139 (1)	AB049927
Paracoccidioides brasiliensis	Pabra2	TTCGGAGCTTTGACGTCTGAGACCTATCAT	30	56.5	158–187 (1)	AY631237
Paecilomyces javanicuss	Pajav	TAGTACTCCAACGCGCACCGGGAA	24	55.7	99–122 (2)	AY830115[d]
Penicillium marneffei	Pemar2	GTCACCACCATATTTACCACGG	22	50.6	468–487 (2)	AB049132
Phialophora richardsiae	Phric3	CCACTAAAACTCTTCTGTATCTCGCGTACC	30	56.5	111–140 (1)	AY179948
Phialophora verrucosa	Phver3	CCAGGACCCGGTCCTTCTCCTTTAAC	26	57.6	521–546 (2)	AF397135
Piedraia hortai var. *hortai*	Pihor2	AAACGATCCGCCCAGCGAGAAT	22	51.6	106–127 (2)	AY839755[d]
Pseudallescheria boydii	Psboy3	GGTTGCCTTCTGCGTAGTAAGTCTCTTTTG	30	56.5	579–608 (2)	AY228118
Rhizopus oryzae	Riory4	GCAGGAATATTACGCTGGTCTCAGGATCTT	30	56.5	486–515 (2)	AB097271
Rhizomucor pusillus	Ripu4	ATCCGTTCAAGCTACCCGAACAATTTGTAT	30	53.8	169–198 (2)	AF117934
Saccharomycodes ludwigii	Salud[f]	CTTGAAATTGTTGCCTAGCAAAGAAGAA	28	55.4	522–549 (2)	AB056135
Scopulariopsis brevicaulis	Scbre3	TGCGTAGTAGATCCTACATCTCGCATCG	28	56.3	500–527 (2)	AY625065
Scytalidium dimidiatum/ *S. hyalinum*	Sydh[e]	AACTCCGGTCAGTGAACGTTGCC	23	53.7	161–183 (2)	AY213688
Scedosporium prolificans	Scpro4	GGCCAGCCGTCAAACCCTCTATTCTTAT	28	56.3	467–494 (2)	AY228117

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TABLE 1—*Continued*

Microorganism	Probe code[a]	Sequence (5′ to 3′)[b]	Length (bp)	T_m (°C)	Location[c]	GenBank accession no.
Trichophyton rubrum/ T. soudanense/ T. violaceum	Trrsv3[e]	CCGCCCTGGCCCCAATCTTTATA	23	53.7	614–636 (2)	Z97993
Trichophyton verrucossum	Trver	GCCTTCCCCCAAATCTCTCTGAGATW	26	54.4	607–632 (1)	Z98003
Trichophyton mentagrophytes/ T. tonsurans/ T. schoenleinii	Trmmist[e]	GCCTCAAAATCTGTTTTATACTTATCAGGT	30	51.1	619–648 (2)	Z97999
Ulocladium consortiale	Ulcon2	CCAAGGTCAGCATCCACAAAGCCTT	25	54.2	477–501 (2)	AY278837

[a] Oligonucleotide probes are arranged on the array as indicated in Fig. 1.
[b] Seven additional bases of thymine were added to the 3′ end of each probe.
[c] The location of probe is shown by the nucleotide number of either ITS 1 or ITS 2; the number (1 or 2) in parenthesis indicates the ITS region from which the probe was designed.
[d] ITS sequences determined in this study and submitted to GenBank.
[e] A group-specific probe used to detect several closely related species.
[f] The probe on the array was used as a positive control of assay.

with homologous species. Finally, 58 probes were selected for fabrication of the array (Fig. 1). For most fungi, a single probe was designed for each species. However, some group-specific probes (Fig. 1, probe codes underlined; Table 1) were designed, i.e., two or more closely related species shared a probe that could not differentiate species within the group. This is due to the fact that some genetically related species have high similarities of both ITS 1 and 2 sequences. For example, the probe Chcgf1 was used to identify three species (*Chaeotomium cochlioides*, *C. globosum*, and *C. fumicola*). Other group-specific probes were Focp (*Fonsecaea compacta/F. pedrosoi*), Fumop (*Fusarium moniliforme/F. oxysporum/F. pallidoroseum*), Macf1 (*Microsporum audouinii/M. canis/M. ferrugineum*), Sydh (*Scytalidium dimidiatum/S. hyalinum*), Trmst1 (*Trichophyton mentagrophytes/T. schoenleinii/T. tonsurans*), and Trrsv3 (*Trichophyton rubrum/T. soudanense/T. violaceum*). The probe Cun4 was a genus-specific (*Cuminghamella*) probe.

Furthermore, strains of some species were found to have high intraspecies divergence of ITS sequences and multiple probes (Fig. 1, probe codes in bold face; Table 1) were used to identify a single species. For example, probes Ackil2 and Ackil3 were used to identify *Acremonium kiliense*, and probes Aupul2, Aupul3, and Aupul4 were designed for identification of *Aureobasidium pullulans*. The melting temperatures (T_m) of probes ranged from 49.7 to 57.9°C (Table 1).

Hybridization of reference strains to the oligonucleotide array. A total of 326 reference strains, including 233 target and 93 nontarget strains, were tested by hybridization to the array. Fig. S2 in the supplemental material shows the hybridization results of reference strains of different species. Of the 233 target strains, 228 (97.9%) were correctly identified to the species or group level, 2 (*Acremonium falciforme* CBS 101427 and *Acremonium strictum* BCRC 32290) were misidentified, and 3 (*Acremonium strictum* CBS 102295, *Bipolaris spicifera* CBS 418.67, and *Hortaea werneckii* ATCC 58301) were not identified (no hybridization signal) (see Table S1 in the supplemental material and Table 2). Strains that produced discrepant identification by the conventional methods and the array method were further analyzed in Table 2.

A. falciforme CBS 101427 hybridized to probes Acfal1 (designed for *A. falciforme*) and Fusol2 (designed for *Fusarium solani*) with almost equal hybridization signals, and no unambiguous species designation for the strain was obtained by the array method. *A. strictum* BCRC 32290 was misidentified as *A. kiliense* (Table 2). The ITS 1 and 2 regions of *A. strictum* BCRC 32290 were sequenced and compared with sequences in the

	1	2	3	4	5	6	7	8	9	10
A	Abcor3	Acfal1	**Ackil2**	**Ackil3**	Acstr2	M	Alalt3	**Aupul2**	**Aupul3**	**Aupul4**
B	Ascla4	Asfla4	Asfum2	Asnid2	Asnig2	M	Aster2	Asver4	Bebas5	Bispi
C	Blder2	Chcgf1	Chfun2	Clban5	Clcar2	M	NC	Corec2	Cun4	Cuber3
D	Epflo2	Exder1	Exjca	Focp	Fumon	M	Fumop	Fusol2	Gecan	Gecap3
E	M	M	M	M	M	NC	M	M	M	M
F	Hower2	Mafil4	Macf1	Migyp3	Micok4	M	Migal3	Minan1	Pabra2	Pihor2
G	Pajav	NC	NC	NC	Pemar2	M	Phric3	Phver3	Psboy3	PC
H	Ripu4	Riory4	Scbre3	Scpro4	Sydh	M	Trmst1	Trver	Trrsv3	Ulcon2

FIG. 1. Layout of oligonucleotide probes on the array (1.1 by 0.9 cm). The probe "PC" (G10) was designed on the basis of the ITS 2 region of *Saccharomycodes ludwigii* BCRC 21378 and used as a positive control. Probes coded "NC" (E6 and G2 to G4) were negative controls (tracking dye only). Probes coded "M" were ITS 4 labeled with digoxigenin at its 5′ end and were used as position markers. Group-specific probes are underlined, and multiple probes used to identify a single species are in bold face. The corresponding sequences of probes are listed in Table 1.

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TABLE 2. List of fungal strains that produced discrepant identification by the conventional methods and array hybridization

Microorganism	Species identified by array hybridization	ITS sequence analysis result[a]	GenBank accession no. or strain no.[b]
Target species			
Acremonium falciforme CBS 101427	*Acremonium falciforme* or *Fusarium solani*	*Acremonium falciforme* (98%/99%)	CBS 475.67
		Fusarium solani (98%/99%)	AY569560
Acremonium strictum BCRC 32290	*Acremonium kiliense*	*Acremonium strictum* genogroup II (100%/95%)	AY138846
		Acremonium kiliense (100%/100%)	CBS 122.29
Acremonium strictum CBS 102295	Not identified	*Acremonium strictum* genogroup II (99%/100%)	AY138844
		Acremonium strictum (69%/70%)	BCRC 32239
Bipolaris spicifera CBS 418.67	Not identified	*Exserohilum rostratum*[c] (98%/99%)	AF163066
		Bipolaris spicifera (84%/75%)	CBS 274.52
Exophiala dermatitidis LM 8	*Exophiala jeanselmei*	*Exophiala jeanselmei* (99%/99%)	AY163552
		Exophiala dermatitidis (48%/56%)	ATCC 38714
Exophiala jeanselmei LM 68	Not identified	*Exophiala mesophila* (97%/98%)	AF542377
		Exophiala jeanselmei (60%/38%)	CBS 835.95
Horteae werneckii ATCC 58301	Not identified	*Exophiala* sp. strain 700-03 (98%/98%)	AY591350
		Horteae werneckii (37%/45%)	ATCC 36317
Trichophyton soudanense LMA 951336	*Trichophyton mentagrophytes*/*T. schoenleinii*/*T. tonsurans*	*Trichophyton tonsurans* (95%/100%)	AF170479
		Trichophyton soudanense (95%/74%)	ATCC 24583
Nontarget species			
Aspergillus oryzae BCRC 30102	*Aspergillus flavus*	*Aspergillus oryzae* (97%/95%)	AY373857
		Aspergillus flavus (97%/95%)	AF453893
Aspergillus sydowii BCRC 33347	*Aspergillus versicolor*	*Aspergillus sydowii* (99%/95%)	AY373868
		Aspergillus versicolor (97%/95%)	AY373882
Rhizomucor miehei BCRC 31627	*Rhizomucor pusillus*	*Rhizomucor miehei* (100%/100%)	AJ278360
		Rhizomucor pusillus (67%/70%)	BCRC 33122

[a] Values in parenthesis are the ITS 1/ITS 2 sequence similarities of the discrepant strain with the indicated fungal species.
[b] The ITS sequences of the discrepant strain were compared with the indicated GenBank accession number or the closest reference strain in our database.
[c] *Exserohilum rostratum* is a new name of *Bipolaris rostratum*.

GenBank and in our database. The results revealed that both ITS sequences of *A. strictum* BCRC 32290 had 100% similarity with those of the type strain (*A. kiliense* CBS 122.29) in our database. However, *A. strictum* BCRC 32290 had sequence similarities of 100% (ITS 1) and 95% (ITS 2), respectively, with *A. strictum* genogroup II (GenBank accession no. AY138844) (Table 2).

Of the three strains not identified (*Acremonium strictum* CBS 102295, *Bipolaris spicifera* CBS 418.67, and *Hortaea werneckii* ATCC 58301), *A. strictum* CBS 102295 had sequence similarities of 99% (ITS 1) and 100% (ITS 2), respectively, with *A. strictum* genogroup II (AY138844), but the similarities were only 69% (ITS 1) and 70% (ITS 2), respectively, with type strain *A. strictum* BCRC 32239 (Table 2). *B. spicifera* CBS 418.67 had sequence similarities of 98% (ITS 1) and 99% (ITS 2), respectively, with *Exserohilum rostratum* (a new name of *B. rostratum*) (AF163066). However, *B. spicifera* CBS 418.67 displayed sequence similarities of only 84% (ITS 1) and 75% (ITS 2), respectively, with *B. spicifera* CBS 274.52 in our database. Therefore, the designation of CBS 418.67 as *B. spicifera* may be questionable. *H. werneckii* ATCC 58301 had high ITS similarities (98 to 99%) with *Exophiala* sp. strain NYSDOH 700-03 (AY591350) by a BLAST search in GenBank (Table 2). However, *H. werneckii* ATCC 58301 had sequence similarities of only 37% (ITS 1) and 45% (ITS 2), respectively, with *H. werneckii* ATCC 36317 (type strain) in our database. For this reason, the designation of the strain ATCC 58301 as *H. werneckii* may be incorrect. Despite the above-described inconsistent results, a third strain of *A. strictum* (BCRC 32239) and a second strain of *B. spicifera* (CBS 274.52) were correctly identified (see Table S1 and Fig. S2, panels 4 and 19, in the supplemental material).

Of the 93 nontarget reference strains, two were misidentified by the array. *Aspergillus sydowii* BCRC 33347 and *Rhizomucor miehei* BCRC 31627 were misidentified as *A. versicolor* and *R. pusillus*, respectively (see Table S1 in the supplemental material and Table 2). A BLAST search revealed that the species designation of the two reference strains is correct. Misidentifications of the two strains were apparently caused by their partial ITS sequence homology with the above-indicated target species (Table 2). Although *R. miehei* BCRC 31627 had low ITS similarities (67 to 70%) with *R. pusillus*, sequence alignment indicated that the probe (Ripu4) designed for *R. pusillus* had an 85% similarity with a partial region of the ITS 2 of *R. miehei* BCRC 31627.

In addition to hybridization to their species-specific probes, each of the strains *Acremonium falciforme* CBS 475.67 (see Fig. 2, panel 2, in the supplemental material), *Alternaria alternata* BCRC 30501 (panel 5), *Aspergillus nidulans* ATCC 11267 (panel 12), *Aspergillus versicolor* BCRC 30225 (panel 15), *Scopulariopsis brevicaulis* ATCC 7903 (panel 55), and *Ulocladium consortiale* CBS 105.21 (panel 65) cross-hybridized to an extra heterologous probe on the array. However, the hybridization signals caused by the heterologous probes were much

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weaker than those produced by their homologous probes, and according to the protocol, these species were correctly identified by the array. The hybridization results for three selected nontarget strains (*Absidia coerulea* BCRC 30897, *Penicillium lividum* BCRC 31673, and *Rhizopus azygosporus* BCRC 31158) are also shown (see Fig. S2, panels 68 to 70, in the supplemental material). For the three nontarget species, no probes were hybridized except the probe for positive control.

Hybridization of clinical isolates to the oligonucleotide array. A total of 71 clinical isolates, including 57 target and 14 nontarget strains, were tested. Of the 57 target strains, 54 were correctly identified (see Table S1 in the supplemental material). *Exophiala dermatitidis* LM 8 and *Trichophyton soudanense* LMA 951336 were identified as *E. jeanselmei* and *Trichophyton mentagrophytes/T. schoenleinii/T. tonsurans*, respectively, by the array method (Table 2). ITS sequence comparison revealed that the identifications of *E. dermatitidis* LM 8 and *T. soudanense* LMA 951336 might have been misidentifications of *E. jeanselmei* and *T. tonsurans*, respectively, because of their high ITS similarities with the later two species and low similarities with their respective reference strains (Table 2). *E. jeanselmei* LM 68 was not identified, and ITS sequence analysis demonstrated that its ITS had similarities of 97% (ITS 1) and 98% (ITS 2), respectively, with *E. mesophila* (GenBank accession no. AF542377), which was not a target strain of this study (Table 2). Therefore, the clinical isolates *E. dermatitidis* LM 8, *E. jeanselmei* LM 68, and *T. soudanense* LMA 951336 should represent misidentifications of *E. jeanselmei*, *E. mesophila*, and *T. tonsurans*, respectively, or their close relatives. On the basis of these results, 100% (57/57) of clinical isolates were correctly identified by the array method. All 14 nontarget clinical isolates produced no hybridization signal with all probes on the array (see Table S1 in the supplemental material).

Performance of the array for fungal identification. Of the 233 target reference strains, 228 (97.9%) were correctly identified, and of the 57 target clinical isolates, 57 (100%) were correctly identified (see Table S1 in the supplemental material). Irrespective of strain sources, an overall sensitivity of 98.3% (285/290) was obtained by the array method. Of the 93 nontarget reference strains, two (*A. sydowii* BCRC 33347 and *Rhizomucor miehei* BCRC 31627) were misidentified and a specificity of 97.9% (91/93) was obtained. For the 14 nontarget clinical isolates, a specificity of 100% (14/14) was obtained. In summary, a specificity of 98.1% (105/107) was obtained irrespective of the sources of nontarget strains.

Hybridization of multiple microorganisms to an array. An array could be used to simultaneously identify several different microorganisms if these microorganisms belonged to distant taxa. For example, the PCR products of *Absidia corymbifera* BCRC 33078 and *Aspergillus fumigatus* BCRC 32120 could concurrently hybridize to their respective probes on an array (see Fig. S2, panel 66, in the supplemental material). Another example was that *Aspergillus flavus* BCRC 30007 and *Penicillium marneffei* CBS 334.59 could be identified on a chip (see Fig. S2, panel 67, in the supplemental material).

Detection limit of the array. Serial 10-fold dilutions of DNAs extracted from two strains (*Aspergillus fumigatus* BCRC 32120 and *Rhizopus oryzae* BCRC 31108) were used to determine the detection limit. The present method was able to detect fungal genomic DNA at a level as low as 10 pg (data not shown).

DISCUSSION

In this study, an oligonucleotide array was developed to identify 64 species (32 genera) of clinically relevant molds. The 64 species covered pathogens causing superficial, cutaneous, subcutaneous, and invasive infections. Several species of dimorphic fungi (*Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Penicillium marneffei*) (see Table S1 in the supplemental material) were also included. The prominent feature of the present method is that it combines the various methods into a single standardized protocol encompassing DNA extraction, PCR amplification of the ITS regions, and hybridization of the PCR products to the array. Another important characteristic is that visualization of fungal reproductive structures, which is essential for classical identification, is not needed for the present method. Since the primer pairs (ITS 1 and 4) used in this study can also amplify the ITS regions of yeasts (5, 31, 46), it is expected that clinically relevant yeasts also could be identified by the same approach used in this study.

Traditionally, the identification of molds causing infections involves isolation of organisms and relies on the expertise of the clinical microbiologist. Identification of filamentous fungi is therefore technical demanding and time consuming, and inaccurate identification is not rare. Taylor et al. (42) have pointed out that there are distinctions between the "evolutionary species" (theoretical species) concept and the "operational species" concept that may include the "morphological species" concept, "biological species" concept, and "phylogenetic species" concept. It has been noted that in general a single morphological species can contain multiple biological or phylogenetic species (42). Besides, strains belong to the same species may display different morphological characteristics at different growth stages. In this study, it was found that even some reference strains (*Bipolaris spicifera* CBS 418.67 and *Hortaea werneckii* ATCC 58301) obtained from collection centers may be misidentified.

The good performance (sensitivity and specificity) of the present array might be due to the fact that the fungal ITS sequences have low intraspecies variation and high interspecies divergence (10, 19, 21, 24, 32). Until now, there has been no report defining the criteria for maximum intraspecies variation in the ITS regions. However, the criteria have been established for the D1/D2 region of large-subunit rRNA genes. Fell et al. (16) established a database of 230 species of basidiomycetous yeasts and suggested that strains differing by two or more nucleotides in the D1/D2 region represented different taxa. Kurtzman and Robnett (29) studied approximately 500 yeast species and proposed that strains showing greater than 1% substitutions in the approximately 600-nucleotide D1/D2 region were likely to be different species. However, the fungal ITS region is more variable than the D1/D2 region. We have sequenced both ITS 1 and 2 regions of many fungal species to establish the intraspecies variation of medically important molds (data not shown) and found that, in general, 2% divergence of both regions (ITS 1 and 2) seems to be a reasonable threshold to differentiate species. Some intraspecies variations

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of ITS 1 (or ITS 2) may be >2%; however, it was rarely found that the divergence of both ITS regions is >2%.

Although a single probe was designed to identify each individual species under most conditions, some exceptions existed. For example, multiple probes were used to identify *Acremonium kiliense* (Ackil2 and Ackil3) and *Aureobasidium pullulans* (Aupul2, Aupul3, and Aupul4) (Table 1 and Fig. 1) because strains within the two species have high intraspecies divergence of ITS sequences. Fig. S2 (panel 16) in the supplemental material shows that *A. pullulans* BCRC 32064 hybridized to the probe Aupul2, while *A. pullulans* BCRC 31981 hybridized to other two probes (Aupul3 and Aupul4) (panel 17). In contrast, some species within a genus displayed high ITS homology and the design of species-specific probes was difficult. Therefore, several probes were designed to identify a "group" of closely related species. For example, the probe Chcgf1 (Table 1) was used to identify species of *Chaetomium cochlioides*, *C. funicola*, and *C. globosum*. However, *C. funicola* had its own species-specific probe (Chfun2) (Table 1). Therefore, when both probe Chcgf1 and probe Chfun2 were hybridized, the microorganism was *C. funicola* (see Fig. S2, panel 22, in the supplemental material). If only the probe Chcgf1 was hybridized, the strain might belong to *C. cochlioides* or *C. globosum* (panels 21 and 23). Similarly, the probe Fumop was designed to identify *Fusarium moniliforme*, *F. oxysporum*, and *F. pallidoroseum*, but an additional probe (Fumon) was designed for *F. moniliforme* (Table 1). Therefore, *F. moniliforme* could be differentiated from *F. oxysporum* (panel 34) and *F. pallidoroseum* (panel 35) by hybridization to probes of both Fumop and Fumon (panel 33).

In this study, four strains (*Acremonium strictum* CBS 102295, *Bipolaris spicifera* CBS 418.67, *Exophiala jeanselmei* LM 68, and *Hortaea werneckii* ATCC 58301) were not identified (Table 2). The anamorphic characteristics of *A. strictum* CBS 102295 are as follows: conidiophores simple, occasionally branched, phialides slender (arising from submerged or slightly fasciculate aerial hyphae), conidia grouped in slimy heads (cylindrical or ellipsoidal, hyaline). These characteristics are typical of the species *A. strictum* (11). *A. strictum* CBS 102295 was not identified, and this might be due to genetic diversity among isolates of the species. Novicki et al. (39) found a greater-than-expected variation among strains previously identified as *A. strictum*. In sequence analyses of the ITS regions and the D1/D2 variable domain of the 28S ribosomal DNA, five clinical isolates phenotypically identified as *A. strictum* were found to have <99% similarities to the *A. strictum* type strain (CBS 346.70) at the ITS and 28S loci. But a sixth isolate phenotypically identified as an *Acremonium* sp. had >99% similarities to the type strain at both loci. They concluded that five out of the six clinical isolates belong to species other than *A. strictum* or that the *A. strictum* taxon is genetically diverse.

Bipolaris spicifera CBS 418.67 had sequence similarities of 98% (ITS 1) and 99% (ITS 2), respectively, with *Exserohilum rostratum* (a new name of *B. rostratum*) (GenBank accession no. AF163066). However, *B. spicifera* CBS 418.67 displayed sequence similarities of only 84% (ITS 1) and 75% (ITS 2), respectively, with *B. spicifera* CBS 274.52 in our database. Therefore, the designation of CBS 418.67 as *B. spicifera* may be questionable. The conidiophores of CBS 418.67 are erect, unbranched, septate, and regularly zig-zagged in the apical part. The conidia of CBS 418.67 are brown, cylindrical with rounded ends, and have three distosepta (conidia subdivided by inner wall layer only). The above-described characteristics of CBS 418.67 are typical of the species of *B. spicifera* (11) and may be why CBS 418.67 was given the name *B. spicifera*.

For *Exophiala jeanselmei* LM 68 (a not-identified clinical isolate), its ITS sequences had similarities of 97% (ITS 1) and 98% (ITS 2), respectively, with *E. mesophila* (GenBank accession no. AF542377), which was not a target strain of this study (Table 2). Members of genus *Exophiala* are often difficult to identify to the species level because of their variable morphological appearances (40). The microscopic morphologies of *E. jeanselmei* LM 68 and *E. mesophila* are similar; both produce annellides that are slender, tubular, sometimes branched, and characteristically tapered to a narrow, elongated tip. Their conidia are oval and gather in clusters at the end and sides of the conidiophore.

Hotaea werneckii ATCC 58301 had high ITS similarities (98 to 99%) with *Exophiala* sp. NYSDOH 700-03 (AY591350) by a BLAST search in GenBank (Table 2). At the early stage, ATCC 58301 produce pale or dark brown yeast-like cells. These cells (2 to 5 by 5 to 10 μm) are actually annellides and are round at one end while tapered and elongated with striations at the other end where conidia are formed. The one- or two-celled annelloconidia form and accumulate at annellidic points along the hyphae. The above-described microscopic characteristics of ATCC 58301 are typical of the species *H. werneckii* (11), and this might explain why ATCC 58301 was given the name *H. werneckii*.

Invasive aspergillosis is a leading cause of infection among patients undergoing treatment for hematological malignancies, solid organ transplantation, and hematopoietic stem cell transplantation (8, 10, 37). *Aspergillus fumigatus* remains the most frequent cause of invasive aspergillosis, followed by *A. flavus*, *A. terreus*, *A. niger*, *A. nidulans*, and *A. versicolor* (12, 22). These six important *Aspergillus* species were all included in this study, and probes designed for them showed satisfactory hybridization results (see Fig. S2, panels 10 to 15, in the supplemental material). The only exception was one strain (BCRC 302225) of *A. versicolor* that cross-hybridized with the probe Asnid2 designed for *A. nidulans* (see Fig. S2, panel 15, in the supplemental material). However, the probe Asver4, designed to identify *A. versicolor*, produced much a stronger hybridization signal than the probe Asnid2.

Recently, Husain et al. (22) prospectively studied 53 liver and heart transplant recipients and found that invasive infections due to filamentous fungi other than *Aspergillus* species were significantly more likely to be associated with disseminated and central nervous system infections than were those due to *Aspergillus* species. The associated mortality rate was 100% for zygomycosis, 80% for non-*Aspergillus* hyalohyphomycosis, and 54% for aspergillosis. Non-*Aspergillus* molds causing sever infections in organ transplant recipients include zygomycetes, *Fusarium* spp., *Pseudallescheria boydii* (*Scedosporium apiospermum*), *Scedosporium prolificans*, and dematiaceous molds (6). Probes for most of these important non-*Aspergillus* species were included in the current study (Table 1).

Some species of dermatophytes are phylogenetically and taxonomically very closely related (19, 25, 34). A high level of ITS homology was observed for several common dermatophyte

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species. Our in-house ITS database demonstrates that the sequence similarities between *Trichophyton rubrum* ATCC 28188 and *T. violaceum* ATCC 28944 are 0.98 (ITS 1) and 0.95 (ITS 2), respectively, whereas the similarities are 1.0 (ITS 1) and 0.97 (ITS 2), respectively, between *T. rubrum* ATCC 28188 and *T. soudanense* ATCC 24583. Sequence similarities of 0.96 (ITS 1) and 0.99 (ITS 2) were observed between *T. mentagrophytes* CBS 361.62 and *T. tonsurans* ATCC 56186, and were 0.95 (ITS 1) and 0.94 (ITS 2) between *T. schoenleinii* ATCC 22775 and *T. tonsurans* ATCC 56186. For this reason, the group-specific probe Trrsv3 was designed to identify species of *T. rubrum*, *T. soudanense*, and *T. violaceum*, whereas Trmst1 was used for identification of *T. mentagrophytes*, *T. schoenleinii*, and *T. tonsurans*. Additional probes designed from other loci such as the D1/D2 or ribosomal intergenic regions (13) may help to generate species-specific probes of dermatophytes. However, separate PCR or multiplex PCR using different sets of primers will be needed to amplify these different regions (13).

Although the T_m values of some probes listed in Table 1 were lower than the array hybridization temperature (55°C), clear hybridization signals were still obtained for these probes (see Fig. S2 in the supplemental material). For example, probes Acfal1 (T_m = 49.7°C) and Gecap3 (T_m = 49.7°C), designed to identify *Acremonium falciforme* and *Geotrichum capitatum*, respectively, produced discernible signals (see Fig. S2, panels 2 and 38, in the supplemental material). This might be partially due to the use of relatively low stringency buffer (high ionic strength [5× SSC] and low detergent concentration [0.02% SDS]) for hybridization reaction. Volokhov et al. (45) used several probes having T_m values (40 to 44°C) lower than the hybridization temperature (45°C) for identification of *Listeria* spp. and still obtained good hybridization results. In contrast, probes Acstr2 (T_m = 55.3°C) and Blder2 (T_m = 56.5°C), used to identify *Acremonium strictum* and *Blastomyces dermatitidis*, respectively, produced relatively weak hybridization signals (see Fig. S2, panels 4 and 20, in the supplemental material). The secondary structure of probes may influence the hybridization efficiency (13).

In conclusion, species identification of clinically important molds by the present oligonucleotide array is reliable and can be used as an effective alternative to the conventional identification methods. The whole procedure can be finished within 24 h starting from isolated colonies, and visualization of fungal reproductive structures is not required. The array used in this study has the potential to be expanded by including more probes in order to identify more species.

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Attachment 22.11

Carlesse F et al. Outbreak of Fusarium oxysporum infections in children with cancer: an experience with 7 episodes of catheter-related fungemia. Antimicrob Resist Infect Control. 2017 Sep 7;6:93. doi: 10.1186/s13756-017-0247-3. PMID: 28912948; PMCID: PMC5588724.

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Antimicrobial Resistance and Infection Control

RESEARCH Open Access

Outbreak of *Fusarium oxysporum* infections in children with cancer: an experience with 7 episodes of catheter-related fungemia

Fabianne Carlesse[1,2], Anna-Paula C. Amaral[2], Sarah S. Gonçalves[3], Hemilio Xafranski[3], Maria-Lucia M. Lee[1], Victor Zecchin[1], Antonio S. Petrilli[1], Abdullah M. Al-Hatmi[4,5], Ferry Hagen[6], Jacques F. Meis[5,6] and Arnaldo L. Colombo[3*]

Abstract

Background: *Fusarium* species are widely spread in nature as plant pathogens but are also able to cause opportunistic fungal infections in humans. We report a cluster of *Fusarium oxysporum* bloodstream infections in a single pediatric cancer center.

Methods: All clinical and epidemiological data related to an outbreak involving seven cases of fungemia by *Fusarium oxysporum* during October 2013 and February 2014 were analysed. All cultured isolates (n = 14) were identified to species level by sequencing of the *TEF1* and *RPB2* genes. Genotyping of the outbreak isolates was performed by amplified fragment length polymorphism fingerprinting.

Results: In a 5-month period 7 febrile pediatric cancer patients were diagnosed with catheter-related *Fusarium oxysporum* bloodstream infections. In a time span of 11 years, only 6 other infections due to *Fusarium* were documented and all were caused by a different species, *Fusarium solani*. None of the pediatric cancer patients had neutropenia at the time of diagnosis and all became febrile within two days after catheter manipulation in a specially designed room. Extensive environmental sampling in this room and the hospital did not gave a clue to the source. The outbreak was terminated after implementation of a multidisciplinary central line insertion care bundle. All *Fusarium* strains from blood and catheter tips were genetically related by amplified fragment length polymorphism fingerprinting. All patients survived the infection after prompt catheter removal and antifungal therapy.

Conclusion: A cluster with, genotypical identical, *Fusarium oxysporum* strains infecting 7 children with cancer, was most probably catheter-related. The environmental source was not discovered but strict infection control measures and catheter care terminated the outbreak.

Keywords: Fusariosis, *Fusarium* sp., *Fusarium oxysporum*, Catheter-related *Fusarium* fungemia, Pediatric invasive fungal infections

* Correspondence: arnaldoicolombo@gmail.com
[3]Division of Infectious Diseases, Escola Paulista de Medicina, Federal University of Sao Paulo (UNIFESP), Rua Pedro de Toledo, 669 e 5° -andar, Sao Paulo CEP 04039-032, Brazil
Full list of author information is available at the end of the article

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Background

Due to prolonged survival of patients with cancer, invasive fungal diseases (IFD) emerged as important cause of morbidity and mortality. In pediatric cancer patients, *Candida* species remain as the most important cause of IFD followed by invasive infections by *Aspergillus* spp. and other moulds [1–3].

Epidemiology of fungal infections varies markedly according to the geographic region. In Brazil, *Fusarium* spp. infections have emerged as major pathogens of systemic infections among cancer patients [4]. *Fusarium* species are widely spread in nature as plant pathogens and are also able to cause superficial, locally invasive and disseminated infections in humans [5]. Infection occurs mainly through airborne transmission, skin breakdown due to trauma, burns or insertion of vascular catheters [6, 7]. The clinical presentation relies mostly on the hosts' immune status, with disseminated infections been reported especially in severe immunocompromised individuals leading to high mortality rates [6, 8].

The lack of data concerning the epidemiology and clinical aspects of invasive infections by *Fusarium* spp. in pediatric patients is notable. Here we report a cluster of *Fusarium oxysporum* bloodstream infections from seven pediatric cancer patients documented in a single Brazilian pediatric cancer center.

Methods

We retrospectively studied all clinical and epidemiological data related to an outbreak enrolling seven cases of fungemia by *Fusarium oxysporum* occurring between October 2013 and February 2014 in the Pediatric Oncology Institute (IOP), located in Sao Paulo, Brazil. IOP is a tertiary care hospital specialized in pediatric oncology which admits 300 new cases per year. The outbreak was documented in patients who had been treated with chemotherapy at the same room used for cancer ambulatory chemotherapy. All long-term intravascular catheters are implanted in the surgery room and cared for by a group of trained nurses.

Clinical and epidemiological data were collected by a single investigator who reviewed all electronic medical records in order to complete a clinical form including information related to gender, age, underlying diseases, presence of neutropenia, exposition to invasive medical procedures and immunosuppressive drugs, imaging, culture results, treatment and clinical outcome.

During the outbreak, all catheters were removed and cultured in accordance with procedures standardized in our division based on cultures of catheter tips and material inside the reservoir. A cut-off of $\geq 10^3$ CFU/plate was used to differentiate significant from insignificant colonization as suggested by Brun–Buisson et al. [9, 10]. All patients were screened for putative deep-seated infection by sinus and chest CT as well as echocardiography and eye fundoscopy. After the diagnosis of fusariosis, at least two serum samples were collected from each patient to check for galactomannan levels and patients were followed for another 90 days for clinical signs and symptoms.

Laboratory procedures

Isolates

All *Fusarium* spp. cultured from blood and catheter samples (swab, flush and tip) were initially identified by morphological characteristics [11] and further identified to species level by sequencing *TEF1* and *RPB2* genes [12].

Besides clinical strains, we cultured environmental samples including air-filters, tap water samples, swab of room surfaces, and different intravenously administered drugs [13, 14]. We finally also evaluated all health care workers for the presence of onychomycosis or other superficial fungal infections.

Molecular identification of *Fusarium* isolates

Genomic DNA of all *Fusarium* isolates was extracted with the PrepMan Ultra Sample Preparation Reagent kit (Applied Biosystems, Palo Alto, CA, USA) according to the manufacturer's instructions. PCRs were performed for the amplification of the largest subunit of RNA polymerase (*RPB2*) and the translation elongation factor-1α (*TEF1α*) following the methods published by Salah et al. [15]. The primer pairs for *TEF1α* were EF1 & EF2 [16] and for *RPB2* were RPB2-7cR & RPB2 -5F [17]. PCR products were sequenced with the same primers used for amplification. The ABI Prism® Big DyeTM Terminator v. 3.0 Ready Reaction Cycle Sequencing Kit (Applied Biosystems) was used for sequencing PCR according to the manufacturer's instructions. The samples were run on an ABI 3730XL automatic sequencer (Applied Biosystems). A BLAST search of *TEF1* and *RPB2* sequences against the database FUSARIUM-ID (http://isolate.fusariumdb.orgl/), the *Fusarium* database (http://www.cbs.knaw.nl/*fusarium*) and GenBank databases (www.ncbi.nlm.nih.gov) were used as an initial step to identify isolates to species and/or species complex. The *TEF1* and *RPB2* nucleotide sequences of all isolates were deposited in GenBank.

Amplified fragment length polymorphism

Amplified fragment length polymorphism (AFLP) fingerprinting was performed as described recently [18]. Briefly, ~50 ng of genomic DNA was digested by using the HpyCH4IV and MseI restriction enzymes (New England Biolabs, Ipswich, MA, U.S.A.) and in the same reaction specific adaptors were ligated to each of the two sticky ends of the DNA fragments. The samples were after a 1 h incubation at room temperature diluted with 10 mM Tris-HCl, 1.0 μl of this diluted product was used as input for the PCR that contains the selective primers HpyCH4IV-C (5′-Flu-

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GTAGACTGCGTACCCGTAC-3′) and MseI-TGAG (5′-GATGAGTCCTGACTAATGAG). After the PCR was performed, the amplicons were 20× diluted using ddH_2O and 1.0 μl of it was mixed with 8.9 μl ddH_2O and 0.1 μl LIZ600 internal size marker (Promega, Leiden, The Netherlands) followed by a heating step for 1 min at 100 °C. Fragment analysis was performed on an ABI3500xL Genetic Analyzer (Applied Biosystems, Foster City, CA, U.S.A.) according to the manufacturer's instructions. Subsequently, the raw data was imported into Bionumerics v7.5 (Applied Maths, Sint Martems-Latum, Belgium), after processing the data a dendrogram was generated by using the UPGMA algorithm.

Results

From October 2013 to February 2014 we were caught by surprise with the occurrence of seven episodes of microbiologic documented catheter-related *F. oxysporum* bloodstream infections (CR-BSI) in our division. This finding led us to believe that we were facing an outbreak because only six cases of invasive fusariosis had been diagnosed in our hospital in the 11 years previously, all caused by *Fusarium solani* species complex strains.

Demographic and clinical data of all seven patients are depictured in Table 1. Ages ranged from 0 to 8 years (3 males), 6 out 7 were treated with chemotherapy for solid tumors, and one for acute lymphoid leukemia (ALL). Two patients (solid tumors) had underwent an autologous stem cell transplantation more than 14 days before and none of the patients received corticosteroids or other immunosuppressive agents. Only one patient had a neutrophil count below 500 cells/mm^3 at the moment of the infection. Fever was the only trigger to collect blood cultures and vascular catheters were removed promptly at the time fungemia was identified. The six intravascular devices removed included 5 totally surgically implanted (Porth-a-Cath) catheters and one peripherally inserted catheter (PICC). All fungemic episodes were documented following 2 days after the last catheter puncture by the nurse. No single patient had any additional skin breakdown or onychomycosis that could explain the portal of entrance for *Fusarium* spp. All catheter tips, reservoir and blood cultures collected through the CVC of the 7 patients yielded *Fusarium oxysporum*. Although they had no signs or symptoms of any organ involvement, further laboratorial investigation was conducted to exclude fungal invasion of target organs. All children had a chest computer tomography (CT), sinus magnetic resonance image, eye fundoscopy and echocardiography done without any evidence of a deep-seated fungal infection. All serum samples were galactomannan negative. Catheters were promptly removed after blood cultures became positive and all patients had good clinical response to antifungal therapy. Oral voriconazole was the therapy of choice for six patients (7 mg/kg/dose) and adequate serum levels (≥1 mg/L) were measured in all patients. One child was treated with liposomal amphotericin B (5 mg/kg/day) due to age restrictions (9 months) for using voriconazole.

It is important to note that during the whole period this cluster occurred, the hospital building was being enlarged, counting with an extensive construction area.

All environmental samples and different intravenous preparations in search for sources of *Fusarium* spp. were negative. Healthcare workers who had previous contact with the patients were checked for the presence of any cutaneous or nail lesions suggestive of fungal infections but nothing was found.

Molecular identification of *Fusarium* isolates

A total of 16 *Fusarium* spp. clinical isolates were identified to genus level by colony and microscopic characteristics of the isolates. Upon molecular identification, based on *TEF1* and *RPB2* partial genes analysis, all *Fusarium* isolates were found to be members of the *F. oxysporum* species complex. All environmental samples were culture negative.

A phylogenetic tree (Additional file 1: Figure S1) was constructed with a total of 20 sequences for two genes, with three strains from the *Fusarium solani* species complex (FSSC) i.e. *F. falciforme* (NRRL32542), *F. keratoplasticum* (FRC-S2477) and *F. petroliphilum* (NRRL32856) as outgroup. The generated tree was separated into two clades. Clade 1 included all members of the *F. oxysporum* species complex (FOSC) and clade 2 represented the *F. solani* species complex (FSSC), the final result of the identification process was that 16 isolates were confirmed as members of FOSC.

Typing results by amplified fragment length polymorphism

All *Fusarium* strains obtained from blood and catheter tips were considered genetically related by AFLP fingerprinting, suggesting that all isolates had a common source. Cluster analysis revealed the presence of two clusters, one with a 95% similarity that includes isolates BRAZIL 1127 (Patient 2 catheter tip culture), 1129 (Patient 2 reservoir culture), 1131 (Patient 2 blood culture) and 1134 (Patient 3 catheter tip culture), and a second one with all other Brazilian isolates that exhibited similarity of 97% (Fig. 1). The reference *F. oxysporum* isolates CBS192.31 and CBS180.29, had a similarity of 90% and 80%, respectively, to the Brazilian isolates.

Discussion

In Brazil, invasive fusariosis is the most common cause of systemic mould infections in hematologic cancer patients [4] and has been associated with a poor prognosis [19]. There is a gap in knowledge with regard to the epidemiology of fusariosis in pediatric patients. Most papers

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Table 1 Demographics and clinical characteristics of 7 patients with catheter-related fungemia due to *Fusarium oxysporum*

Case	Underlying diseases	HSCT	Age (years)	Gender	Neutropenia	CVC	GMI	Time interval between CVC placement and infection	Chest CT	ECHO	Fundoscopic exam	Therapy	Duration (days)	Outcome
1	Solid tumor	Auto	3	Male	Yes	Port-a-cath	Negative	665 days	Normal	Normal	Normal	Voriconazole	21	Alive
2	Solid tumor	No	2	Female	No	Port a cath	Negative	89 days	Normal	Normal	Normal	Voriconazole	21	Alive
3	Solid tumor	No	1	Male	No	Port a cath	Negative	114 days	Normal	Normal	Normal	Voriconazole	21	Alive
4	Solid tumor	No	9 months	Female	No	Port a cath	Negative	125 days	Normal	Normal	Normal	L-Ampho B	16	Alive
5	Solid tumor	Auto	1	Female	No	Port a cath	Negative	112 days	Normal	Normal	Normal	Voriconazole	21	Alive
6	Solid tumor	No	2	Female	No	Port a cath	Negative	282 days	Normal	Normal	Normal	Voriconazole	21	Alive
7	ALL in remission	No	8	Male	No	PICC	Negative	158 days	Normal	Normal	Normal	Voriconazole	14	Alive

ALL acute lymphoblastic leukemia, *Auto* Autologous, *CVC* central venous catheter, *PICC* peripherally inserted central catheter, *GMI* galactomannan index, *ECHO* echocardiography, *Chest CT* chest computed tomography, *L-Ampho B* liposomal amphotericin B

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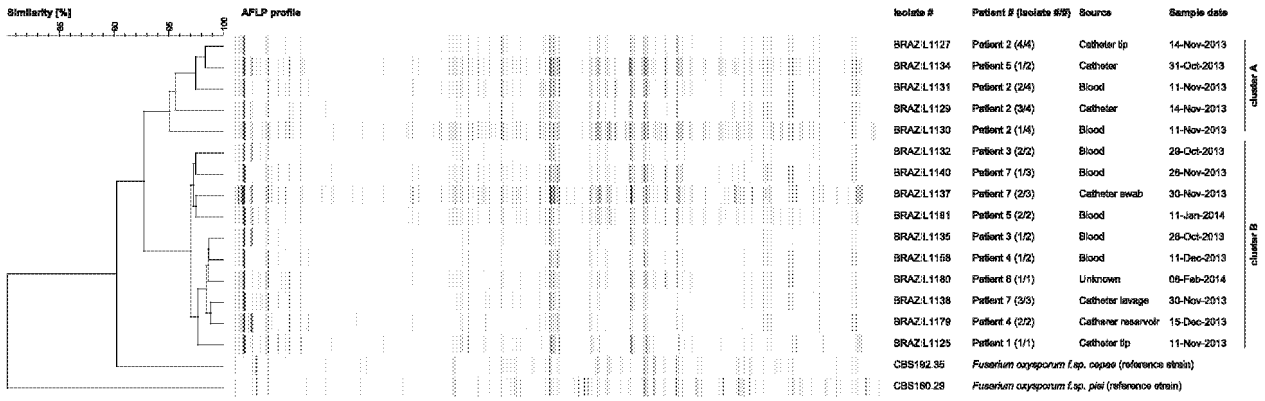


Fig. 1 AFLP fingerprint analysis was performed on 16 clinical *Fusarium oxysporum* species complex isolates. The dendrogram was generated by using the Pearson correlation similarity coefficient followed by single linkage cluster analysis

represent single case reports, with the exception of two outbreaks that were also documented in Brazilian medical centers and a review paper [20–22]. Information provided by the largest pediatric series of fusariosis published in the medical literature shows that the most common underlying condition was leukemia. Lung, blood and skin were the most commonly reported sites of infection and mortality rates are usually higher than 50% [22].

There is a consensus in the literature that the respiratory tract is the main portal of entry for this fungal infection, followed by skin breakdown due trauma and/or burns [23–31]. Despite some reports suggesting that fusariosis may also be acquired by contamination of a central venous catheter, the real prevalence and the natural history of intravascular catheter related fusariosis remains unclear [32–36].

Velasco and colleagues reported four immunocompromised children between 4 and 12 years, having neuroblastoma (n = 1) or hematologic malignancies (n = 3) who developed catheter-related *Fusarium* spp. infections without neutropenia. Fungemia was followed by skin lesions in only one patient and there was no clinical or radiological evidence of respiratory tract involvement. All patients survived after cathether removal and treatment with conventional amphotericin B [21].

Recently, Colombo et al. [35] described a case of a 13-year-old boy in Italy diagnosed with ALL readmitted 1 month after the start of chemotherapy due to intermittent fever of unknown origin, without any clinical or radiological evidence of invasive infection. Patient had his Broviac central venous catheter removed and blood cultures taken from the CVC were positive only for *F. solani* species complex. In addition, scanning electron microscopy of the catheter tip demonstrated the formation of a large mycelium in the catheter lumen that yielded a positive culture of *F. solani* complex. This finding represents a strong support for the hypothesis that fungemia was related to fungal colonization of the catheter. Fungemia resolved without any evidence of deep-seated infection after prompt CVC removal and therapy with voriconazole.

We report an outbreak of *F. oxysporum* infection enrolling 6 children with solid cancers and one with ALL in complete remission without persistent neutropenia. Fever was the only clinical manifestation of infection and the trigger to collect blood cultures in all episodes. Patients were carefully examined, and no single event of fungal deep tissue infection was documented. Finally, in the absence of respiratory infection as well as any type of skin breakdown that could be the port of entry, we are convinced that the intravascular catheter was the source of all episodes of *F. oxysporum*. Indeed, by typing all isolates with AFLP we confirmed our hypothesis that the 7 cases of *F oxysporum* were related, and all cultures of catheter tips and reservoirs had similar or identical genotypes to isolates obtained from blood cultures. Because all environmental investigations were negative for the presence of *Fusarium* spp., we were not able to identify the presumed common source of all infections. On the other hand, we may not exclude the possibility that medical devices were colonized by *Fusarium* during inappropriate management of intravascular catheters by health care workers or by the contamination of intravascular fluids.

Disseminated fusariosis is a difficult to treat fungal infection with an overall mortality ranging between 50% and 80% mostly due to uncontrolled hematologic malignant disease, prolonged neutropenia and the exposition to corticosteroids [19, 37]. Indeed, during a recent outbreak among children with cancer, fungemia and deep-seated infections due to *Fusarium* the mortality rate was 50% [20].

In contrast, in the present series, and as documented by previous reports of catheter related fusariosis [21, 33], we observed a complete clinical recovery of all patients after removal of the intravascular catheter and initiation of appropriate antifungal therapy. The good outcome

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documented with our patients may be explained also because there was no neutropenia or exposition to corticosteroids at the time they developed fusariosis.

F. oxysporum was the etiologic agent responsible for all fungemias documented in the present outbreak. This finding is in accordance with previous reports where seven out ten cases of *Fusarium* spp. fungemias and intravascular catheter related infections were due non-*solani Fusarium* species [21, 23, 33–36, 38].

Measures taken to control the outbreak were lowering the level of humidity in the CVC storage room and the implementation of a multidisciplinary quality-improvement intervention, including a central line insertion care bundle, consisting of hand hygiene, maximal sterile barrier use upon insertion and use of chlorhexidine skin disinfection. After the introduction of these actions, no further cases were noted.

In conclusion, *Fusarium* fungemia may be acquired by intravascular catheter colonization without any further deep-seated infections. In case of *Fusarium* outbreaks, especially involving non-*F. solani* species, clinicians should be aware that contamination of central venous catheter may be the potential source of infection.

Conclusions

We described 7 episodes of *Fusarium oxysporum* fungemia where we presented strong clinical and laboratorial documentation supporting the hypothesis that the portal of entry for all cases of fusariosis was the intravascular central catheter. In case of *Fusarium* outbreaks, especially involving non-*F. solani* species, clinicians should be aware that contamination of central venous catheter may be a potential source. Finally, we added information suggesting that the clinical outcome of catheter related fungemia due to *Fusarium* may be favorable in patients without neutropenia who were submitted to prompt CVC removal and early initiation of antifungal therapy.

Additional file

Additional file 1: Figure S1. Phylogenetic tree resulting from RAxML analysis for the RPB2 and TEF1genes (values of 85% for maximum likelihood are shown). List of the 16 isolates examined in this study (Brazil) and controls. (TIFF 330 kb)

Abbreviations

AFLP: Amplified fragment length polymorphism; ALL: Acute lymphoid leukemia; CFU: Colony forming unit; CR-BSI: Catheter-related blood stream infections; CT: Computer tomography; CVC: Central venous catheter; FOSC: Fusarium solani species complex; FSSC: Fusarium solani species complex; IFD: Invasive fungal diseases; PICC: Peripherally inserted central catheter

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Availability of data and materials

Please contact author for data requests.

Authors' contributions

FC and ALC performed epidemiological data analysis and initial draft preparation. FC, APCA, MLML, VZ, and ASP took care of patients and were involved in outbreak control. SSG, HX, FH and AMA, performed molecular studies. JFM and ALC provided expert advice and methodology. FC, JFM, and ALC finalized the draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the local institutional review board with approval IRB number 1.093.913.

Consent for publication

Not applicable.

Competing interests

FC received educational grants from Pfizer, United Medical and Astellas. ALC received educational grants from Pfizer, Gilead, United Medical and Astellas, and funding for research from Pfizer and Astellas. JFM received grants from Astellas, Basilea and Merck. He has been a consultant to Astellas, Basilea and Merck and received speaker's fees from Merck, United Medical and Gilead. All other authors no conflict of interest.

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Author details

[1]Oncology Pediatric Institute (IOP-GRAACC), Escola Paulista de Medicina, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil. [2]Department of Pediatrics, Escola Paulista de Medicina, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil. [3]Division of Infectious Diseases, Escola Paulista de Medicina, Federal University of Sao Paulo (UNIFESP), Rua Pedro de Toledo, 669 e 5° -andar, Sao Paulo CEP 04039-032, Brazil. [4]Westerdijk Fungal Biodiversity Centre, Utrecht, The Netherlands. [5]Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands. [6]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital (CWZ), Nijmegen, The Netherlands.

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CLINICAL REPORT

Chronic Infection Due to *Fusarium oxysporum* Mimicking Lupus Vulgaris: Case Report and Review of Cutaneous Involvement in Fusariosis

M. PEREIRO Jr.[1], M. T. ABALDE[1], A. ZULAICA[2], J. L. CAEIRO[2], A. FLÓREZ[1], C. PETEIRO[1] and J. TORIBIO[1]

Departments of Dermatology, [1]Faculty of Medicine, Complejo Hospitalario Universitario, Santiago de Compostela, Spain and [2]Hospital Xeral CiesVigo, Spain

A 67-year-old female presented with a 20-year-old lesion involving the right ear and preauricular area mimicking tuberculous lupus. *Fusarium oxysporum* infection was confirmed by biopsy studies and cultures. The biopsy specimen showed an unusually extensive dermal invasion with fungal hyphae. This is an uncommon clinical presentation for *Fusarium* infection in a healthy patient. When referred to us, the patient had received antifungal therapy with itraconazole without any benefit. Improvement was obtained with fluconazole therapy. The spectrum of cutaneous involvement related to *Fusarium* spp. includes toxic reactions, colonization, superficial indolent infection, deep cutaneous or subcutaneous infections and disseminated infection.

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Manuel Pereiro Jr., MD, PhD, Departamento de Dermatología, Facultad de Medicina, C/. San Francisco, s/n, 15705 Santiago de Compostela, Spain.
E-mail: manuelpe@usc.es

Fusarium spp. are soil and plant saprophytes commonly associated with human and animal myco-toxicosis. However, species in this genus play an emerging role as pathogens in human infections. *F. solani*, *F. oxysporum* and *F. verticilloides* are the species most frequently reported as human pathogens in localized and disseminated infections (1).

Reports on localized *Fusarium* infections have mainly described therapeutic and diagnostic difficulties in onycho-mycosis and keratitis and other extra-cutaneous involvement. There have been few reports of atypical cutaneous fusariosis. We report a well-documented case of long-standing localized cutaneous fusariosis mimicking lupus vulgaris that responded well to fluconazole therapy. Cutaneous diseases related to *Fusarium spp*. infections are reviewed.

CASE REPORT

A 67-year-old female with a history of type II diabetes, which had been treated orally, was referred to our hospital for diagnosis and management of a 20-year-old lesion in the right ear. The patient did not recall any previous traumatic injury in the affected area. In 1980 she was diagnosed with infectious granuloma caused by fungi or mycobacteria. At that time, all complementary tests for mycobacteriosis were negative. No mycological cultures were carried out. However, based on clinical and histological findings she then received treatment with rifampicin, isoniazid and ethambutol for 2 months, followed by rifampicin and isoniazid for 7 months. In 1982 she received tentative cryotherapy. In 1990, as a result of the presence of fungal elements in biopsy specimens, she was diagnosed with cutaneous mycosis and received treatment with itraconazole 200 mg/day for 6 months followed by terbinafine 250 mg/day for 2 months, without any benefit.

In January 2000 she was referred to us, presenting with an infiltrated, soft plaque involving the whole helix, slight pruriginous, resembling lupus vulgaris (Fig. 1). Routine tests, including blood cell count, biochemistry and X-ray examination were normal. A standard multi-test for cellular immunity (tetanus, diphtheria, Streptococci, proteus, tuberculin, glycerol, Candidin, trichophytin) gave normal results. All laboratory tests for mycobacteria, including cultures and PCR detection, were negative. A biopsy specimen was taken for histological examination. Hematoxylin–eosin staining showed a chronic inflammatory response produced by epithelioid cells, eosinophils and numerous giant foreign body cells. Inside the foreign



Fig. 1. Infiltrated plaque with erythematous areas, covered by slight scaling and scars and with badly defined margin in the right ear.

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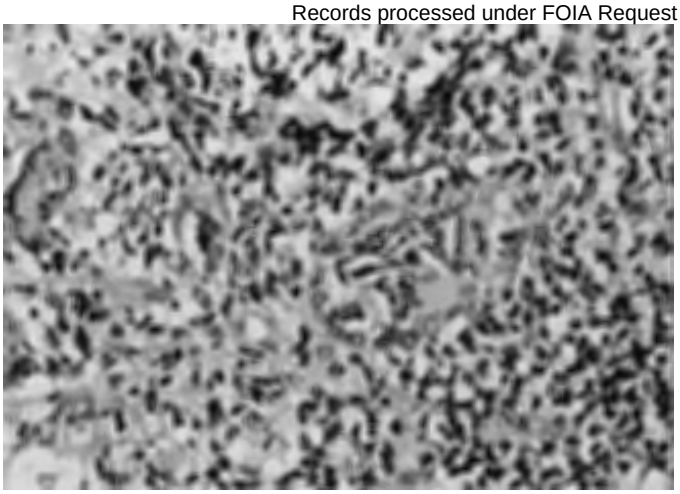


Fig. 2. PAS-positive hyphae sparsely distributed in the dermis (original magnification × 400).

body cells, pale structures resembling fungal hyphae were observed. Periodic acid–Schiff (PAS) staining showed numerous hyphae sparsely distributed in the dermis and also inside giant cells (Fig. 2).

A new biopsy specimen for mycological identification was sampled onto chloramphenicol–gentamicin–Sabouraud's agar and cyclohexamide–Sabouraud's agar at 25°C and 37°C. Chloramphenicol–gentamicin–Sabouraud's agar cultures yielded velvety colonies, white to pale gray in color at 25°C and orange at 37°C. Old cultures developed violet areas at both 25°C and 37°C. Subcultures and slide cultures were prepared for species identification onto oatmeal agar, potato sucrose and potato dextrose agar. Microscopic examination revealed wide vegetative aerial mycelium with septate, branched hyphae, scarce fusiform, 3–5-celled, slightly curved, macroconidia, pointed at the tip, numerous, single-celled, oval/ellipsoid, non-chain microconidia developed on short lateral conidiophores and intercalary, single or paired, hyaline, smooth-walled chlamydospores (Fig. 3).

On the basis of these data we identified the colony as *F. oxysporum* Schlecht.:Fr. (2), and started treatment with oral fluconazole 150 mg/day. After 3 months the patient showed a marked improvement.

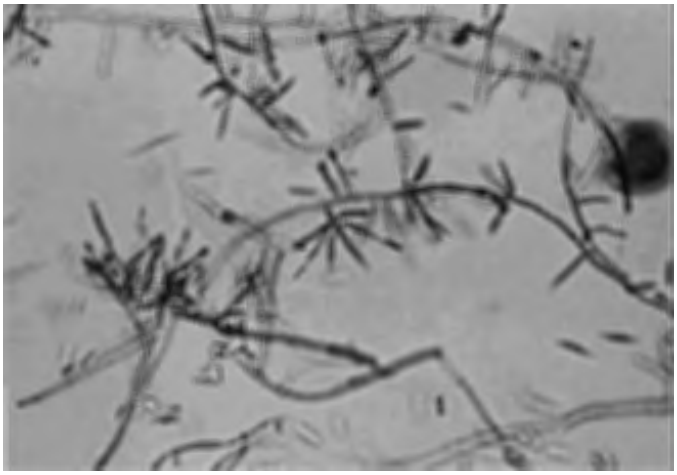


Fig. 3. Slide cultures on Sabouraud's agar reveal the presence of well-ramified, septate, hyaline hyphae, with lateral, short, simple, sometimes branched, conidiophores and sparse, ellipsoid, single-celled microconidia.

DISCUSSION

Cutaneous diseases related to *Fusarium* spp. can appear in both immunocompromised and healthy hosts and include toxic reactions, colonization, superficial infection, deep cutaneous or subcutaneous infections and disseminated infection.

Exposure to the toxin deoxynivalemol caused lesions of the skin and mucous membranes, suggesting a toxic reaction, in grass planters in The Netherlands (3). Chronic indolent superficial fusariosis limited to the skin appendages or corneal layer, namely onychomycosis and intertrigo, is frequent (4). *F. oxysporum* was reported as causing distal subungual, proximal subungual (5) and superficial white toenail mycosis in a patient who presented with a low extremity temperature after cranial trauma (6). Colonization in surgical wounds, severe burns, venous and arterial leg ulcers is a common finding (1, 7, 8) and was related to diabetes in one case (7). However, *F. oxysporum* was also reported as being the only causative agent of a large foot ulcer (9). When fungal hyphae reach the dermis and subcutaneous tissue, subcutaneous nodules (10, 11), sporotrichoid nodules (12), panniculitis (13), mycetoma (14, 15) or chronic granuloma (16, 17) can be observed in both immunocompromised and healthy hosts.

In healthy hosts, localized papular and pustular lesions that developed after trauma were reported (18, 19). A case presenting with extensive chronic granulomatous lesions involving the 2 arms, in which the authors could not demonstrate any known immune defect, was caused by *F. oxysporum* (20). Our case report described a diabetic patient who denied any trauma at the onset of the process. However, over the years she had received several treatments, including tentative cryotherapy. This cryotherapy injury possibly facilitated the deep invasion and later clinical appearance, as well as further antifungal resistance.

Host responses in localized cutaneous chronic *Fusarium* infections have included granuloma (16), pseudocarcinomatous hyperplasia (15), sometimes with carcinomatous changes (21), and eccrine syringofibroadenomatous hyperplasia (22). Despite the long evolution time, granuloma without carcinomatous changes was observed in the present case.

The first case of systemic infection by *Fusarium* spp. was published in 1973 (23). Since then, a number of systemic infections caused by *Fusarium* spp. alone (24, 25) or in association with other agents (26) have been published. Neutropenia is probably the most important predisposing factor for disseminated infections in immunocompromised hosts. The clinical picture is characterized by fever and muscular pain refractory to treatment. Cutaneous involvement is common, including painful erythematous maculae, palpable or non-palpable purpura, flaccid pustules and necrosis on the trunk, face, scalp, extremities, palms and soles (1, 23–26).

There is no agreement between the *in vitro* and *in vivo* results in the reports describing the management of *Fusarium* infections and therefore none of the therapeutic regimens reported can be considered ideal (1). The gold standard for the treatment of disseminated infection continues to be amphotericin B, either alone or in combination with 5-fluorocytosine, rifampicin or azole derivatives (1, 23–26). In deeply located infections, good results were obtained by

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combining surgical excision with antifungal treatment (27). However, reported treatments have produced contradictory results depending on the patient's condition (3, 6–27). In the case reported here the patient's history, which revealed itraconazole resistance, and the benign condition of a 20-year-old infection caused us to reject the use of a more aggressive therapy. Fluconazole has little activity on intracellular fungi (28), but does enhance the killing activity of neutrophils, monocytes and macrophages (29). In our case clinical improvement was obtained after 3 months of fluconazole therapy.

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MAJOR ARTICLE

Cutaneous Infection by *Fusarium* Species in Healthy and Immunocompromised Hosts: Implications for Diagnosis and Management

Marcio Nucci[1] and Elias Anaissie[2]

[1]University Hospital, Universidade Federal do Rio de Janeiro, Brazil; and [2]University of Arkansas for Medical Sciences, Little Rock

Infections by *Fusarium* species frequently involve the skin, either as the primary or the metastatic site. To better understand the pathophysiology of these infections, 43 new patients with fusariosis were evaluated, and the literature was reviewed. A total of 259 patients (232 immunocompromised and 27 immunocompetent) were identified. Skin involvement was present in 70% of patients, particularly in immunocompromised patients (72% vs. 52%; $P = .03$). In immunocompetent patients, cutaneous infections were characterized by preceding skin breakdown, localized involvement, slow pace of progression, and good response to therapy. In contrast, skin involvement in immunocompromised patients was only occasionally preceded by skin breakdown and typically was presented as rapidly progressive disseminated lesions at various stages of evolution. Metastatic skin lesions were associated with fungemia, neutropenia, and death. Skin was the single source of diagnosis for the majority of immunocompromised and immunocompetent patients. Recommendations for the prevention of fatal fusariosis originating from skin are presented.

Fungal infections represent an important complication for immunosuppressed patients and are associated with high morbidity and mortality [1, 2]. The limited diagnostic tools available usually delay the diagnosis and treatment of these infections. Therapy is complicated further by the variable susceptibilities of pathogens to antifungal agents [3]. Thus, any clue to the early diagnosis of infection with a specific pathogen may lead to changes in antifungal therapy and may be critical for an improved outcome. *Fusarium* species have long been recognized as a cause of localized infections in immunocompetent individuals [4] and disseminated infections among those who are severely immunocompromised [5]. *Fusarium* species now represent the second most frequent mold-causing invasive fungal infections in this latter population [5, 6].

One of the most frequent aspects of infection by *Fusarium* species is the development of skin lesions, which are frequently the only source of diagnostic material. Therefore, it is important to characterize the clinicopathological features of skin infection involvement in fusariosis and to establish their role in the diagnosis and management of this infection. We describe the characteristics of fusarial skin infections in immunocompetent and immunocompromised hosts and make practical recommendations for management.

PATIENTS AND METHODS

A computerized search of MEDLINE from January 1966 to October 2001 was performed; we used the keywords "*Fusarium*" and "fusariosis." In addition, 45 previously unpublished cases of fusariosis from Brazil were included in our analysis [7]. We selected studies that provided a detailed description of the clinical presentation, treatment, and outcome. Reports with limited

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Reprints or correspondence: Dr. Elias J. Anaissie, Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, 4301 W. Markham, Slot 776, Little Rock, AR 72205 (anaissieeliasj@exchange.uams.edu).

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information, those published in languages other than English, and duplicate publications were excluded, as were cases of onychomycosis without an associated soft-tissue infection.

The following data were reviewed: underlying disease and its therapy, presence of neutropenia (<500 neutrophils/mm^3) and other immunosuppression, results of blood cultures, skin lesions (presence, distribution, type [localized or disseminated], culture results, and histopathology), and clinical outcome. Localized infection was defined as the presence of a single skin lesion or >1 lesion clustered in a single cutaneous segment; disseminated infection was defined as the presence of >1 skin lesion in noncontiguous sites. Categorical variables were analyzed by χ^2 or Fisher's exact test. Registration and analysis of data were performed by EpiInfo 6.04 software (Centers for Disease Control and Prevention). $P \leq .05$ was considered to be statistically significant.

RESULTS

There were 157 reports describing fusarial infections between 1970 and 2001. Cases described in 31 reports were excluded because of publication in languages other than English ($n = 15$), lack of detailed clinical description ($n = 12$), and duplicate publication ($n = 4$). Thus, we examined 126 publications reporting 216 patients with fusariosis [5, 8–131]. Forty-three previously unpublished cases of fusarial infections from a multicenter Brazilian study [7] also were included, for a total of 259 patients. The 259 evaluated patients included 232 who were immunocompromised (90%) and 27 who were immunocompetent (table 1). Skin involvement by fusariosis was present in 181 patients (70%) and was more common among immunocompromised patients (72% vs. 52%; $P = .03$).

Table 1. Underlying conditions in 259 cases of fusariosis in immunocompromised and immunocompetent patients.

Condition	No. (%) of patients
Immunocompromised	232
Cancer	205 (88)
Aplastic anemia	15 (6)
Solid-organ transplantation	7 (3)
Renal	4
Heart and lung	1
Heart and liver	1
Lung	1
Other	5 (2)
AIDS	2
Diabetes	1
Chronic neutropenia	1
Chronic granulomatous disease	1
Immunocompetent	27
None	15 (56)
Motor vehicle accident	4 (15)
Renal failure, chronic ambulatory peritoneal dialysis	3 (11)
Burns	2 (7)
Alcohol abuse	1 (4)
Heatstroke	1 (4)
Injection drug abuse	1 (4)

Type of skin lesions in immunocompetent hosts. Thirteen of the 14 immunocompetent patients with fusarial skin involvement presented with localized lesions (figure 1). The majority of these patients ($n = 10$) had a history of recent skin breakdown at the site of the fusarial infection, either as a result of trauma (7 patients) or of preexisting onychomycosis (3 patients). Fusarial infection presented as cellulitis among these latter 3 patients. The 7 patients who developed infection after trauma presented with necrotic lesions of the skin and soft tissues after a motor vehicle accident (2 patients) [35]; cellulitis with necrosis after severe burns (2 patients) [10, 18]; chronic, painful toe ulcer that developed 1 year after surgery on the same toe [19] (1 patient); subcutaneous abscess after direct trauma, 1 year earlier, with a small bamboo chip (1 patient) [84]; and a plaque with several vesicles and pustules and a central superficial ulcer on a finger 3 weeks after minor trauma (1 patient) [32]. In 3 patients, a history of skin breakdown or trauma was not reported. Two of the latter patients presented with ulcerated lesions resembling chromoblastomycosis. One patient had 1 large ulcerated lesion extending from the left shoulder to the upper forearm, as well as another circular indurated ulcer on the right forearm, which had evolved over years [28]. The second patient had 2 large, deep ulcers covering the entire skin surface of the dorsum of both feet, which had been present for 1 year [56]. A third patient without a history of skin breakdown had a 5 × 5–mm erythematous pustule on the dorsum of the hand [12]. The single case of disseminated metastatic skin lesion occurred in a child with fever, pulmonary infiltrates, multiple erythematous papules and nodules, and several blood cultures yielding *Fusarium* species. The results of an extensive workup for an underlying immunosuppressive illness were negative [7].

Type of skin lesions in immunocompromised hosts. Of 167 patients, localized cutaneous lesions occurred in only 20 (12%), of whom 11 had a recent history of skin breakdown. The most frequent lesion among the latter 11 patients was cellulitis at the site of preexisting onychomycosis (8 patients). The skin lesions in the remaining 3 patients were necrotic lesions on the feet after local trauma (2 neutropenic patients with acute lymphoid leukemia) [7] and an abscess on the left calf (a bone marrow transplant recipient with acute lymphoid leukemia) [42].

Among the 9 patients without a history of skin breakdown,

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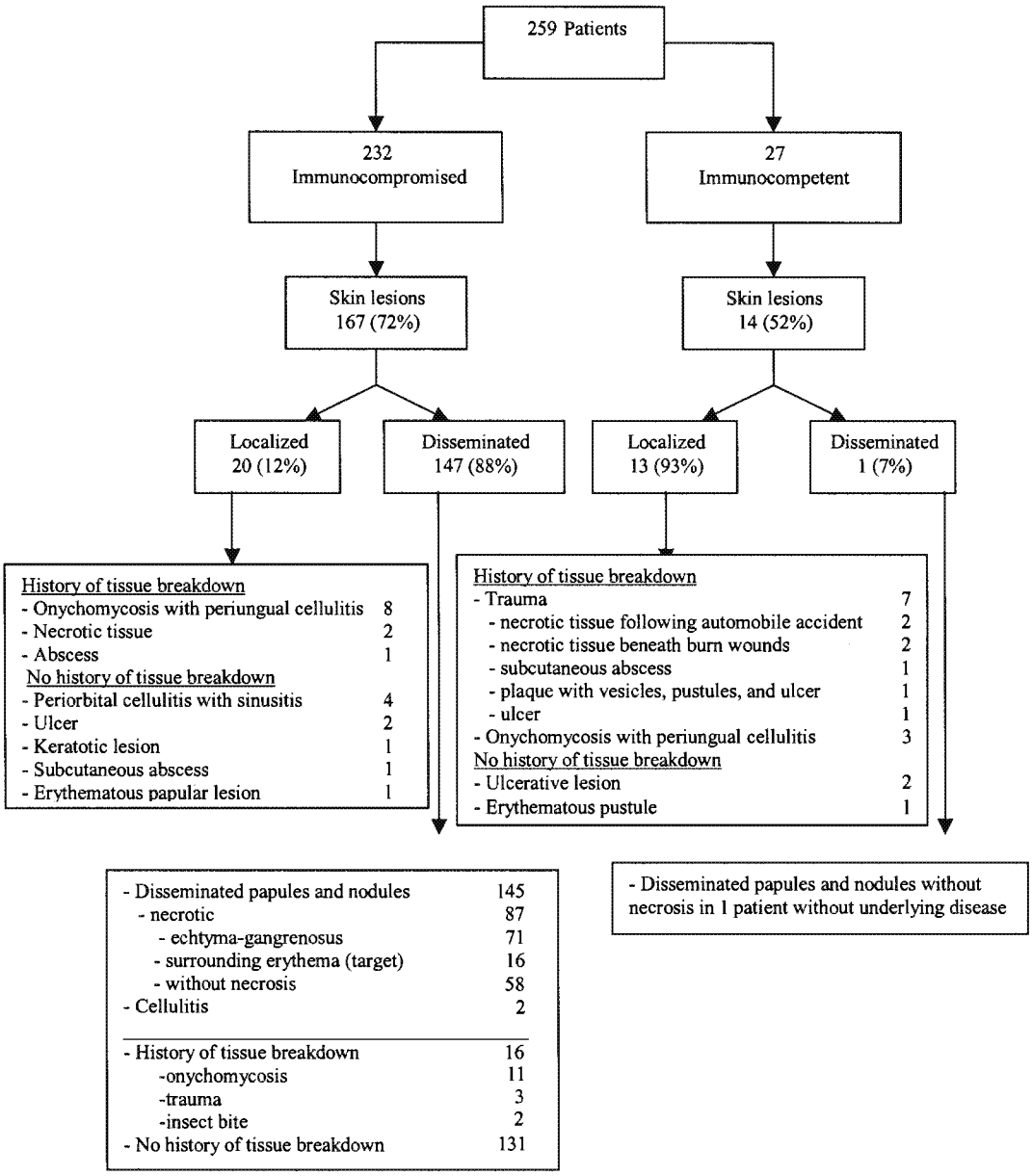


Figure 1. Type and extent of skin lesions caused by *Fusarium* species, according to immune competence of host. Among the 65 immunocompromised patients without skin lesions, infections included fungemia (37 patients), pneumonia (10 patients), sinusitis (9 patients), brain abscess (2 patients), arthritis (1 patient), liver involvement (1 patient), and endophthalmitis (1 patient). No data were available for the remaining 4 patients. Infections among 13 immunocompetent patients without skin involvement included peritonitis following peritoneal dialysis (3 patients), sinusitis (2 patients), pneumonia (2 patients), arthritis following motor vehicle accident (2 patients), endophthalmitis (2 patients [1 injection drug user]), and fungemia following heat stroke and allergic bronchopulmonary fusariosis (1 patient each).

the skin lesions included periorbital cellulitis (4 patients with sinusitis) and ulcerative lesions (2 patients): a leg ulcer in a patient with diabetes [16], and a left heel ulcer in a kidney transplant recipient [91]. One patient with chronic granulomatous disease developed a keratotic lesion on the cheek that evolved over 6 months [8]. One renal transplant recipient presented with a subcutaneous abscess on the dorsum of the foot [121], and 1 patient with acute lymphoid leukemia developed a single 2×2–cm erythematous, tender, raised lesion on the forearm [48]. Ten of 12 patients with cellulitis were neutropenic, and 4 of the 5 patients with ulcers or abscesses had adequate neutrophil counts ($P = .02$).

The most frequent skin lesions among patients with disseminated disease were multiple painful erythematous papular or nodular lesions with (87 patients) or without (58 patients) central necrosis. Most necrotic lesions had an ecthyma gan-

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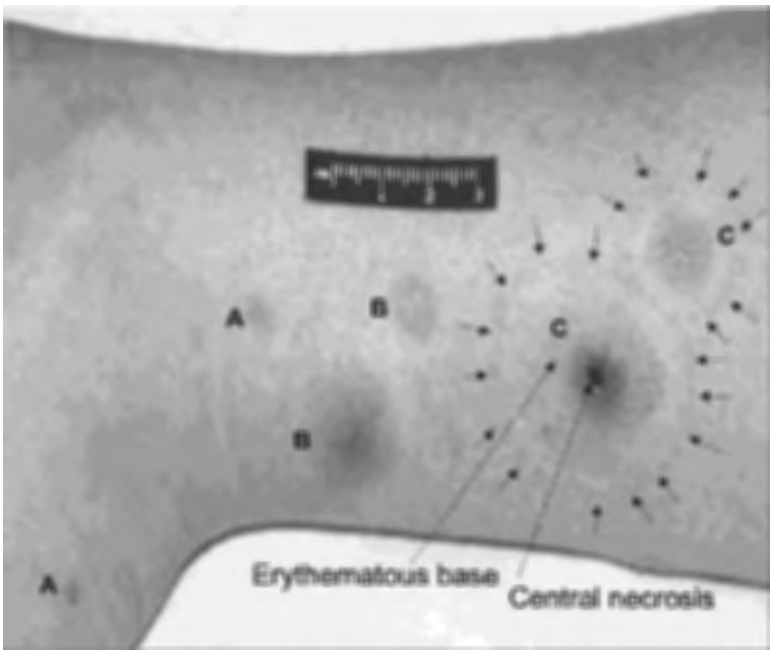


Figure 2. Lower extremity involvement, with several *Fusarium* skin lesions of different types and ages. *A,* Small macular lesions. *B,* Papular lesions of different sizes. *C,* Two target lesions: central necrosis surrounded by an erythematous base, an area of normal skin, and an outer rim of thin erythema *(arrows).* Patient was a 32-year-old woman with relapsed leukemia who had undergone allogeneic bone marrow transplantation and developed disseminated and fatal fusarial infection.

grenosum-like appearance (71 patients), whereas target lesions (a thin rim of erythema of 1–3 cm in diameter surrounding the above-mentioned papular or nodular lesions) were reported in the remaining 16 patients (figure 2). One patient developed bullae in addition to nodular lesions (figure 3). These lesions involved practically any skin site, with predominance in the extremities. The lesions evolved rapidly, usually over a few days (range, 1–5 days). Lesions at different stages of evolution were

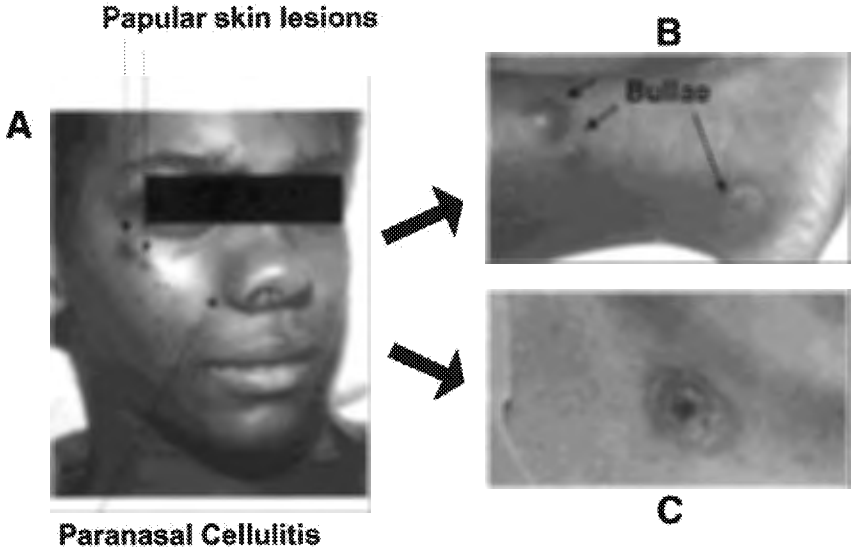


Figure 3. *A,* Paranasal cellulitis in a 15-year-old girl with aplastic anemia who presented with *Fusarium* sinusitis with subsequent development of cutaneous nodules on the face *(A),* extremities *(B),* and chest *(C)* caused by *Fusarium* species. Note the appearance of bullae in some fusarial lesions *(B).* The chest lesion became necrotic *(C);* the patient developed endophthalmitis with blindness and died a few days later. Panels *B* and *C* are reprinted with permission from [65].

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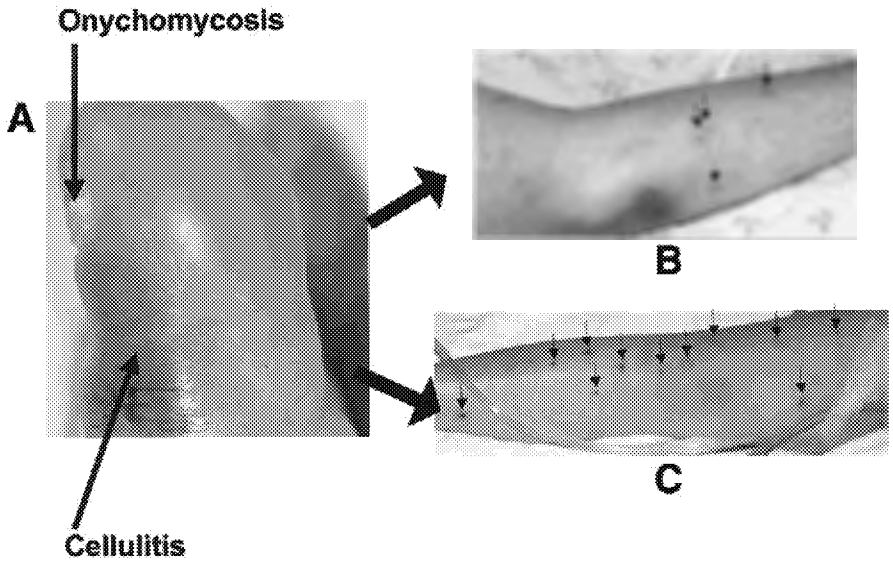


Figure 4. *Fusarium* toe cellulitis developing at the site of onychomycosis *(A)* after cytotoxic chemotherapy in a 45-year-old woman with lymphoma who underwent allogeneic bone marrow transplantation. Disseminated *Fusarium* skin lesions developed subsequently in upper *(B)* and lower *(C)* extremities. Several blood cultures were positive for *Fusarium* species. Panel *A* is reprinted with permission from [5].

described in 51 patients (usually a combination of papules, nodules, and necrotic lesions; figure 1), and myalgias (suggesting muscle involvement) were reported in 23 patients.

Among 16 patients with metastatic skin lesions, a recent history of cellulitis at the site of onychomycosis (11 patients; figures 4 and 5), local trauma (3 patients), or an insect bite (2 patients) were reported, suggesting that skin was the primary site of infection that led to disseminated fusariosis in these 16 patients. Only 2 patients with metastatic skin lesions did not have papular or nodular lesions. In these 2 patients, a fusarial cellulitis developed in one toe after trauma and was followed by cellulitis at another toe in the other foot [45, 46]. The pattern of skin lesions did not appear to be associated with any particular *Fusarium* species.

Compared with nonneutropenic immunocompromised patients, patients with neutropenia had a higher rate of skin lesions (78% vs. 45%; $P = .0001$), and these lesions were disseminated more frequently (94% vs. 41%; $P < .0001$). Patients

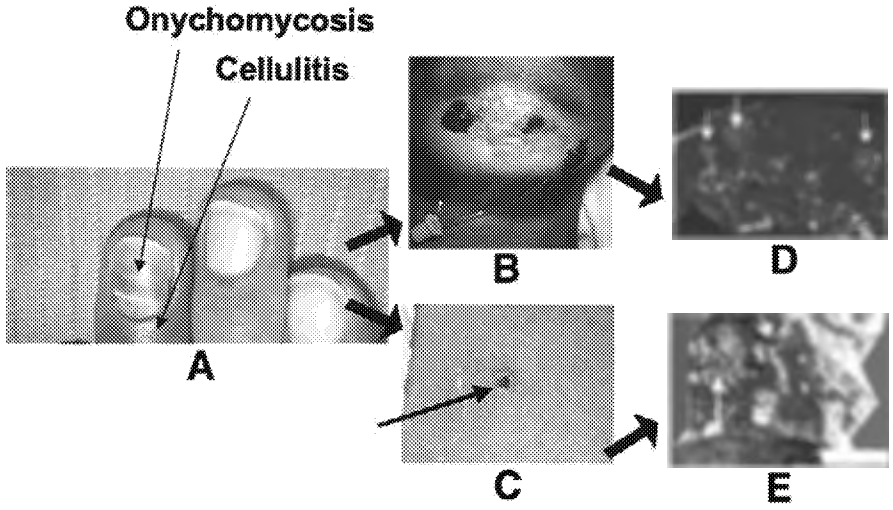


Figure 5. *Fusarium* finger cellulitis developing at the site of onychomycosis *(A)* after autologous bone marrow transplantation in a 43-year-old man with Hodgkin's disease. Disseminated *Fusarium* skin lesions developed subsequently on the face *(B)* and trunk *(C)*. Fatal multiorgan involvement followed, with liver *(D)* and lung *(E)* involvement. Panel *A* is reprinted with permission from [5].

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Table 2. Differentiating features of cutaneous infection with *Fusarium* species between immunocompetent and immunocompromised hosts.

Feature	Immunocompetent host	Immunocompromised host
Risk factor		
Tissue breakdown (trauma, onychomycosis, insect bite)	Very common (>70%); may precede infection by up to 1 year	Uncommon (<10%)
Neutrophil count	Adequate	Usually immediately before infection; neutropenia
Type of skin lesion	Necrosis, cellulitis, ulcer, abscess, rarely chromoblastomycosis-like	Multiple, painful erythematous papules or nodules with necrosis; some with evolution into target lesions; different stages of evolution; less commonly, cellulitis (usually site of tissue breakdown)
Histopathology		
Inflammation	Marked	Scant
Necrosis	Variable	Marked
Vascular invasion	No	Abundant
Neutrophils	Abundant	No
Hyphae	Few	Abundant
Extent	Localized	Disseminated
Pace of clinical progression	Slow, over months	Rapid, over days
Blood cultures	Negative	Positive (50%)
Skin cultures, histopathology	Positive	Positive
Treatment	Local debridement; systemic antifungal therapy; perhaps local antifungal therapy	Perhaps systemic antifungal therapy with newer agents; perhaps granulocyte transfusion
Mortality	Very low	Very high, unless immunosuppression can be resolved promptly

with disseminated lesions also were more likely to have blood cultures positive for *Fusarium* species than those whose lesions were localized (57% vs. 7%; $P < .0001$).

Contribution of cutaneous infection to the diagnosis of fusariosis. Skin lesions were the single source of diagnosis of fusarial infection in the majority of patients (100 [55%] of 181), including in the 148 patients whose skin lesions were disseminated. Of these 148 patients, 78 had blood cultures negative for *Fusarium* species, and the skin was the only source of diagnostic material in all except 2 patients (sinus was the source in 2 patients). Detailed information on the timing of positive blood cultures and the occurrence of skin lesions was provided for 18 of the remaining 71 patients whose blood cultures yielded *Fusarium* species

In these latter patients, skin lesions preceded fungemia in 11 patients by a median of 5 days (range, 1–10 days), occurred on the same day (4 patients), and did not appear until after the diagnosis of fungemia was made (3 patients, at 3, 5, and 13 days after diagnosis). Seventy-six of the 82 patients for whom information on histopathologic examination was available had hyaline acute-branching septate hyphae invading the skin. Hyphal invasion extended into the blood vessels, with thrombosis and skin necrosis in those patients with metastatic lesions.

Patient outcome in relation to cutaneous involvement. The overall death rate of patients with fusarial infections was 66% (170 of 259 patients), with a 100% mortality among persistently neutropenic patients, compared with only 30% among those who ultimately recovered from immunosuppression ($P < .0001$). A higher mortality also was observed among patients with skin lesions (70% vs. 56%; $P = .04$), particularly among those whose lesions were disseminated (76% vs. 39%; $P < .0001$). However, a stratified analysis of patients with metastatic lesions by neutrophil count revealed that the higher mortality rate remained significant only among those who had an adequate neutrophil count throughout the course of their illness. In this group of patients with persistently adequate neutrophil counts, the mortality rate was 67% for those with metastatic lesions and 21% for those with localized lesions ($P = .03$). The mortality among neutropenic patients was high, regardless of whether the lesions were localized or metastatic (64% vs. 77%; $P = .33$), respectively, which reflects the contribution of severe immunosuppression to the fatal outcome.

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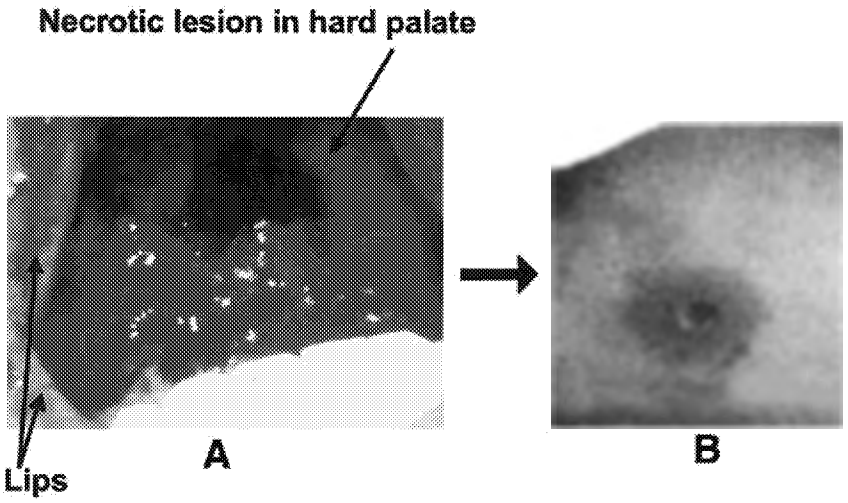


Figure 6. Black necrotic hard palate ulcer *(A)* caused by *Fusarium* species in a 29-year-old patient with leukemia and fusarial sinusitis and pneumonia. The infection later became disseminated and involved multiple organs, including the skin *(B)*.

DISCUSSION

This is the first attempt to characterize the cutaneous involvement in infections with *Fusarium* species in immunocompetent and immunosuppressed hosts and to compare the findings in these 2 patient populations. Our analysis yielded several findings. First, skin lesions represent a frequent manifestation (>50%) of infection by *Fusarium* species, especially among immunocompromised patients, in contrast to the rare cutaneous involvement (<10%) in infection with other opportunistic fungi, such as *Candida* species or *Aspergillus* species. Second, skin is the primary site of disseminated and life-threatening infections among a subset of highly immunocompromised patients. Third, skin is also the most common source of diagnostic material (and frequently the only one). Fourth, distinct patterns of skin involvement by *Fusarium* species exist, depending on the immune status of the host (table 2). Fifth, the mortality rate among neutropenic patients is high, regardless of whether fusarial skin lesions are localized or disseminated. This is in contrast to the immunocompromised patients with adequate neutrophil count and in whom localized skin lesions are associated with a lower mortality rate. We also describe the first patient with skin bullae as a manifestation of disseminated fusariosis.

Among immunocompetent individuals, skin lesions typically are localized and develop after skin breakdown at the site of

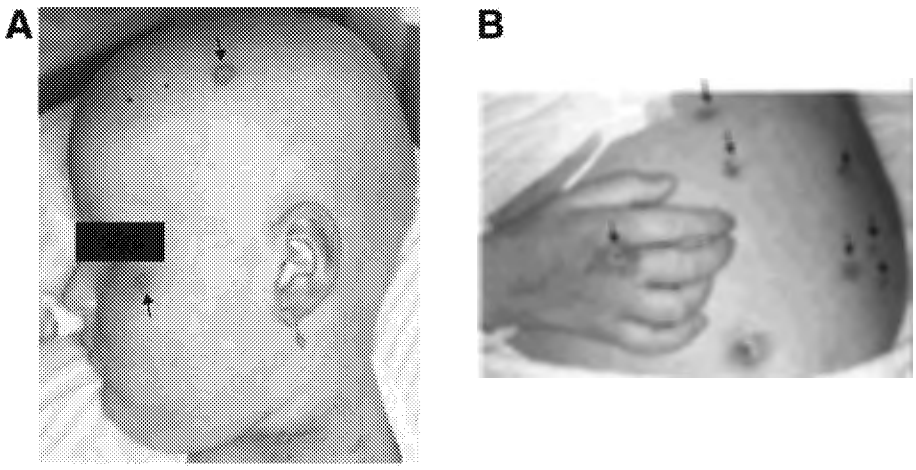


Figure 7. Multiple cutaneous fusarial skin lesions on the face and scalp *(A)* and abdomen *(B)* of an 8-year-old girl who experienced relapse of leukemia. The infection started as paranasal sinusitis, which was followed by pneumonia and skin lesions. Patient died 30 days later with persistent fusariosis and leukemia. Courtesy of Dr. Flavio Queiroz-Telles, University Hospital, Universidade Federal do Paraná, Curitiba, Brazil.

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infection. It is of note that skin breakdown may precede infection by up to 1 year. Cutaneous infections in these immunocompetent hosts present most commonly as necrotic lesions that complicate extensive wounds (burns and trauma), cellulitis secondary to underlying onychomycosis, or chronic ulcers and abscesses. Skin infection may rarely resemble chromoblastomycosis, an infection caused by dematiaceous fungi.

By contrast, the majority of immunocompromised patients have disseminated skin lesions that evolve over a much shorter period of time, particularly among neutropenic patients. Lesions in these patients typically consist of multiple painful erythematous papules or nodules with necrosis, occur among neutropenic patients, and are associated frequently with cultures positive for *Fusarium* species (blood and skin) and death. These disseminated lesions may result from a skin breakdown in some patients with preexisting onychomycosis. When such patients undergo severely immunosuppressive therapy, toe or finger cellulitis develops at the site of the onychomycosis and is followed by disseminated infection (figures 4 and 5). It is likely that the preexisting skin damage allows for entry of these pathogenic fungi into the underlying soft tissues, which leads to the development of cellulitis and subsequent dissemination in a manner reminiscent of bacterial infections. The nasal sinuses are yet another primary site of fusarial infections that may lead to dissemination after severe immunosuppression (figures 6 and 7).

Our study is limited by its retrospective nature and, thus, may underestimate the true incidence of some of our findings, such as the history of previous trauma and the presence of lesions at different stages of evolution. However, the consistency of findings across various reports from different institutions and over a long period of time suggests that our analysis is an accurate reflection of the nature of the cutaneous involvement in infection by *Fusarium* species

Our findings have several implications for the clinical management of immunocompromised patients. Because skin may be the source for disseminated and frequently life-threatening fusarial infections, we recommend that patients likely to undergo severely immunosuppressive therapy undergo a thorough skin evaluation before commencing immunosuppressive therapy (table 3). All areas of tissue breakdown should be identified and suspicious skin lesions cultured, and a biopsy should be performed. The histopathological findings of infection with *Fusarium* species (branching hyaline hyphae) cannot be distinguished from those caused by infection with other opportunistic molds, such as *Aspergillus* species. Because of these remarkable similarities and the differences in susceptibility to antifungal agents between *Fusarium* species and various hyaline molds, identification by culture is critical.

Local debridement should be performed and topical antifungal agents (e.g., natamycin and amphotericin B) considered if *Fusarium* species are identified. In addition, severely immunocompromised patients with skin or other exposed tissue breakdown should avoid exposure to environmental sources of *Fusarium* species, such as tap water. Indeed, we have shown that hospital water may be contaminated with *Fusarium* species and may lead to patient infection [132].

Table 3. Prevention of fusarial infections during severe immunosuppression.

Educate patients about need to avoid the following:
Activities associated with increased risk of skin breakdown
Contact of areas with skin breakdown (onychomycosis, dermatomycosis, or other) with tap water
History and physical examination before commencing immunosuppression should ascertain the following:
History of skin lesions during previous immunosuppression
Presence of areas of skin breakdown (onychomycosis, dermatomycosis, or other) and skin lesions that imply presence of fungal infection
Preventive measures (before immunosuppression) for patients with skin breakdown include the following:
Perform local debridement with biopsy and culture of areas with skin breakdown
Apply topical antifungal agents active against *Fusarium* species and other pathogenic molds (terbinafine, natamycin, or other) at site of skin breakdown before and throughout immunosuppression
Consider delaying severely immunosuppressive therapies (when possible) until areas of skin breakdown have healed
Maintain lowest immunosuppression possible throughout therapy
Select donors very carefully in settings of organ or stem, cell transplantation (to avoid immunosuppressive effects of GVHD and organ rejection and their therapies)
Consider in vitro susceptibility testing of *Fusarium* species isolated from skin breakdown areas and incorporation of active agents in antifungal prophylactic regimen

NOTE. GVHD, graft-versus-host disease.

Because infection with *Fusarium* species is more likely to involve the skin than infections by *Candida* species or *Aspergillus* species and because skin is the most likely source of diagnostic material, the presence of skin lesions in immunocompromised patients should raise the index of suspicion for this infection. Because of the relatively high yield of blood cultures among patients with fusarial skin lesions, immunocompromised patients with skin lesions should have blood samples collected and cultured. Identifying the specific pathogen is critical, because *Fusarium* species have variable susceptibilities to the antifungal agents that are currently used. Newer antifungal triazole agents that may have good activity against *Fusarium* species have become available. These include itraconazole, voriconazole, and posaconazole [133–139]. The development of these new antifungal drugs with activity against *Fusarium* species and the promising role of granulocyte transfusions in severely neutropenic

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patients should prompt considerations for such approaches in patients with fusariosis and may improve the otherwise dismal prognosis of these patients.

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Attachment 22.14

Hidron, et.al., Infect Control Hosp Epidemiol 2008;29:996-1011.

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INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY NOVEMBER 2008, VOL. 29, NO. 11

NHSN ANNUAL UPDATE

Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Annual Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007

Alicia I. Hidron, MD; Jonathan R. Edwards, MS; Jean Patel, PhD; Teresa C. Horan, MPH; Dawn M. Sievert, PhD; Daniel A. Pollock, MD; Scott K. Fridkin, MD; for the National Healthcare Safety Network Team and Participating National Healthcare Safety Network Facilities

OBJECTIVE. To describe the frequency of selected antimicrobial resistance patterns among pathogens causing device-associated and procedure-associated healthcare-associated infections (HAIs) reported by hospitals in the National Healthcare Safety Network (NHSN).

METHODS. Data are included on HAIs (ie, central line–associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia, and surgical site infections) reported to the Patient Safety Component of the NHSN between January 2006 and October 2007. The results of antimicrobial susceptibility testing of up to 3 pathogenic isolates per HAI by a hospital were evaluated to define antimicrobial-resistance in the pathogenic isolates. The pooled mean proportions of pathogenic isolates interpreted as resistant to selected antimicrobial agents were calculated by type of HAI and overall. The incidence rates of specific device-associated infections were calculated for selected antimicrobial-resistant pathogens according to type of patient care area; the variability in the reported rates is described.

RESULTS. Overall, 463 hospitals reported 1 or more HAIs: 412 (89%) were general acute care hospitals, and 309 (67%) had 200–1,000 beds. There were 28,502 HAIs reported among 25,384 patients. The 10 most common pathogens (accounting for 84% of any HAIs) were coagulase-negative staphylococci (15%), *Staphylococcus aureus* (15%), *Enterococcus* species (12%), *Candida* species (11%), *Escherichia coli* (10%), *Pseudomonas aeruginosa* (8%), *Klebsiella pneumoniae* (6%), *Enterobacter* species (5%), *Acinetobacter baumannii* (3%), and *Klebsiella oxytoca* (2%). The pooled mean proportion of pathogenic isolates resistant to antimicrobial agents varied significantly across types of HAI for some pathogen-antimicrobial combinations. As many as 16% of all HAIs were associated with the following multidrug-resistant pathogens: methicillin-resistant *S. aureus* (8% of HAIs), vancomycin-resistant *Enterococcus faecium* (4%), carbapenem-resistant *P. aeruginosa* (2%), extended-spectrum cephalosporin-resistant *K. pneumoniae* (1%), extended-spectrum cephalosporin-resistant *E. coli* (0.5%), and carbapenem-resistant *A. baumannii, K. pneumoniae, K. oxytoca,* and *E. coli* (0.5%). Nationwide, the majority of units reported no HAIs due to these antimicrobial-resistant pathogens.

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WOUND CARE



Medical Adhesives and Patient Safety: State of the Science

Consensus Statements for the Assessment, Prevention, and Treatment of Adhesive-Related Skin Injuries

Laurie McNichol ■ Carolyn Lund ■ Ted Rosen ■ Mikel Gray

ABSTRACT

Skin injury related to medical adhesive usage is a prevalent but underrecognized complication that occurs across all care settings and among all age groups. If proper technique for application and/or removal of adhesive products is not used, tissue trauma can occur, impacting patient safety and quality of life and increasing healthcare costs. Little guidance exists in the literature regarding appropriate selection and proper use of adhesive products to minimize medical adhesive–related skin injury, as well as best practices for skin care preventive strategies, application and removal techniques, and assessment and treatment of such injuries. In an effort to define best practices for prevention of such injury, a consensus panel of 23 recognized key opinion leaders convened to establish consensus statements on the assessment, prevention, and treatment of medical adhesive–related skin injury. The consensus summit was held in December 2012 and was made possible by an unrestricted educational grant from 3M. This document details the consensus definitions and statements and identifies research priorities for development of new adhesive technologies and protocols for skin protection.

KEY WORDS: Bandages, Dressings, Medical adhesive, Skin integrity, Skin stripping, Skin tear, Surgical tape

Introduction

Medical adhesives comprise an integral part of healthcare delivery and are used by virtually every medical specialty in all care settings. Medical adhesives are a component of a variety of products, including tapes, dressings, electrodes, ostomy supplies, and patches; they provide securement for both critical and noncritical devices and products, facilitate skin protection and healing, and allow noninvasive monitoring.

Skin injury related to medical adhesive usage is a prevalent but underrecognized complication that occurs across all care settings, from healthy patients in the ambulatory environment to acute and critically ill patients. Although often described as being limited to the extremes of age, such skin injury occurs across all age groups. If proper technique is not used, superficial layers of the skin are removed along with the adhesive product, which not only affects skin integrity but can cause pain and the risk of infection, increase wound size, and delay healing, all of which reduce patients' quality of life.[1] However, under certain circumstances, adhesive products can also cause deeper tissue injuries beyond loss of superficial skin layers. Medical adhesive-related skin injury (MARSI) has a significant negative impact on patient safety. In addition, treating skin damage is costly in terms of service provision, time, and additional treatments and supplies.[2] The average cost of treating a skin tear in an extended

■ Laurie McNichol, MSN, RN, GNP, CWOCN, WOC Nurse and Clinical Nurse Specialist, Cone Health System, Greensboro, North Carolina.
■ Carolyn Lund, MSN, RN, CNS, Neonatal Clinical Nurse Specialist, Children's Hospital, Oakland, California; and Associate Clinical Professor, School of Nursing, University of California San Francisco.
■ Ted Rosen, MD, Professor of Dermatology, Baylor College of Medicine and Chief of Dermatology, Houston Veterans Affairs Medical Center, Houston, Texas.
■ Mikel Gray, PhD, PNP, FNP, CUNP, CCCN, FAANP, FAAN, Professor and Nurse Practitioner, University of Virginia, Charlottesville, Virginia.

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Laurie McNichol, Carolyn Lund, and Ted Rosen are standing members of the 3M Skin Integrity Advisory Board. Carolyn Lund is also a member of the 3M Gentleness Test Methods Advisory Panel. Mikel Gray has no relevant disclosures.

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Correspondence: Mikel Gray, PhD, Department of Urology, University of Virginia, PO Box 800422, Charlottesville, VA 22908 (MG5K@hscmail.mcc.virginia.edu).

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convalescent center was recently reported to be $21.96 per patient per incident.[3]

Healthcare providers play an important role in medical adhesive safety, but literature review reveals little guidance regarding appropriate selection and proper use of adhesive products in order to minimize MARSI. In addition, outside of clinical textbooks on wound and ostomy care,[4-6] there is a paucity of information regarding best practices for skin care preventive strategies and application and removal techniques, as well as assessment and treatment of MARSI. For example, only 2 relevant guidelines were identified in the literature: the Association of Women's Health, Obstetric and Neonatal Nurses Neonatal Skin Care Guideline[7] and evidence-based recommendations/national guidelines in Portuguese resulting from the 1st InterPele: Symposium on Skin Integrity Prevention Strategies, held in Angra dos Reis, Brazil, in March 2011.[8]

In an effort to increase awareness of MARSI and define best practices for its prevention, a consensus panel of 23 key opinion leaders convened to establish consensus statements on the assessment, prevention, and treatment of MARSI. Additional goals included defining knowledge gaps regarding medical adhesives and skin safety, documenting the spectrum of care settings and medical applications where MARSI occurs, and identifying research priorities for development of new adhesive technologies and protocols for skin protection. The interdisciplinary Medical Adhesives & Patient Safety Consensus Summit was held December 10 to 11, 2012, in St. Paul, Minnesota. An industry partner, 3M provided an unrestricted grant for the consensus summit, and a third party (Magellan Medical Technology Consultants) was contracted to manage the project.

▩ Methods

Three standing members of the 3M Skin Integrity Advisory Board were invited and agreed to serve an advisory role (Task Force). Medical specialties and/or practice settings where medical adhesives are used were identified and used as a guide to extend invitations to potential panel members. Specialty practice areas represented by the panel members were critical care; dermatology; electrophysiology; geriatrics; infection prevention; infusion therapy; neonatology; oncology; orthopedics; pediatrics; perioperative; physical therapy; plastic surgery; and wound, ostomy and continence. Researchers in the area of skin and wound care, including pressure ulcers, were also among the invited participants.

Literature reviews were conducted during September and October 2012. An initial search was conducted in the Scopus database using terms identified by the Task Force, which included adhesive(s), adhesive surgical tape, allergic contact dermatitis, bandages, barrier film, dressing, epidermal injury, epidermal stripping, fragile skin, irritant contact dermatitis, maceration, medical adhesive, medical adhesive tape, medical bandage, skin abrasion, skin injury, tape blister, and tape burn. As many of these key terms are broad, search limiters such as adhesive(s), adverse effects, skin injury, skin protection, and/or trauma were incorporated using the Boolean function "AND." After initial review of records, results were limited to articles published in English since 1990. An additional review was completed for studies investigating medical adhesive stripping published in English since 1990. This review included the following five electronic databases: MEDLINE, EMBASE, BIOSIS Previews, CHEMICAL ABSTRACTS, and EMcare. Search terms included keywords for bandage or dressing or tape combined with key words for skin stripping. A separate search was conducted for relevant practice guidelines or procedures. Textbooks were not included in these searches.

In addition to randomized clinical trials and comparison cohort studies, individual case studies, multiple cases series, clinical practice guidelines, consensus documents, practice surveys, laboratory studies, preclinical research studies, technical articles, letters to the editor, and product-related articles were retrieved. Publications outside the scope of the topic were excluded and all remaining articles (n = 167) were reviewed on a case-by-case basis by the Task Force; of these, 88 (52.6%) were considered relevant. In order to obtain a manageable cross section of key publications for consensus statement development and background information for invited panel members, each relevant article was categorized according to medical specialty and practice setting. Task Force members then ranked each article on a scale of 1 to 3 (where 1 defined the lowest level of information and 3 the highest), while also including as many representative specialties/practice settings as feasible. The 31 top-scoring articles (articles totaling 10 points or more) were identified as key publications.

The 2-day Summit began with a presentation summarizing pre-Summit activities and state of the science, which was followed by a review of draft consensus statements. An interactive PowerPoint software program and wireless response system pads (IML ViewPoint Express and IML Click, IML, Minneapolis, Minnesota) were used to allow anonymous interactive voting by the panel members and Task Force and to capture responses. Consensus on each statement was obtained based on general principles outlined in Murphy and colleagues,[9] using 80% agreement as the criterion for consensus. If consensus was not achieved on the first vote, the statement was edited based on participant input and a second, and sometimes third, vote was taken. In cases where consensus could not be reached, or if a statement was considered not relevant, consensus regarding deletion of the statement was obtained. Additional background on the establishment of the Medical Adhesives and Patient Safety Consensus Summit and its methodology can be found in Supplemental Digital Content 1, http://links.lww.com/JWOCN/A18.

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Background

Medical Adhesives and Medical Adhesive Products

Literature review identified several definitions for medical adhesives and medical adhesive tapes/bandages (Supplemental digital content 2, http://links.lww.com/JWOCN/A20). A medical adhesive can be defined as a product used to affix an external component (ie, tape, dressing, catheter, electrode, ostomy pouch, or patch) to the skin. However, selected tapes, dressings, and devices can also function as medical adhesives. According to Widman and colleagues,[10] medical adhesive tape can be simply defined as a pressure-sensitive adhesive and a backing that acts as a carrier for the adhesive. The US Food and Drug Administration more specifically defines a medical adhesive tape or adhesive bandage as "a device intended for medical purposes that consists of a strip of fabric material or plastic, coated on one side with an adhesive, and may include a pad of surgical dressing without a disinfectant. The device is used to cover and protect wounds, to hold together the skin edges of a wound, to support an injured part of the body, or to secure objects to the skin."[11]

Medical adhesive tapes/dressings/devices are composed of several layers (Figure 1). The type of backing and adhesive incorporated into the design determines the properties and performance of the adhesive product. For example, tape backings may consist of paper or a paper blend, plastic, silk (woven polyester), soft (nonwoven) cloth, traditional cloth, or foam and/or elastic. Examples of types of adhesives used in tapes and dressings include acrylates, silicones, hydrogels, hydrocolloids, and polyurethanes, as well as those that are natural-rubber latex based or contain zinc oxide.[1,12] Technical considerations demand that some adhesives are only paired with certain backings. Examples of adhesive dressings and dressing-adhesive combinations include hydrocolloids, hydrogel sheets, foams (silicone, acrylate, polyurethane, or hydrocolloid), semipermeable transparent films (silicone or acrylate), and hydrofiber dressings (Table 1).

Medical adhesives are pressure sensitive; firm pressure applied to the surface of the medical tape/dressing/device will activate the adhesive by increasing the surface area contact.[12] Over time, the adhesive will warm and flow to fill in gaps between the adhesive and the irregularities in the skin surface, increasing the strength of the bond. The length of time for this process differs among the various types of adhesive products. Some softer adhesives, such as silicone, have a lower surface tension and fill in these gaps quickly and maintain the same level of adherence over time. Others adhesives, such as the acrylates, act more slowly, and adherence increases over time.

Medical Adhesive–Related Skin Injury

The pathophysiology of MARSI is only partially understood. Skin injury results when the skin to adhesive attachment is stronger than skin cell to skin cell attachment. Cohesive failure occurs when adhesive strength exceeds the strength of skin cell to skin cell interactions. As a result, the epidermal layers separate or the epidermis separates completely from the dermis. Even when there is no visible trauma, adhesive removal commonly results in detachment of varying amounts of superficial epidermal cell layers; repeated application and removal result in compromised skin barrier function and initiate inflammation and the wound healing response. The association of a specific product with skin stripping or

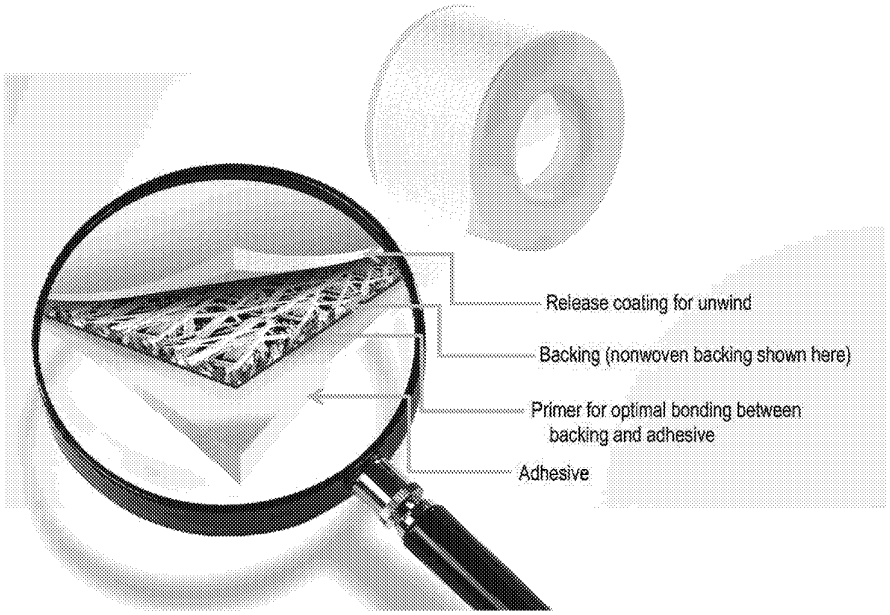


FIGURE 1. Anatomy of medical adhesive tape.

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TABLE 1

Common Adhesives/Backings Used in Medical Tapes[a]

Adhesive	Backing	Advantages	Disadvantages	Clinical Implications
Natural rubber latex based	elastic traditional cloth	Oldest class of adhesives, used for 100+ y Very strong tape when paired with woven cloth backing Generally tolerates moisture better than acrylate or silicone adhesive	Adhesive can be very aggressive on skin Can cause damage if applied and/or removed incorrectly Natural rubber latex is known to cause sensitization and allergic reactions	Good backing strength for securement of heavy tubes, dressings and appliances Can be used for selected applications where contact with moisture and secretions are a consideration (eg, endotracheal tubes)
Acrylate	Elastic foam paper plastic silk soft cloth traditional cloth	This class of adhesives has been used for 50+ y This type of is low sensitizing and usually termed hypoallergenic Can be formulated to be gentler or more aggressive depending on adhesive formulation	Widely and safely used; however, incorrect selection, application, or removal of this tape can lead to skin damage and pain upon removal	Select the tape with the appropriate adhesion level. Higher adhesion than needed may increase risk of skin damage Considerations for tape selection include gentleness, stretch, backing strength, and moisture tolerance
Silicone	paper plastic	Newest class of adhesive available Very gentle to skin Very low sensitizing	Not recommended for primary securement of critical tubing and appliances Less tolerant to moist conditions compared to acrylate or rubber-based adhesives	Good choice for securement of lightweight dressings and tubing on at-risk skin or where frequent retaping is required Better securement can be achieved by increasing surface area covered by tape Tape removes easily and painlessly over hairy areas
Hydrocolloids	film	Initially adheres to dried surfaces, and nature of adhesion varies over time according to water content of the hydrocolloid mass, eventually weakening Molds well to skin surfaces	Has been shown to cause skin trauma equal to acrylate tape when removed at 24 h	Used in wound dressings and over skin as taping platforms
Hydrogels and polyurethanes	These types of adhesives are not frequently used. Consult manufacturer instructions for information.			

[a]This is general information only. Attributes and performance characteristics may vary by brand.

injury arises from a combination of factors, including energy required to remove the adhesive (often measured in Newtons), the rheology of the adhesive, its occlusiveness, and the rigidity of the material used as tape backing.[13] For example, rigid tape backing can lead to injury if there is skin movement due to edema or joint movement.[14,15] Trapping of moisture beneath an occlusive tape may result in maceration and irritation, which renders the skin more vulnerable to mechanical trauma. Types of MARSI are described in Figure 2.

Various intrinsic and extrinsic factors also influence the risk of skin injury (Table 2). For example, age-related physiologic factors exert a major impact on a patient's susceptibility to MARSI.[1,12,23] Neonatal skin is 40% to 60% thinner than adult skin, largely due to the presence of fewer epidermal cell layers in the stratum corneum.[12] This underdeveloped stratum corneum provides a less-efficient barrier, particularly in premature infants, resulting in increased transepidermal water loss, evaporative heat loss, and permeability.[24] Removal of any layers of the neonatal stratum corneum during the process of adhesive removal can further reduce the skin's barrier function, which significantly compromises fluid balance and homeostasis and increases skin permeability; this leads to potential toxicity and irritation from topically applied substances, as well as an increased risk of infection. In addition, the cohesion between the dermis and epidermis is lower in neonatal skin than in adult skin, increasing the risk for select skin injuries.[12]

A number of skin changes inherent to the aging process increase the risk of skin injury in older adults. These include loss of dermal matrix and subcutaneous tissue; epidermal thinning; reduced cohesion between the dermal and epidermal layers; reduced vascularity, elasticity, tensile strength; and loss of moisture.[1,23,24]

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Mechanical

Skin (Epidermal) stripping—Removal of one or more layers of the stratum corneum occurring following removal of adhesive tape or dressing; lesions are frequently shallow and irregular in shape and the skin may appear shiny; open lesions may be accompanied by erythema and blister formation[1,16,17]

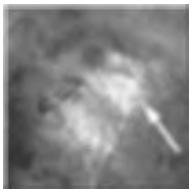


Photo courtesy of 3M

Tension injury or blister—Injury (separation of the epidermis from the dermis) caused by shear force as a result of distension of skin under an unyielding adhesive tape or dressing, inappropriate strapping of tape or dressing during application, or when a joint or other area of movement is covered with an unyielding tape[16,18,19]



Photo courtesy of 3M

Skin tear—Wound caused by shear, friction and/or blunt force resulting in separation of skin layers; can be partial- or full-thickness[20]

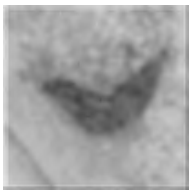


Photo courtesy of 3M

Dermatitis

Irritant contact dermatitis—Non-allergic contact dermatitis occurring as a result of a chemical irritant; a well-defined affected area correlates with the area of exposure; may appear reddened and swollen and vesicles may be present; typically of shorter duration[10,21]



Photo courtesy of 3M

Allergic dermatitis—Cell-mediated immunologic response to a component of tape adhesive or backing; typically appears as an area of erythematous, vesicular, pruritic dermatitis corresponding to the area of exposure and/or beyond; persists for up to a week[10,21,22]



Photo courtesy of Ted Rosen

Other

Maceration—Changes in the skin resulting from moisture being trapped against the skin for a prolonged period; skin appears wrinkled and white/gray in color; softening of the skin results in increased permeability and susceptibility to damage from friction and irritants



Photo courtesy of 3M

Folliculitis—Inflammatory reaction in hair follicle caused by shaving or entrapment of bacteria; appears as small inflamed elevations of skin surrounding the hair follicle; may be nonsuppurative (papules) or contain pus (pustules)



Photo courtesy of Teresa Conner-Kerr

FIGURE 2. Types of adhesive-related skin injury.

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TABLE 2

Factors That Can Increase the Risk of Medical Adhesive–Related Skin Injury[1,4,12,20,23]

Intrinsic Factors	Extrinsic Factors
Extremes of age (neonate/premature infant and the elderly)	Drying of the skin due to harsh skin cleansers, excessive bathing, low humidity, etc
Race/ethnicity	Prolonged exposure to moisture
Dermatologic conditions (ie, eczema, dermatitis, chronic exudative ulcers, epidermolysis bullosa)	Certain medications (ie, anti-inflammatory agents, anticoagulants, chemotherapeutic agents, long-term corticosteroid use)
Underlying medical conditions (ie, diabetes, infection, renal insufficiency, immunosuppression, venous insufficiency, venous hypertension, peristomal varices)	Radiation therapy
	Photodamage
	Tape/dressing/device removal
	Repeated taping
Malnutrition	
Dehydration	

TABLE 3

Preventable Causes of Medical Adhesive–Related Skin Injury[4,45]

Improper choice of tape
Using tape with excessive adhesion for the purpose
Wrong choice of tape (ie, not using a tape with stretch for an area where swelling or movement is anticipated)
Improper application technique
Tension on application (ie, strapping)
Applying in wrong direction (ie, not allowing stretch in direction of expected swelling/movement)
Applying to wet/moist skin
Use of alcohol-based skin preps, which are drying to the skin
Not allowing skin preps/barriers to dry (a common cause of irritant contact dermatitis)
Not clipping/trimming hair prior to application
Excessive use of substances that increase the stickiness of adhesives (ie, tackifiers, bonding agents)
Leaving occlusive tapes or dressings on too long
Improper removal technique
Quick removal
Removal at a high angle
Insufficient support of the skin at the peel line when removing the adhesive product
Repeated taping or dressing changes

Emerging evidence suggests that differences in skin structure and function among various ethnic groups may affect their risk of skin injury. These include racial differences in percutaneous absorption rates of various substances as well as stratum corneum lipid (ceramide) content, which is highest in African Americans.[25] More recently, ethnic differences in tensile mechanical properties of the dermis have been demonstrated, suggesting that African American skin is more rigid than non-Hispanic white skin, which may affect risk of injury.[26]

Additional intrinsic factors that can increase the risk of MARSI include a number of dermatologic and underlying medical conditions, malnutrition, and dehydration; extrinsic factors such as drying of the skin, prolonged exposure to moisture, certain medications, radiation therapy, photodamage, and previous use of adhesive products also play an important role in enhanced susceptibility to skin injury (Table 3)[21,22].

Epidemiology

The prevalence of skin injury due to adhesives is largely unknown. In one prospective cohort study of older individuals admitted to a long-term care facility, the cumulative incidence of skin injury caused by adhesive tape was reported to be 15.5% (incident density 38 per 1000 person-days).[27] Clinical manifestations of MARSI observed in this study included contact dermatitis (71%), trauma (21%), and infection (9%). The use of adhesives was also identified as the primary cause of skin breakdown among neonatal intensive care unit patients in a nursing research utilization project involving 2820 newborns.[28]

Tape-related skin (epidermal) stripping can occur at any age and in any clinical setting, but it is especially prevalent at the extremes of life (in the elderly and neonates).[1,16,29,30] In a 1-day prevalence audit, 8% of hospitalized infants and children were found to have tape-related skin stripping.[29] In the 2003 National Pediatric Pressure Ulcer and Skin Breakdown Prevalence Survey, the prevalence of skin stripping related to adhesive tape was reported as 17%.[30]

One clinical setting where the incidence of MARSI has been fairly well documented is orthopedic surgery. Tension injuries or blisters are more prominent in this setting as a result of multiple factors, including the use of large amounts of tape to hold large compression bandages securely. In this setting, the risk of tape damage is compounded by joint movement, skin friction, and the presence of tissue edema, which creates a strapping effect. The incidence of tension blisters has been reported to be in the range of 6% to 41% following knee or hip surgery[18,19,31-33] and 0% to 6% following knee arthroscopy.[34]

Medical adhesives are a common contributor to skin tears[20,35] and are a critical concern in caring for the elderly and for patients with compromised skin. In the International 2010 Skin Tear survey, dressing removal was cited as one of the top causes of skin tears.[20] During a 12-month period, the Pennsylvania Patient Safety Authority reported tape as the third most common cited cause of skin tears, following hospital beds and patient

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transfers.[35] The units where skin injury occurred most often included medical/surgical, intermediate care, rehabilitation, and specialty units.

Consensus Definitions

Medical Adhesive

Panel members established the following definition for a medical adhesive:

A medical adhesive is a product used to approximate wound edges or to affix an external device (ie, tape, dressing, catheter, electrode, pouch, or patch) to the skin.

Medical Adhesive–Related Skin Injury

Konya and associates define skin injury due to adhesive tape as "a condition in which persistent erythema or other skin injury is evident even 60 minutes after removal of the tape."[27(p1237)] Building upon this terminology, and based on the use of a 30-minute timeframe to define erythema persistence in the definition of stage 1 pressure ulcers in guidelines developed by the Wound, Ostomy and Continence Nurses Society in 1988[36] and in measurement of alterations in skin barrier function following adhesive removal in some research trials (eg, Lund and colleagues[37]), as well as clinical practice, panel members established the following definition for MARSI:

A medical adhesive–related skin injury is an occurrence in which erythema and/or other manifestation of cutaneous abnormality (including, but not limited to, vesicle, bulla, erosion, or tear) persists 30 minutes or more after removal of the adhesive.

Consensus Statements

Assessment—General

1. During use of adhesive-containing products, the skin should be assessed for evidence of damage on a daily basis or with adhesive device changes; this is especially important for those patients deemed to be at high risk for adhesive-related injury.

It is a widely accepted standard of care that skin be assessed on all patients on admission to a healthcare facility and then at regular intervals, with more frequent assessment of patients at higher risk for skin breakdown or damage.[7,38,39] Assessment of the skin is particularly important during the use of adhesive-containing products, particularly in patients at high risk for adhesive-related injury. Skin inspection requires thorough observation and data collection, followed by interpretation.[40] Good lighting is essential for this process. The skin should be assessed for color, texture, uniformity of appearance, and integrity. Any lesions should be described accurately with regard to type, color, arrangement, size, and distribution. Accurate description of the skin and any lesions can help distinguish adhesive-related skin damage from other nontraumatic dermatologic disorders or conditions and may help identify an infectious process if present. In patients with deeply pigmented skin, mild erythema may not be apparent and lesion color may vary from that seen in persons with lighter skin tones.

2. For all medical adhesive–related skin injuries, a comprehensive assessment should be performed to determine severity and guide management.

If an MARSI is noted during a skin assessment or device change, the injury should be assessed and the severity determined in order to guide management. As a whole, mechanical injuries (skin stripping, tension injuries, and skin tears) may be assessed as general wounds and classified according to depth (ie, superficial, partial thickness, or full thickness).[41] The Neonatal Skin Condition Scale,[42] a validated assessment tool that incorporates evaluation of dryness, erythema, and skin breakdown, provides an objective measurement of skin condition and may be used in clinical practice to assess MARSI in this patient population. Existing skin tear assessment and classification systems, such as the Payne-Martin or Skin Tear Audit Research instruments, are not widely accepted,[20] and there currently are no such systems for other adhesive-related injuries in clinical practice. Although it may be difficult to clinically distinguish between irritant and allergic dermatitis, a thorough assessment may identify distinguishing features and enable determination of severity, thus guiding appropriate management.[43] Identification of allergic dermatitis is important, since the patient should be advised regarding future avoidance of the same or similar materials (see the following section). Assessment for evidence of infection should be performed in all cases of MARSI.

Assessment—Allergy/Sensitivity

3. Obtain a history of patients' known or suspected allergies and sensitivities to minimize the risk of medical adhesive–related skin injury.

Medical adhesive products are a common cause of nonallergic irritant contact dermatitis,[10,27,44] and such reactions are more likely to occur with extended exposure.[10] Allergic contact dermatitis related to adhesive products occurs much less frequently than irritant contact dermatitis, although numerous case reports of allergic reactions to components of adhesive products can be found in the literature.[10,44] Because avoidance of the causative substance is key to the prevention and management of dermatitis,[43] it is prudent to obtain a history of a patient's known or suspected allergies, as well as any previous episodes of irritant contact dermatitis, before using an adhesive product.

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4. The incidence of true allergic contact dermatitis related to adhesives is not known; suspected allergic contact dermatitis should prompt consideration for referral and/or appropriate investigation (such as patch or scratch tests).

If there is a high suspicion of allergic contact dermatitis and/or irritant contact dermatitis cannot be ruled out, one should consider referring the patient for further evaluation. If avoidance and empiric treatment do not resolve a suspected case of allergic contact dermatitis, patch testing may be indicated.[43] The clinician can contact the manufacturer of the adhesive product in question for further assistance in identifying potential allergens. However, while the components of the adhesive may contribute in some way to the adverse reaction, it is neither logical nor possible in many cases to separate out these components for testing; it is the final combination that is the product, not necessarily its constituent parts.

Prevention—General

5. Identification of patients at high risk for medical adhesive–related skin injury is a key component of prevention.

As noted previously, a number of physiologic and pathologic conditions and extrinsic factors have an adverse effect on skin structure and function and thus can increase the risk of skin injury (refer to Table 2). Therefore, identification of patients who may be at increased risk for MARSI is a key component of prevention, as extra precautions can often be taken to help protect the skin from injury. These include the use of gentler adhesives, barrier products, and medical adhesive removers.

6. Care of the skin, including prevention of adhesive-related injury, should be a standard of care for all healthcare providers.

Skin care is an important aspect of patient care. Because medical adhesives play such an integral part of healthcare delivery and affect nearly every patient, prevention of MARSI is paramount to good patient care. A number of preventable causes of MARSI were found in the literature or identified by the consensus panel members (Table 4). By addressing these issues, the risk of skin injury can be reduced.

7. Prevention of medical adhesive–related skin injuries is facilitated by good nutrition and hydration.

Proper nutrition and hydration are important aspects of good skin care and overall patient health. Overall nutrition should include adequate calories, amino acids, carbohydrates, and fats, as well as trace minerals and vitamins that are essential components for maintaining intact and healthy skin.

Prevention—Selection, Application, and Removal

Selection

8. Select the most appropriate adhesive product based on its intended purpose, the anatomic location, the adhesive will be applied to, and the ambient conditions present at the application site.

9. Appropriate product selection entails consideration of properties of adhesive-containing products such as adhesive gentleness, breathability, stretch, conformability, and flexibility.

When selecting an adhesive product, one must consider both patient- and product-related factors. Perhaps the

TABLE 4.

Recommended Procedures for Applying and Removing Adhesive-Containing Products[4,5,45,58]

Application	Removal
Ensure that the area is clean and dry.	Loosen the edges of the adhesive product. If there is no folded edge/tab already in place, a small piece of tape may be affixed to an edge of the product to form a tab to facilitate removal.
Clip hair if necessary.	With the fingers of the opposite hand, push the skin down and away from the adhesive.
Apply an alcohol-free skin barrier film to protect at-risk skin.	Remove the adhesive product low and slow back over itself in the direction of hair growth, keeping it horizontal and close to the skin surface.
Allow all preps to dry thoroughly before applying the adhesive product.	As the product is removed, continue moving fingers of the opposite hand as necessary to support newly exposed skin.
Apply the adhesive product without tension, pulling, or stretching. If desired, an edge could be folded over to form a tab to facilitate removal.	Nonbordered transparent film dressings may also be removed by loosening a corner of the dressing and stretching it horizontally in the opposite direction of the wound (stretch and relax technique). Walk fingers under dressing to continue stretching it. One hand continuously supports the skin adhered to the film dressing. The process can be repeated around the dressing.
Smooth the adhesive product into place with firm gentle pressure, avoiding gaps and wrinkles.	Tape strips may be removed by slowly removing each side toward the wound. When both sides are completely loosened, lift the strip up from the center of the wound.
Use gentle, stretchable adhesive products if edema/movement is anticipated, considering the direction of the stretch when securing the product.	Use medical adhesive remover if needed to loosen the adhesive bond. Consider using lotion, petrolatum, or mineral oil if not reapplying an adhesive product to the same area.
If compression is needed, stretch the adhesive over the dressing only and press remaining tape onto skin without tension.	

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foremost patient consideration is the intended use or purpose of the product (ie, securement of a critical device, noncritical device, or dressing; wound closure; etc). The intended use of the product, in turn, influences anticipated wear time. The clinician should then consider anatomic location and skin thickness, as well as the ambient conditions present at the site. Key considerations include whether the area is smooth or contoured, subject to movement or friction, or exposed to moisture, perspiration, humidity, irritants, exudate, and/or body fluids.

The intrinsic characteristics of all components of an adhesive product must then be taken into account to address these patient factors. Properties of the adhesive to be considered include cohesiveness over time and gentleness; properties of the tape/backing/dressing to be considered include breathability, stretch, conformability, flexibility, and strength. The goal is to select a product that will fulfill the intended purpose for the anticipated wear time, at the specific anatomic location, and under the conditions present. The clinician must remember that it is the combination of the adhesive and the backing that give the adhesive product its overall characteristics.

Silicone adhesives represent a newer type of medical adhesive, and limited evidence suggests that these products are gentler than other types of adhesives and associated with lower risk of skin injury due to their physical properties.[1,15,46,47,49] Silicone adhesives have lower surface tension than traditional adhesives, which allows them to conform to the skin's natural contours and to rapidly create a secure bond.[48] In contrast to conventional adhesives, which gradually increase contact with the skin surface and therefore increase adhesion over time, silicone adhesives contact the entire skin surface quickly and the adhesion then remains constant over time. These properties result in less peel force (defined as the average amount of force required to remove an adhesive product from the skin), less propensity for epidermal cell stripping, and less discomfort upon removal. In addition, some silicone adhesive products can be repositioned if needed.

10. Consider the potential adverse consequences of insufficient adhesion and/or adhesive failure, when selecting medical adhesive products for use in securing a critical device.

Critical devices include those for which there is a risk of significant clinical impact to a patient if the device is dislodged or does not perform as expected. Examples include vascular access devices, endotracheal tubes, nasogastric feeding tubes, and indwelling urinary catheters. Proper securement of critical devices is paramount to patient safety. For example, inadequately secured vascular access devices increase the risk of phlebitis, infection, and catheter migration or displacement.[49] Displacement of a small-bore nasogastric feeding tube can have dire consequences; for example, aspiration of a substance because a tube has moved out of position.[50] As such, the more critical the device, the greater the need for use of a higher-adhesion product and/or a stronger backing. Higher-adhesion products and/or stronger backings are usually necessary for securing items such as heavy tubing and immobilization splinting.

11. Exercise caution when using silicone adhesives to secure some devices as this may result in suboptimal adherence or adhesion failure.

Silicone adhesives adhere poorly to other silicone products, and research into medical silicone technology has not produced a silicone adhesive formulation that adheres well to plastics.[51] While silicone adhesives are commonly used for wound dressings and in securement of lightweight tubes and devices, products such as silicone adhesive tapes have not been evaluated for use as primary securement of critical tubing. For this reason, caution should be exercised when using silicone adhesives to secure critical tubes and devices and frequent monitoring is essential to ensure that proper securement is maintained.

Selection and Application

12. Anticipate changes in skin and/or joint movement following injury and operative or other procedures when selecting and applying medical adhesive products.

Tension injuries or blisters represent a separation of the epidermis from the dermis, which is more likely to occur when the skin is stretched underneath an unyielding tape or when a joint or other area of movement is covered with an unyielding tape.[31] As noted earlier, the incidence of tension injuries in the orthopedic surgery setting can be high. For example, in the case of hip surgery, tension forces can develop beneath the posterior dressing when the skin moves as a result of flexion of the hip.[33] However, skin movement can normally be expected in any area of the body affected by joint articulation or tissue expansion or movement. In addition, skin movement may occur in other areas of the body due to edema resulting from inflammation, injury, or operative and other procedures. To minimize the risk of tension injuries in these situations, an adhesive product that stretches should be applied so that the direction of stretch corresponds with the direction of movement.

13. Anticipate skin movement with edema when selecting and applying medical adhesive products.

Potential skin movement should also be considered in cases of edema that occur unrelated to inflammation, injury, or operative and other procedures. Edema can occur in a wide

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range of medical conditions, including allergic reactions, cirrhosis, congestive heart failure, deep vein thrombosis, hypoalbuminemia, chronic kidney disease, burns, sepsis, and fluid overload, such as might be seen in critical care settings.

Application

14. Consider the role of skin tension (Langer's lines) and the effects of medical adhesive products when applied with the lines or against/across these lines.

Langer's lines, also known as tension or cleavage lines, correspond to the alignment of collagen fibers within the dermis and the direction in which the skin is under the highest tension and has the least extensibility.[52] Surgical incisions, and especially cosmetic procedures, are made parallel to the direction of Langer's lines because this approach is associated with better healing and less scarring. Skin movement is more likely across Langer's lines, where the skin tension is lower; if it is necessary to apply adhesive products across these lines, it would be beneficial to use products that stretch. In contrast, reduced skin movement and potentially fewer tension injuries are anticipated if a rigid adhesive product is applied parallel to Langer's lines. Nevertheless, evidence supporting clinical applications of these principles is lacking and additional research is needed to more clearly define application of adhesive devices along or in parallel to the direction of Langer's lines.

15. Consider application of a skin barrier prior to applying an adhesive product.

Skin barrier products provide a protective interface between the skin and adhesives and are recommended to reduce the risk of MARSI and to protect the skin from body fluids, exudates, urine, and stool.[4,5] Most commonly available as liquid barrier films (foams, wipes, or sprays), they may be composed of silicones, acrylates, organic polymers, or inorganic compounds dispersed in a solvent. Following application of a liquid barrier film, the solvent evaporates, forming a transparent, breathable, protective coating. Some barrier films also include an added component (plasticizer) that allows flexibility in the applied product. Pectin-based products are also available.

Clinical studies have demonstrated the ability of barrier films to reduce erythema and skin stripping following medical adhesive removal in various patient populations, including neonates,[53,54,55] as well as their ability to protect periwound skin.[56] For these reasons, the use of barrier products prior to adhesive product application should be considered, particularly in patients at high risk for skin injury. Use of barrier products in neonates and in the periwound and ostomy setting is particularly important, given the propensity for compromised skin integrity. However, current neonatal skin care guidelines recommend avoidance of alcohol because of its drying effects.[7,12] Due to the neonate's high body surface-to-weight ratio, deficient stratum corneum, and certain skin immaturity factors, the guidelines also recommend avoidance of solvents containing hydrocarbon derivatives or petroleum distillates due to risk of toxicity. These guidelines also recommend that barrier products be limited to use of pectin or hydrocolloid barriers, or barrier films, such as an alcohol-free skin protectant, which is recommended for use in infants over 30 days of age. In clinical practice, pectin and hydrocolloid barriers are used more often in neonates as a platform for adhesives because they allow better molding and attachment. However, limited evidence suggests that skin injury can occur with the use of these products.[37] As a result, silicone-based skin barrier films are often used off label in neonates regardless of age. Use of these barrier films has been described in neonates[54] and premature infants,[57] but further research is needed.

16. Limit or avoid substances, such as compound tincture of benzoin, which increase the stickiness of adhesives.

Substances that increase the stickiness of adhesives, sometimes referred to as tackifiers or bonding agents, may be used to increase the cohesive strength of an adhesive, particularly when it is subject to stress. They increase the flow and spread of an adhesive on the surface of the skin, thus increasing immediate adhesion. Such agents are usually low-molecular-weight materials that are derived from natural products, such as rosin (eg, tincture of benzoin) or citrus peels, or from petroleum-based compounds. However, the enhanced adherence provided by such substances may lead to skin injury with adhesive removal and should be avoided, particularly in neonates.[7,12] Panel members concurred that the use of these agents should be limited to selected adult patients when enhanced adhesive adherence is needed.

Application and Removal

17. Use proper application and removal techniques for adhesive-containing products.

Proper application and removal of adhesive-containing products are critical to minimizing skin damage. Recommended procedures for applying and removing adhesive-containing products are summarized in Table 3. It is important that adhesive-containing products not be applied under tension (strapping), as this can lead to tension injuries.[45,58] In addition, rapid, vertical pulling has been shown to generate a higher peel force than slow removal while keeping the adhesive product horizontal and folded onto itself.[59]

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18. Consider use of medical adhesive removers to minimize discomfort and skin damage associated with removal of adhesive products.

Removing medical adhesive products can strip layers of the stratum corneum, causing skin injury and pain to the patient. Medical adhesive removers are used in clinical practice to aid in removal of adhesive products and to remove adhesive and barrier film residues. The 3 main types of medical adhesive removers are alcohol or organic solvent-based, oil-based, or silicone-based. They may be formulated as wipes, pads, or sprays. Of these, the silicone-based removers are the newest, often being promoted as being "no-sting" because they do not contain alcohol.

Medical adhesive removers have not been studied in neonates. Current neonatal skin care guidelines recommend avoidance of alcohol and organic solvent-based medical adhesive removers and recommend slow and careful removal using water-soaked cotton balls to continuously wet the adhesive-skin interface.[7] Alternatively, mineral oil or petrolatum can be used to loosen tape in cases where retaping is not necessary.

Prevention—Electrodes

19. To prevent electrochemical burns under adhesive electrodes, powered (battery and line voltage) equipment should be maintained and monitored for dangerous leakage currents.

Electrical components and devices are encased in nonconducting insulation to ensure that the electric current is contained within the unit and follows the intended pathway through the device's electrical circuit. If this insulation deteriorates or is damaged, current will leak through the insulation and flow to the ground. These leakage currents can cause electrochemical burns under adhesive electrodes, as the electrode connection and/or the adhesive itself are electrically conductive. Direct current leakage currents, such as from batteries, are particularly dangerous.

Normally, leakage currents are felt by the patient as a shocking or tingling sensation near an applied electrode. However, electrochemical injuries have been reported in anesthetized patients connected to battery-operated medical devices as a result of leakage currents.[60] Typically, these injuries can be differentiated from other electrical injuries such as burns due to allergic or chemical reactions or thermal burns, due to the fact that they appear different on the anode, where the reaction is acidic versus the cathode, where the reaction is alkaline.[60,61]

All types of powered equipment should be properly maintained and monitored to measure leakage currents to verify that they are electrically safe.[61] Each piece of equipment should be examined prior to use to ensure that it has been recently inspected and tested, that insulation and connectors are clean and intact, and if battery operated, that any batteries are secure and covered.

Infection Prevention

20. Adhesives may promote overgrowth of microorganisms. Monitor sites exposed to adhesive materials for manifestations of infection.

Several researchers have documented increased bacterial growth beneath occlusive tapes.[62,63] Adhesives may also promote overgrowth of yeasts and saprophytic fungi.[64,65] Therefore, any site exposed to adhesive materials should be monitored for evidence of localized or systemic infection. Signs and symptoms of localized bacterial infection include increased pain, edema, erythema, warmth, or suppuration (eg, presence of pustules, folliculitis, or furunculosis). Signs and symptoms of localized fungal infection include, but are not limited to, an erythematous maculopapular rash with satellite papular or pustular lesions.

As with any skin injury, those that result from the use of adhesive-containing products may lead to localized or systemic infections, particularly in vulnerable populations.[1,12,18] These include patients with factors or comorbid conditions that compromise immune function, such as diabetes, renal failure, malignancy, solid organ transplantation, or a history of or current use of immunosuppressive drugs; surgical patients; as well as the elderly, neonates, and premature infants.

21. Store and use adhesive-containing products in a manner that prevents contamination.

Medical adhesive products have been documented in the literature as potential reservoirs of pathogenic microorganisms as early as 1974.[66–70] For example, one study demonstrated that 59 of 80 tape specimens (74%) collected at various clinical areas in one hospital were found to be colonized by pathogenic bacteria.[65] More recently, Harris and colleagues[70] documented that 11 of 21 samples (52%) of partially used surgical adhesive tapes collected from several clinical areas of three hospitals in Australia were contaminated with multiresistant organisms (methicillin-resistant *Staphylococcus aureus* and/or vancomycin-resistant enterococci).[70]

These reports represent case studies or investigations with small sample sizes where only rates of colonization were determined. However, as medical adhesive products are used to affix items that come into contact with blood, normally sterile tissue, or mucous membranes, there is the potential for infection with use of products that are not packaged as single use, particularly many tape products, as well as certain barrier products, ostomy supplies, and other medical adhesive devices. For example, pectin-based adhesive skin barrier sheets were implicated in a 5-year outbreak of *S aureus* in a neonatal unit in the United Kingdom.[71] In addition, outbreaks of cutaneous *Rhizopus* infection have been reported with the use of adhesive products such as polyethylene tape,[72] ostomy pouches,[73] and elasticized adhesive dressings used over surgical wounds.[67,68] Cases of cutaneous mucormycosis associated

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with the use of temperature probes and monitoring electrodes in neonates have also been reported.[74,75]

As such, any medical adhesive product that is not packaged as single use should be stored and used in a manner that prevents contamination. Boxes containing multiple items should remain closed and ideally, individual items brought to the patient's bedside as needed. Clean items should be separated from those that are frequently touched and/or have already been used (eg, adhesive tape rolls). Items such as adhesive tape rolls should not be left on contaminated surfaces or carried around in pockets or on stethoscopes, and strips of tape should not be placed on bedrails, tables, or other potentially contaminated surfaces prior to application on the patient.

22. Single-patient-use adhesive products are preferred.

Federal and Centers for Disease Control guidelines suggest that, to help prevent cross-contamination, nondisposable patient items that cannot be cleaned and disinfected between patients, such as adhesive tape, should be dedicated for use only on a single patient.[76,77] Because adhesive tape has the potential to act as a significant fomite, Harris and colleagues[70] recommend that short rolls of medical adhesive tape be supplied in sealed packets for individual patient use. Many adhesive products, such as dressings, are already packaged as single-use items and manufacturers now offer adhesive tape in single-patient-use rolls for the reasons cited previously.[78] Therefore, single-patient-use adhesive products should be used whenever possible.

Treatment

23. Apply evidence-based wound care principles when treating medical adhesive–related skin injuries.

24. Consult an appropriate skin or wound care specialist if a medical adhesive–related skin injury does not respond to conservative management within 7 days or if the wound deteriorates despite conservative care.

The same general principles used to manage other acute wounds should be employed when treating adhesive-related skin injuries (refer to the National Guidelines Clearinghouse, http://www.guidelines.gov, for examples of wound care guidelines). Specific guidance regarding the management of skin tears has recently been published.[20]

After an initial assessment to determine the severity of the adhesive-related injury, the wound should be cleansed with a noncytotoxic solution to remove adhesive residue, bacteria, and cellular debris. Afterward, a therapy that supports moist wound healing should be applied. Irritant contact dermatitis can be managed with use of lipid-rich moisturizers to improve the damaged skin barrier and use of cool compresses for acute inflammation. Although topical steroids are often used initially to control inflammation in this form of dermatitis, there is some evidence that they may compromise barrier function and some recommend steroids be avoided.[43] Cool compresses and low- to mid-potency topical steroids (eg, hydrocortisone butyrate, desonide, or triamcinolone) can be used to reduce the inflammation seen with allergic contact dermatitis. Folliculitis should be treated with proper skin hygiene and topical and/or oral antibiotics as needed. If an MARSI does not respond to conservative management within 7 days or if the wound deteriorates despite conservative care, an appropriate skin or wound care specialist should be consulted.

Future Research

25. Further research is needed to expand the scientific knowledge of adhesive performance and use, including mechanisms of medical adhesive–related skin injury, prediction, prevention, assessment and documentation, and treatment.

Consensus panel members identified a number of areas where further research is needed to expand the scientific knowledge of adhesive performance and use (Table 5).

TABLE 5
Recommended Areas for Further Research

Mechanisms of MARSI	Although much physiologic data regarding wounds and wound healing exists in the literature, there is less adhesive-specific research in this area, particularly how the various components of adhesive products interact to cause injury, as well as specific adhesive measurements, such as surface energy, viscosity, and skin adherence.
Prediction	Further clarification of adhesive-specific risk factors for skin injury is needed.
Prevention	There is a need to study potentially beneficial products (eg, skin protectants and silicone adhesive removers) in neonates and premature infants, as there are limited data of use of these products in this patient population.
Assessment and documentation	Tools for clinical assessment and documentation of MARSI are lacking. Currently, the relative degree of MARSI can be estimated only by in vivo, side-by-side comparisons of objective and subjective measurements under identical experimental conditions. Objective measurements include TEWL, the number of cells or amount of protein removed, cutaneous confocal microscopy, and colorimetric measurement of erythema.[13,37] Subjective measurements, which are typically used in the clinical setting, include overall skin appearance (ie, presence of vesicles or bullae) and degree of erythema or dryness following repeated adhesive applications.
Treatment	Identification of best practices to facilitate healing of MARSI is needed.

Abbreviations: MARSI, medical adhesive–related skin injury; TEWL, transepidermal water loss.

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Conclusions and Recommendations for Practice

Panel members were in agreement that MARSI is far-reaching and affects patients of all ages across all settings of care. The care of the skin, including its protection against MARSI, is a basic requirement for patient care. Healthcare providers should strive to prevent and reduce the incidence of MARSI but first must be made aware of the problem and its causes. They, as well as patients and caregivers, need to be provided with the knowledge and tools necessary for preventing and managing adhesive-related injury. Best practice guidelines are needed to assist those who use medical adhesives in using them appropriately, identifying patients at risk for skin injury, and implementing prevention and management strategies. A glossary of terms used in this document can be found in Supplemental Digital Content 2, http://links.lww.com/JWOCN/A19.

KEY POINTS

✔ Expert opinion suggests that appropriate selection of adhesive products and the use of proper application and removal techniques can help minimize MARSI.

✔ Expert opinion recommends considering the role of skin tension and anticipating skin and/or joint movement when selecting and applying medical adhesive products.

✔ Expert opinion recommends that adhesive-containing products be stored and used in a manner that prevents contamination, and that single-patient-use products be used whenever possible.

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BOX

Medical Adhesives & Patient Safety Consensus Panel Members:

- Trudy Adamson, MSN, RN, DNC, Mayo Clinic, Rochester, Minnesota
- Barbara Bor, BSN, CIC, Infection Prevention Coordinator, Gillette Children's Specialty Health Care, St. Paul, Minnesota; President, APIC Minnesota Chapter
- Ruth Bryant, MS, RN, CWOCN, Washington State University College of Nursing, Spokane, Washington
- Janice C. Colwell, MSN, RN, CWOCN, FAAN, University of Chicago Medical Center, Chicago, Illinois
- Teresa Conner-Kerr, PT, PhD, CWS, CLT, Department of Physical Therapy, Winston-Salem State University, Winston–Salem, North Carolina
- Evelyn G. Duffy, DNP, G/ANP-BC, FAANP, Nurse Practitioner Program/Associate Director, University Center on Aging and Health, Frances
- Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio
- Laura Edsberg, PhD, Director, Center for Wound Healing Research, Daemen College, Amherst, New York
- Sharon Fritzsche, MSN, RN, FNP-BC, CPSN, Plastic Surgery Department, Loma Linda Medical Center, Loma Lina, California
- Steven Hoath, MD, Professor/Attending Neonatologist, Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio
- Laurie Kennedy-Malone, PhD, RN, GNP-BC, FGSA, FAANP, School of Nursing, University of North Carolina at Greensboro
- Diane Langemo, PhD, RN, FAAN, College of Nursing, University of North Dakota, Grand Forks
- Carolyn Lund, MSN, RN, CNS,* Neonatal Clinical Nurse Specialist, Children's Hospital, Oakland, California
- Laurie McNichol, MSN, RN, GNP, CWOCN, WOC* Nurse/Clinical Nurse Specialist, Cone Health, Greensboro, North Carolina
- David M. Mercer, MSN, RN, ACNP-BC, CWOCN, CFCN, University of Virginia, Charlottesville
- Brett Netherton, MS, FASNM, CNIM, Technical Director, ROCWorks, LLC, Columbia, South Carolina
- Kathy Puglise, MSN/ED, BSN, RN, CRNI, Vice President, Infusion Nursing, BioScrip, Inc, Norfolk, Virginia
- Sandy Quigley, MSN, CWOCN, CPNP, Boston Children's Hospital, Boston, Massachusetts
- Ted Rosen, MD,* Professor of Dermatology, Baylor College of Medicine, Chief of Dermatology, Houston Veterans Affairs Medical Center, Texas
- Amelia Ross, MSN, RN, APRN, CCNS, Critical Care, University of North Carolina Health Care, Chapel Hill
- Sharon A. Van Wicklin, MSN, RN, CNOR/CRNFA, CPSN, PLNC, Perioperative Nursing Specialist, Association of periOperative Registered Nurses (AORN), Denver, Colorado
- Carolyn Watts, MSN, RN, CWON, Vanderbilt Medical Center, Nashville, Tennessee
- Mary K. Wollan, BAN, RN ONC, National Association of Orthopaedic Nurses (NAON), Minneapolis, Minneapolis
- Stephanie Yates, MSN, RN, CWOCN, ANP-BC, Duke University Cancer Center, Durham, North Carolina

*Members of the Medical Adhesives & Patient Safety Consensus Task Force.

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Attachment 22.16

LeBlanc, et al., "Skin Tears: State of the Science: Consensus Statements for the Prevention, Prediction, Assessment, and Treatment of Skin Tears" Advances in Skin and Wound Care. 2011; 24(9): 2-15.

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Skin Tears: State of the Science: Consensus Statements for the Prevention, Prediction, Assessment, and Treatment of Skin Tears©

Kimberly LeBlanc, MN, RN, CETN(C), and Sharon Baranoski, MSN, RN, CWCN, APN-CCNS, FAAN

Cochairpersons of Skin Tear Consensus Panel: Kimberly LeBlanc, MN, RN, CETN(C), KDS Professional Consulting, Ottawa, Ontario, Canada; kimleblanc@rogers.com; and Sharon Baranoski, MSN, RN, CWCN, APN-CCNS, FAAN, Wound Care Dynamics Inc, Shorewood, Illinois; nrsebear@aol.com

Skin Tear Consensus Panel Members: Karen Campbell, PhD, RN, APN, University of Western Ontario, London, Ontario, Canada; Keryln Carville, PhD, RN, Associate Professor, Domiciliary Nursing, Silver Chain Nursing Association and Curtin University, Perth, Australia; Dawn Christensen, MHSc, RN, CETN(C), KDS Professional Consulting, Ottawa, Ontario, Canada; Karen Edwards, MSS, BSN, RN, CWOCN, WOCN, University of Alabama at Birmingham, Alabama; Mary Gloeckner, MS, RN, COCN, CWCN, Ostomy/Wound Specialist, Trinity Regional Health System, Iowa Health System, Bettendorf, Iowa; Samantha Holloway, MSc, RN, Senior Professional Tutor/Course Director (MSc in Wound Healing and Tissue Repair), Department of Dermatology and Wound Healing, School of Medicine, Cardiff University, Cardiff, Wales, United Kingdom; Diane Langemo, PhD, RN, FAAN, Langemo & Associates, Grand Forks, North Dakota; Alicia Madore, MSN, RN, CCNS, WCC, Army Nurse Corps; Mary Ann Sammon, BSN, CWCN, Manager, Pressure Ulcer/Consult Team, Cleveland Clinic, Cleveland, Ohio; Ann Williams, BSN, RN, BC, CWOCN, Wound/Ostomy Care Coordinator, Inova Fair Oaks Hospital, Fairfax, Virginia; Mary Regan, PhD, RN, CNS, CWCN, Hollister Wound Care, Libertyville, Illinois.

Medical Writer: Karen Beach

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The statements from the consensus document are designed to facilitate the implementation of knowledge-transfer-into-practice techniques for quality patient outcomes. This implementation process should include interprofessional teams (clinicians, laypeople, and policy makers) concerned with the care of individuals at risk for or who suffer from skin tears, to adequately address medical, social, legal, and financial ramifications of skin tears.

The content of this document is based on the results of a 2-day roundtable discussion held January 27–28, 2011, in Orlando, Florida, and was made possible by an unrestricted educational grant from Hollister Wound Care, Libertyville, Illinois. Additional input was received from an international panel of 68 distinguished reviewers using a modified Delphi Method process. The information contained herein does not necessarily represent the opinions of all panel members, distinguished reviewers, or Hollister Wound Care.

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ABSTRACT

The appropriate management of patients with skin tears is an ongoing challenge for healthcare professionals. Skins tears are often painful, acute wounds resulting from trauma to the skin and are largely preventable. Healthcare professionals must be able to identify individuals at risk for skin tears and aid in the prevention of these wounds and in their treatment when they occur. Despite preliminary studies that suggest skin tears may be more prevalent than pressure ulcers, there remains a paucity of literature to guide prevention, assessment, and treatment of skin tears. As a result, these wounds are often mismanaged and misdiagnosed, leading to complications, including pain, infection, and delayed wound healing. In addition, skin tears increase caregiver time and facility costs, cause anxiety for patients and families, and may reflect poorly on the quality of care delivered in a facility. In an effort to shift awareness toward this largely unheeded healthcare issue, a consensus panel of 13 internationally recognized key opinion leaders convened to establish consensus statements on the prevention, prediction, assessment, and treatment of skin tears. The initial consensus panel meeting was held in January 2011 and was made possible by an unrestricted educational grant from Hollister Wound Care. This document details the consensus definition and statements, as well as recommendations for future research and steps toward establishing a validated, comprehensive program for managing skin tears.

KEYWORDS: skin tears, traumatic injury

ADV SKIN WOUND CARE 2011;24(9)(suppl 1):2-15

BACKGROUND FOR ESTABLISHING SKIN TEAR CONSENSUS PANEL

Development of an international pressure ulcer advisory panel has resulted in a universal definition and classification system for pressure ulcers, as well as international guidelines for the prevention, prediction, assessment, and management of pressure ulcers. The acceptance and utilization of a common

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language and classification system has facilitated best practice and research in this area.[1] In contrast, despite arguments that skin tears may be more prevalent than pressure ulcers, a universally accepted classification and management system for skin tears has yet to be established.

The most commonly cited definition of skin tear is that of Payne and Martin[2]: "A skin tear is a traumatic injury occurring on the extremities of older adults as a result of shearing or friction forces, which separate the epidermis from the dermis." Payne and Martin[3] revised this definition in 1993 to state, "A skin tear is a traumatic injury occurring principally on the extremities of older adults as a result of shearing or friction forces which separate the epidermis from the dermis (partial-thickness wound) or which separate both the epidermis and the dermis from underlying structures (full-thickness wound)." The revised Payne-Martin 1993 definition was later adapted by Carville et al[1] as part of the Skin Tear Audit Research (STAR) skin tear classification system. LeBlanc et al[4] defined skin tears as "the result of shearing, friction, or blunt trauma that causes separation of skin layers. The subsequent wounds are partial- or full-thickness depending upon the degree of tissue damage." Regardless of definition, skin tears commonly occur in the extremes of age, the critically ill or medically compromised, and in individuals requiring assistance with personal care.[1,4–6]

A literature review revealed limited literature addressing the prevalence, incidence, or economic impact of skin tears on the global population. Carville et al[1] asserted that skin tears are perceived to be common wounds and occur more frequently than pressure ulcers. Early research estimated that 1.5 million skin tears occur each year in institutionalized adults in the United States.[7] A 1994 study[8] in a 347-bed facility in Western Australia demonstrated a 41.5% skin tear prevalence rate within its population.[8] Studies of community settings have reported skin tear prevalence rates between 5.5% in known wounds among all age groups[9] and 20% of known wounds in the veteran population.[10] Canadian and European prevalence and incidence of skin tears are not known.

An international survey, aimed at exploring current practices in the assessment, prediction, prevention, and treatment of skin tears, was conducted by LeBlanc et al[11] from June 2010 to December 2010. A total of 1127 healthcare professionals from 16 countries completed an online survey. More than half (69.6%) of respondents reported a problem with current assessment and documentation of skin tears in their practice settings. The vast majority (89.5%) favored a simplified method for documenting and assessing skin tears. A total of 80.9% of respondents admitted to not using any tool or classification system for assessing and documenting skin tears (Tables 1A-D).

Tables 1A-D.
INTERNATIONAL SKIN TEAR SURVEY RESULTS FROM A TOTAL OF 1127 RESPONSES (2010)

Table 1A.
Do you believe that there is a problem with skin tear assessment and documentation at your healthcare setting?

Answer options	Response %	Response n
Yes	69.6	695
No	30.4	303
Other (please specify)		39
	Answered question	**998**
	Skipped question	**129**

Table 1B.
Would you like a more simplistic method of documenting skin tears?

Answer options	Response %	Response n
Yes	89.5	891
No	10.5	104
Other (please specify)		23
	Answered question	**995**
	Skipped question	**132**

Table 1C.
Does your facility/hospital/home care agency use any of the following scales for assessing and documenting skin tears?

Answer options	Response %	Response n
Payne-Martin Classification for Skin Tears	10.0	98
CAWC Best Practice Recommendations	3.3	32
STAR Skin Tear Classification System	5.8	57
None	80.9	790
Other (please specify)		48
	Answered question	**977**
	Skipped question	**150**

Table 1D.
What is your country of practice?

Answer options	Response %	Response n
United States	74.8	843
Canada	11.6	131
Australia	7.0	79
United Kingdom	4.9	55
Europe	1.4	16
Japan	0.3	3
Other (please specify)		20
	Answered question	**1127**
	Skipped question	**0**

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CLASSIFYING SKIN TEARS

The Payne-Martin Classification System[2] was the only known method for classifying skin tears documented in the literature, until the STAR Classification System evolved (Figure 1).

Payne and Martin[3] published a critique of the classification system in 1993. The authors maintained that the system demonstrated internal and external validity, although they raised concerns about the usefulness of the skin tear classification system among clinicians and care providers. White et al[12] found that despite the internal and external validity of the Payne-Martin classification system, it was not widely used in clinical practice. Similarly, an online survey[11] revealed that only 10% of those surveyed used the classification system in practice.

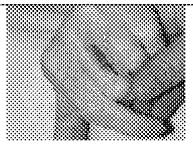
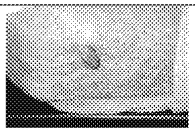
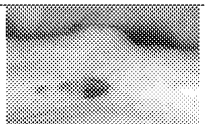
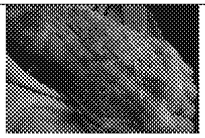
In response to the need for a universally accepted validated skin tear classification system, Carville et al[1] established and validated the STAR Classification System in 2006 (Figure 2). Although only 5.8% of international survey respondents answered that they used the STAR Classification System in clinical practice, it is important to note that the STAR Classification System has only recently been disseminated outside Australia, and of the 1127 respondents to the survey, only 79 were from Australia (Table 1D).

The need for a universally accepted definition and a comprehensive international strategy addressing all aspects of skin tear management prompted establishment of a consensus panel of wound care experts. An initial consensus meeting was held in January 2011 to initiate global discussion and develop consensus statements surrounding the prevention, prediction, assessment, and treatment of skin tears. The resulting skin tear definition and consensus statements, as well as future recommendations for research, are described in this document.

GOALS AND OBJECTIVES

The primary goal for establishing a skin tear expert panel was to initiate an ongoing global discussion regarding skin tears in all healthcare settings. Objectives of the initial meeting were to generate a skin tear definition and series of statements that would serve as a guide for future consensus-building discussions. The panel-developed definition and statements would subsequently be subject to global review and input from a wide group

Figure 1.
ADAPTED PAYNE-MARTIN SKIN TEAR CLASSIFICATION TOOL[2]

Category IA	Linear type skin tear, epidermis and dermis pulled apart, without tissue loss	
Category IB	Epidermal Flap completely covers the dermis within one millimeter of the wound margin	
Category IIA	Scant tissue loss type<25% of the epidermal flap lost	
Category IIB	>25% of the epidermal flap lost	
Category III	Epidermal flap is absent	

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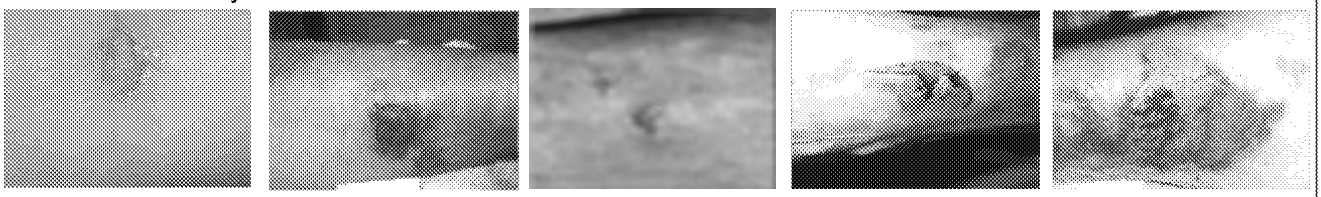
Figure 2.
STAR CLASSIFICATION SYSTEM

STAR Skin Tear Classification System

STAR Skin Tear Classification System Guidelines

1. Control bleeding and clean the wound according to protocol.
2. Realign (if possible) any skin or flap.
3. Assess degree of tissue loss and skin or flap colour using the STAR Classification System.
4. Assess the surrounding skin condition for fragility, swelling, discolouration or bruising.
5. Assess the person, their wound and their healing environment as per protocol.
6. If skin or flap colour is pale, dusky or darkened reassess in 24-48 hours or at the first dressing change.

STAR Classification System



Category 1a	Category 1b	Category 2a	Category 2b	Category 3
A skin tear where the edges **can** be realigned to the normal anatomical position (without undue stretching) and the skin or flap colour **is not** pale, dusky or darkened.	A skin tear where the edges **can** be realigned to the normal anatomical position (without undue stretching) and the skin or flap colour **is** pale, dusky or darkened.	A skin tear where the edges **cannot** be realigned to the normal anatomical position and the skin or flap colour **is not** pale, dusky or darkened.	A skin tear where the edges **cannot** be realigned to the normal anatomical position and the skin or flap colour **is** pale, dusky or darkened.	A skin tear where the skin flap is completely absent.

Skin Tear Audit Research (STAR). Silver Chain Nursing Association and School of Nursing and Midwifery, Curtin University of Technology. Revised 4/2/2010.

STAR Skin Tear Classification System Glossary

- ***Skin Tear:*** "a traumatic wound occurring principally on the extremities of older adults, as a result of friction alone or shearing and friction forces which separate the epidermis from the dermis (partial thickness wound) or which separate both the epidermis and the dermis from underlying structures (full thickness wound)"[1].
- ***Pale, dusky or darkened skin or flap colour:*** when compared to the individual's 'normal' surrounding skin, may indicate ischaemia or the presence of haematoma, which may affect skin or flap viability.
- ***Ischaemia:*** inadequate tissue perfusion as evidenced by pale, dusky or darkened tissue.
- ***Haematoma:*** a collection of blood or clot under the flap or realigned skin.
- ***Realign:*** to replace the skin or flap into the normal anatomical position without undue stretching.
- ***Linear skin tear:*** a skin split or the skin splitting in a straight line.
- ***Flap skin tear:*** a segment of skin or skin and underlying tissue that is separated from the underlying structures.

References:

1 Payne, R., & Martin, M. (1993). Defining and classifying skin tears: Need for a common language ... a critique and revision of the Payne-Martin Classification system for skin tears. *Ostomy Wound Management, 39*(5), 16-20.
2 Photographs courtesy of the Skin Tear Audit Research (STAR) photographic library, Silver Chain Nursing Association and School of Nursing and Midwifery, Curtin University of Technology.
3 Carville, K., Lewin, G., Newall, N., Haslehurst, P., Michael, R., Santamaria, N., & Roberts, P. (2007). STAR: A consensus for skin tear classification. *Primary Intention, 15*(1), 18-28.

STAR Tool G 4/2/2010

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of international reviewers. The purpose of this document is to disseminate the globally agreed skin tear definition and consensus statements and to generate further research on this topic.

METHODOLOGY

A 3-phase modified Delphi Method[13] was used to reach consensus on the skin tear definition and 12 statements proposed in this document.

Phase 1

An expert panel was convened to develop consensus statements pertaining to the assessment, prediction, prevention, and treatment of skin tears. The panel consisted of 13 key opinion leaders in the field of wound care from the United States, Canada, United Kingdom, and Australia. The initial consensus meeting was held January 27–28, 2011, in Orlando, Florida, and was made possible by an unrestricted educational grant from Hollister Wound Care. Notes from this meeting were used to generate a preliminary consensus document. A recording of the meeting was available for review.

Phase 2

Consensus statements were disseminated to all consensus panel members, who then distributed the statements to a wider global group of distinguished reviewers. Each panel member collected and summarized feedback from the global reviewers, then returned feedback to the consensus panel's 2 co-chairpersons. A total of 68 reviewers with noted expertise in wound care were selected to be the distinguished international external review panel.

Phase 3

Written input received from the international panel members and the expert panel members was used to generate a final consensus document. This final consensus document was then returned to the original expert panel and the 68 external reviewers for voting on the definition and each of the 12 statements for consensus. A quorum of 80% who strongly or somewhat agree was used as a predetermined point for consensus on the definition and each of the 12 statements. The definition and statements received 99% from those who agreed or somewhat agreed with the statements.

PANEL STATEMENTS

Skin Tear Definition

Building upon the literature and work of Payne and Martin,[3] Carville et al,[1] and LeBlanc et al,[4] the consensus panel, established the following skin tear definition:

A skin tear is a wound caused by shear, friction, and/or blunt force resulting in separation of skin layers. A skin tear can be partial-thickness (separation of the epidermis from the dermis) or full-thickness (separation of both the epidermis and dermis from underlying structures).

CONSENSUS STATMENTS

Statement 1

Intrinsic and extrinsic factors contribute to the occurrence of skin tears; some of these factors are yet to be determined.

Normal wound healing occurs in a well-orchestrated sequence of events. The cascade starts with hemostasis and progresses through inflammation, proliferation, and maturation, each stage overlapping the others while remaining distinct in terms of time after injury.[14] Factors known to alter the wound healing process include age; nutritional status; medications, such as immunosuppressives, anti-inflammatory agents, and anticoagulants; smoking; underlying disease states; and local wound conditions.[15] The use of anticoagulants increases the risk of ecchymosis,[4] which has been identified as a contributing extrinsic factor to skin tear development.[1]

Individuals suffering from skin tears often suffer from a long history of skin tears. It is worthwhile to note that as with any wound, once closed the area of injury will have reduced tensile strength, and with each subsequent skin tear, the individual will be at greater risk for skin tears.[4,15]

These factors, in addition to numerous other intrinsic and extrinsic factors (Table 2), are thought to be associated with increased risk of skin tears as well.

Intrinsic factors, such as age, pertain to an individual's inherent biologic or genetic makeup. Extremes in age impact not only on how individuals heal but also on their susceptibility to developing a wound.[14] With increasing age, individuals experience dermal and subcutaneous tissue loss, epidermal thinning, and serum composition changes, all of which cause decreased skin surface moisture. In turn, the skin's elasticity and tensile strength decrease.[16,17] Risk of skin tears is further increased by dehydration, poor nutrition, cognitive impairment, altered mobility, and decreased sensation.[18,19] These factors are common in the elderly in all care settings and combine to increase the skin's vulnerability to trauma.[20]

Neonates and infants are also susceptible to skin tears. Neonates have underdeveloped skin, and children have only 60% of adult epidermal thickness.[21] Neonates have decreased epidermal-to-dermal cohesion; deficient stratum corneum; impaired thermoregulation; a body surface/weight ratio of nearly 5 times greater than that of an adult; and immaturities in the immune, hepatic, and renal systems. A combination of these factors places this population at increased risk for epidermal stripping, infection, increased transepidermal

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Table 2.
INTRINSIC AND EXTRINSIC FACTORS ASSOCIATED WITH AN INCREASED RISK OF SKIN TEARS[1,2,4,5,7,16]

- Very young (neonate) and very old (>75 years old)
- Sex (female)
- Race (Caucasian)
- Immobility (chair- or bed-bound)
- Inadequate nutritional intake
- Long-term corticosteroid use
- History of previous skin tears
- Altered sensory status
- Cognitive impairment
- Limb stiffness (joint stiffness/contractures) and spasticity
- Neuropathy
- Having blood drawn
- Polypharmacy
- Presence of ecchymosis
- Dependence for activities of daily living
- Using assistive devices
- Applying and removing stockings
- Removing tape or dressings
- Vascular problems
- Cardiac problems
- Pulmonary problems
- Visual impairment
- Transfers and falls
- Prosthetic devices
- Continence/incontinence
- Skin cleansers
- Improper use of skin sealants

water loss with resultant heat loss, and toxicity from percutaneous absorption.[5,21–24]

Extrinsic factors also play an important role in the development of skin tears. There is an increased risk for mechanical trauma when assistance is required for bathing, dressing, toileting, and transferring. Soap reduces the skin's natural lubrication, and as a result, frequent bathing, coupled with the natural decrease in lubrication associated with aging, can result in dry skin. Dry skin is more susceptible to friction and shearing, increasing the individual's susceptibility to skin tears.[12] In a case-control study of a 500-bed Australian tertiary hospital, 6 statistically significant factors were identified as being associated with a predisposed risk of acquiring a skin tear[1]:

- senile purpura
- ecchymosis
- hematoma
- evidence of previously healed skin tears
- presence of edema
- inability to reposition independently

Additional research is required to validate the risk factors associated with skin tears. The literature to date has also not addressed the impact of elder abuse/domestic violence and its potential impact on skin tear prevalence.

Statement 2

Skin tears are more prevalent with, but not limited to, the extremes of age.

Skin tears commonly occur in individuals at the extremes of age, the critically ill or medically compromised, and in those requiring assistance with personal care.[1,4,6] Although elderly and neonatal populations are at the highest risk for skin tears, it is imperative that all patients be assessed for skin tear risk. Individuals who are critically ill, at the end of life, or who suffer from multiple intrinsic and extrinsic risk factors, regardless of age, are also at higher risk. Special attention should be paid to individuals in the critical care setting or those who have suffered major trauma or surgery.[1,5,6]

Statement 3

Physiological changes related to the aging process affect the skin's ability to resist shear, friction, and/or blunt force.

Known physiological changes related to the skin and aging process are listed in Table 3. Aging skin undergoes a process of dermal and subcutaneous tissue loss, epidermal thinning, and serum composition changes that cause decreased skin surface moisture.[22,23,25,26] The most obvious change is the flattening of the dermal-epidermal junction. In aging skin, dermal thickness can be decreased by as much as 20%, a contributing factor in the paper-thin appearance of skin in the elderly. The skin's elasticity and tensile strength decrease as these other changes occur.[22,23,25,26]

With the aging process, skin becomes more susceptible to dryness. *Xerosis cutis*, or dry skin, is extremely common in the elderly and occurs as the result of diminished or loss of sebaceous and sweat gland activity. It is seen most often on the lower legs but also occurs on the hands and trunk.[27] Bathing removes the body's natural oils from the skin surface, which exacerbates the potential for dry skin, particularly in the elderly, as natural oil production is already diminished.[23] In addition, the use of alkaline soaps increases the skin's pH and thus reduces the skin's protective acid mantle.[4,23] This drying of the skin may be potentiated in certain regions during the colder months with centrally heated homes that dry the air and contribute to dry skin.[4]

Malone et al[7] identified site-specific atrophy over time of subcutaneous tissue on the shins, face, dorsal aspect of the hands, and plantar aspect of the foot. In sustained trauma, these areas absorb more energy that can result in skin tears.

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Table 3.
PHYSIOLOGICAL CHANGES RELATED TO THE AGING PROCESS[22,23,25,26]

- Thinning and flattening of the dermal-epidermis junction
- Thinning and atrophy of dermis due to decreased collagen production
- Impaired vascularity of the dermis and hypodermis/subcutaneous tissue
- Atrophy of the hypodermis/subcutaneous tissue
- Loss of dermal and hypodermis/subcutaneous tissue
- Reduced function of sweat gland secretion
- Increased need for handling due to physical and cognitive disabilities
- Decreased sebum production
- Decreased inflammatory/immune response
- Decrease in the cellular growth rate or apoptosis
- Degeneration of collagen and elastin fibers
- Delayed angiogenesis
- Increase in capillary fragility in body mass
- Slower epithelialization
- Increased vascular lesions
- Reduced sensation

Statement 4

Physiological characteristics of neonatal/infant skin may affect the skin's ability to resist shear, friction, and/or blunt force.

Studies have shown that epidermal stripping is listed among the most common wound types occurring in hospitalized neonates and children.[21,22] At 24 weeks' gestation, premature neonates have little stratum corneum and attenuated rete ridges. They lack subcutaneous tissue, and their dermis lies directly over the muscle. Consequently, skin stripping secondary to adhesive dressing and/or tape removals can result in full-thickness tissue loss. Between 26 and 29 weeks' gestation, subcutaneous fat deposition begins. However, the barrier function of the skin remains poor. Additional intrinsic characteristics of neonatal and infant skin also increase their risk of skin tears.

At 30 weeks, subcutaneous tissue is evident, and the stratum corneum is 2 to 3 cell layers thick, compared with 40 weeks when it is 30 layers thick. Functional integumentary maturity occurs at 33 weeks. The epidermis is fully keratinized, and the dermal/epidermal junction is stronger but remains fragile and easily damaged. At 36 weeks (full-term), the skin is structurally similar to the adult but the epidermal and dermal layers are only up to 60% as thick as an adult.[21–24]

In addition, if a skin tear does occur, the normally rapid wound healing response of neonatal and pediatric populations can be compromised by protein-calorie malnutrition, hypotension requiring inotropic therapy, edema, infection, and physiological instability that prevents safe redistribution of pressure.[21,22]

Statement 5

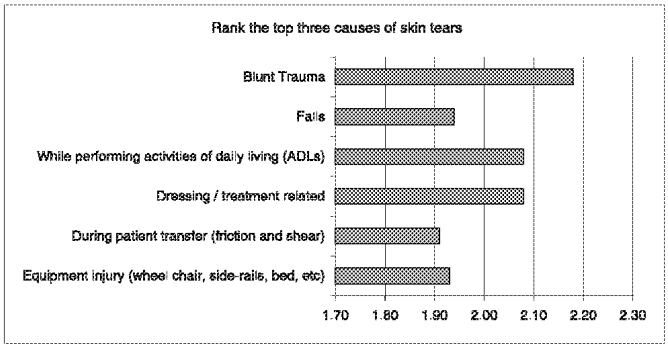
Individuals with impaired activity, mobility, sensation, or cognition have increased risk of shear, friction, and/or blunt force injury related to the need for increased assistance.

When skin tears are reported, the causative factor is often not known. When the cause is known, skin tears are frequently linked to wheelchair injuries, blunt trauma from accidently bumping into objects, transfers, or falls.[4,20] White et al[12] concluded that key times skin tears occur are during the peak activity hours of 6:00 AM to 11:00 AM and 3:00 PM to 9:00 PM.

In the elderly population, skin tears are often related to the environment.[26] In 1990, Payne and Martin[2] conducted a 3-month, descriptive study in 10 long-term-care facilities to describe skin tears, identify risk factors, and determine the rate of healing of skin tears. Among the predominant risk factors, impaired activity, mobility, sensation, and cognition all demonstrated an increased risk for skin tear development. McGough-Carny and Kopac[19] conducted a similar study in a Veterans Affairs nursing home and concluded that dependency in activities of daily living, sensory loss, limited mobility, use of assistive devices, and impaired cognition were risk factors for skin tear development.[19]

Patients who are dependent on others for total care are at the greatest risk for skin tears.[12] Dependent patients frequently acquire skin tears during routine activities, such as dressing, bathing, repositioning, and transferring. Independent ambulatory patients are at the second highest risk, and the majority of their skin tears occur on their lower extremities. In the 2011 survey conducted by LeBlanc et al,[11] the top causes of skin tears included equipment injury, patient transfers, falls, activities of daily living, and treatment and dressing removal (Figure 3).

Figure 3.
2011 SURVEY RESULTS FOR TOP CAUSES OF SKIN TEARS



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Statement 6

A comprehensive assessment of risk factors for skin tears should be conducted for all individuals within the context of their environment.

In addition to understanding factors that contribute to the development of skin tears, a systematic approach is required to accurately predict skin tear risk. Guidelines recommend a risk assessment be conducted and include a comprehensive head-to-toe assessment upon admission to a healthcare service and thereafter whenever the individual's condition changes or per agency/facility policies.[28–32] The Registered Nurses' Association of Ontario (RNAO)[28,29] and National Pressure Ulcer Advisory Panel (NPUAP)[32] support the use of validated risk assessment tools.

Although validated risk assessment tools are available to predict pressure ulcers and are well utilized, the same is not true for skin tears. The Skin Integrity Risk Assessment Tool developed by White et al[12] (Figure 4) does not appear to be widely used. A validated and widely accepted tool is needed to predict and identify those at high risk for skin tears so that an appropriate prevention program can be implemented before injury occurs.[1,4,23,33]

Cause, duration, and history of alteration in skin integrity; other coexisting health issues; medications; and mobility level are a few of the issues that should be included in the risk assessment. If all of these issues are taken into account, a comprehensive prevention plan can be developed, addressing physical, social, and emotional needs.[3,4,23,26,33] Despite the lack of risk assessment tools for the prediction of skin tears, there is consistency in the literature in terms of appropriate prevention strategies (Table 4).

Statement 7

A collaborative multidisciplinary approach should be utilized for skin tear prevention and management.

Numerous organizations, advisory panels, and authors have recommended an organized multidisciplinary team approach to managing wounds.[4,28,29,31,32] Although patients, families, and caregivers greatly benefit from the wound care expert's professional knowledge, they also require added expertise of other members of an multidisciplinary team. Team members can include occupational therapists, physical therapists, dieticians, social workers, general physicians, general nurses, wound care speciality nurses, enterostomal therapy nurses, tissue viability specialists, WOC nurses (wound ostomy, continence), pharmacists, discharge planners, and others.[34] Healthcare professionals involved in the care of patients with skin tears must be willing and able to work together toward positive patient outcomes.

Figure 4.

SKIN INTEGRITY RISK ASSESSMENT TOOL[12]

White et al[12] recommend implementing a skin-tear risk prevention care plan for patients who meet any of the criteria in group I below, patients who meet 4 or more criteria in group II, patients who meet 5 or more criteria in group III, and patients who meet 3 criteria in group II and three or more criteria in group III.

Group I
- History of skin tears within last 90 days
- Actual number of skin tears

Group II
- Decision-making skills impaired
- Vision impaired
- Extensive assistance/total dependence for activities of daily living (ADLs)
- Wheelchair assistance needed
- Loss of balance
- Bed or chair confined
- Unsteady gait
- Bruises

Group III
- Physically abusive
- Resists ADL care
- Agitation
- Hearing impaired
- Decreased tactile stimulation
- Wheels self
- Manually or mechanically lifted
- Contracture of arms, legs, shoulders, hands
- Hemiplegia or hemiparesis
- Trunk: partial or total inability to balance or turn body
- Pitting edema of legs
- Open lesions on extremities
- 3 to 4 senile purpura on extremities
- Dry, scaly skin

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Table 4.
STRATEGIES IN PREVENTING SKIN TEARS[4,16,20,26,33–36]

1. Assess for risk upon admission to healthcare service and whenever the individual's condition changes
2. Implement a systematic prevention protocol
3. Have individuals at risk wear long sleeves, long pants/trousers, or knee-high socks
4. Provide shin guards for those individuals who experience repeat skin tears to shins
5. Ensure safe patient handling techniques and equipment/environment
6. Involve individuals and families in preventive strategies
7. Educate registered and nonregistered staff and caregivers to ensure proper techniques for providing care without causing skin tears
8. Consult dietitian to ensure adequate nutrition and hydration
9. Keep skin well lubricated by applying hypoallergenic moisturizer at least 2 times per day
10. Protect individuals at high risk from trauma during routine care and from self-injury

A team of healthcare professionals working together is more effective than one healthcare professional working in isolation.[34] At the core of the team should be the patient. Patients and their family/caregiver should be involved in their plan of care, and the team should work to keep them involved. The patient's desires and wishes must be respected even if they differ from the ultimate goals of the healthcare team.[34]

Statement 8

Skin tears are to be assessed and documented on a regular basis according to healthcare setting practice and policy.

The RNAO[28,29] and National Guidelines Clearinghouse (NGCH) guidelines[30] provide recommendations related to the classification of wounds. To accurately document and treat skin tears, it is important that a common language be used to describe them. Proper documentation is vital to understanding the extent of the problem. As with other wound types, skin tear documentation requires a systematic framework for assessment, treatment, and evaluation of outcomes.

Although pressure may be a related cause of skin tears, the etiology of skin tears differs from that of pressure ulcers. Skin tears need to be documented as separate occurrences and not grouped into pressure ulcer categories.[1,16] Because of the current lack of a well-accepted skin tear classification system, additional research is needed in this area. It is important to note that if pressure, friction, and shear become evident, then the skin tear should be reclassified as a pressure ulcer.[30]

Statement 9

Evidence-based wound care principles should guide treatment of skin tears.

The same principles used to manage other wounds should be employed when treating skin tears.[16] The Wales Tissue Viability Nurse Forum: Best Practice Statements,[36] Canadian Best Practice Recommendations for the Prevention and Treatment of Skin Tears,[4] Pennsylvania Safety Authority Skin Tear Initiative,[37] RNAO,[28,29] and NGCH[30] guidelines provide a number of recommendations regarding wound assessment and treatment. Prevention of future skin tears should remain a primary focus. Healthcare professionals must be educated and equipped to manage these challenging wounds when they occur. Several areas must be addressed, including coexisting factors, nutritional support, pain management, local wound conditions, and optimal dressing selection.[4,36–40] The following are some of the general guidelines.

Wound Assessment

Before initiating any treatment, the first step is to assess the wound, skin flap, or pedicle and determine the type or category of skin tear using a validated documentation system.[1,23,38] Based on literature review, the Payne-Martin[3] or STAR tools[1]are the only systems currently available to classify skin tears.

Wound Cleansing

Skin tears should be cleansed following assessment. Bacteria, debris, and/or necrotic tissue must be removed. Depending on the healthcare setting, a tetanus immunoglobulin may be administered.[4] Optimal wound healing cannot occur unless surface slough, biofilms, and foreign debris have been removed, thus lowering the bioburden.[15,41] Cleansing is the easiest method for accomplishing this goal.[16]

Krasner,[34] as well as Gardner and Frantz,[42] have outlined best practices for cleansing wounds with necrotic debris. They suggest irrigating with noncytotoxic solutions such as normal saline or nonionic surfactant cleansers using safe pressures of less than 10 to 15 pounds per square inch (psi), achieved by using a 19-gauge angiocatheter and a 35-cc piston syringe. Uncomplicated tears (ie, those without debris) should be gently cleansed with noncytotoxic solutions, such as normal saline or nonionic surfactant cleansers at a low pressure of less than 8 psi to protect granulating tissue.[15,42,43]

Moist Wound Healing

The importance of moist wound healing in healable wounds cannot be understated.[15] High-level evidence supports moist wound healing as an integral part of any wound management

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plan.[29] Sibbald et al[15] indicated that when compared with dry wounds, a moist wound environment accelerates wound healing. Moist wound therapy dressings can enhance the wound healing environment by maintaining optimal moisture levels to promote cell growth and healing.[15,44]

Dressing Selection

RNAO recommendations[29] support the need for a systematic approach to dressing selection for all wound types. Ovington and Peirce[41] cited several dressing recommendations, which were also endorsed by the RNAO. Recommendations include choosing a dressing that will

- maintain constant moisture,
- suit the local wound environment,
- protect the periwound skin,
- control or manage exudates,
- control or manage infection, and
- optimize caregiver time.

These recommendations, in conjunction with local formularies, should be followed when assessing wounds and choosing wound care products.[45]

Unlike pressure ulcers and other chronic wounds, skin tears are acute wounds with the potential to be closed by primary intention.[4] Wounds closed by primary intention are traditionally secured with suture or staples. Given the fragility of elderly skin, sutures and staples are not a viable option; other methods are required.[33] Sutton and Pritty[46] conducted a randomized controlled study comparing pretibial laceration management options. They reported that most pretibial lacerations responded best to conservative management and that adhesive strips were preferable to suturing. This research supporting the use of adhesive strips is outdated, and while more research is needed, case studies and expert opinion suggest that adhesive strips are not the current treatment option of choice for skin tears.[47–50]

Recently published regimens for topical treatment of skin tears include lipido-colloid based mesh and foam dressings, soft silicone-based mesh or foam dressings, calcium alginate dressings, absorbent clear acrylic dressings, and skin glue.[47,48,51] Nazarko[51] reviewed a skin tear protocol that included use of calcium alginates to control bleeding postinjury, then treatment according to category: Payne-Martin Category I skin tears were treated with adhesive strips anchor, Category II skin tears were treated with combination of adhesive strips and soft silicone or low tack foam dressings, and Category III skin tears were treated with soft silicone or low tack foam dressings. Dressings were held in place with stocking-like products or cotton gauze wraps. The review indicated that when using this protocol, skin tears tended to achieve wound closure within 7 to 10 days.[51]

O'Regan[33] reviewed existing literature on the treatment of skin tears and concluded that wounds should be treated in a systematic way to include cleaning with normal saline, control of bleeding, clot removal, and an appropriate dressing to address wound bed characteristics.

Best practice supports that a skin flap (the pedicle) should be approximated if possible, and a hydrogel, alginate, lipido-colloid based mesh and foam dressings, soft silicone, foam, or nonadherent dressing applied depending on wound characteristics.

In more recent literature,[47,48,50] absorbent clear acrylic dressings have been successfully used to treat Payne-Martin Category I to III skin tears with low to moderate exudate. These dressings are semipermeable and can be left in place for up to 21 days. LeBlanc and Christensen[47] and LeBlanc et al[48] examined a convenience sample of 5 patients with Category I to II skin tears who were treated with absorbent clear acrylic dressings and found complete wound closure with no wound infection and minimal reported pain in all 5 patients. Dressings were removed at 21 days, and complete wound closure was seen in all patients.

In treating Payne-Martin Category I and II skin tears with less than 25% of epidermal flap loss that require close approximation of the edges of the skin tear/flap tissue, successful use of 2-octyl cyanoacrylate topical bandage (skin glue) has been reported.[47–50] Milne and Corbett[52] studied a convenience sample of 20 patients with category II to III skin tears who were treated with 2-octyl cyanoacrylate topical bandage. Complete wound closure was seen with one application per skin tear, with no reported wound infection. The average cost was less than US $1 per application at the time of the study.

Hydrocolloids, or traditional transparent film dressings, are not recommended over skin tears, as they may cause skin stripping and injury to the healing skin tear if not removed properly.[53] If the skin tear is infected or extensive, the wound should be assessed by a physician or a wound care specialist to determine the best treatment options.[54]

When skin tears occur on the lower limb, peripheral edema as a comorbidity is often associated with the elderly. Therefore, it is important to rule out any significant degree of peripheral vascular disease. This should be done prior to the application of compression therapy for edema control and can be established through a clinical history and the use of Doppler ultrasound to determine the ankle brachial pressure index.[55]

Statement 10

Patients, caregivers, and healthcare providers should be educated regarding prevention and management of skin tears.

The RNAO,[28,27] Wound Ostomy Continence Nurses Society (WOCN),[31] and NGCH guidelines[30] support the need to educate patients, caregivers, and healthcare professionals

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on the prevention and treatment of skin tears. Patients, family, and healthcare professionals require ongoing education and support to ensure current evidence-based practice is being followed.[56]

Education is a key component in any successful prevention or treatment program[26,38] and particularly important in the prevention of skin tears, as little has been written to support universal care strategies. All healthcare providers and caregivers must be made aware of proper lifting/transferring/positioning techniques for providing care without traumatizing the skin. Skin tear education and dressing competency should be part of every annual skin and wound care educational review. A list of recommended education points for preventing skin tears is listed in Table 5.

Table 5.
SUGGESTED EDUCATION POINTS FOR SKIN TEAR PREVENTION[4,23,26,34,36,39,47,48,57]

- Perform skin hygiene according to individual need using warm/tepid, not hot, water and soapless or pH-neutral cleanser, followed by a hypoallergenic moisturizer. Hygiene frequency is based on personal, cultural, and healthcare organization practices and policies.
- Lubricate the skin by applying hypoallergenic moisturizer at least twice per day. After showering, apply moisturizers while skin is still damp but not wet.
- Provide protection from trauma during routine care, activities of daily living, and from self-injury; ensure proper transfer and moving and handling techniques and equipment are utilized to avoid shear and friction insult when transferring or moving individuals.
- Pad bed rails (where applicable), wheelchair legs, furniture edges, or other objects that may lead to blunt trauma; remove unnecessary equipment from the room or hallway.
- Promote and monitor adequate nutrition and hydration; offer fluids between meals and during rounds.
- Avoid use of adhesive products on frail skin. If dressings or tapes are required, use paper tapes or nonadherent or silicone dressings to avoid skin tears. Use gauze wraps, stockinettes, or other bandages to secure dressings rather than tape.
- Create a safe environment, such as clothing or protective devices that cover the extremities; initiate fall precaution protocol to reduce risk of falls and blunt trauma.
- Caregivers should take caution to ensure that their own nails are kept short and that they are not wearing jewelry that can catch and contribute to skin tear formation.
- Extremes of weight (bariatric, cachetic, or excessively thin) require extra care to prevent skin tears.

It is also important to involve those at risk, their family members, and their caregivers in the prevention process, thus empowering them to play a proactive role in skin tear prevention.[4,56] A needs assessment of patients and caregivers should be performed and documented, including baseline information pertaining to knowledge, beliefs, health practices, and perceived learning needs of patients, families, and caregivers. Cultural and psychological variables will also be factors in developing prevention and management strategies.[4,56]

Statement 11

Not all skin tears are preventable.

The Skin Changes at Life's End© (SCALE) consensus document[58] proposes that not all wounds are preventable or healable. Individuals suffering from multiple comorbidities, dementia with aggression, or multiorgan failure are especially at risk for skin tears, which may not be preventable.

As the body's largest organ, the skin can be greatly compromised during multiorgan failure, such as at end of life. Shunting of blood away from the skin in order to support vital organs may result in decreased skin and soft tissue perfusion and reduction of the normal cutaneous metabolic process. Even minor trauma can lead to skin tears.[58] Every effort should be made to prevent skin tears whenever possible and to provide evidence-based, best practice care when they do occur.

Statement 12

Further research is needed to expand scientific knowledge to determine best practice in skin tear prediction, prevention, assessment, treatment, and documentation.

The skin tear consensus panel recommends the following future research and tool development projects in order to fill the gaps in current literature:

- Develop an accepted definition and classification system for skin tears that may be used reliably by individuals in all healthcare settings (prerequisite for any future research).
- Conduct an international prevalence and incidence studies across different healthcare settings.
- Develop a valid and reliable risk assessment tool applicable to skin tears in all healthcare settings.
- Conduct randomized controlled trials to determine best practices for the prevention and treatment of skin tears.
- Identify unpreventable skin tear situations as protective measure to the healthcare systems.

CONCLUSIONS

The International Skin Tear Panel members were in agreement that skin tears represent a specific and challenging type of

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wound. Skin tears affect all ages and continue to be a common problem in all healthcare settings. Prevention of these wounds is the primary focus for managing this growing concern. Although management of skin tears may vary according to institution and product availability, the basic goal remains to control bleeding, prevent infection, control pain, restore skin integrity, and promote a healing environment. Literature pertaining to the prevention and treatment of these wounds is limited. Further research is needed to determine the prevalence and incidence of skin tears across healthcare settings, identify and validate an internationally accepted skin tear classification system, and validate a risk scale or predictive document. Lastly, best practice prevention and treatment guidelines are needed to assist healthcare professionals in managing skin tears and identifying those at risk for these wounds.

GLOSSARY OF TERMS

Dermis: lower or inner layer of the main 2 layers of cells that make up the skin; consists of a bed of vascular connective tissue and contains nerves, organs of sensation, hair roots, and sebaceous and sweat glands[4]

Epidermis: outermost layer of the skin[4]

Extrinsic: from the outside of a body or organ[59]

Delphi Method: a structured communication technique, originally developed as a systematic, interactive forecasting method, which relies on a panel of experts.[13]

Friction: the resistance to motion in a parallel direction relative to the common boundary of 2 surfaces[32]

Full-thickness skin loss: ulceration that extends through the dermis to involve subcutaneous tissue[4]

Healable: ability of the individual's body to support the phases of wound healing[4]; the physical capacity to heal, and the system and client can support optimal treatment choices

Healed: restoration of tissue/skin integrity after insult[59]

Intrinsic: coming from within[59]

Interprofessional: collaborative efforts of physicians, nurses, therapists, and all other healthcare providers[59]

Ischemia: inadequate tissue perfusion as evidenced by pale, dusky, or darkened tissue[59]

Nonhealable: inability of an individual's body to repair/restore a skin/tissue defect due to multiple comorbidities[59]; the patient/client does not have the physical capacity to heal

Laceration: a torn or jagged tear of the skin; often used to describe a skin tear[59]

Partial-thickness skin loss: skin damage that involves the epidermis and can penetrate into but not through the dermis[29]

Pedicle: a flap composed of skin with or without its subjacent subcutaneous tissue, attached to the original site[59]

Pressure ulcer: localized injury to the skin and/or underlying tissue over a bony prominence, as a result of pressure, or in combination with friction or shear[29]

Responsible bathing: bathing should be based on individual need and preference, should be performed with either soapless products or pH-balanced soaps, involves limiting baths: showering instead with warm not hot water and includes the application of hypoallergenic moisturizers post showering while skin is still damp but not wet[4]

Risk assessment: an assessment to determine which, if any, risk factors are present that might contribute to the development of a skin tear[29]

SCALE©: Skin Changes at Life's End[58]

Shear: the force per unit area exerted parallel to the plane of interest.[32]

INTERNATIONAL LIST OF REVIEWERS

Elizabeth A. Ayello, PhD, RN, ACNS-BC, CWON, MAPWCA, FAAN—USA
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Helen LeBlanc, RN—Canada
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Lynne Watret, CNS, Tissue Viability Nurse—UK
Lorne Wiesenfeld, MD, CM, FRCPC—Canada
Trudie Young, Tissue Viability Nurse—UK
Karen Zulkowski, DNS, RN, CWS—USA

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Attachment 22.17

Rayner, et al., "A review of patient and skin characteristics associated with skin tears" Journal of Wound Care 2015; 24(9): 406-414.

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A review of patient and skin characteristics associated with skin tears

• **Objective:** Skin tears are the most common wound among the elderly and have the potential to cause infection, form chronic wounds, reduce quality of life and increase health-care costs. Our aim was to identify studies that reviewed patient and skin characteristics associated with skin tears.

• **Method:** A review of skin tear studies reported in the English literature between 1980 and 2013 was undertaken using the following electronic databases: PubMed, Medline, CINAHL, Embase, Scopus, Evidence Based and Medicine Reviews (EBM). Search terms included aged, skin, tears or lacerations, skin tearing, geri tear, epidermal tear and prevalence.

• **Results:** There were 343 articles found with using the search terms. After abstract review nine were found to be relevant to the search. The principle findings from these eight published articles and one unpublished study revealed that the most common patient characteristics were a history of skin tears, impaired mobility and impaired cognition. Skin characteristics associated with skin tears included senile purpura, ecchymosis and oedema.

• **Conclusion:** This review provides an overview of identified patient and skin characteristics that predispose the elderly to skin tears and exposes the lack of research within this domain.

• **Declaration of interest:** R. Rayner is a recipient of a 2013 Australian Postgraduate Award, Curtin University Postgraduate Scholarship and a Wound Management Cooperative Research Centre (CRC) PhD stipend. The School of Nursing, Midwifery and Paramedicine, Curtin University and the Silver Chain Group, Western Australia are participants in the Wound Management Innovation CRC. No conflict of interest exists among the authors.

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White, Karam, and Cowell, "Skin Tears in Frail Elders: A Practical Approach to Prevention" Geriatric Nursing. 1994; 15(2), 95-99.

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Skin Tears in Frail Elders: A Practical Approach to Prevention

If practical preventive skin tear interventions are made in the very old geriatric population, what are the outcomes?

By Marguerite W. White/Sandra Karam/Barbara Cowell

Skin tears are common in the frail elderly population.[1] Normal physiologic changes of the skin and vascular system predispose an aged person to skin tears caused by minor trauma.[2] Skin changes that occur with aging include thinning of the epidermis, changes in cell reproduction, and decreased skin strength and elasticity due to collagen changes and a decrease in the number and size of the epithelial cells and blood vessels. The blood vessels become thinner and more fragile, leading to appearances of hemorrhaging known as *senile purpura*.[3-5] According to Malone et al.,[1] skin tears often occur at sites of senile purpura. A reduced immunity, combined with the tendency for delayed healing of wounds, places the person 85 years or older at a greater risk for complications from any interruption in skin integrity.[5,6]

A search of the medical and nursing literature reveals that there has been very limited study of this phenomena, and no studies were found of outcomes resulting from practical application of preventive measures. This article represents an attempt to study outcomes derived from practical applications of preventive skin tear interventions for residents of a long-term care facility.

Scope of Problem

Beth Sholom Home of Eastern Virginia is a 120-bed Jewish nursing facility. Ninety-eight percent of residents require nursing facility level of care, and 2% require skilled nursing care. There is a mean age of 85 years. The average length of stay is 3 years.

The philosophy of the nursing home promotes the provision of an improved quality of life by continuing cultural and religious traditions. Wellness is emphasized through a wide variety of therapeutic social interactions. Even the most debilitated residents get out of bed daily, dress in street clothes, attend all meals in the dining room, and participate in appropriate activities, unless this is contraindicated by the interdisciplinary care plan. This approach results in dependent residents being transferred in and out of bed several times a day.

Wound and skin rounds are conducted weekly on each of the three 40-bed units that make up the facility. Rounds are conducted by the gerontological clinical nurse specialist and attended by the responsible RN supervisor and LPN team leaders. The sessions provide an opportunity for teaching and a collaborative exchange of ideas for improving care. Through weekly observation and documentation, it was ascertained that the majority of incidents of interruptions in skin integrity were due to skin tears caused by minor trauma, not pressure sores. Therefore nursing administrators recognized the need to investigate the extent of the problem through a retrospective study.

Retrospective Study

We defined *skin tears* as a separation of the dermis from the epidermis because of rubbing or shearing. Included in the definition were lacerations involving several layers of skin—linear or with flaps, superficial or those requiring sutures—and abrasions involving only the first layer of skin.

In January 1991 a retrospective review of all incident reports involving lacerations or abrasions, or both, due to

MARGUERITE W. WHITE, BSN, RNC, CNA, is director of nursing services, SANDRA KARAM, MS, RN, CNS, CS, is a gerontological nurse specialist, and BARBARA COWELL, RNC, is an associate director of nursing services at the Beth Sholom Home of Eastern Virginia, in Virginia Beach, Virginia.

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CRITICAL REVIEW

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Skin tear prevalence and associated factors: a systematic review

Prevalência de lesão por fricção e fatores associados: revisão sistemática

Prevalencia de lesión por fricción y factores asociados: revisión sistemática

Kelly Cristina Strazzieri-Pulido[1], Giovana Ribau Picolo Peres[1], Ticiane Carolina Gonçalves Faustino Campanili[1], Vera Lúcia Conceição de Gouveia Santos[2]

[1] Universidade de São Paulo, Escola de Enfermagem, Programa de Pós-Graduação em Enfermagem na Saúde do Adulto, São Paulo, SP, Brazil.

[2] Universidade de São Paulo, Escola de Enfermagem, Departamento de Enfermagem Médico-Cirúrgica, São Paulo, SP, Brazil.

ABSTRACT

Objective: To identify and analyse skin tear prevalence and factors associated with its occurrence. **Method**: Systematic review of literature of studies published until June 2014 including studies published in full in English, Spanish or Portuguese. The studies were analysed according to the Strengthening the Reporting of Observational Studies in Epidemiology and the Guidelines for Critically Appraising Studies of Prevalence or Incidence of a Health Problem. **Results:** The analysis of eight studies showed skin tear prevalence of 3.3% to 22% in the hospital setting and 5.5% to 19.5% in homecare. Advanced age, dependence on basic activities of daily life, frail elderly, level of mobility, agitated behavior, non-responsiveness, greater risk for concurrent development of pressure ulcers, cognitive impairment, spasticity and photoaging were cited as risk factors. **Conclusion**: Skin tear prevalence ranged from 3.3% to 22% and is mainly associated with advanced age and dependence on basic activities of daily life.

DESCRIPTORS

Wounds and Injuries; Prevalence; Cross-Sectional Studies; Epidemiology; Review.

Correspondence Addressed to:
Kelly Cristina Strazzieri Pulido
Rua Voluntários da Pátria, 3744 – Santana
CEP 02402-400 - Sao Paulo, SP Brazil
kellycspulido@gmail.com

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INTRODUCTION

Caring for people with fragile skin is a challenge when a minor trauma can result in Skin Tear (ST)[1-3].

Although some researchers suggest that Skin Tear is more prevalent than pressure ulcers and burns[4-5], ST go unnoticed as they are shallow traumatic wounds, occurring mainly in elderly ends resulting from friction or a combination of friction and shear, leading to separation of the epidermis from the dermis (partial thickness wound) or completely separating the epidermis and the dermis from the underlying structures (total thickness wound)[6]. They are regarded as inherent to the age, inducing the feeling of an irrelevant condition, however, they cause pain and can easily be infected[2-4,7].

Because they are relegated as mere casual unavoidable incidents, there is little interest and therefore, they are underdiagnosed. The lack of diagnostic accuracy and understanding of the causes involved, contributes to increasing pain and suffering, healing time and treatment costs, negatively affecting the quality of care[2-4,7-8].

For less than 25 years, researchers have slowly begun to monitor the epidemiology of ST in order to build and refine appropriate nomenclature and risk assessment instruments and classification[8-9], fundamental instruments for the evaluation of the wound and planning care actions, which are essential for its prevention[10-11].

Simple measures such as the identification of patients at risk and the implementation of prevention protocols are proving to be effective to prevent ST or minimize its severity[12]. Researches[1,13] show that the occurrence of ST decreases as soon as an individual is identified at risk and preventive measures are implemented.

In order to bring tangible foundations on all scientific knowledge that still needs to be built on the ST, the International Skin Tear Advisory Panel[3] recommends and encourages the development of studies to elucidate the epidemiology of ST in the health services and in the community.

This review aimed at identifying and analyzing the information available in the literature on the prevalence of ST, as well as factors associated with its occurrence in children, adults and elderly.

METHOD

Systematic review of the literature according to the recommendations of the Cochrane Collaboration[14].

The guiding question of this review was: *What is the information available in the literature on the prevalence and factors associated with ST in children, adults and elderly*? To clarify it, the following electronic databases were consulted: CINAHL, Cochrane, EBM Reviews, Embase, LILACS, PubMed, SciELO, Scopus and Web of Science up to June 2014. For the selection of studies, we used the following criteria: to be published in English, Spanish or Portuguese until June 2014, to be available in full and to be an epidemiological research, that is, directed at the investigation of the prevalence of ST. Book chapters, conference abstracts, review articles, case reports, consensus, editorials, guidelines, correspondences, clinical trials, cohort studies and case-control studies were excluded.

The search strategy was based not only on indexed descriptors by Medical Subject Headings Section and Descriptors in Health Sciences - bold in Box 1 - but also on keywords used in narrative reviews and up to date studies, since the terminology about ST is not uniform. The search for studies was performed using Boolean operators AND and OR, respecting the peculiarities of each database searched. Chart 1 shows the search strategy.

Chart 1 – Search strategy - Sao Paulo, 2014.

Number	Descritor MeSH/ DeCS or key-word
# 1	**Older people**
# 2	**Adult**
# 3	**Child**
# 4	**Skin aging** OR Elderly skin
# 5	**Prevalence** OR **Epidemiology**
# 6	**Lacerations** OR Mangled wounds OR Tear wounds OR Rag wounds OR Skin lacerations OR Traumatic laceration OR Pretibial laceration OR Skin tears OR Skin trauma OR Skin stripping
# 7	**(#1 OR #2 OR #3 OR #4) AND (#5) AND (#6)**

The search for studies was conducted by one of the authors in each of the electronic databases. The search results were exported to EndNote Web® program, which stored the following data from each study: title, authors, journal title, number, volume, page, section, abstract and keywords.

The initial selection of studies was performed from the title and abstract analysis. The studies were randomized among the authors, and each of them had to be analyzed by two authors. Studies, which generated doubts about the relevance of their inclusion, were analyzed by a third author.

Studies that had their abstracts selected were redeemed in full and randomly distributed among the authors, and each one of them had to be analyzed by two authors. A third author judged the validation of analysis, evaluating and comparing 30% of the studies, chosen through a raffle.

The studies were analyzed descriptively and the results were grouped and presented with respect to: year of publication, country where the study was conducted, methods (population/sample; prevalence of ST; ST instruments used for classification, and statistics strategies analysis) and the main results found by the authors (prevalence of ST and factors associated with ST, when identified).

To assess the quality of the studies included in this review both the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE)[15] and the *Guidelines for Critically Appraising Studies of Prevalence or Incidence of a Health Problem*[16] were used.

STROBE, translated into Portuguese by Malta et al.[15], contains 22 items with recommendations on what should be included in a more accurate and full description of observational studies. Each of the 22 criteria received a score of 0

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to 1. The total score was converted into percentage to better assess the quality of the studies. The items that reached a percentage higher than 50% were considered of good quality.

The *Guidelines for Critically Appraising Studies of Prevalence or Incidence of a Health Problem,* developed by Loney et al.[16] consist of eight questions on the adequacy and accuracy of the study relating to the validity of the methods, interpretation and applicability of the results. Each item was rated with a point, generating maximum score of 8 points. Loney et al.[16] did not establish quality categories neither for the score obtained nor for the cut-off score. Studies which reached more than 4 points were considered of good quality. The system is presented in Chart 2.

Chart 2 – Guidelines for Critically Appraising Studies of Prevalence or Incidence of a Health Problem - Sao Paulo, 2014.

Guidelines for Critically Appraising Studies of Prevalence or Incidence of a Health Problem	
Item	**Score**
1. Random sample or whole population	1 point
2. Unbiased sampling frame	1 point
3. Adequate sample size	1 point
4. Measures were the standard	1 point
5. Outcomes measured by unbiased assessors	1 point
6. Adequate response rate, refusers described	1 point
7. Confidence intervals, subgroup analysis	1 point
8. Study subjects described	1 point
Maximum score	8 points

Source: Loney PL, Chambers LW, Bennett KJ, Roberts JG, Stratford PW. Critical appraisal of the health research literature: prevalence or incidence of a health problem. Chronic Dis Can. 1998;19(4):170-6.[16]

RESULTS

The search in the nine databases resulted in 8,095 studies. After removing 2,426 duplicates, 5,669 studies were directed to title screening. After reading the titles, 5,433 studies were removed, leaving 236 studies for abstract analysis. Of these, book chapters, conference abstracts, review studies, case reports, consensus, editorials, guidelines, correspondences, clinical trials, cohort studies and case-control were excluded. Remaining only nine studies on the prevalence of ST, of which eight[17-24] met the inclusion criteria and were read in full. The only excluded study[25] did not meet the language criterion, since it was published in Chinese.

Embase (57.42%) and PubMed (34.48%) were the databases that found the largest number of studies. The less representative databases were Cochrane (0.84%), CINAHL (0.21%), SciELO (0.10%), EBM Reviews (0.09%) and LILACS (0.01%), as shown Table 1.

Chart 3 presents a summary of the six selected articles.

Table 1 – Studies identified according to databases - Sao Paulo, 2014.

Databases	**Identified studies**	
	N	**%**
CINAHL	17	0.21
Cochrane	68	0.84
EBM Reviews	07	0.09
Embase	4644	57.42
LILACS	01	0,01
PubMed	2788	34,48
SciELO	08	0,10
Scopus	283	3.50
Web of Science	279	3.45
Total	8087	100

Chart 3 – Study stratified by author, year of publication, country, methods, results and quality score - Sao Paulo, 2014.

Author/Year of publication	**Country**	**Methods**	**Results (prevalence of ST)**	**STROBE**	**LONEY**
Carville K e Lewin G, 1998[17]	Australia	Retrospective study n=1,146 patients in homecare. Auditing charts. It does not cite instrument for ST classification. It does not cite statistical methods	5,5% (excluding ST of lower limbs) (It does not have CI) Advanced age	48%	4.0
Carville K e Smith JA, 2004[18]	Australia	Cross-sectional study n=492 war veterans in homecare Physical examination It does not cite instrument for Skin tear classification Cox regression analysis	19.5% (It does not have CI) Advanced age Frail elderly	61%	6.0
McErlean B, Sandison S, Muir D, Hutchinson B e Humphreys W, 2004[19]	Australia	Cross-sectional study n=187 patients admitted to a tertiary hospital Physical examination Payne-Martin Classification System for Skin Tears It does not cite statistical methods	11% (It does not have CI) Level of dependency and mobility	68%	6.5

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Author/Year of publication	Country	Methods	Results (prevalence of ST)	STROBE	LONEY
McLane KM, Bookout K, McCord S, McCain J e Jefferson LS, 2004[20]	United States of America	Cross-sectional study n=1,064 patients in children's hospitals (up to 17 years) Physical examination It does not cite instrument for ST classification It does not cite statistical methods	17% (It does not have CI) It does not refer to associated factors	58%	4.5
Santamaria N, Carville K e Prentice J, 2009[21]	Australia	Cross-sectional study n=5,800 admitted patients in public health institutions Physical examination It does not cite instrument for ST Confidence intervals for wounds in general, z-score and p value	8% (It does not have CI) Advanced age	58%	5.0
Amaral AFS, Strazzieri-Pulido KC e Santos VLG, 2012[22]	Brazil	Cross-sectional study n=157 admitted patients with cancer Physical examination STAR Skin Tear Classification System Chi-square test and p value	3.3% (It does not have CI) Less independence and autonomy for self-care Agitated behavior or Non-responsiveness; Higher risk for concurrent development of pressure ulcers	87%	7.5
LeBlanc K, Christensen D, Cook J, Culhane B e Gutierrez O, 2013[23]	Canada	Cross-sectional study n=113 patients in long-stay institutions Physical examination Payne-Martin Classification System for Skin Tears t-student, Chi-square, adherence and Bonferroni tests	22% (It does not have CI) Dependence for basic activities of daily life Cognitive impairment Spasticity	90%	6.5
Koyano Y, Nakagami G, Iizaka S, Minematsu T, Noguchi H, Tamai N, et al., 2014[24]	Japan	Cross-sectional study n=410 patients admitted to retirement geriatric hospital Physical examination STAR Skin Tear Classification System Calculation of prevalence	3.9% (It does not have CI) photoaging	87%	7.0

The studies are mostly from Australia (4)[17-19,21], predominantly from hospital settings (6)[19-24] or homecare (2)[17,18]. Physical examination was the main strategy for data collection, being held in seven studies[18-24]. Payne-Martin Classification System for Skin Tears was used by one of the Australian[19] and the Canadian[23] studies. The Brazilian study[22], as well as Japanese[24], used the Classification System STAR – Skin tears STAR Skin Tear Classification System. However, most studies (4)[17-18,20-21] did not mention which instrument was used for the classification of ST.

The prevalence of ST ranged from 3.3% to 22% in the hospital setting[19-24] and 5.5% to 19.5% in homecare[17-18]. With regard to risk factors associated with ST, advanced age (3)[17-18,21] and dependence for basic activities of daily life (3)[19,22-23] were the most cited. Other factors mentioned were frail elderly[18], level of mobility, agitated behavior, non-responsiveness, greater risk for concurrent development of pressure ulcers[22], cognitive impairment, spasticity[23] and photoaging[24]. One study[20] did not mention risk factors associated with ST.

Only one study[17] was not considered of good quality, reaching 48% of STROBE and 4 points in the system developed by Loney et al.[16]. However, the performance of all studies[17-24] was hampered, since none of them had confidence intervals on the estimates of prevalence, and most (4)[17,19-21] did not describe the study subjects.

DISCUSSION

In the hospital setting, the ST prevalence ranged from 3,3%[22] to 22%[23]. The lowest rates (3.3%, 3.9% and 8%) were identified, respectively, in the studies developed in Brazil[22], in Japan[24] and in Australia[21]. The Brazilian study[22] identified the prevalence of ST in adult patients hospitalized with cancer, the Japanese study[24] in a geriatric retired hospital and the Australian study[21] quantified the epidemiology of wounds, including ST, in all patients, regardless of age, admitted to hospitals/linked to the public health system hospitals of Western Australia.

Studies conducted in Australia[19], in the United States of America[20] and in Canada[23] identified the highest prevalence of ST (11%, 17% and 22%). The Australian study[19] identified ST prevalence in adult patients admitted to a tertiary hospital, the American study[20] documented the prevalence of pressure ulcers and other wounds, including ST, in hospitalized children, and the Canadian study[23] identified it on patients admitted to a long-term care facility.

Regarding homecare, all studies were conducted in Western Australia and the ST prevalence ranged from 5.5%[17] to 19.5%[18]. The lowest prevalence (5.5%) was identified in the study in patients with wounds being cared at home[17]. At that time, the authors chose to exclude ST in lower limbs. In a later study[18], conducted with patients

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from the Department of Veterans' Affairs in homecare for wound, the authors found a significantly higher prevalence (19.5%). When lower limb ST were included, there was a 10% increase in the prevalence of this type of wound[18].

As for the factors associated with ST, advanced age was identified in three studies analyzed[17-18,21], and frail elderly in one study[18]. Physiological changes associated with aging expose the elderly population to ST more than any other risk group. There is consensus among experts that it happens for two reasons: the weakening of the skin and susceptibility to trauma[3-4,7-8,11,13,26-27].

In the first case, with skin aging, or intrinsic aging, that is, premature increase in the keratinization of the epidermis and enlargement and flattening of skin grooves, along with the loss of the folding of the basal lamina. Consequently, the anchoring system between the layers of epidermis and dermis do not withstand well as to friction and shear[27].

On the other hand, in the dermis, fibroblasts begin to produce less collagen type I and more type III. Collagen fibers become tenuous, fragmented and separated by large areas occupied by fundamental amorphous substance. The mucopolysaccharides lose its structural function and is present as an amorphous pellet. The skin loses tensile strength, toughness, elasticity and extensibility[27].

The production of sweat and sebaceous glands is also reduced with age, skin becomes dehydrated, dry and inelastic. The subcutaneous layer becomes thinner and the fat pad less efficient in absorbing impact. The skin thickness decreases progressively, reaching a 20% loss in thickness[27].

The findings obtained in another study[24], infer that the risk factors for ST are not related only to the effects of skin aging but also to photoaging, or extrinsic aging. In the epidermis, exposure to ultraviolet radiation leads to thinning of the spinous layer and the flattening of the dermal-epidermal junction, while the dermis, is related to decreased collagen synthesis, as well as the increase of its degradation[28]. Photoaging, therefore, when enhancing skin aging, contribute further to their fragility, increasing thereby the risk for ST[24].

Added to the fragile skin of the elderly, they also present susceptibility to trauma. That happens because, over the years, the increase of musculoskeletal stiffness and muscle spasticity reduce sensory sensitivity, visual acuity and cognitive ability, leading to loss of physical mobility and increasing dependence for basic activities of daily life. All of these changes contribute to the considerable increase in the risk for trauma and make advanced age a major risk factor for ST[3-4,7-8,11,13,26-27].

Dependence for basic activities of daily living[19,22-23], non-responsiveness (which incurs total dependence), levels of mobility[22] and spasticity[23] were also identified as risk factors associated with ST.

In a study conducted with fully dependent elderly, who required assistance for basic activities of daily life, had large number of ST, particularly in the upper limbs[11]. They occurred during routine care, such as dressing and bathing, and during placements and transfers. Almost half of the ST (48%) occurred in bedridden elderly and 11% in those who required assistance to walk. In a descriptive study during six months of observation, it was found that the chances of presenting ST increased in the presence of gait difficulties[7]. Wheelchairs were also associated with 25% of occurred traumas[9].

Agitated behavior also figured as a risk factor associated with the occurrence of ST[22]. Researchers[11] considered it as a predisposing factor to trauma and therefore, ST, and included psychomotor agitation as one of the risk items being investigated for their risk ST assessment instrument, the Skin Integrity Risk Assessment Tool.

The decline in cognitive ability stems from the physiological processes of normal aging or a transitional stage for dementias, reflecting in other cognitive domains beyond memory and interfering with work capacity and social life[3]. Some authors[7,23] found in their studies that the chances of presenting ST increased in the presence of cognitive impairment.

Newborns and children are also susceptible to ST and constitute the second largest risk group. The authors of the study confirmed that ST prevalence (17%) is higher than the pressure ulcer (4%) in the pediatric population[20]. The age group up to 3 months old showed to be the most susceptible, because, besides having poor stratum corneum and dermal-epidermal junction undeveloped at birth, the dermis is thin, with only 60% of the thickness when compared to adult dermis. Tapes and adhesive bandages are identified as the main responsible for ST in this age group[20,29].

Clinical experience, however, provides strong evidence that ST is not restricted to the extremes of age[4,29-30]. Although elderly and newborns constitute the largest risk groups for ST, there are other groups which are prone to embrittlement of the skin and should not be ignored, such as critically ill individuals (in intensive care, or who have suffered major trauma or large surgery) at the end of life, or suffering from multiple extrinsic and intrinsic risk factors for ST regardless of age[29-30].

While studying patients hospitalized with cancer, the authors found many individuals under 50 years old with ST[22]. The skin, like any other organ, can also fail. A severe medical condition certainly compromise the body's homeostatic mechanisms, which can cause skin to divert blood to vital organs, resulting in decreased skin and soft tissue perfusion and, consequently, compromising the metabolic processes of the skin. Small traumas would be able to cause major complications such as bleeding, gangrene, infection, pressure ulcers and ST. The tolerance to pressure and friction decreases in such a way that these conditions can make it impossible to prevent the breakage of the skin integrity[30].

Hospitalized patients with cancer and ST also had a higher risk for pressure ulcer development (60%) than those without ST (12.5%)[22]. Similarly to this study[22] other authors[8] also found that most elderly with ST (60%) had the lowest Braden scores and hence higher risk for developing pressure ulcers. Although developed with other age groups, study subjects have similar characteristics to those patients with cancer cited at the beginning of this paragraph, especially some precarious conditions of global health, especially

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the activity and mobility and therefore, they were also at higher risk for developing pressure ulcers[8].

There is still a lot to be done in order to elucidate the epidemiology of ST. The methodological diversity of the studies, as data collection and statistical processing of data and the different criteria used in the classification of ST, besides the multitude of scenarios and the target population, make it difficult and sometimes impossible to generalize the results. It was also highlighted the importance of the presentation of the quantitative results of prevalence studies with their respective confidence intervals, which statistically estimate how reliable the values found are[16]. Also, they recommend that such prevalence should be analyzed in subgroups such as gender and age, among other variables that may be considered relevant. Unfortunately, this recommendation was not performed in any of the eight studies analyzed.

Restriction of the publication language was one limitation of this study, resulting in the exclusion of a study, published in Chinese[25].

Nevertheless, it is considered that the present study, through the summary of the knowledge about the prevalence of ST and factors associated with its occurrence, contributes to the development of protocols for prevention, and risk screening instruments for those wounds in the light of evidence-based practice.

CONCLUSION

The prevalence of ST ranged from 3.3% to 22% in hospital settings, and from 5.5% to 19.5%, in homecare. It was mainly associated with advanced age and dependence on basic activities of daily life.

RESUMO

Objetivo: Identificar e analisar a prevalência de lesão por fricção e os fatores associados à sua ocorrência. **Método:** Revisão sistemática da literatura publicada até junho de 2014 com a inclusão de estudos publicados na íntegra em inglês, espanhol ou português. Os estudos foram analisados segundo o *Strengthening the Reporting of Observational Studies in Epidemiology* e o *Guidelines for Critically Appraising Studies of Prevalence or Incidence of a Health Problem*. **Resultados:** As análises de oito estudos mostraram prevalência de lesão de 3,3% a 22% no cenário hospitalar e 5,5% a 19,5% no domiciliar. Idade avançada, dependência para as atividades básicas de vida diárias, idoso frágil, nível de mobilidade, comportamento agitado, arresponsividade, maior risco para o desenvolvimento concomitante de úlcera por pressão, comprometimento cognitivo, espasticidade e fotoenvelhecimento foram os fatores de risco citados. **Conclusão**: A prevalência de lesão variou de 3,3% a 22%, estando associada principalmente à idade avançada e dependência para as atividades básicas de vida diárias.

DESCRITORES

Ferimentos e Lesões; Prevalência; Estudos Transversais; Epidemiologia; Revisão.

RESUMEN

Objetivo: Identificar y analizar la prevalencia de lesión por fricción y los factores asociados con su ocurrencia. **Método:** Revisión sistemática de la literatura publicada hasta junio de 2014 con la inclusión de estudios publicados integralmente en inglés, español o portugués. Los estudios fueron analizados según el *Strengthening the Reporting of Observational Studies in Epidemiology* y el *Guidelines for Critically Appraising Studies of Prevalence or Incidence of a Health Problem*. **Resultados:** Los análisis de ocho estudios mostraron prevalencia de lesión del 3,3% al 22% en el escenario hospitalario y del 5,5% al 19,5% en el domiciliario. Edad avanzada, dependencia para las actividades básicas de vida diarias, anciano frágil, nivel de movilidad, comportamiento agitado, falta de responsividad, mayor riesgo para el desarrollo concomitante de úlcera por presión, afectación cognitiva, espasticidad y fotoenvejecimiento fueron los factores de riesgo citados. **Conclusión:** La prevalencia de lesión varió del 3,3% al 22%, estando asociada principalmente con la edad avanzada y la dependencia para las actividades básicas de vida diarias.

DESCRIPTORES

Heridas y Traumatismos; Prevalencia; Estudios Transversales; Epidemiología; Revisión.

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Attachment 22.20

Cutting. "Impact of adhesive surgical tape and wound dressings on the skin, with reference to skin stripping" Journal of Wound Care 2008; 17(4): 157-162.

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Impact of adhesive surgical tape and wound dressings on the skin, with reference to skin stripping

Age- and disease-related factors can cause the skin to become susceptible to damage, particularly at dressing change. This review recommends ways of avoiding skin trauma when removing adhesive dressings and surgical tapes

review; skin stripping; adhesive tapes; adhesive dressings; soft silicone dressings

K.F Cutting, MN, RN, Cert Ed (FE), Principal Lecturer, Buckinghamshire New University, UK. Email: info@healthdirections.co.uk

Care of the skin, including its protection against mechanical/chemical injury, is a requirement for those involved in dermatological care. Tissue trauma, caused by the removal of adhesives tapes and dressings, can exacerbate pain, increase wound size and delay healing, thereby increasing health-care costs and reducing patients' quality of life.[1] Adhesives can either be separate entities (eg, tapes) or an integral component of a dressing (eg, incorporated over the entire dressing surface or around the central absorptive pad).

This article briefly describes how age- and disease-related pathological changes can adversely affect skin integrity. It then focuses on trauma (skin stripping) related to the use of adhesive surgical tapes and wound dressings, and the potential impact on patients, particularly those with ageing skin and/or skin that has been compromised by disease. Following a review of experimental and clinical data, recommendations are given on how to avoid these problems.

The literature search

Searches of bibliographic databases (Medline 1950–2008 and Embase 1974–2008), the Cochrane Library and *World Wide Wounds* websites, and journals relating to dermatology and wound management were undertaken to identify relevant data. The following search terms were used: 'skin' and ['structure' or 'morphology' or 'function' or 'physiology'] and ['abnormality' or 'defect' or 'damage' or 'injury' or 'lesion' or 'trauma' or 'ulcer' or 'wound'] and ['aging' or 'disease'] and 'adhesive' and ['tape' or 'dressing'].

Age-related pathological changes to skin

Skin integrity is adversely affected by both age-related and disease-related pathologies.

Progressive detrimental changes, caused primarily by cumulative exposure to harmful ultraviolet wavelengths in sunlight, occur in the skin with ageing. Progressive changes lead to epidermal hyperplasia and neoplasia, with concomitant dermal changes including enhanced inflammatory processes, elastosis and reduction of cutaneous vessel size.[2,3] Changes in the mechanical properties of skin, in particular tissue hydration and its resiliency, are intimately linked with age. Skin can show a tendency for decreased blood flow with increasing age.[4,5]

Disease-related pathological changes to skin

Various pathological conditions, affecting both adults and children, have an adverse affect on skin structure and function. Early presenting aetiological factors play a pivotal role in skin integrity. For example, infantile eczema and atopic dermatitis may predispose towards inherently friable skin.[6,7] Extreme infantile congenital skin disorders such as epidermolysis bullosa (EB) and skin ectodermal dysplasia/skin fragility syndrome (EDSFS) can severely affect skin integrity from an early age.

Epidermolysis bullosa is characterised by extremely fragile skin and recurrent blister formation ending in scars, as a result of minor mechanical friction or trauma.[8]

Skin ectodermal dysplasia/skin fragility syndrome is associated with severe cutaneous changes including skin fragility and blistering, with detachment of the upper epidermal layers as a result of skin disadhesion.[9]

Dermatological changes associated with diabetes are common, with many factors being responsible for the formation of skin abnormalities in almost one-third of diabetic patients. These include:

- Skin reactions to diabetic treatments
- Pathological skin involvement (eg, diabetic dermopathy and scleroderma
- Infections.[10,11]

Skin adjacent to chronic wounds resulting from venous insufficiency may be subject to additional pathologies. For example, patients may develop

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characteristic changes in the skin of the lower limb known as lipodermatosclerosis (LDS). This is generally associated with dry, flaky skin, induration and hyperpigmentation as a result of acute inflammation, and may also become ulcerated.[12,13] Venous hypertension can lead to the trapping and activation of neutrophils and monocytes and the expression of pro-inflammatory cytokines. Subsequent endothelial cell damage in the epidermal microvasculature increases the susceptibility of peri-wound skin to physical injury in patients with LDS.[14]

Skin stripping: causes and pathologies

When adhesive tapes or dressings are removed from skin, varying amounts of superficial stratum corneum are removed with them. The repeated application and removal of adhesive tapes or dressings to and from the same site cause exogenous damage to the skin (skin stripping).[15] Skin stripping may, in turn, lead to inflammatory skin reactions, oedema and soreness, all of which can have an adverse effect on skin barrier function.[16,17]

Another consequence of skin stripping is pain.[18] Dressing removal, which has the potential to cause trauma to delicate healing tissue in wounds and the surrounding skin, is considered one of the most painful wound-care interventions[19] and can affect quality of life.[20] According to an international survey of wound-care practitioners, dried out dressings and adherent products were most likely to cause trauma and pain at dressing changes. Furthermore, there appeared to be a close association between dressings that caused wound trauma and those that caused pain.[21]

Damage to the stratum corneum and irritation due to skin stripping are subject to many variables; these may be patient-related (age, skin pathology) and adhesive-related (type and strength).[17,22] The quantity and depth of corneocytes that are removed have a direct relationship with the degree of skin irritancy and adhesive applied. Repeated applications of adhesives enhance these detrimental effects.[17,23]

The damage caused by skin stripping may be amplified in patients that have skin problems associated with ageing, disease (such as EB) or clinical interventions (such as radiation-induced skin damage).[15]

Comparisons of adhesive tapes and dressings in terms of their propensities to cause skin stripping

Different types of adhesives are used in tapes and wound dressings, including acrylics, hydrocolloids, polyurethanes, soft silicones and zinc oxide. The removal of acrylic, hydrocolloid, polyurethane and zinc-oxide adhesives can cause trauma (skin stripping) and pain[16,24-26] as well as, in the case of hydrocolloid and polyurethane adhesives, maceration.[1,18] Soft silicone adhesives, on the other hand, provide an effective and safe level of adhesion to skin that, unlike some other adhesive types, such as acrylics, does not increase with time.[1]

The literature search identified a number of studies involving either volunteers[16,25,26] or patients with wounds/skin injuries,[27,28] in which comparative data on the propensity for different adhesive tapes and dressings to cause skin stripping are presented.

Experimental models of normal human skin in healthy volunteers, although not totally indicative of clinical use, have addressed aspects of skin-surface adhesive interactions and demonstrated differences in the level of skin stripping related to various adhesive tapes and dressing adhesives and associated peel force.[16,25,26]

In two of the volunteer studies[25,26] and in a clinical study involving patients with venous ulcers discussed later in this article,[27] measurements of transepidermal water loss (TEWL) and skin surface hydration were undertaken.

An inverse relationship exists between TEWL and skin surface hydration (measured by cutaneous conductance), representing water barrier function and the stratum corneum hydration state respectively. These two parameters are good indicators of skin barrier stasis.

Water is normally retained in the stratum corneum, thus maintaining a viable skin-surface hydration state and barrier function, as well as helping to retain skin suppleness and flexibility.[29] Transepidermal water loss tends to be minimal in normal skin because of the water barrier function of the stratum corneum. Dry pathological skin, in comparison, demonstrates increased TEWL and low stratum corneum water content.[30]

Peel force, skin stripping and cutaneous damage were assessed in a study involving 11 healthy volunteers who had daily applications of two ostomy adhesive strips (one with zinc oxide based adhesive (Smith & Nephew) and the other with a hydrocolloid-based adhesive (Assura, Coloplast), to the skin of their forearms for a four-week period.[26]

The peel force of the zinc oxide adhesive increased significantly during the first two weeks, and was significantly higher ($p=0.007$) than that of the hydrocolloid adhesive for the rest of the study period. The zinc oxide adhesive was found to have a significantly higher TEWL than the hydrocolloid adhesive ($p<0.05$) in the first two weeks, after which no statistically significant difference in TEWL between the two adhesives was observed.

Throughout the study, the two adhesives were associated with significantly higher TEWL than the control sites ($p<0.05$). At the end of the study period, the mean water content of the skin treated with the zinc oxide adhesive was lower than that of the

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control sites, whereas the mean water content of the skin treated with the hydrocolloid adhesive was statistically higher ($p<0.05$). Both adhesives caused skin tears at the edges of the treated areas.

The hydrocolloid adhesive was associated with TEWL and skin hydration levels that are consistent with those of non-pathological skin, although the hydrocolloid adhesive-treated skin exhibited erythema as a result of local irritation. In contrast, the zinc oxide adhesive induced pathophysiological cutaneous changes, including epidermal thickening and parakeratosis, which has similarities to skin diseases such as psoriasis and atopic dermatitis. Although this study related to ostomy adhesive strips, it is relevant to wound care as the adhesive systems used in the products evaluated are also used to facilitate dressing retention.

To quantify the peel force required to remove five different adhesive dressings and relate this to the amount of stratum corneum removed, an experimental study involving 20 healthy volunteers was undertaken.[16] After staining the forearm skin of volunteers with a blue dye, three consecutive 24-hour applications of each dressing were made. Peel force measurements were undertaken at 24, 48 and 72 hours. After removal of the dressings, the amount of dye remaining on the skin was sampled and measured as a means of gauging skin damage (ie, on the assumption that the more dye was left on the skin, the less damage had been incurred, and vice versa).

Statistically significant differences were observed between some of the dressings, with a rank order from highest to lowest peel force as follows:

- Foam dressing with an acrylic adhesive (Allevyn Adhesive, Smith & Nephew)
- Foam dressing with a polyurethane adhesive (Tielle, Johnson & Johnson)
- Hydrocolloid dressing (Duoderm Extra Thin, ConvaTec)
- Foam dressing with Safetac soft silicone adhesive (Mepilex Border, Mölnlycke)
- Foam dressing with hydrocolloid adhesive (Biatain Adhesive, Coloplast).

Differences between the dressings in terms of the level of damage to the stratum corneum were also observed (Fig 1). For most of the dressings evaluated, the amount of damage to the stratum corneum appeared to be related to the peel force — for example, the foam dressing with Safetac soft silicone adhesive was associated with a low peel force and a low percentage of damage, whereas a high peel force and a high percentage of damage were observed for the foam dressing with an acrylic adhesive.

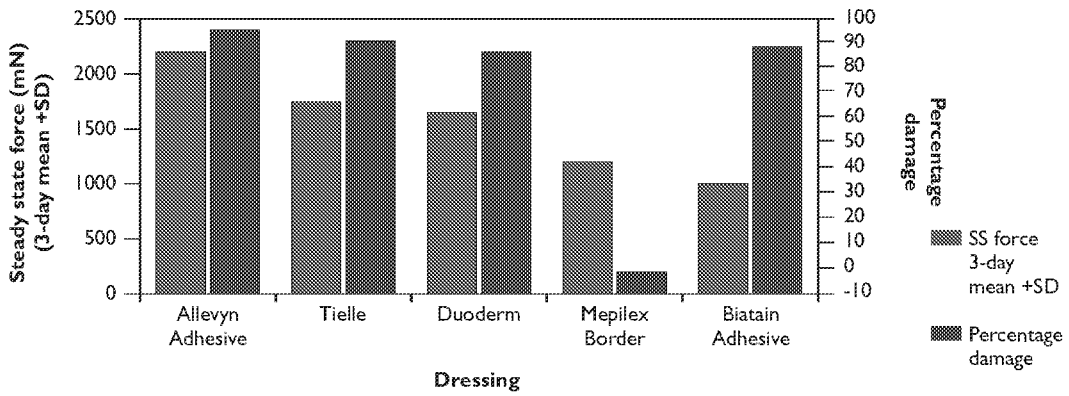
However, peel force did not always correlate with the degree of skin stripping observed — for example, the foam dressing with hydrocolloid adhesive was associated with a low peel force but a high percentage of damage, suggesting that factors other than peel force are involved in determining the level of skin stripping caused by adhesive dressings.

A more recent study involving 30 healthy volunteers set out to assess the effect of repeated application and removal of adhesive edges from six dressings on cutaneous irritancy and barrier function.[25] Six applications to the same test site were done over a 14-day period for the following dressings:

- Foam dressing with Safetac soft silicone technology (Mepilex Border Lite, Mölnlycke)
- Foam dressing with acrylic adhesive (Allevyn Adhesive, Smith & Nephew)
- Foam dressing with hydrocolloid adhesive (Biatain, Coloplast)
- Foam dressing with a polyurethane adhesive (Tielle Plus, Johnson & Johnson)
- Hydrocolloid dressing (Duoderm Extra Thin, ConvaTec)
- Hydrocolloid dressing (Comfeel Plus Transparent, Coloplast).

A cumulative irritancy score for each test site was determined by adding erythema scores (based on an

Fig 1. Comparison of adhesive dressings in terms of peel force and skin damage on removal[1]



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established ranking scale for cutaneous erythema) recorded at six time points during the study period. The skin barrier function of each site was assessed by measuring TEWL at the end of the study period.

The acrylic-, polyurethane-, and soft silicone-based adhesive foam dressings were associated with lower cumulative irritancy scores than both of the hydrocolloid dressings and the foam dressing utilising a hydrocolloid adhesive system (Fig 2). The acrylic-, polyurethane- and soft silicone-based adhesive foam dressings were associated with TEWL that was not significantly different from normal skin ($p<0.05$), whereas the other dressings were associated with a significantly higher TEWL (Fig 3).

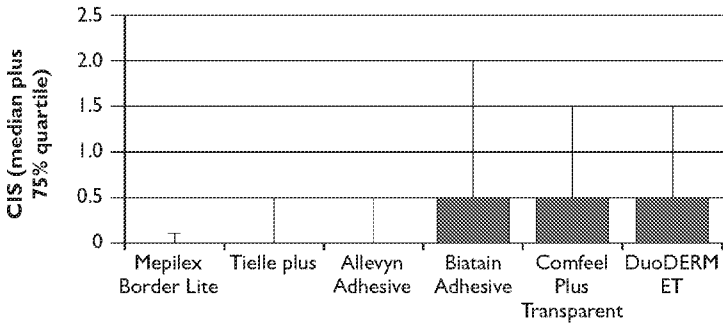
Reflecting on the findings of the studies described above, it is important to consider the relevance of volunteer studies to assessing the potential for adhesives to cause skin stripping in the clinical setting. The best indicator comes from the clinical study involving patients with venous leg ulcers[27] in which adhesive dressings were applied to both peri-wound skin and normal forearm skin. Interestingly, the TEWL measurements showed very similar responses on the peri-wound and forearm skin. However, as peri-wound skin is often more friable than normal healthy skin, it could be argued that the level of skin stripping observed in volunteer studies may not necessarily reflect the severity of skin stripping or the true difference between dressings in terms of their propensity to cause skin stripping in the clinical situation.

A clinical study involving 45 patients with venous leg ulcers was undertaken to assess the effects of repeated removal of adhesive dressings on the barrier function (measured by TEWL) and hydration (measured by electrical conductance) of peri-wound skin. Patients were randomised to treatment with one of four dressings:

- Foam dressing with hydrocolloid adhesive (Biatain, Coloplast)
- Foam dressing with polyurethane adhesive (Tielle, Johnson & Johnson)
- Hydrocolloid dressing (Duoderm Extra Thin, ConvaTec)
- Foam dressing with Safetac soft silicone adhesive (Mepilex Border, Mölnlycke).

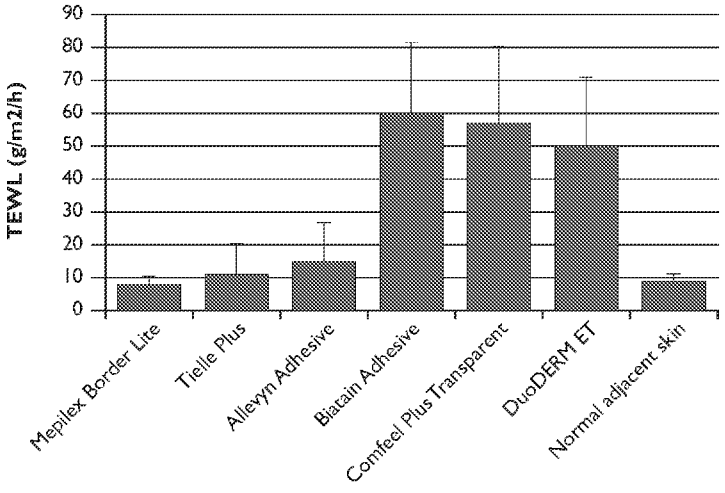
The peri-wound skin was treated for 14 days with patches of the dressings (replaced every two days); normal skin on the patients' forearms were treated identically as controls. The foam dressing with hydrocolloid adhesive and the hydrocolloid dressing were associated with increased TEWL and conductance (indicating that they induced major functional alterations of the stratum corneum), while the foam dressing with polyurethane adhesive and the foam dressing with Safetac soft silicone adhesive did not influence these parameters significantly, when compared with non-treated peri-wound skin (Fig 4).[27,28]

Fig 2. Comparison of adhesive dressings in terms of cumulative irritancy scores (CIS) associated with repeated application and removal[25]



The following pairs are significantly different ($p < 0.05$): Mepilex Border Lite versus DuoDERM ET, Mepilex Border Lite versus Comfeel, Mepilex Border Lite versus Biatain, Tielle versus Biatain, and Allevyn versus Biatain

Fig 3. Comparison of adhesive dressings in terms of transepidermal water loss (TEWL) associated with repeated application and removal[25]



Avoiding skin stripping

Recommendations for preventing or minimising skin stripping include:

- Identifying at-risk patients (elderly and/or those with underlying pathologies)
- Closely monitoring patients for signs of skin stripping by performing regular pain assessments and examinations of peri-wound skin
- Choosing appropriate dressings that are designed to minimise skin stripping.

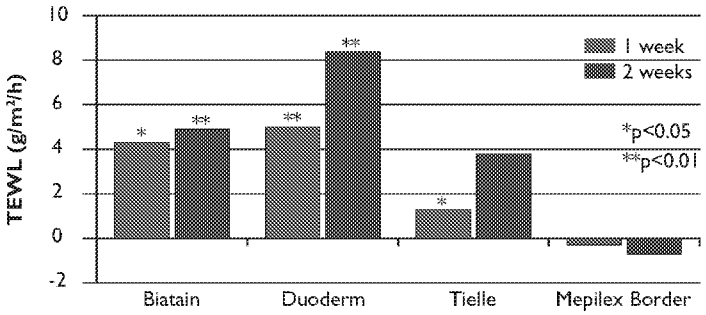
Adhesive-skin interactions are clearly key considerations in dressing choice, especially in relation to inherently friable and compromised skin as found in many and varied skin conditions. A fundamental requirement for appropriate dressing choice would

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Fig 4. Comparison of adhesive dressings in terms of transepidermal water loss (TEWL) associated with repeated application and removal (peri-wound skin)[28]



appear to be based on clinical requirements with close reference to dressing adhesive and skin adhesion. Ideally, the adhesive would be compatible with local skin conditions including age, anatomical site and pathological state, thus having the ability to reduce the incidence of skin stripping and related adverse cutaneous reactions such as erythema.

According to a consensus document issued by the World Union of Wound Healing Societies,[20] it is important that clinicians consider dressings that are known to be atraumatic on removal (ie, soft silicones). The atraumatic and virtually pain-free removal of soft silicone dressings has been demonstrated in a number of clinical studies involving adults, children and neonates with a variety of wound types (such as grafts, burns/scars, leg/foot ulcers, pressure ulcers, skin tears, amputation/surgical wounds, pressure ulcers, skin tears and amputations) as well as skin disorders (such as radiation-induced skin damage congenital skin disorders like EB),[31] many of which are associated with friable and damaged skin. If soft silicone dressings have proved to be of benefit where the most fragile skin is encountered, then similarly advantageous outcomes can be expected in less challenging situations.

In relation to the management of damaged/friable skin and successful wound healing, several key issues need to be considered. Importantly, patient care plans frequently address issues related to the protection of skin integrity at dressing change, including dressing choice, pain control, body fluids and patient comfort.[32] Despite this, a 2001 survey of 1000 clinicians involved in wound care in the UK found that over one-third of respondents were unaware of products specifically designed to reduce cutaneous pain and trauma at dressing change.[19] Dressing change represents a clinical challenge, particularly in patients with fragile skin that may be easily damaged and cause considerable pain.

A large number of advanced wound dressings aim to provide moist wound healing environments conducive to healing. However, the benefits of such an approach may be limited as a result of trauma and pain caused by the repeated application and removal of adhesive tapes and dressings. With this in mind, the selection and use of atraumatic wound dressings is extremely important. Unfortunately, appropriate care and intervention is dictated by the limitations imposed by human and financial resources. However, dressing choice based on initial low expenditure costs does not necessarily equate with best value for money when trying to achieve a successful patient outcome.[32]

It is important, therefore, that the process of wound dressing selection is based on all aspects influencing the cost of treatment (ie, materials, labour and non-medical costs to society) and not solely on the unit costs of dressings.[33]

Conclusion

Trauma following repeated removal of skin adhesive causes an erythematous reaction, which has an adverse effect on skin barrier function. Adhesive-skin interactions are clearly key components in dressing choice in modern wound care. The accurate assessment of a patient's needs, followed by application of the most appropriate dressing, should dominate dressing choice if unnecessary skin damage is to be avoided. Dressings utilising soft silicone adhesive technology have been shown to be effective in the treatment of a variety of wounds, most notably those associated with conditions which may predispose towards inherently friable skin. These dressings should be strongly considered in the treatment of wounds where care has to be exercised in avoiding trauma to the wound bed and peri-wound skin. ■

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3 January 2018 Global guidelines for the prevention of surgical site infection, 2nd ed. (Link accessed 27 May 2022).

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Overall coordination and writing of the guidelines

Benedetta Allegranzi (Department of Service Delivery and Safety, WHO) coordinated and led the development and writing of the guidelines. Peter Bischoff (Charité-University Medicine Berlin, Germany), Zeynep Kubilay (Department of Service Delivery and Safety, WHO), Stijn de Jonge (University of Amsterdam, Amsterdam, the Netherlands) and Bassim Zayed (Department of Service Delivery and Safety, WHO) helped coordinate the development and writing of the guidelines. Mohamed Abbas (University of Geneva Hospitals, Switzerland), Nizam Damani (Southern Health and Social Service Trust, UK) and Joost Hopman (Radboud University Medical Center Nijmegen, the Netherlands) also contributed to the writing of specific chapters. Rosemary Sudan provided professional editing assistance. Thomas Allen and Jose Luis Garnica Carreno (Library and Information Networks for Knowledge, WHO) provided assistance with the systematic reviews searches. Susan Norris (Guidelines Review Committee Secretariat, WHO) provided guidance on the document development.

WHO Guideline Steering Group

The following WHO staff formed the Guideline Steering Group:

Department of Service Delivery and Safety: Benedetta Allegranzi, Edward Kelley, Walter Johnson, Bassim Zayed.

Department of Pandemic and Epidemic Diseases: Sergey Eremin.

Regional Office for the Americas: Valeska Stempliuk.

WHO Guidelines Development Group

The chair of the Guidelines Development Group was Joseph S Solomkin (University of Cincinnati College of Medicine/OASIS Global, USA).

The GRADE methodologist of the WHO Guidelines Development Group was Matthias Egger (University of Bern, Bern, Switzerland).

The following experts served on the Guidelines Development Group:

Hanan H Balkhy (King Saud Bin Abdulaziz University for Health Sciences, Kingdom of Saudi Arabia); Javier F Belda (University of Valencia, Spain); Sean Berenholtz (Johns Hopkins Medicine, Baltimore, USA); Marja A Boermeester (University of Amsterdam, the Netherlands); Nizam Damani (Craigavon Area Hospital, UK); E Patchen Dellinger (University of Washington, USA); Mazen S Ferwana (King Saud Bin Abdulaziz University for Health Sciences, Kingdom of Saudi Arabia); Petra Gastmeier (Institute of Hygiene and Environmental Medicine, Charité-University Medicine Berlin, Germany); Robert Greif (Hospital University of Bern, Switzerland); Asad Latif (Johns Hopkins Medicine, Baltimore, USA); Xavier Guirao (Parc Tauli Hospital Universitari, Spain); Nordiah Jalil (University Kebangsaan Malaysia Medical Centre, Malaysia); Robinah Kaitiritimba (Uganda National Health Consumers' Organization, Uganda); Fauzia Khan (Aga Khan University Karachi, Pakistan); Janet Martin (School of Medecine/Dentistry Western University, Ontario, Canada); Regina Kamoga (Community Health and Information Network, Uganda); Claire Kilpatrick (KS Healthcare Consulting (S3 Global, UK); Shaheen Mehtar (Stellenbosch University and Infection Control Africa Network, Republic of South Africa); Jannicke Mellin-Olsen (World Federation of Societies of Anesthesiologists, London, UK); Babacar Ndoye (Infection Control Africa Network Board, Senegal); Peter Nthumba (AIC Kijabe Hospital, Kenya); Bisola Onajin Obembe (University of Port Harcourt,

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Members of the Systematic Reviews Expert Group

The following experts served on the Systematic Reviews Expert Group (names of team leaders are underlined):

Jasper J Atema, Marja A Boermeester, Quirne Boldingh, Sarah Gans, Stijn de Jonge, Fleur de Vries, and Elon D Wallert (University of Amsterdam, the Netherlands); Stacey M Gomes (OASIS Global, USA); and Joseph S. Solomkin (University of Cincinnati College of Medicine, USA); Jan Kluytmans and Miranda van Rijen (Amphia Hospital Breda, the Netherlands); Jianan Ren and Yiuwen Wu (Nanjing University, People's Republic of China); Xavier Guirao and Sandra Pequeno (Parc Taulí Hospital Universitari, and Centre Cochrane Iberoamericà de l'Hospital de la Santa Creu i Sant Pau, Spain); Petra Gastmeier and Peter Bischoff (Institute of Hygiene and Environmental Medicine, Charité-University Medicine Berlin, Germany); Didier Pittet and Caroline Landelle (University of Geneva Hospitals, Switzerland); Nizam Damani (Southern Health and Social Service Trust, UK); Benedetta Allegranzi, Zeynep Kubilay and Bassim Zayed (Department of Service Delivery and Safety, WHO); Yoon K Loke, K. Mattishent, A. Peel, A. Sinha, M. Thavarajah (University of East Anglia Norwich, UK).

External Peer Review Group

The following experts served as external peer reviewers of the draft guideline documents:

Emmanuel Ameh (Ahmadu Bello University, Nigeria); Kamal Itani (VA Boston Healthcare System & Boston University School of Medicine, USA); Fernando Otaíza (Infection Prevention and Control Unit, Ministry of Health, Chile); Val Robertson (University of Zimbabwe, Zimbabwe); Ilker Uçkay (University of Geneva Hospitals, Switzerland).

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ABBREVIATIONS AND ACRONYMS

ABHR	alcohol-based handrub
AMR	antimicrobial resistance
ASHP	American Society of Health-System Pharmacists
CDC	Centers for Disease Control and Prevention
CHG	chlorhexidine gluconate
CI	confidence interval
ECDC	European Centre for Disease Prevention and Control
ESBL	extended spectrum beta-lactamase
FiO2	fraction of inspired oxygen
GDFT	goal-directed fluid therapy
GDG	Guidelines Development Group
GRADE	Grading of Recommentations Assessment, Development and Evaluation
HAI	health care-associated infection
IDSA	Infectious Diseases Society of America
IPC	infection prevention and control
LMICs	low- and middle-income countries
MBP	mechanical bowel preparation
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
MTX	methotrexate
NHSN	National Healthcare Safety Network
NICE	National Institute for Health and Care Excellence
NNIS	National Nosocomial Infections Surveillance System
OR	odds ratio
PAHO	Pan American Health Organization
PHMB	polyhexamethylene biguanide
PICO	Population, Intervention, Comparison, Outcomes
pNPWT	prophylactic negative pressure wound therapy
PVP-I	povidone-iodine
RCT	randomized clinical trial
SAP	surgical antibiotic prophylaxis
SHEA	Society of Healthcare Epidemiology of America
SIGN	Scottish Intercollegiate Guidelines Network
SREG	Systematic Reviews Expert Group
SSI	surgical site infection/s
THA	total hip arthroplasty
TKA	total knee arthroplasty
TNF	tumour necrosis factor
UK	United Kingdom
USA	United States of America
v/v	volume/volume
WHO	World Health Organization
WFSA	World Federation of Societies of Anesthesiologists
WP	wound protectors

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GLOSSARY OF TERMS

Alcohol-based handrub refers to an alcohol-based preparation designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients and humectants.

Antimicrobial skin sealants refer to sterile, film-forming cyanoacrylate-based sealants that are commonly used as additional antimicrobial skin preparation after antisepsis and prior to skin incision. These sealants are intended to remain in place and block the migration of flora from surrounding skin into the surgical site by dissolving for several days postoperatively.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) is an approach used to assess the quality of a body of evidence and to develop and report recommendations.

Health care-associated infection, also referred to as "nosocomial" or "hospital" infection, is an infection occurring in a patient during the process of care in a hospital or other health care facility, which was not present or incubating at the time of admission. Health care-associated infections can also appear after discharge. They represent the most frequent adverse event during care.

Hygienic handrub refers to the treatment of hands with an antiseptic handrub to reduce the transient flora without necessarily affecting the resident skin flora. These preparations are broad spectrum and fast-acting, and persistent activity is not necessary.

Hygienic handwash refers to the treatment of hands with an antiseptic handwash and water to reduce the transient flora without necessarily affecting the resident skin flora. It is broad spectrum, but it is usually less efficacious and acts more slowly than hygienic handrub.

Interactive (advanced) wound dressings refer to modern (post-1980) dressing materials that are designed to promote the wound healing process through the creation and maintenance of a local, warm, moist environment underneath the chosen dressing when left in place for a period indicated through a continuous assessment process. Examples are alginates, semipermeable film membranes, foams, hydrocolloids and fibrous hydrocolloids, non-adherent wound contact materials and combinations of those.

Iodophors refer to a preparation containing iodine complexed with a solubilizing agent, such as a surfactant or povidone (forming povidone-iodine). The result is a water-soluble material that releases free iodine when in solution. Iodophors are prepared by mixing iodine with the solubilizing agent; heat can be used to speed up the reaction.

Low- and middle-income countries: WHO Member States are grouped into four income groups (low, lower-middle, upper-middle, and high) based on the World Bank list of analytical income classification of economies for the 2014 fiscal year, calculated using the *World Bank Atlas* method. For the current (2016) fiscal year, low-income economies are defined as those with a gross national income (GNI) per capita of US$ 1045 or less in 2014; middle-income economies are those with a GNI per capita of more than US$ 1045, but less than US$ 12 736; (lower-middle-income and upper-middle-income economies are separated at a GNI per capita of US$ 4125) high-income economies are those with a GNI per capita of US$ 12 736 or more.

Mechanical bowel preparation refers to the

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preoperative administration of substances to induce voiding of the intestinal and colonic contents.

Paediatric population: infants, children, and adolescents, within an age limit usually ranging from birth up to 18 years of age.

Point prevalence (survey) refers to the proportion of individuals with a particular disease or attribute measured on a particular date.
Note: Prevalence differs from incidence in that prevalence includes all cases, both new and preexisting, in the population at the specified time, whereas incidence is limited to new cases only.

Primary closure is defined as closure of the skin level during the original surgery, regardless of the presence of wires, wicks, drains, or other devices or objects extruding through the incision. This category includes surgeries where the skin is closed by some means. Thus, if any portion of the incision is closed at the skin level, by any manner, a designation of primary closure should be assigned to the surgery.

Resident flora refers to microorganisms residing under the superficial cells of the *stratum corneum* and found also on the surface of the skin.

Surgical antibiotic prophylaxis refers to the prevention of infectious complications by administering an effective antimicrobial agent prior to exposure to contamination during surgery.

Surgical hand preparation refers to an antiseptic handwash or antiseptic handrub performed preoperatively by the surgical team to eliminate transient flora and reduce resident skin flora. Such antiseptics often have persistent antimicrobial activity.

Surgical handrub(bing) refers to surgical hand preparation with a waterless alcohol-based handrub.

Surgical handscrub(bing)/presurgical scrub refers to surgical hand preparation with antimicrobial soap and water.

Surgical procedure refers to an operation where at least one incision (including a laparoscopic approach) is made through the skin or mucous membrane, or reoperation via an incision that was left open during a prior operative procedure AND takes place in an operating room.

Surgical site infection refers to an infection that occurs after surgery in the part of the body where the surgery took place. Surgical site infections can sometimes be superficial infections involving the skin only. Other surgical site infections are more serious and can involve tissues under the skin, organs, or implanted material.
(Source: United States Centers for Disease Control and Prevention. https://www.cdc.gov/HAI/ssi/ssi.html, accessed 11 July 2016).

Surgical site infection is also defined as an infection that occurs within 30 days after the operation and involves the skin and subcutaneous tissue of the incision (superficial incisional) and/or the deep soft tissue (for example, fascia, muscle) of the incision (deep incisional) and/or any part of the anatomy (for example, organs and spaces) other than the incision that was opened or manipulated during an operation (organ/space).
(Source: European Centre for Disease Prevention and Control. http://ecdc.europa.eu/en/publications/Publications/120215_TED_SSI_protocol.pdf, accessed 16 August 2016).

SSI-attributable mortality refers to deaths that are directly attributable to SSI. The numerators refer to surgical patients whose cause of death was directly attributable to SSI and the denominator usually refers to all surgical patients in a patient population.

Surgical site infection rates per 100 operative procedures are calculated by dividing the number of surgical site infections by the number of specific operative procedures and multiplying the results by 100. Surgical site infection rate calculations can be performed separately for the different types of operative procedures and stratified by the basic risk index.

Surgical instruments are tools or devices that perform such functions as cutting, dissecting, grasping, holding, retracting, or suturing the surgical site. Most surgical instruments are made from stainless steel.

Surgical wound refers to a wound created when an incision is made with a scalpel or other sharp cutting device and then closed in the operating room by suture, staple, adhesive tape, or glue and resulting in close approximation to the skin edges.

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Transient flora refers to microorganisms that colonize the superficial layers of the skin and are more amenable to removal by routine handwashing/handrubbing.

Underweight is a term describing a person whose body weight is considered too low to be healthy. The definition usually refers to people with a body mass index of under 18.5 or a weight 15-20% below the norm for their age and height group.

Surgical wounds are divided into four classes.

1. Clean refers to an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital or uninfected urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria.

2. Clean-contaminated refers to operative wounds in which the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

3. Contaminated refers to open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (for example, open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered ,including necrotic tissue without evidence of purulent drainage (for example, dry gangrene), are included in this category.

4. Dirty or infected includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.
(Source: United States Centers for Disease Control and Prevention. https://www.cdc.gov/hicpac/SSI/table7-8-9-10-SSI.html, accessed 11 July 2016.)

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DECLARATION OF INTERESTS

In accordance with WHO regulations, all members of the Guidelines Development Group (GDG) were required to complete and submit a WHO Declaration of interests form prior to participating in each meeting. External reviewers and members of the Systematic Reviews Expert Group were also required to submit a Declaration of interest form. The secretariat then reviewed and assessed each declaration. In the case of a potential conflict of interest, the reason was presented to the GDG.

Procedures for the management of declared conflicts of interest were undertaken according to the WHO *guidelines for declaration of interests (WHO experts)*. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were only required to openly declare the potential conflict at the beginning of the Technical Consultation. However, the declared conflicts were considered irrelevant on all occasions and did not warrant any exclusion from the GDG. Therefore, all members participated fully in the formulation of the recommendations and no further action was taken.

The following interests were declared by GDG members:

Joseph Solomkin, chair of the GDG, is also the chief executive officer of OASIS Global (USA), at the time of the guidelines development an organization that provided funds to partially support the salary of a WHO consultant assisting in initiating the guideline development process.

Andreas Widmer declared that he received a research support grant of 200 000 Swiss francs from the Swiss National Science Foundation for a study on antibiotic prophylaxis in 2014.

Peter Nthumba declared that his attendance at a workshop on surgical site infections in 2014 was supported by Ethicon Surgical Care (Johnson & Johnson).

Javier Belda declared that he obtained a research grant of € 132 624 from Air Liquide Sante for the Project iPROVE-O2 (https://clinicaltrials.gov/ct2/show/NCT02776046).

Marja A Boermeester declared that her attendance at a meeting was supported by Johnson & Johnson in 2014 and that she obtained a research grant of € 49 000 from Johnson & Johnson on a subject not related to these guideline recommendations. She also received grants or honoraria for delivering lectures on surgical site infection or serving on scientific advisory boards for Abbott/Mylan, Acelity, Bard, Baxter, GSK, Ipsen and Johnson & Johnson.

E Patchen Dellinger declared that he received honoraria for delivering lectures on surgical site infection. He also received fees for serving on scientific advisory boards for Astellas, Baxter, Cubist, Durata, Merck, Ortho-McNeil, Pfizer, Rib-X, R-Pharm, Targanta, Tetraphase and 3M. These honoraria and fees varied between US$ 1000 and US$ 5000 but the activities were not related to the guideline recommendations.

Robert Greif declared that he is the first author of a paper published in the New England Journal of Medicine in 2000, which demonstrates benefit of use high FiO_2 to reduce SSI.

Xavier Guirao declared that he received personal fees of about € 1000 from Merck, Pfizer, Astra-Zeneca, and Novartis; these activities were not related to the guideline recommendations.

Fauzia Khan declared that as the chair of the World Federation of Societies of Anesthesiologists (WFSA) Safety & Quality of Practice Committee, he discussed the WHO recommendation on high FiO_2 within this group in the past.

Akca Ozan declared that he contributed to a review article on high FiO_2 published in the Turkish Journal of Anaesthesiology and Reanimation in 2017.

Apart from Marja Boermeester, Joseph Solomkin and Xavier Guirao (see above), no member of the Systematic Reviews Expert Group declared any conflict of interest. One external reviewer declared the following interests which were considered irrelevant by the WHO Steering Group:
Val Robertson declared that she received a research grant of US$ 3500 from the International Federation of Infection Control in 2015 and that she currently receives a monthly honorarium of US$ 2241 as a technical advisor to the Zimbabwe Infection Prevention and Control Project.

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EXECUTIVE SUMMARY

Introduction

Health care-associated infections (HAI) are acquired by patients while receiving care and represent the most frequent adverse event affecting patient safety worldwide.

Recent work by the World Health Organization (WHO) shows that surgical site infection (SSI) is the most surveyed and frequent type of HAI in low- and middle-income countries and affects up to one third of patients who have undergone a surgical procedure. Although SSI incidence is lower in high-income countries, it remains the second most frequent type of HAI in Europe and the United States of America (USA).

Many factors in the patient's journey through surgery have been identified as contributing to the risk of SSI. Therefore, the prevention of these infections is complex and requires the integration of a range of preventive measures before, during and after surgery. However, the implementation of these measures is not standardized worldwide. No international guidelines are currently available and inconsistency in the interpretation of evidence and recommendations among national guidelines is frequently identified.

The aim of these guidelines is to provide a comprehensive range of evidence-based recommendations for interventions to be applied during the pre-, intra- and postoperative periods for the prevention of SSI, while also considering aspects related to resource availability and values and preferences.

Although the guidelines are intended for surgical patients of all ages, some recommendations do not apply to the paediatric population due to lack of evidence or inapplicability and this is clearly stated.

Target audience

The primary target audience for these guidelines is the surgical team, that is, surgeons, nurses, technical support staff, anaesthetists and any professionals directly providing surgical care. Pharmacists and sterilization unit staff will also be concerned by some aspects of these guidelines. The recommendations are also intended to be used by policy-makers, senior managers and infection prevention and control (IPC) professionals as the basis for developing national and local SSI protocols and policies, and supporting staff education and training.

Guideline development methods

The guidelines were developed according to the processes described in the WHO *Handbook for guideline development* issued in 2014. In summary, the process included:
(1) identification of the primary critical outcomes and priority topics and formulation of a series of questions structured in a PICO (Population, Intervention, Comparison, Outcomes) format;
(2) retrieval of the evidence through specific systematic reviews of each topic using a standardized agreed methodology;
(3) assessment and synthesis of the evidence;
(4) formulation of recommendations; and
(5) writing of the guideline content and planning for its dissemination and associated implementation strategy.

The development of the guidelines involved the formation of four main groups to guide the process: the WHO Guideline Steering Group; the Guidelines Development Group (GDG); the Systematic Reviews Expert Group; and the External Review Group.

Using the list of priority topics, questions and critical outcomes identified by the WHO Guideline

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Steering Group, the GDG and the guideline methodologist in a scoping meeting convened by WHO in September 2013, the Systematic Reviews Expert Group conducted 27 systematic reviews to provide the supporting evidence for the development of the recommendations; summaries of the systematic reviews are available as web appendices of the guidelines. The scientific evidence was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. WHO convened four GDG technical consultations between June 2014 and November 2015 to formulate and approve the recommendations based on the evidence profiles. In agreement with the methodologist and the WHO Guidelines Review Committee secretariat, five recommendations were re-discussed through GDG on-line consultations after the meetings and slightly modified, based on either comments by the external peer reviewers or emerging new evidence.

Following the issue of the guidelines in November 2016, some concerns were raised by experts and users during 2017 on the strong recommendation regarding the use of 80% fraction of inspired oxygen (high FiO_2) in surgical patients under general anaesthesia with tracheal intubation. The arguments were related to the analysis of the evidence on the benefit and safety of this intervention. Therefore, between 2017 and 2018 WHO re-assessed the evidence by updating the systematic review related to the effectiveness of high FiO_2 and commissioning an independent systematic review on adverse events potentially associated with the recommended use of high FiO_2. The GDG membership was also broadened to include an additional eight anaesthetists. Based on the evidence reviews up to April 2018, the GDG decided to revise the strength of the recommendation from *strong* to *conditional* and to update the chapter of the guidelines dedicated to this topic.

The guidelines consist of a core section including a dedicated chapter for each recommendation, which is divided into subsections according to their application in the pre-, intra- and postoperative periods. This is preceded by a section including other important issues in the approach to SSI prevention that were not the subject of recommendations, but of which users should be fully aware. A summary of main existing national guidelines on SSI prevention is also provided as a web appendix of the guidelines.

Recommendations

The WHO technical consultations led to the adoption of 29 recommendations covering 23 topics for the prevention of SSI in the pre-, intra- and postoperative periods (see Table). For four topics, the GDG considered that the available evidence was not sufficient to develop related recommendations. For each recommendation, the quality of evidence was graded as "very low", "low", "moderate" or "high". The GDG qualified the direction and strength of each recommendation by considering the quality of evidence and other factors, including the balance between benefits and harms, the values and preferences of stakeholders and the resource implications of the intervention. To ensure that each recommendation is correctly understood and applied in practice, the GDG has provided additional remarks where needed. Guideline users should refer to these remarks, as well as to the summary of the evidence provided in each chapter of the recommendations. The summaries of the systematic reviews, including the risk of bias assessments and the GRADE tables, are available in full as on-line appendices of the guidelines. Each chapter also features a research agenda identified by the GDG for each topic.

The recommendations for the prevention of SSI to be applied or considered in the pre-, intra- and postoperative periods are summarized in the Table below, together with the associated PICO questions and their strength and evidence quality. In accordance with WHO guideline development procedures, these recommendations will be reviewed and updated following identification of new evidence at least every five years. WHO welcomes suggestions regarding additional questions for inclusion in future updates of the guidelines.

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Table 1. **Summary of core topics, research questions and recommendations for the prevention of surgical site infection**

Topic	Research questions	Recommendations	Strength	Quality of evidence
Preoperative measures				
Preoperative bathing	1. Is preoperative bathing using an antimicrobial soap more effective in reducing the incidence of SSI in surgical patients compared to bathing with plain soap? 2. Is preoperative bathing with CHG-impregnated cloths more effective in reducing the incidence of SSI in surgical patients compared to bathing with antimicrobial soap?	It is good clinical practice for patients to bathe or shower prior to surgery. The panel suggests that either plain soap or an antimicrobial soap may be used for this purpose. The panel decided not to formulate a recommendation on the use of CHG-impregnated cloths for the purpose of reducing SSI due to the very low quality of evidence.	Conditional	Moderate
Decolonization with mupirocin ointment with or without CHG body wash for the prevention of *Staphylococcus aureus* infection in nasal carriers	Is mupirocin nasal ointment in combination with or without CHG body wash effective in reducing the number of *S. aureus* infections in nasal carriers undergoing surgery?	The panel recommends that patients undergoing cardiothoracic and orthopaedic surgery with known nasal carriage of *S. aureus* should receive perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash. The panel suggests considering to treat also patients with known nasal carriage of *S. aureus* undergoing other types of surgery with perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash.	Strong Conditional	Moderate Moderate
Screening of ESBL colonization and the impact on antibiotic prophylaxis	1. Should SAP be modified in high (>10%) ESBL prevalence areas? 2. Should SAP be modified in patients who are colonized with or a carrier of ESBL? 3. Should patients be screened for ESBL prior to surgery?	The panel decided not to formulate a recommendation due to the lack of evidence.	NA	NA

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Topic	Research questions	Recommendations	Strength	Quality of evidence
Preoperative measures				
Optimal timing for preoperative SAP	How does the timing of SAP administration impact on the risk of SSI and what is the precise optimal timing?	The panel recommends that SAP should be administered prior to the surgical incision when indicated (depending on the type of operation). The panel recommends the administration of SAP within 120 minutes before incision, while considering the half-life of the antibiotic.	Strong Strong	Low Moderate
Mechanical bowel preparation and the use of oral antibiotics	Is mechanical bowel preparation combined with or without oral antibiotics effective for the prevention of SSI in colorectal surgery?	The panel suggests that preoperative oral antibiotics combined with mechanical bowel preparation should be used to reduce the risk of SSI in adult patients undergoing elective colorectal surgery. The panel recommends that mechanical bowel preparation alone (without administration of oral antibiotics) should **not** be used for the purpose of reducing SSI in adult patients undergoing elective colorectal surgery.	Conditional Strong	Moderate Moderate
Hair removal	1. Does hair removal affect the incidence of SSI? 2. What method and timing of hair removal is associated with the reduction of SSI?	The panel recommends that in patients undergoing any surgical procedure, hair should either **not** be removed or, if absolutely necessary, it should be removed only with a clipper. Shaving is strongly discouraged at all times, whether preoperatively or in the operating room.	Strong	Moderate
Surgical site preparation	Should alcohol-based antiseptic solutions or aqueous solutions be used for skin preparation in surgical patients and, more specifically, should CHG or PVP-I solutions be used?	The panel recommends alcohol-based antiseptic solutions based on CHG for surgical site skin preparation in patients undergoing surgical procedures.	Strong	Low to moderate

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Topic	Research questions	Recommendations	Strength	Quality of evidence
Preoperative measures				
Antimicrobial skin sealants	Should antimicrobial sealants (in addition to standard surgical site skin preparation) be used in surgical patients for the prevention of SSI compared to standard surgical site skin preparation only?	The panel suggests that antimicrobial sealants should **not** be used after surgical site skin preparation for the purpose of reducing SSI.	Conditional	Very Low
Surgical hand preparation	1. What is the most effective type of product for surgical hand preparation to prevent SSI? 2. What is the most effective technique and ideal duration for surgical hand preparation?	The panel recommends that surgical hand preparation should be performed by scrubbing with either a suitable antimicrobial soap and water or using a suitable alcohol-based handrub before donning sterile gloves.	Strong	Moderate
Preoperative and/or intraoperative measures				
Enhanced nutritional support	In surgical patients, should enhanced nutritional support be used for the prevention of SSI?	The panel suggests considering the administration of oral or enteral multiple nutrient-enhanced nutritional formulas for the purpose of preventing SSI in underweight patients who undergo major surgical operations.	Conditional	Very Low
Perioperative discontinuation of immunosuppressive agents	Should immunosuppressive agents be discontinued perioperatively and does this affect the incidence of SSI?	The panel suggests not to discontinue immunosuppressive medication prior to surgery for the purpose of preventing SSI.	Conditional	Very Low
Perioperative oxygenation	How safe and effective is the perioperative use of an increased fraction of inspired oxygen in reducing the risk of SSI?	The panel suggests that adult patients undergoing general anaesthesia with tracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen intraoperatively and, if feasible, in the immediate postoperative period for 2-6 hours to reduce the risk of SSI.	Conditional	Moderate

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Topic	Research questions	Recommendations	Strength	Quality of evidence
Preoperative and/or intraoperative measures				
Maintaining normal body temperature (normothermia)	Should systemic body warming vs. no warming be used for the prevention of SSI in surgical patients?	The panel suggests the use of warming devices in the operating room and during the surgical procedure for patient body warming with the purpose of reducing SSI.	Conditional	Moderate
Use of protocols for intensive perioperative blood glucose control	1. Do protocols aiming to maintain optimal perioperative blood glucose levels reduce the risk of SSI? 2. What are the optimal perioperative glucose target levels in diabetic and non-diabetic patients?	The panel suggests the use of protocols for intensive perioperative blood glucose control for both diabetic and non-diabetic adult patients undergoing surgical procedures to reduce the risk of SSI. The panel decided not to formulate a recommendation on this topic due to the lack of evidence to answer question 2.	Conditional	Low
Maintenance of adequate circulating volume control/ normovolemia	Does the use of specific fluid management strategies during surgery affect the incidence of SSI?	The panel suggests the use of goal-directed fluid therapy intraoperatively to reduce the risk of SSI.	Conditional	Low
Drapes and gowns	1. Is there a difference in SSI rates depending on the use of disposable non-woven drapes and gowns or reusable woven drapes and gowns? 1.1. Is there a difference in SSI rates depending on the use of disposable non-woven or reusable woven drapes? 1.2. Is there a difference in SSI rates depending on the use of disposable non-woven or reusable woven gowns?	The panel suggests that either sterile, disposable non-woven or sterile, reusable woven drapes and gowns can be used during surgical operations for the purpose of preventing SSI. No specific evidence was retrieved to answer to questions 1.1 and 1.2.	Conditional	Moderate to very low
	2. Does the use of disposable, adhesive, incise drapes reduce the risk of SSI?	The panel suggests **not** to use plastic adhesive incise drapes with or without antimicrobial properties for the purpose of preventing SSI.	Conditional	Low to very low

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Topic	Research questions	Recommendations	Strength	Quality of evidence
Preoperative and/or intraoperative measures				
Wound protector devices	Does the use of wound protector devices reduce the rate of SSI in open abdominal surgery?	The panel suggests considering the use of wound protector devices in clean-contaminated, contaminated and dirty abdominal surgical procedures for the purpose of reducing the rate of SSI.	Conditional	Very low
Incisional wound irrigation	Does intraoperative wound irrigation reduce the risk of SSI?	The panel considered that there is insufficient evidence to recommend for or against saline irrigation of incisional wounds before closure for the purpose of preventing SSI.	NA	NA
		The panel suggests considering the use of irrigation of the incisional wound with an aqueous PVP-I solution before closure for the purpose of preventing SSI, particularly in clean and clean-contaminated wounds.	Conditional	Low
		The panel suggests that antibiotic incisional wound irrigation should **not** be used for the purpose of preventing SSI.	Conditional	Low
Prophylactic negative pressure wound therapy	Does prophylactic negative pressure wound therapy reduce the rate of SSI compared to the use of conventional dressings?	The panel suggests the use of prophylactic negative pressure wound therapy in adult patients on primarily closed surgical incisions in high-risk wounds for the purpose of the prevention of SSI, while taking resources into account.	Conditional	Low
Use of surgical gloves	1. When is double-gloving recommended? 2. What are the criteria for changing gloves during an operation? 3. What type of gloves should be used?	The panel decided not to formulate a recommendation due to the lack of evidence to assess whether double-gloving or a change of gloves during the operation or the use of specific types of gloves are more effective in reducing the risk of SSI.	NA	NA

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Topic	Research questions	Recommendations	Strength	Quality of evidence
Preoperative and/or intraoperative measures				
Changing of surgical instruments	At the time of wound closure, is there a difference in SSI when instruments are changed for fascial, subcutaneous and skin closure using a new set of sterile instruments?	The panel decided not to formulate a recommendation on this topic due to the lack of evidence.	NA	NA
Antimicrobial -coated sutures	Are antimicrobial-coated sutures effective to prevent SSI? If yes, when and how should they be used?	The panel suggests the use of triclosan-coated sutures for the purpose of reducing the risk of SSI, independent of the type of surgery.	Conditional	Moderate
Laminar flow ventilation systems in the context of OR ventilation	1. Is the use of laminar air flow in the OR associated with the reduction of overall or deep SSI?	The panel suggests that laminar airflow ventilation systems should **not** be used to reduce the risk of SSI for patients undergoing total arthroplasty surgery.	Conditional	Low to very low
	2. Does the use of fans or cooling devices increase SSIs? 3. Is natural ventilation an acceptable alternative to mechanical ventilation?	The panel decided not to formulate a recommendation on these topics due to the lack of evidence to answer questions 2 and 3.	NA	NA
Postoperative measures				
SAP prolongation	Does continued postoperative SAP reduce the risk of SSI compared with preoperative and (if necessary) intraoperative prophylaxis only?	The panel recommends **against** the prolongation of SAP after completion of the operation for the purpose of preventing SSI.	Strong	Moderate
Advanced dressings	In surgical patients, should advanced dressings vs. standard sterile wound dressings be used for the prevention of SSI?	The panel suggests **not** using any type of advanced dressing over a standard dressing on primarily closed surgical wounds for the purpose of preventing SSI.	Conditional	Low
Antimicrobial prophylaxis in the presence of a drain and optimal timing for wound drain removal	1. In the presence of drains, does prolonged antibiotic prophylaxis prevent SSI?	The panel suggests that preoperative antibiotic prophylaxis should **not** be continued in the presence of a wound drain for the purpose of preventing SSI.	Conditional	Low
	2. When using drains, how long should they be kept in place to minimize SSI as a complication?	The panel suggests removing the wound drain when clinically indicated. No evidence was found to allow making a recommendation on the optimal timing of wound drain removal for the purpose of preventing SSI.	Conditional	Very low

SSI: surgical site infection; PICO: Population, Intervention, Comparison, Outcomes; CHG: chlorhexidine gluconate; SAP: surgical antibiotic prophylaxis; ESBL: extended-spectrum beta-lactamase; PVP-I: povidone-iodine; NA: not applicable.

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1. BACKGROUND

Health care-associated infections (HAIs) are acquired by patients when receiving care and are the most frequent adverse event affecting patient safety worldwide. Common HAIs include urine, chest, blood and wound infections. HAIs are caused mainly by microorganisms resistant to commonly-used antimicrobials, which can be multidrug-resistant.

Although the global burden remains unknown because of the difficulty to gather reliable data, it is estimated that hundreds of millions of patients are affected by HAIs each year, leading to significant mortality and financial losses for health systems. At present, no country is free from the burden of disease caused by HAIs and antimicrobial resistance (AMR).

Of every 100 hospitalized patients at any given time, seven in developed and 15 in developing countries will acquire at least one HAI. The endemic burden of HAI is also significantly (at least 2-3 times) higher in low- and middle-income countries (LMICs) than in high-income nations, particularly in patients admitted to intensive care units, and neonates.

Recent work by the World Health Organization (WHO) *Clean Care is Safer Care* programme (http://www.who.int/gpsc/en) shows that surgical site infection (SSI) is the most surveyed and frequent type of HAI in LMICs and affects up to one third of patients who have undergone a surgical procedure. In LMICs, the pooled incidence of SSI was 11.8 per 100 surgical procedures (range 1.2 to 23.6) *(1, 2)*. Although SSI incidence is much lower in high-income countries, it remains the second most frequent type of HAI in Europe and the United States of America (USA). In some European countries, it even represents the most frequent type of HAI. The European Centre for Disease Prevention and Control (ECDC) reported data on SSI surveillance for 2010-2011. The highest cumulative incidence was for colon surgery with 9.5% episodes per 100 operations, followed by 3.5%for coronary artery bypass graft, 2.9% for caesarean section, 1.4% for cholecystectomy, 1.0% for hip prosthesis, 0.8% for laminectomy and 0.75% for knee prosthesis *(3)*.

Many factors in a patient's journey through surgery have been identified as contributing to the risk of SSI. The prevention of these infections is complex and requires the integration of a range of measures before, during and after surgery. However, the implementation of these measures is not standardized worldwide and no international guidelines are currently available.

No full guidelines have been issued by WHO on this topic, although some aspects related to the prevention of SSI are mentioned in the 2009 WHO *guidelines for safe surgery (4)*. Some national guidelines are available, especially in Europe and North America, but several inconsistencies have been identified in the interpretation of evidence and recommendations and validated systems to rank the evidence have seldom been used. Importantly, none of the currently available guidelines have been based on systematic reviews conducted ad hoc in order to provide evidence-based support for the development of recommendations. In addition, important topics with a global relevance that can lead to potentially harmful consequences for the patient if neglected are mentioned in only a few guidelines, for example, surgical hand antisepsis or the duration of surgical antibiotic prophylaxis (SAP). Of note, the prolongation of antibiotic prophylaxis is one of the major determinants of AMR.

Given the burden of SSI in many countries and the numerous gaps in evidence-based guidance,

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there is a need for standardization based on strategies with proven effectiveness and a global approach. International, comprehensive SSI prevention guidelines should include also more innovative or recent approaches. To ensure a universal contribution to patient safety, recommendations should be valid for any country, irrespective of their level of development and resources.

The aim of these guidelines is to provide a comprehensive range of evidence-based recommendations for interventions to be applied during the pre-, intra- and postoperative periods for the prevention of SSI, while taking into consideration resource availability and values and preferences.

1.1 Target audience

The primary target audience for these guidelines is the surgical team, that is, surgeons, nurses, technical support staff, anaesthetists and any professionals directly providing surgical care. Pharmacists and sterilization unit staff will be concerned also by some recommendations or aspects of these guidelines. The guidelines will be an essential tool for health care professionals responsible for developing national and local infection prevention protocols and policies, such as policy-makers and infection prevention and control (IPC) professionals. Of note, it will be crucial to involve senior managers, hospital administrators, individuals in charge of quality improvement and patient safety and those responsible for staff education and training to help advance the adoption and implementation of these guidelines.

1.2 Scope of the guidelines

Population and outcome of interest

The guidelines focus on the prevention of SSI in patients of any age undergoing any surgical procedure. However, there are recommendations that are either not proven for the paediatric population due to lack of evidence or inapplicable. The primary outcomes considered for developing the recommendations were the occurrence of SSI (SSI incidence rates) and SSI-attributable mortality.

Priority questions

The priority research questions guiding the evidence review and synthesis according to each topic addressed by these guidelines are listed in the table of recommendations included in the executive summary. These were further developed as a series of questions structured in a PICO (Population, Intervention, Comparison, Outcomes) format (available in full in web Appendices 2-27) (https://www.who.int/infection-prevention/publications/ssi-web-appendices/en/).

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2. METHODS

2.1 WHO guideline development process

The guidelines were developed following the standard recommendations described in the WHO *Handbook for guideline development (5)* and according to a scoping proposal approved by the WHO Guidelines Review Committee.

In summary, the process included: (i) identification of the primary critical outcomes and priority topics and formulation of the related PICO questions; (ii) retrieval of the evidence through specific systematic reviews of each topic using an agreed standardized methodology; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations; and (v) writing of the guidelines' content and planning for the dissemination and implementation strategy; and (vi) revision of the recommendation regarding the use of 80% fraction of inspired oxygen (high FiO_2) in surgical patients under general anaesthesia with tracheal intubation.

The initial plan for the guidelines included a section dedicated to best implementation strategies for the developed recommendations, based on a systematic review of the literature and expert advice. However, given the very broad scope and length of the present document and following consultation with the methodologist and the Guidelines Review Committee secretariat, the Guideline Steering Group decided not to include this section. A short chapter is included to address this aspect in the guidelines and two separate implementation documents *(6, 7)* were developed and launched by WHO in 2018.

The development of the guidelines involved the formation of four main groups to guide the process and their specific roles are described in the following sections.

WHO Guideline Steering Group

The WHO Guideline Steering Group was chaired by the director of the Department of Service Delivery and Safety (SDS). Participating members were from the SDS IPC team, the SDS emergency and essential surgical care programme, the Department of Pandemic and Epidemic Diseases, and the IPC team at the WHO Regional Office of the Americas.

The Group drafted the initial scoping document for the development of the guidelines. In collaboration with the Guidelines Development Group (GDG), it then identified the primary critical outcomes and priority topics and formulated the related questions in PICO format. The Group identified systematic review teams, the guideline methodologist, the members of the GDG and the external reviewers. It supervised also the evidence retrieval and syntheses, organized the GDG meetings, prepared or reviewed the final guideline document, managed the external reviewers' comments and the guideline publication and dissemination. The members of the WHO Steering Group are presented in the Acknowledgements section and the full list including affiliations is available in the Annex (section 6).

Guidelines Development Group

The WHO Guideline Steering Group initially identified 20 external experts and stakeholders from the six WHO regions to constitute the GDG. GDG membership was updated in September 2018 to include an additional eight anaesthetists. Representation was ensured from various professional and stakeholder groups, including surgeons, nurses, IPC and infectious disease specialists, researchers and patient representatives. Geographical representation and gender balance were also considerations when selecting GDG members. Members provided input for the drafting of the scope of the guidelines, the PICO questions and participated in the identification of the

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methodology for the systematic reviews. In addition, the GDG appraised the evidence that was used to inform the recommendations, advised on the interpretation of the evidence, formulated the final recommendations based on the draft prepared by the WHO Steering Group and reviewed and approved the final guideline document. The members of the GDG are presented in the Annex (section 6.1).

Systematic Reviews Expert Group

Given the high number of systematic reviews supporting the development of recommendations for the guidelines, a Systematic Reviews Expert Group (SREG) was created. This group included researchers and professionals with a high level of expertise in the selected topics and the conduct of systematic reviews. While some of the reviews were conducted by the WHO IPC team, most SREG experts volunteered to conduct the systematic reviews as an in-kind contribution of their institutions to the development of the guidelines.

The SREG undertook the systematic reviews and meta-analyses and prepared individual summaries, which are available as web appendices to the guidelines. It assessed also the quality of the evidence and prepared the evidence profiles according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Some SREG members were also part of the GDG. However, according to the Guideline Review Committee's instructions and to avoid any intellectual conflict, experts leading the systematic reviews were excluded from consensus decision-making for the development of recommendations related to the topic they reviewed, in particular when voting was necessary. As a member of the SREG, the GDG chair was equally excluded from decision-making on recommendations that were based on systematic reviews conducted by himself and his team. Furthermore, in sessions where the chair presented the evidence from systematic reviews conducted by his team, another GDG member was identified to act as the chair. The members of the GDG are presented in the Acknowledgements and the full list including affiliations is available in the Annex (section 6.1).

External Peer Review Group

This group included five technical experts with a high level of knowledge and experience in the fields of surgery and IPC. The group was geographically balanced to ensure views from both high- and LMICs; no member declared a conflict of interest. The group reviewed the final guideline document to identify any factual errors and commented on technical content and evidence, clarity of the language, contextual issues and implications for implementation. The group ensured that the guideline decision-making processes had incorporated contextual values and preferences of potential users of the recommendations, health care professionals and policy-makers. It was not within the remit of this group to change the recommendations formulated by the GDG. However, very useful comments were provided in some cases, which led to modifications of the recommendation text or the explanations provided within the remarks. The members of the WHO External Peer Review Group are presented in the Acknowledgements and the full list including affiliations is available in the Annex (section 6.4).

2.2 Evidence identification and retrieval

The SREG retrieved evidence on the effectiveness of interventions for the prevention of SSI from randomized controlled trials (RCTs) and non-randomized studies as needed. The Guideline Steering Group provided the SREG with the methodology and a briefing on the desired output of the systematic reviews and the members of these groups agreed together on the format and timelines for reporting. Using the assembled list of priority topics, questions and critical outcomes from the scoping exercise identified by the WHO Guideline Steering Group, the GDG and the guideline methodologist, the SREG conducted 27 systematic reviews between December 2013 and October 2015 to provide the supporting evidence for the development of the recommendations. The systematic review used as the basis for the recommendation on the use of high FiO_2 was updated to April 2018 and an additional independent systematic review on adverse events potentially associated with the recommended use of high FiO_2 was commissioned and conducted up to April 2018.

To identify relevant studies, systematic searches of various electronic databases were conducted, including Medline (Ovid), the Excerpta Medica Database, the Cumulative Index to Nursing and Allied Health Literature, the Cochrane Central Register of Controlled Trials and WHO regional databases. All studies published after 1 January 1990 were considered. In a few reviews, the GDG and the SREG judged that relevant studies had been published before 1990 and no time limit was used. Studies in at least English, French and Spanish were included; some reviews had no language restrictions. A comprehensive list of search terms was used, including Medical Subject Headings.

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Criteria for the inclusion and exclusion of literature (for example, study design, sample size and follow-up duration) for the reviews were based on the evidence needed and available to answer the specific research questions. Studies from LMICs and high-income countries were considered. Search strategies and summaries of evidence for each systematic review are reported in web Appendices 2-27 (https://www.who.int/infection-prevention/publications/ssi-web-appendices/en/). The GDG was consulted again for re-evaluation of the updated evidence and reconsideration of the recommendation on the use of high FiO_2, first in December 2017/January 2018 and then in October/December 2018.

Two independent reviewers screened the titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained and then reviewed independently by two authors based on inclusion criteria. Duplicate studies were excluded. Both authors extracted data in a predefined evidence table and critically appraised the retrieved studies. Quality was assessed using the Cochrane Collaboration tool to assess the risk of bias of RCTs *(8)* and the Newcastle-Ottawa Quality Assessment Scale for cohort studies *(9)*. Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons were performed using Review Manager version 5.3 *(10)*, as appropriate. Crude estimates were pooled as odds ratios (OR) with 95% confidence intervals (CI) using a random effects model. The GRADE methodology (GRADE Pro software; http://gradepro.org/) was used to assess the quality of the body of retrieved evidence *(11, 12)*. Based on the rating of the available evidence, the quality of evidence was graded as "high", "moderate", "low" or "very low" (Table 2.2.1).

Table 2.2.1. **GRADE categories for the quality of evidence**

High: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

The results of the systematic reviews and meta-analyses were presented at four GDG meetings held in June 2014, in February, September and November 2015, and online GDG consultations were held between December 2017 and December 2018 for the re-assessment of the updated evidence on high FiO_2. The evidence profiles and decision-making tables were reviewed to ensure understanding and agreement on the scoring criteria. According to a standard GRADE decision-making table proposed by the methodologist, recommendations were formulated based on the overall quality of the evidence, the balance between benefits and harms, values and preferences and implications for resource use. These were assessed through discussion among members of the GDG. The strength of recommendations was rated as either "strong" (the panel was confident that the benefits of the intervention outweighed the risks) or "conditional" (the panel considered that the benefits of the intervention probably outweighed the risks). Recommendations were then formulated and the wording was finalized by consensus. If full consensus could not be achieved, the text was put to the vote and the recommendation was agreed upon according to the opinion of the majority of GDG members.

In some conditional recommendations, the GDG decided to use the terminology "the panel suggests considering..." because they considered that it was important to stimulate the user to undertake a thorough decision-making process and to give more flexibility, especially because these recommendations involve important remarks about resource implications and feasibility in LMICs. Areas and topics requiring further research were also identified. After each meeting, the final recommendation tables were circulated and all GDG members provided written approval and comments, if any.

The systematic reviews targeted patients of any age. In general, these guidelines are valid for both adult and paediatric patients unless specified in the text of the recommendation or in the remarks. In several systematic reviews, no study was retrieved on the paediatric population and thus the GDG

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discussed whether the recommendations are valid in this population topic by topic. As a result, there are recommendations that are either inapplicable in the paediatric population or not proven due to lack of evidence. Based on the evidence reviews up to April 2018, the strength of the recommendation on the use of high FiO_2 was revised from *strong* to *conditional* following consultation of the GDG, and the chapter of the guidelines dedicated to this topic update was duly revised. The updated guidelines were then issued in December 2018.

Draft chapters of the guidelines containing the recommendations were prepared by the WHO secretariat and circulated to the GDG members for final approval and/or comments. Relevant suggested changes were incorporated in a second draft. If GDG comments involved substantial changes to the recommendation, all members participated in online or telephone discussions to reach a final agreement on the text. The second draft was then edited and circulated to the External Peer Review Group and the Guideline Steering Group. The draft document was further revised to address their comments. Suggested changes to the wording of the recommendations or modifications to the scope of the document were not considered in most cases. However, in 3 specific recommendations, most reviewers suggested similar changes and these were considered to be important by the Guideline Steering Group. In these cases, further discussions were undertaken with the GDG through teleconferences and consensus was achieved to make slight changes in the text of the recommendations to meet the reviewers' comments under the guidance of the methodologist.

The guideline methodologist ensured that the GRADE framework was appropriately applied throughout the guideline development process. This included a review of the PICO questions and the results of the systematic reviews and meta-analyses, including participation in re-analyses when appropriate, thus ensuring their comprehensiveness and quality. The methodologist also reviewed all evidence profiles and decision-making tables before and after the GDG meetings and provided guidance to the GDG in formulating the wording and strength of the recommendations.

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3. IMPORTANT ISSUES IN THE APPROACH TO SURGICAL SITE INFECTION PREVENTION

3.1 Surgical site infection risk factors: epidemiology and burden worldwide

Background

SSIs are potential complications associated with any type of surgical procedure. Although SSIs are among the most preventable HAIs *(1, 2)*, they still represent a significant burden in terms of patient morbidity and mortality and additional costs to health systems and service payers worldwide *(3-11)*. SSI is both the most frequently studied and the leading HAI reported hospital-wide in LMICs *(3, 4)*. For these reasons, the prevention of SSI has received considerable attention from surgeons and infection control professionals, health care authorities, the media and the public. In particular, there is a perception among the public that SSIs may reflect a poor quality of care *(12)*. The aim of this review is to provide an update of the global data on SSI with a special focus on LMICs, notably to assess infection rates, associated risk factors and the economic burden.

Summary of the available evidence

1. Burden of SSI

a. Evidence from high-income countries

i. USA

In 2010, an estimated 16 million surgical procedures were performed in acute care hospitals in the USA *(13)*. In a recent report on the rates of national and state HAIs based on data from 2014, 3654 hospitals reported 20 916 SSI among 2 417 933 surgical procedures performed in that year *(5)*.

Of note, between 2008 and 2014 there was an overall 17% decrease in SSI in the 10 main surgical procedures. As an example, there was a decrease of 17% in abdominal hysterectomy and 2% in colon surgery *(5)*.

By contrast, a multi-state HAI prevalence survey conducted in 2011 estimated that there were 157 000 SSIs related to any inpatient surgery and SSI was ranked as the second most frequently reported HAI between 2006 and 2008 *(14)*. Another study reported data from the National Healthcare Safety Network (NHSN) between 2006 and 2008 that included 16 147 SSIs following 849 659 surgical procedures across all groups, representing an overall SSI rate of 1.9% *(15)*.

AMR patterns of HAI in the USA have been described *(16)* and compared to a previous report *(17)*. Among the 1029 facilities that reported one or more SSI, *Staphylococcus aureus* was the most commonly reported pathogen overall (30.4%), followed by coagulase-negative staphylococci (11.7%), *Escherichia coli* (9.4%) and *Enterococcus faecalis* (5.9%). Table 3.1.1 summarizes the distribution of the top seven reported pathogens *(16)*.

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Table 3.1.1. **Distribution and percentage of pathogenic isolates associated with SSI and resistant to selected antimicrobial agents, NHSN, 2009-2010***

Rank	Pathogen	No. of pathogens/ total SSI pathogens reported (%)	Antimicrobial agent (s)	No. of isolates tested (%)	Resistance (%)
1	*S. aureus*	6415 (30.4)	OX/METH	6304 (98.3)	43.7
2	Coagulase-negative staphylococci	2477 (11.7)	NA	NA	NA
3	*E. coli*	1981 (9.4)	ESC4	1627 (82.1)	10.9
			FQ3	1876 (94.7)	25.3
			Carbapenems	1330 (67.1)	2
			MDR1	1390 (70.2)	1.6
4	*E. faecalis*	1240 (5.9)	VAN	1187 (95.7)	6.2
5	*Pseudomonas aeruginosa*	1156 (5.5)	AMINOS	664 (57.4)	6
			ESC2	1097 (94.9)	10.2
			FQ2	1111 (96.1)	16.9
			Carbapenems	872 (75.4)	11
			PIP/PIPTAZ	818 (70.8)	6.8
			MDR2	1053 (91.1)	5.3
6	*Enterobacter spp.*	849 (4.0)	ESC4	816 (96.1)	27.7
			Carbapenems	594 (70.0)	2.4
			MDR1	648 (76.3)	1.7
7	*Klebsiella spp.*	844 (4.0)	ESC4	710 (84.1)	13.2
			Carbapenems	582 (69.0)	7.9
			MDR1	621 (73.6)	6.8

* Modified from reference *16*.
NHSN: National Healthcare Safety Network; SSI: surgical site infection; OX/METH: oxacillin/methicillin; ESC4: extended-spectrum (ES) cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone); FQ3: fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin); MDR1: multidrug resistance 1 gene (pathogen must test as "I" [intermediate] or "R" [resistant] to at least one drug in 3 of the 5 following classes: ESC4, FQ3, aminoglycosides, carbapenems§, and piperacillin [PIP] or piperacillin/tazobactam [PIP/TAZ]); NA: not available; VAN: vancomycin; AMINOS: aminoglycosides (amikacin, gentamicin, tobramycin); ESC2: ES cephalosporins (cefepime, ceftazidime); MDR2: multidrug resistance 2 gene (pathogen must test as I or R to at least 1 drug in 3 of the 5 following classes: ESC2, FQ2, AMINOS, carbapenems, and PIP or PIP/TAZ.
§ Carbapenems are imipenem and meropenem.

To investigate the costs of SSI, a study used the 2005 hospital stay data from the US Nationwide Inpatient Sample, which represents 1054 hospitals from 37 states. Extra hospital stay attributable to SSI was 9.7 days with increased costs of US$ 20 842 per admission. From a national perspective, SSI cases were associated with 406 730 extra hospital days and hospital costs exceeding US$ 900 million. An additional 91 613 readmissions for the treatment of SSI accounted for a further 521 933 days of care at a cost of nearly US$ 700 million *(18)*.

Applying two different consumer price index adjustments to account for the rate of inflation in hospital resource prices, the Centers for Disease Control and Prevention estimated that the aggregate attributable patient hospital costs for SSI infection ranged between US$ 1087 and US$ 29 443 per infection (adjusted for the 2007 US$ level). Using the consumer price index for urban consumers and inpatient hospital services, SSI is considered as the HAI with the largest range of annual costs (US$ 3.2–8.6 billion and US$ 3.5–10 billion, respectively) *(19)*.

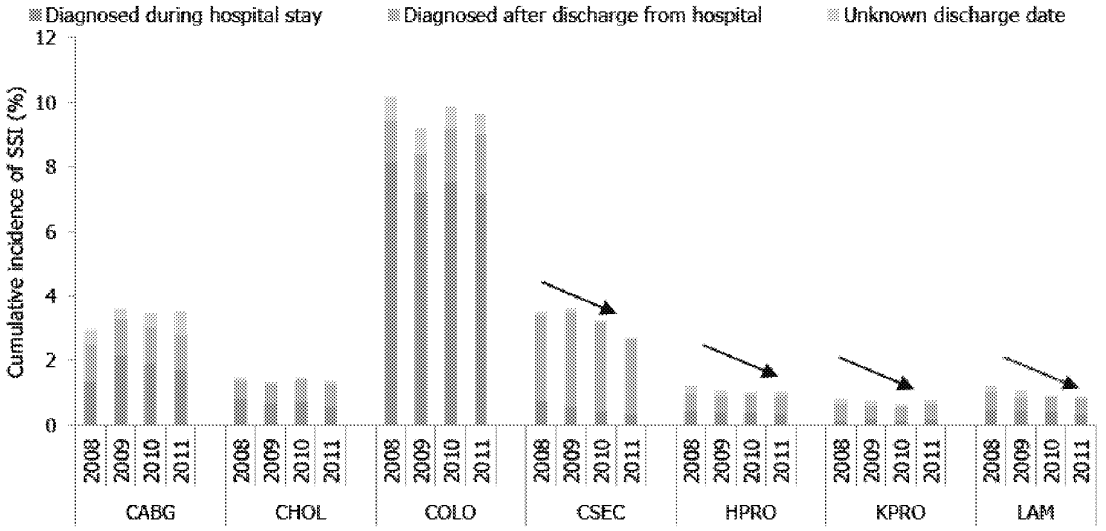
ii. European countries

The European point prevalence survey of HAIs and antimicrobial use conducted in 2011-2012 showed that SSIs are the second most frequent HAI in hospitals *(20)*. A recent report from the ECDC on SSI surveillance of SSI provided data for 2010

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and 2011 *(6)* from 20 networks in 15 European Union countries and one European Economic Area country using a standardized protocol *(21)*. Hip prosthesis was the most frequently reported surgical procedure and represented 33% of all operations. The cumulative incidence of patients with SSI was the highest in colon surgery with 9.5% (episodes per 100 operations), followed by 3.5% for coronary artery bypass graft, 2.9% for caesarean section, 1.4% for cholecystectomy, 1.0% for hip prosthesis, 0.8% for laminectomy and 0.75% for knee prosthesis *(6)*. The results showed also decreasing trends in SSI incidence in several types of procedure (caesarean section, hip prosthesis and laminectomy) (Figure 3.1.1), thus suggesting that prevention efforts, including surveillance, were successful in participating hospitals *(6, 22)*.

Figure 3.1.1. **Cumulative incidence for SSI by year and type of procedure: European Union/European Economic Area countries, 2008–2011**



Data source: ECDC, HAI-Net SSI patient-based data 2008–2011 (http://ecdc.europa.eu/en/activities/surveillance/Pages/data-access.aspx#sthash.hHYRJ9ok.dpuf, accessed 21 May 2016).

SSI: surgical site infection; CABG: coronary artery bypass graft; CHOL: cholecystectomy; COLO: colon; CSEC: caesarean section; HPRO: hip prosthesis; KPRO: knee prosthesis; LAM: laminectomy.

A study published in 2004 reviewed data from 84 studies and estimated the economic costs of SSIs in Europe to range between € 1.47–19.1 billion. It predicted also that the average patient stay would increase by approximately 6.5 days and cost 3 times as much to treat an infected patient. The analysis suggested that the SSI-attributable economic burden at that time was likely to be underestimated *(10)*.

In **France**, it was estimated that 3% of surgical procedures resulted in infection for a total annual cost of nearly € 58 million. Moreover, patients who experienced SSI had a significantly increased mortality risk (from 4- to 15-fold) and a 3-fold increased length of hospital stay *(23)*.

The prevalence of SSI in **Switzerland** was reported to be 5.4% in a study conducted in 50 acute care hospitals participating in the Swiss Nosocomial Infection Prevalence surveillance programme *(24)*. Another study described a 13-year multicentre SSI surveillance scheme performed from 1998 to 2010. Reported SSI rates were: 18.2% after 7411 colectomies; 6.4% after 6383 appendicectomies; 2.3% after 7411 cholecystectomies; 1.7% after 9933 herniorrhaphies; 1.6% after 6341 hip arthroplasties; and 1.3% after 3667 knee arthroplasties *(25)*.

In **Italy**, the SSI rate reported by the "Sistema Nazionale di Sorveglianza delle Infezioni del Sito Chirurgico" (national SSI surveillance system) from

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355 Italian surgical wards between 2009 and 2011 was 2.6% episodes per 100 procedures (1628 cases/60 460 procedures); 60% of SSIs were diagnosed through 30-day post-discharge surveillance. SSI rates were higher in colon (9.0%) and rectal surgery (7.0%), laparotomy (3.1%) and appendectomy (2.1%) *(26)*.

In **England**, the most recent summary of data collected by National Health Service hospitals reported cumulative SSI rates from January 2008 to March 2013. The highest rate was reported among large bowel surgery (8.3%; 95% CI: 7.9–8.7 per 1000 inpatient days), followed by small bowel surgery (4.9%; 95% CI: 4.3–5.7), bile duct, liver and pancreatic surgery (4.9%; 95% CI: 4.1–5.9) and cholecystectomy (4.6%; 95% CI: 3.1–6.6). The lowest rate was reported for knee prosthesis (0.4%; 95% CI: 0.3–0.4) *(8)*.

Data collected from April 2010 to March 2012 estimated that the median additional length of stay attributable to SSI was 10 days (7-13 days), with a total of 4694 bed-days lost over the 2-year period *(27)*.

iii. Australia

A study evaluated the time trends in SSI rates and pathogens in 81 Australian health care facilities participating in the Victorian Healthcare Associated Infection Surveillance System. A total of 183 625 procedures were monitored and 5123 SSIs were reported. *S. aureus was* the most frequently identified pathogen, and a statistically significant increase in infections due to ceftriaxone-resistant *E. coli* was observed (relative risk: 1.37; 95% CI: 1.10–1.70) *(9)*.

iv. Japan

Data from the Japan nosocomial infection surveillance system showed that 470 hospitals voluntarily participated in SSI surveillance in 2013 *(28, 29)*. A retrospective study evaluated also the influence of SSI on the postoperative duration of hospitalization and costs between 2006 and 2008 after abdominal or cardiac surgery. Overall, the mean postoperative hospitalization was 20.7 days longer and the mean health care expenditure was US$ 8791 higher in SSI patients. SSI in abdominal surgery extended the average hospitalization by 17.6 days and increased the average health care expenditure by US$ 6624. Among cardiac surgical patients, SSI extended the postoperative hospitalization by an average of 48.9 days and increased health care expenditure by an average of US$ 28 534 *(30)*. A recent study assessed SSI rates and risk factors after colorectal surgery using the Japan nosocomial infection surveillance system national database. The cumulative incidence of SSI for colon and rectal surgery was 15.0% (6691/44 751 procedures) and 17.8% (3230/18 187 procedures), respectively *(31)*.

v. Republic of Korea

A prospective multicentre surveillance study published in 2000 concluded that SSI constituted 17.2% of all HAIs reported from 15 acute care hospitals *(32, 33)*. The 2009 national SSI surveillance system report described the incidence and risk factors for SSI in 7 types of procedures. The SSI rate per 100 operations was 3.68% (22/1169) after craniotomies, 5.96% (14/235) for ventricular shunt operations, 4.25% (75/1763) for gastric operations, 3.37% (22/653) for colon surgery, 5.83% (27/463) for rectal surgery, 1.93% (23/1190) for hip joint replacement and 2.63% (30/1139) for knee joint replacement *(34)*.

A web-based surveillance of SSIs was performed between 2010 and 2011 to determine the incidence of SSIs after 15 surgical procedures in 43 hospitals. The overall SSI rate represented 2.10% of the total of 18 644 operations and differed after various types of surgery *(35)*. In addition, a systematic review of the literature published between 1995 and 2010 on the epidemiological and economic burden of SSI in the Republic of Korea reported an overall incidence of SSI ranging from 2.0% to 9.7% *(36)*. SSIs were associated with increased hospitalization costs and each episode of SSI was estimated to cost around an additional 2 000 000 Korean Republic won (approximately US$ 1730). Postoperative stays for patients with SSIs were 5 to 20 days longer *(36)*.

In a recent study conducted between 2008 and 2012, the SSI rate following gastrectomy was 3.12% (522/16 918), 2.05% (157/7656) for total hip arthroplasty and 1.90% (152/7648) for total knee arthroplasty. There was a significant trend of decreased crude SSI rates over 5 years *(37)*.

vi. Gulf Council Countries

We were not able to retrieve published national data on SSI rates from any of the Gulf Council Countries (Bahrain, Kingdom of Saudi Arabia, Kuwait, Oman, Qatar and the United Arab Emirates). However, in Saudi Arabia, a 5-year analysis of SSI in orthopaedic surgery in one hospital estimated a rate of 2.55% *(38)*. Another

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study from the King Abdulaziz Medical City (Saudi Arabia) compared SSI rates for herniorraphy and cholecystectomy in 2007 to 1999-2001. In 2007, SSI rates per 100 operations in 2007 were 0.88% for herniorrhaphy and 0.48% for cholecystectomy, while in 2007, rates were reduced by 80% for herniorrhaphy (P=0.049) and 74% for cholecystectomy (P=0.270) *(39)*.

vii. Singapore

In a systematic literature review (2000 to 2012) *(40)* of the burden of HAI in South-East Asia, the pooled incidence of SSI was 7.8% (95% CI: 6.3–9.3). A study conducted between January and March 2008 in a tertiary care hospital in Singapore reported an SSI incidence of 8.3% for general, neurologic and orthopaedic surgical procedures *(41)*.

viii. Uruguay

The national incidence data on SSI for 2012-2013 reported that the incidence rate for appendectomy was 3.2%, 2.5% for cardiac surgery, 6.2% for cholecystectomy and 15.4% for colon surgery *(42)*.

ix. Chile

The 2013 national report on HAI surveillance showed a SSI rate of 3.09% for coronary bypass surgery and 1.89% for hip joint replacement. Infection rates in cholecystectomy performed via laparotomy were 4.12% (95% CI: 2.8-6.11) times higher than laparoscopic cholecystectomy (P<0.0001) *(43)*.

Table 3.1.2. **Summary of SSI rates in different countries**

Country (reference)	SSI rate (%) (95% CI [when provided])	Year*	Measurement used	Study design
USA *(5, 15)*	0.9 17% decrease in SSI related to the 10 selected procedures (2014 compared to 2008)	2014	Cumulative incidence (episodes per 100 operations)	NHSN data (incidence design)
European Union *(6)*	9.5 (COLO) 3.5 (CABG) 2.9 (CSEC) 1.4 (CHOL) 1.0 (HPRO) 0.8 (LAM) 0.75 (KPRO)	2010–2011	Cumulative incidence (episodes per 100 operations)	ECDC HAI SSI protocol *(21)*
England *(8)*	Large bowel surgery: 8.3 (7.9–8.7) Small bowel surgery: 4.9 (4.3–5.7) Bile duct, liver and pancreatic surgery: 4.9 (4.1–5.9) CHOL: 4.6 (3.1–6.6) KPRO: 0.4 (0.3–0.4)	2008–2013	Incidence density (episodes per 1000 patient-days)	SSI surveillance - incidence design
Australia *(9)*	2.8	2002–2013	Incidence density (episodes per 1000 patient-days)	Victorian Healthcare Associated Infection Surveillance System
Japan *(29, 31)*	COLO: 15.0 (669 1/44 751) Rectal surgery: 17.8 (3230/18 187)	2008–2010	Cumulative incidence (episodes per 100 operations)	National nosocomial infection surveillance system – incidence design

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Country (reference)	SSI rate (%) (95% CI [when provided])	Year*	Measurement used	Study design
Republic of Korea *(35, 37)*	Overall: 2.1 Gastrectomy: 3.1 (522/16 918) Total hip arthroplasty: 2.0 (157/7656)	2010–2011 2008–2012	Cumulative incidence (episodes per 100 operations)	National surgical site infection surveillance system – incidence design
Uruguay *(42)*	Appendectomy: 3.2 Cardiac surgery: 2.5 Cholecystectomy: 6.2 COLO: 15.4	2014	Cumulative incidence (episodes per 100 operations)	National nosocomial infection surveillance system
Chile *(43)*	Coronary bypass surgery: 3.1 Hip joint replacement: 1.9	2013		National HAI infection surveillance system
LMICs-WHO	Average: 5.9 (4.8–7.1)	1995–2015	Cumulative incidence (episodes per 100 operations)	Incidence/prospective
South-East Asia *(40)*	7.8 (6.3–9.3)	2000–2012	Pooled incidence review	Systematic literature

* Year of the most recent publication assessing the national SSI rates.
Unpublished WHO data.

SSI: surgical site infection; CI: confidence interval; NHSN: National Healthcare Safety Network; ECDC: European Centre for Disease Prevention and Control; HAI: health care-associated infection; COLO: colon surgery; CABG: coronary artery bypass graft; CSEC: caesarean section; CHOL: cholecystectomy; HPRO: hip prosthesis; LAM: laminectomy; LMIC: low- and middle-income countries; KPRO: knee prosthesis; UK: United Kingdom.

b. WHO systematic reviews on SSI in LMICs

The 2011 WHO report on the global burden of endemic HAI provided SSI data from LMICs. The pooled SSI incidence was 11.8 per 100 surgical patients undergoing surgical procedures (95% CI: 8.6–16.0) and 5.6 per 100 surgical procedures (95% CI: 2.9–10.5). SSI was the most frequent HAI reported hospital-wide in LMICs and the level of risk was significantly higher than in developed countries *(3, 4)*.

Recently, WHO conducted an update of the systematic literature review from 1995 to 2015 with a special focus on SSI in LMICs (WHO unpublished data). A total of 231 articles in English, French, German, Spanish and Portuguese were included. The pooled SSI rate was 11.2 per 100 surgical patients (95% CI: 9.7–12.8) for incidence/prospective studies. There was no statistical difference in SSI rates when stratified by study quality, patient age groups, geographic regions, country income, SSI definition criteria, type of setting or year of publication. However, there were statistical differences between studies according to the type of surgical population procedures (P=0.0001) and the number of patients per study (P=0.0004).

In incidence studies, the SSI rate was higher for procedures in oncology (17.2%; 95% CI: 15.4–19.1), orthopaedic (15.1%; 95% CI: 10.2–20.6), general surgery (14.1%; 95% CI: 11.6–16.8) and paediatric surgery (12.7%; 95% CI: 6.7–20.3). The SSI rate expressed as the number of SSI infections per 100 surgical operations was reported in 57 (24.7%) studies. The pooled SSI rate using this measure was 5.9% (95% CI: 4.8–7.1) for incidence/prospective studies.

Some studies *(44-50)* investigated SSI rates after caesarean section surgery and showed a substantial variability in the definition of SSI and in reported rates. High rates of SSI following caesarean section were reported in several LMICs: 16.2% in a study from Nigeria *(44)*, 19% from Kenya *(45)*, 10.9% from Tanzania *(46)* and 9.7% by Viet Nam *(47)*. In 2 studies from Brazil, one reported a rate of 9.6% *(48)* and the other a higher rate of 23.5% *(49)*. Overall, SSI pooled incidence following caesarian section was 11.7% (95% CI: 9.1–14.8); a much lower average SSI rate of 2.9% is reported in Europe *(6, 21)*.

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2. Factors increasing the risk of SSI

Many factors influence surgical wound healing and determine the potential for infection *(51)*. These include patient-related (endogenous) and process/procedural-related (exogenous) variables that affect a patient's risk of developing an SSI. Some variables are obviously not modifiable, such as age and gender. However, other potential factors can be improved to increase the likelihood of a positive surgical outcome, such as nutritional status, tobacco use, correct use of antibiotics and the intraoperative technique.

The usefulness of risk assessment and the definition of risk is debatable as there are very few studies that have an altered patient outcome based on information gained by risk assessment *(52, 53)*. One study analysed a 2-year data report of the NHSN for all surgical procedures and used stepwise logistic regression to develop specific risk models by procedure category. The study concluded that a set of new models using existing data elements collected through the NHSN improved predictive performance, compared to the traditional NHSN risk index stratification *(15)*.

A systematic review of 57 studies from both high-income countries and LMICs identified the following factors associated with an increased risk of SSI in adjusted analysis: a high body mass index; a severe score according to the US National Nosocomial Infections Surveillance (NNIS) risk index; severe wound class; diabetes; and a prolongation of surgery duration *(54)*. A meta-analysis of prospective cohort studies suggested that diabetes mellitus is significantly associated with an increased risk of SSI *(55)*. The national nosocomial surveillance system protocol in Italy identified a longer duration of surgery, an American Society of Anesthesiologists score of at least 3 and a pre-surgery hospital stay of at least 2 days as factors associated with an increased risk of SSI, while videoscopic procedures reduced SSI rates *(26)*. In the Republic of Korea, a systematic review of the epidemiological and economic burden identified diabetes, the absence or >1 hour administration of antibiotic prophylaxis and the type of wound classification (contaminated or dirty) as risk factors significantly associated with SSI by multivariate analyses *(36)*. In addition, the NNIS risk index identified trauma, re-operation and age (60-69 years) as risk factors for SSI after total hip arthroplasty *(37)*.

In a recent unpublished systematic review conducted by WHO, a total of 14 observational studies (no RCTs) *(56-69)* describing the relationship between surgical volume and the risk of SSI were identified. There was a substantial heterogeneity in the definitions of volume, surgical procedures studied and SSI measurement. Thus, separate meta-analyses were performed to evaluate SSI rates between high vs. low and medium vs. low hospital volume, and high vs. low and medium vs. low surgeon volume. A moderate quality of evidence showed that surgical procedures performed in high-/medium-volume hospitals have lower SSI rates compared to low-volume hospitals (OR: 0.69; 95% CI: 0.55-0.87 and OR: 0.80; 95% CI: 0.69-0.94, respectively). In addition, there was a moderate quality of evidence that surgical procedures performed by high- or medium-volume surgeons have lower SSI rates (OR: 0.67; 95% CI: 0.55-0.81 and OR: 0.73; 95% CI: 0.63-0.85, respectively) compared to low-volume hospitals. However, there was controversial evidence when high- and medium-volume hospitals were compared and it remains unclear whether there is a linear relationship between procedure/surgeon volume and the SSI rate.

Conclusions

Despite robust data on the burden of SSI in some countries or regions, accurate estimates of the global burden in terms of SSI rates and the economic aspects still remain a goal for the future. As an example, SSI and overall HAI data are not yet included in the list of diseases for which the global burden is regularly estimated by WHO or other international organizations gathering data on global health. Although SSI rates vary between countries and geographical regions, they represent an important problem, with a significantly higher burden in developing countries. If SSI rates are to serve as a quality indicator and comparison benchmark for health care facilities, countries and the public, they must be determined in a reliable way that produces robust infection rates to ensure valid comparisons. There is a global need to address changes to SSI definitions, strengthen and validate SSI data quality, and to conduct robust SSI economic and burden studies.

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3.2 Surgical site infection surveillance: definitions, methods and impact

The surveillance of HAI is one of the core components of an effective IPC programme *(1, 2)*. However, defining, detecting, reporting and interpreting HAI, including SSI, is challenging and requires expertise, time and resource dedication.

Definitions of surveillance and SSI

Surveillance is defined as "the ongoing, systematic collection, analysis, interpretation and evaluation of health data closely integrated with the timely dissemination of these data to those who need it" *(3)*.

There are many definitions of SSI and a systematic review identified as many as 41 different definitions. However, only five were described as being standardized definitions created by multidisciplinary groups (Table 3.2.1) *(4)*. More than one third of included studies used the US CDC definitions (either 1988 or 1992). While the authors of this review suggest that a single definition allows longitudinal analysis and benchmarking, they conclude by stating that "there is no single, objective gold standard test for surgical wound infection" *(4)*. In addition, many countries use the HAI SSI protocol developed by the ECDC (http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/surgical-site-infections/Pages/SSI.aspx, accessed 20 May 2016).

Table 3.2.1. **Definitions of SSI***

Criterion	CDC 1988	CDC 1992	SISG	NPS	PHLS
Purulent discharge in or exuding from the wound or observed on direct examination	I		✓	✓	✓
Painful spreading erythema indicative of cellulitis			✓	✓	
Purulent drainage	D	SI/D			
Purulent drainage from a drain placed beneath the fascial layer	D				
Purulent drainage from a drain placed through a stab wound into the organ/space		OS			
Organisms isolated from fluid or tissue from the wound	I	SI			
Organisms isolated from fluid or tissue in the organ/space		OS			
Surgeon/physician diagnosis	I/D	SI/DI/OS			
Surgeon deliberately opens wound, unless wound is culture-negative	I/D	SI/DI			
Wound spontaneously dehisces	D	SI/DI			
Pain	D	SI/DI			
Tenderness	D	DI	✓	✓	
Fever > 38°C	D	DI	✓	✓	
Localized swelling (oedema)		SI	✓	✓	
Redness or extending margin or erythema		SI	✓	✓	
Patient still receiving active treatment for a wound with discharged pus				✓	
Heat		SI			
Abscess or other evidence of infection found on direct examination	D	DI/OS			

*Reproduced from reference 4.

CDC: Centers for Disease Control and Prevention; SISG: Surgical Infection Study Group; NPS: National Prevalence Survey; PHLS; Public Health Laboratory Service.

CDC 1988 definitions: I, incisional surgical wound infection; D, deep surgical wound infection. CDC 1992 definitions: SI, superficial incisional; DI, deep incisional; OS, organ/space. The SISG and NPS allow fever (>38°C), tenderness, oedema, an extending margin of erythema or if the patient is still receiving treatment for the wound.

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Aims of surveillance

The primary aim of surveillance is the collection of data on SSI rates in order to obtain a measure of the magnitude of the problem. These data must then be analysed to identify and investigate trends, including a careful interpretation of results. Finally, surveillance data should guide the identification of improvement actions and evaluate the effectiveness of these interventions. In this context, the feedback of SSI rates to relevant stakeholders is important.

Should surveillance be conducted?

The positive impact of HAI surveillance was first described in the landmark study on the efficacy of a nosocomial infection control programme conducted in the USA in the 1970s. In this trial, it was shown that an IPC programme with both surveillance and control components could lower SSI rates significantly *(5)*. Importantly, surveillance of SSI is part of the WHO safe surgery guidelines *(6)*. Many countries have introduced mandatory surveillance of HAI, including SSI, such as the UK and certain states in the USA, whereas other countries have voluntary-based surveillance, such as France, Germany and Switzerland. However, there are considerable differences related to the types of surveillance, as well as in the length and type of surveillance *(7, 8)*. Increasingly, national networks and "networks of networks" are being created, such as the CDC NHSN, the ECDC HAI Surveillance Network (HAI-Net) and the International Nosocomial Infection Control Consortium.

By using standardized definitions of HAI and specifically SSI, these networks allow inter-hospital comparisons and benchmarking. An essential component of these surveillance networks is feedback to individual hospitals, as discussed below.

It has been postulated that a "surveillance effect" might occur, similar to the Hawthorne effect in clinical trials, that is, the simple fact of being conscious that one is being observed may independently lead to improved practices or improved adherence to guidelines *(9)*.

Another way in which a successful surveillance programme may decrease SSI rates is that the feedback given to the institution may prompt investigation of why its rates are higher than the benchmark. Certain process indicators (if not already collected) may then identify the reason for "underperformance" and prompt local initiatives to improve performance on these indicators. There is conflicting evidence that conducting surveillance as part of a network has a positive impact on SSI rates (Table 3.2.2). Some studies report a successful reduction of SSI rates after participation in a surveillance network *(10-12)*, while others report no effect *(13)*. However, there is an important methodological issue that could "dilute" the reduction in the time trend of SSI rates, which is the fact of adding smaller hospitals in a network without taking into account their year of participation in the network. This obstacle was overcome in an analysis of German data where hospitals were stratified by year of participation *(9)* and in an analysis of Dutch *(14)* and Swiss *(13)* data where SSI rates were stratified by surveillance time to operation in consecutive one-year periods using the first year of surveillance as a reference. The Dutch and German studies reported decreasing time trends of SSI rates after surveillance, whereas the Swiss study did not.

Conversely, as shown in clinical trials, intensive surveillance may lead to the detection of higher SSI rates than under standard surveillance conditions. As an example, in a recent clinical trial comparing skin antiseptic agents for caesarean section, the SSI rate was 4.0% in one arm and 7.3% in the other *(15)*.These rates seem higher than the most recently available data from the ECDC, which show an SSI rate of 2.9% (inter-country range: 0.4%-6.8%) *(16)*.

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Table 3.2.2. **Temporal trends of SSI rates after surveillance in selected networks***

Country (name of network)	Duration of surveillance (years)	Procedures	Change in SSI rate	Reference
England (SSISSF)	5	Orthopaedic	-64 to -69%	*(17)*
France (ISO-RAISIN)	8	Various	-30%	*(11)*
Germany (KISS)	4	Various	-25%	*(10)*
The Netherlands (PREZIES)	5	Various	-57%	*(14)*
Switzerland (regional network)	13	Various	3% to 22%	*(13)*
USA (SENIC)	5	Various	-35%	*(18)*

* Adapted from reference *19*.

SSISS: surgical site infection surveillance service; ISO-RAISIN: Infections du Site Opératoire-Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales; KISS: Krankenhaus Infektions Surveillance System; PREZIES: Preventie Ziekenhusinfecties door surveillance; SENIC: study on the efficacy of nosocomial infection control.

Establishing a surveillance system

According to the US Association for Professionals in Infection Control and Epidemiology *(20)*, there is "no single or "right" method of surveillance design or implementation" *(21)*. However, the following minimal requirements for ensuring quality of surveillance have been identified by the Association *(21)*.

- A written plan that states goals, objects and elements of surveillance process
- Constant rigour of intensity of surveillance
- Consistent elements of surveillance (for example, definitions, calculation methods)
- Adequate human resources (professionals trained in epidemiology)
- Informatic services, computer support
- Evaluation methods.

For a surveillance programme to be successful, there should be a method of data validation to ensure that data are accurate and reliable *(22)*, particularly for benchmarking purposes, as discussed further *(23)*.

Methods for conducting surveillance

In the field of SSI, most surveillance systems target colorectal surgery and total hip and knee arthroplasty. The most common outcome indicator is the cumulative SSI incidence (or SSI rate). Detecting SSI using prevalence methods is less reliable given the high proportion of SSIs that manifest after discharge.

For any given period, denominator data represent the total number of procedures within each category. The number of patients can be used also as the denominator, but it is less precise because more than one infection can occur in the same patient. Numerator data will be the number of SSIs in that same period. Demographic data (age, sex, timing and choice of antimicrobial prophylaxis, American Society of Anesthesiologists score, duration of the operation and wound contamination class) are recorded for all patients, including the site of infection and type of SSI (superficial, deep, organ/space) for those with SSI. Linkage with microbiological data may also be useful.

The gold standard is prospective direct surveillance, although it is time- and labour-intensive and costly *(24)*. The CDC recommendations describe indirect methods of surveillance (sensitivity of 84-89%; specificity 99.8%) as a combination of:

1. Review of microbiology reports and patient medical records.
2. Surgeon and/or patient surveys.
3. Screening for readmission and/or return to the OR.
4. Other information, such as coded diagnoses, coded procedures, operative reports or antimicrobials ordered. *(24)*

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The importance of post-discharge surveillance

It is estimated that a significant proportion of SSIs are detected following patient discharge. This proportion varies across settings and according to different definitions, but it has been estimated to be between 13% to 71% *(25)*. The fact that hospital length of stay has been steadily decreasing over the past decades has probably contributed to shifting the burden from inpatient to outpatient infections. Moreover, implant-associated infections may not become apparent until one year after the procedure. For this reason, many surveillance networks recommend the practice of post-discharge surveillance. There is no known gold standard procedure for post-discharge surveillance and a systematic review identified only 7 reports of studies comparing different surveillance methods *(26)*. Due to variations in data collection and classification, as well as missing information regarding diagnostic criteria, no synthesis of post-discharge surveillance data was possible. The authors concluded that more research is required regarding the measurement of SSI after hospital discharge.

There has been recent controversy regarding the CDC decision to shorten post-discharge surveillance to 90 days instead of one year after certain procedures *(27)*. This change was aimed at simplifying post-discharge surveillance and reducing delayed feedback, but it has not been universally adopted as yet *(28)*. A report compared historical prospective SSI surveillance data from a USA network to the retrospective application of the new CDC definitions *(29)*. The authors found that 9.6% of SSIs detected by the former definition went undetected with the new definitions; 28.8% of these undetected SSIs concerned hip and knee prostheses. The proportion of missed SSIs varied by procedure, but they were high for hip (8.8%) and knee prostheses (25.1%). Another report from the Dutch SSI surveillance network analysed the influence of the duration and method of post-discharge surveillance on SSI rates in selected procedures *(30)*. The proportion of missed SSIs was variable, but they were 6% and 14% for hip and knee prostheses, respectively. More importantly, the study showed that the new CDC method of performing post-discharge surveillance was associated with a higher risk of not detecting a SSI when compared with the former method.

How to report surveillance data

Although most surveillance systems report SSI rates, there has been debate in the literature regarding the best choice of outcome indicator. Some authors argue that the incidence density of in-hospital SSI is a more suitable choice of outcome indicator by taking into account different lengths of hospital stay and different post-discharge surveillance methods *(31)*. This indicator requires recording the date of patient discharge.

In order to adjust for variations in case-mix, it is recommended to present risk-adjusted SSI rates in addition to crude rates *(32)*. The most commonly used method of risk adjustment is the NNIS risk index whose aim is to predict the occurrence of an SSI in a given patient *(33)*. This risk index has been updated and includes procedure-specific factors that improve its predictive power, but it is not widely used *(28, 34)*. Of note, collecting data for the NNIS risk index may be difficult in settings with limited resources where very limited information is reported in patient records. As an example, in a recent systematic review conducted by WHO, only 14 of 231 SSI surveillance studies from developing countries reported using the NNIS risk index (WHO unpublished data).

Some surveillance systems report standardized infection ratios, which is the ratio between the observed and the expected infection rates *(35, 36)*. A ratio higher than 1.0 indicates that more SSIs occurred than were expected, whereas a ratio lower than 1.0 indicates the opposite *(36)*. The simplest manner to calculate the expected number of SSIs is by multiplying the number of operations in each procedure category by the SSI rate and dividing by 100. This accounts for the case-mix and is therefore a risk-adjusted summary measure *(36)*.

Other surveillance systems (UK, Switzerland) use a funnel plot to improve the precision of the estimates of SSI rates, which are dependent on the number of operations performed. SSI rates are plotted against the number of procedures for each hospital and 95% CIs are drawn. In this manner, outliers (hospitals with unusually high rates) can be easily identified *(37)*.

Difficulties associated with surveillance

Active surveillance is a resource- and time-consuming activity. Constraints can be both in financial terms and/or in the availability of trained and dedicated staff. Surveillance data need validation and interpretation by supervising IPC professionals and/or epidemiologists. A major and very common constraint to HAI surveillance

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in developing countries is the lack of reliable microbiology support. However, this may have a less significant impact on SSI surveillance as a clinical diagnosis can often be made without microbiological confirmation. Thus, the correct collection of clinical data (preferably electronically) is essential for a successful surveillance system. Another difficulty in low-income countries is the high loss of patient follow-up for post-discharge surveillance due to long distances between surgical care services and the patient's place of residence and/or the patient's financial constraints. Based on some interesting publications *(38)*, WHO has developed an adapted approach to SSI post-discharge surveillance by issuing pre-discharge instructions to the patient to allow him/her to recognize signs of infection and maintain follow-up through telephone calls. Finally, in the absence of effective infection control programmes and societies (local and national), it is difficult to introduce a sustainable surveillance system.

Use of surveillance for benchmarking

The use of HAI surveillance data, including SSIs, has been advocated for benchmarking purposes *(23)*. Benchmarking can be used for several purposes, including for the publication of "league tables" as in the UK and USA *(39)*. In addition, it is also used in the USA as the basis for modifying hospital payments to facilities paid by Medicare *(24)*. There are advantages and disadvantages of benchmarking as there are important pitfalls that should be actively avoided. There is a possibility that surveillance systems with more intensive and sensitive surveillance methods that result in higher SSI rates may be unfairly penalised.

Even in the presence of uniform standardized definitions, several studies have shown that inter-rater agreement for SSI is rather low *(40-42)*. One study evaluated inter-rater agreement by submitting 12 case-vignettes of suspected SSI to IPC physicians and surgeons from 10 European countries *(41)*. It was found that there was poor agreement regarding SSI diagnosis and the type of SSI, with variations between and within countries. An analysis of data submitted from 11 countries to the ECDC HELICS (Hospitals in Europe for Infection Control through Surveillance) network showed that there was a substantial variation not only in terms of case-mix (as measured by the NNIS risk index score), but also in the reporting of SSI (highly variable inter-country proportions of superficial SSI ranging from 20-80%) and the length and intensity of postoperative follow-up *(31)*.

An audit of SSI surveillance methods in England showed that differences in data collection methods and data quality were associated with large differences in SSI rates *(43)*. What is striking is that even in the presence of mandatory surveillance with a clearly defined national protocol, a substantial proportion of responders (15%) used alternative definitions *(43)*.

Conclusions

Ideally, surveillance of SSI should be an integral part of IPC programmes of health care organizations and priorities for public health agencies worldwide. However, caution must be exerted when interpreting SSI data, especially when making comparisons, due to a possible heterogeneity of definitions used, surveillance methods, risk stratification and reporting.

Further studies are needed to determine the most sensitive methods of diagnosing SSI, both for in-patients and as part of PDS, and the most efficient methods of collecting data. It is of the utmost importance to develop and test reliable adapted definitions and surveillance methods for settings with limited resources. The role of automated computerized algorithms needs to be also further evaluated. Similarly, the role of SSI surveillance data for benchmarking purposes needs to be clarified, especially when public reporting is involved.

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3.3 Importance of a clean environment in the operating room and decontamination of medical devices and surgical instruments

3.3.1 Environment

For many years, environmental contamination was considered to be less important than many other factors in contributing to HAI. However, recent evidence shows that a contaminated health care environment plays a significant role in the transmission of microorganisms *(1,2)*. It is essential that the operating room (OR) is thoroughly cleaned on a daily basis. Proper mechanical ventilation is also necessary to prevent surgical wound contamination from unfiltered air drawn into the OR and to dilute and remove microorganisms shed in skin scales *(3)*. Specific guidance on the most appropriate ventilation systems in the OR and an evidence-based recommendation on laminar flow are included in chapter 4.23 of these guidelines.

Environmental cleaning and waste management in the OR

Cleaning consists of the removal of dust, soil and contaminants on environmental surfaces and ensures a hygienic and healthy environment both for patients and staff. The environment should be thoroughly cleaned and general principles of good practice should be taken into consideration (Box 3.3.1). Cleaning requirements for various surfaces are detailed in Table 3.3.1.

At the beginning of each day, all flat surfaces should be wiped with a clean, lint-free moist cloth to remove dust and lint. Between cases, hand-touch surfaces (Figure 3.3.1) and surfaces that may have come in contact with patients' blood or body fluids, should be wiped clean first by using a detergent solution and then disinfected according to hospital policy and allowed to dry.

Box 3.3.1. General principles for environmental cleaning

- Cleaning is an essential first step prior to any disinfection process to remove dirt, debris and other materials.
- The use of a neutral detergent solution is essential for effective cleaning. It removes dirt while improving the quality of cleaning by preventing the build-up of biofilms and thus increasing the effectiveness of chemical disinfectants.
- If disinfectants are used, they must be prepared and diluted according to the manufacturer's instructions. Too high and/or too low concentrations reduce the effectiveness of disinfectants. In addition, high concentrations of disinfectant may damage surfaces.
- Cleaning should always start from the least soiled areas (cleanest) first to the most soiled areas (dirtiest) last and from higher levels to lower levels so that debris may fall on the floor and is cleaned last *(4)*.
- Detergent and/or disinfectant solutions must be discarded after each use.
- Avoid cleaning methods that produce mists or aerosols or disperse dust, for example dry sweeping (brooms, etc.), dry mopping, spraying or dusting.
- Routine bacteriological monitoring to assess the effectiveness of environmental cleaning is not required, but may be useful to establish the potential source of an outbreak and/or for educational purposes *(5)*.

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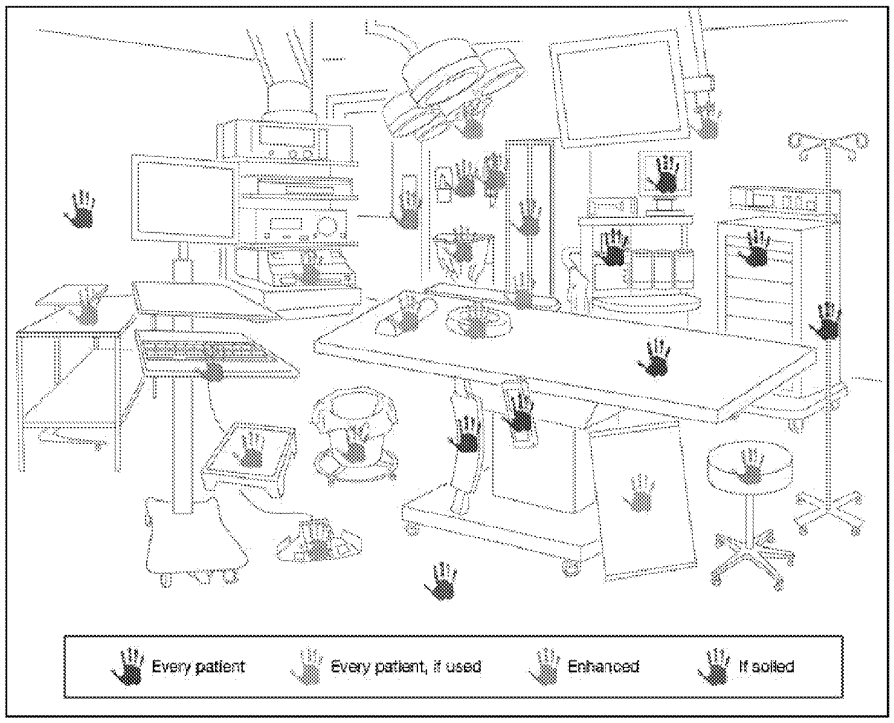
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Table 3.3.1. **Cleaning requirements for various surface types**

Surface type	Definition	Cleaning requirement
High hand-touch surface	Any surface with frequent contact with hands.	Requires special attention and more frequent cleaning. *After* thorough cleaning, consider the use of appropriate disinfectants to decontaminate these surfaces.
Minimal touch surface (floors, walls, ceilings, window sills, etc.)	Minimal contact with hands. Not in close contact with the patient or his/her immediate surroundings.	Requires cleaning on a regular basis with *detergent only* or when soiling or spills occur. Also required following patient discharge from the health care setting.
Administrative and office areas	No patient contact.	Require normal domestic cleaning with *detergent only*.
Toilet area	–	Clean toilet areas at least twice daily and as needed.
Medical and other equipment	–	Require cleaning according to written protocols (for example, daily, weekly, after each patient use, etc.). This should include the use of appropriate personal protective equipment, cleaning methods conforming to the type/s of surface and cleaning schedules, etc. Schedules and procedures should be consistent and updated on a regular basis and education and training must be provided to all cleaning staff. Please refer to the manufacturer's instructions for medical equipment to ensure that the item is not damaged by the use of disinfectants.
Surface contaminated with blood and body fluids	Any areas that are visibly contaminated with blood or other potentially infectious materials.	Requires prompt cleaning and disinfection.

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Figure 3.3.1. **Example of cleaning frequencies in preoperative and postoperative care areas**



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All spills must be carefully cleaned up and the surface cleaned and disinfected according to hospital policy. Domestic heavy duty gloves should be always worn to undertake this task. Use a single-use plastic apron if contamination of the body is likely. Use of a gown and mask is *not* necessary. If there is a risk of spills with chemicals, the use of a face shield or goggles should be considered, depending on the type of chemical products used for disinfection. All waste from the OR should be collected and removed in closed leak-proof containers; soiled linen should be placed in plastic bags for collection. All reusable medical devices should be sent for reprocessing to the sterile services department or the decontamination unit. The operating table should be cleaned and wiped with a detergent solution, including the mattress and the surface. All surfaces that have come in contact with a patient or a patient's body fluids must be cleaned and disinfected using an appropriate disinfectant solution according to local protocols.

At the end of every day, it is necessary to perform a total cleaning procedure. All areas of the surgical suite, scrub sinks, scrub or utility areas, hallways and equipment should be thoroughly cleaned, regardless of whether they were used or not during the last 24 hours. Soiled linen should be removed in closed leak-proof containers. All contaminated waste containers should be removed and replaced with clean containers. Sharps' containers should be closed and removed when they are three quarters full. All surfaces should be cleaned from top to bottom using a detergent, followed by a disinfectant if necessary, and then allowed to dry. To reduce the microbial contamination of environmental surfaces, such as walls, ceilings and floors, they should be thoroughly cleaned from top to bottom with a detergent and allowed to dry. The routine use of a disinfectant or fumigation of the OR is *not* necessary even after contaminated surgery.

3.3.2 Decontamination of medical devices and surgical instruments

Decontamination is a complex and highly specialized subject. This section provides a brief summary on the decontamination and reprocessing of reusable medical devices and patient care equipment.

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In countries with established programmes, decontamination is a speciality in its own right and is an independent, quality-assured and accountable service delivered to health care institutions. The entire process of decontamination is highly regulated and governed by clearly defined guidelines and standards, which are established at both national and international (International Organization for Standardization) levels. This ensures validation of the processes and patient safety *(7-10)*.

In LMICs, decontamination science is in its infancy and few structured decontamination programmes exist, as was evident during the recent Ebola outbreak. In these countries, where the lack of sterile instruments and/or the availability of a properly designed OR and sterile services department have a considerable impact, SSI can be described as surgery-associated infection *(11,12)*. In response to this need, the WHO/Pan American Health Organization (PAHO) have produced a decontamination and reprocessing manual for health care facilities *(13)* to support and guide operational activities to improve standards of care.

In the USA, the term decontamination does not include cleaning and refers to all reprocessing following on thereafter. In the UK and Europe, decontamination relates to the entire process, including cleaning, and this term is used in this chapter (see Table 3.3.2).

Table 3.3.2. **Glossary of terms**

Decontamination	The use of physical or chemical means to remove, inactivate or destroy pathogenic microorganisms from a surface or item to the point where they are no longer capable of transmitting infectious particles and the surface or item is rendered safe for handling, use or disposal. This term is used to cover cleaning, disinfection and sterilization. A risk assessment based on the sections below must be conducted to decide the appropriate level of decontamination required.
Cleaning	The removal, usually with detergent and water, of adherent visible soil, blood, protein substances, microorganisms and other debris from the surfaces, crevices, serrations, joints and lumens of instruments, devices and equipment by a manual or mechanical process that prepares the items for safe handling and/or further decontamination. Cleaning is *essential* prior to the use of heat or chemicals.
Disinfection	Either thermal or chemical destruction of pathogenic and other types of microorganisms. Disinfection is less lethal than sterilization because it destroys most recognized pathogenic microorganisms, but not necessarily all microbial forms (for example, bacterial spores). It reduces the number of microorganisms to a level that is not harmful to health or safe to handle.
Sterilization	The complete destruction of all microorganisms including bacterial spores.

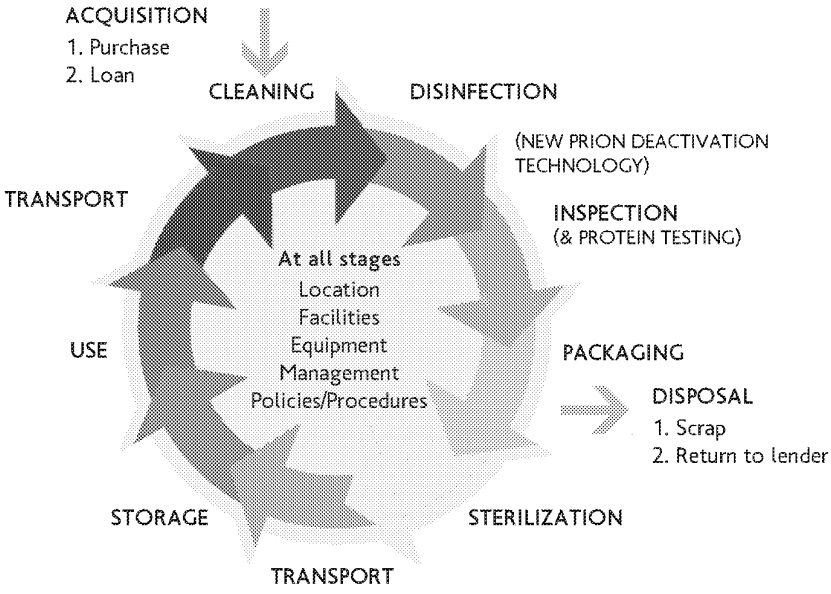
Essentials of decontamination

All medical devices that are reprocessed, such as surgical instruments, must undergo rigorous cleaning prior to decontamination and sterilization procedures. Soaking contaminated medical devices prior to cleaning in disinfectants of any kind is not sufficient or recommended *(14)*. Regardless of the type of operative procedure, the decontamination steps in reprocessing surgical instruments and other medical devices are the same. The life cycle of decontamination illustrates *(Figure 3.3.2)* the salient features of decontamination, with each step being as important as the next.

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Figure 3.3.2. **The cycle of decontamination of a reusable surgical instrument**



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Risk assessment of contaminated instruments

The risk of transferring microorganisms from instruments and equipment is dependent on the following factors:

- the *presence of microorganisms*, their number, and their virulence;
- the *type of procedure* that is going to be performed (invasive or non-invasive);
- the *body site* where the instrument or equipment will be used.

Risk assessment for the reprocessing of medical devices was best described by Spaulding *(15)* and has since been modified. After thorough cleaning, the decision to disinfect or sterilize is based on whether the device is stable to heat or not. In addition, the body site where the instrument or equipment will be used/have contact with will determine whether cleaning or high level disinfection or sterilization is required. According to the Spaulding classification, medical devices are categorized as critical, semi-critical or non-critical according to the degree of risk of infection transmission (Table 3.3.3).

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Table 3.3.3. **Spaulding classification of equipment decontamination**

Category	Definition	Level of microbicidal action	Method of decontamination	Example of common items/equipment
High (critical)	Medical devices involved with a break in the skin or mucous membrane or entering a sterile body cavity.	Kills all microorganisms.	Sterilization (usually heat if heat-stable or chemical if heat-sensitive).	Surgical instruments, implants, prostheses and devices, urinary catheters, cardiac catheters, needles and syringes, dressing, sutures, delivery sets, dental instruments, rigid bronchoscopes, cystoscopies, etc.
Intermediate (semi-critical)	Medical devices in contact with mucous membranes or non-intact skin.	Kills all microorganisms, except high numbers of bacterial spores.	High-level disinfection by heat or chemicals (under controlled conditions with minimum toxicity for humans).	Respiratory therapy and anaesthetic equipment, flexible endoscopes, vaginal specula, reusable bedpans and urinals/ urine bottles, patient bowls, etc.
Low (non-critical)	Items in contact with intact skin.	Kills vegetative bacteria, fungi and lipid viruses.	Low level disinfection (cleaning).	Blood pressure cuffs, stethoscopes, electrocardiogram leads, etc. Environmental surfaces, including the OR table and other environmental surfaces.

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Decontamination facility

The work space

All reprocessing of medical devices must take place in the sterile services department, which should be a separate demarcated department or in a designated decontamination area. Many countries have centralized decontamination areas (central sterile services department) and provide services to the OR, wards and clinical areas. Centralized decontamination processes make the decontamination process cheaper, increase the process safety and enhance its quality. A structured transportation system for clean and used equipment must also be in place. Of note, when the decontamination area space is very limited (usually just one room) and reprocessing is expected to take place in the smallest and least appropriate space with old equipment and overcrowded surfaces, the risk of contamination of clean trays is highly likely. Decontamination of medical devices in clinical areas is not recommended.

Standard operating procedures for decontamination and sterilization

All decontamination units must have written policies and procedures for each stage of the decontamination process and should include:

- formal staff qualification, education/training and competency assessment;
- cleaning;
- high-level disinfection (all processes available);
- preparation and packaging of medical devices;
- sterilizer operating procedures;
- monitoring and documenting of chemical or cycle parameters;
- workplace health and safety protocols specific to the chemical sterilant;
- handling, storage and disposal of the sterilant according to the manufacturer's instructions for use and local regulations;
- use of physical, chemical and/or biological indicators;
- quality systems;
- validation of cleaning, disinfection and sterilization.

Provisions for hand hygiene and personal protective equipment

Equipped hand hygiene stations should be available at the entrance and exit of the sterile services department or decontamination areas. Appropriate personal protective equipment must be provided at each entry point into the sterile services department or decontamination area. Personal protective equipment is designed to be disposable, but it is reused in some low-resource settings. This is acceptable provided that the personal protective equipment, for example, an apron, is cleaned by wiping with a damp cloth and allowed to dry. The apron should then be wiped with 70% alcohol and allowed to dry. A discard bucket for used personal protective equipment must be provided at the exit point, preferably near the wash hand basin.

The workflow

There should be clearly demarcated areas during the reprocessing of medical devices, such as the dirty area where the items are received and cleaned, the inspection-assembly-packaging and the sterilization or high-level disinfection areas, and finally those dedicated to the storage of sterile packs and their transportation. It is recommended that these areas be physically demarcated to avoid cross-contamination from dirty to clean. When this is not possible because of lack of space, obstacles should be placed in order to only permit a unidirectional movement of staff and equipment from dirty to clean without any possibility of overlap.

Transportation of used medical devices

Once devices have been used in the clinical area such as the OR, they should be prepared for transportation to the sterile services department by counting and collecting the devices, rinsing them under cold running water, allowing excess water to drain away, and placing them in a closed container or tray, which will keep them moist until they are removed. These trays (and the accompanying checklist) should be transported in a robust trolley, preferably with closed sides, to the decontamination area. Soaking of medical devices in disinfectant prior to cleaning or during transportation is not recommended as there is a danger of spilling contaminated fluids *(13)* (Box 3.3.2). Used devices should be received, checked and sorted for cleaning in the "dirty" area. Cleaning is normally done either manually or by automated methods.

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Box 3.3.2. Recommendations related to the soaking of instruments in disinfectant prior to cleaning

Do not soak instruments in desinfectant prior to cleaning

Soaking instruments in 0.5% hypochlorite solution or any other disinfectant before cleaning is not recommended for the following reasons.

- It may damage/corrode the instruments.
- The disinfectant may be inactivated by blood and body fluids, which could become a source of microbial contamination and formation of biofilm.
- Transportation of contaminated items soaked in chemical disinfectant to the decontamination area may pose a risk to health care workers and result in inappropriate handling and accidental damage.
- Soaking may contribute to the development of antimicrobial resistance to disinfectants.

Manual cleaning

Cleaning by hand will require well-trained operators to wear appropriate personal protective equipment (waterproof aprons, domestic heavy duty gloves, face cover to protect mucous membranes and head cover [optional]), dilute the detergent accurately according to the manufacturer's guidelines, open up all the hinges on the devices and clean these by holding the item below the surface of the water (water temperature no more than 50° C) while using a soft nylon brush to remove debris. Visual inspection of the hinges, teeth and serrated edges should be carried out to ensure cleanliness. There is no controlled validation of manual cleaning apart from protein detection, which is expensive. Water or air pressure guns are used to blow through and clear lumen devices.

Automated cleaning

Reprocessing medical devices through a washer disinfector is safer and usually more efficient. Devices are cleaned using water jets, then washed with detergent and warm water, followed by a thermal disinfection cycle (some machines have a drying cycle). The load is substantial, although some washer disinfectors are capable of reprocessing up to 60 trays per hour. Most importantly, each cycle is validated with physical and biological parameters *(13)*.

Inspection, assembly and packaging

Using a magnifying glass and good lighting, clean devices are carefully checked to confirm cleanliness and being fit for purpose and then reassembled. If the medical device is found not to be clean, it is returned for re-cleaning; damaged devices are replaced and the completed tray is wrapped ready for sterilization. Packaging is usually done by double wrapping for surgical trays or sterilization pouches for single items. Packaging material should be robust, permeable to steam, but maintain a fluid barrier, and should protect the sterility of the package prior to use.

Methods of decontamination

Steam sterilization

Most surgical devices are heat-resistant and therefore steam is the preferred sterilizing agent globally. It is inexpensive, efficient, easily maintained and widely available, compared with chemical sterilizers. There are several types of autoclaves/sterilizers. All of them work on the same principle of converting water to steam and holding the steam just below boiling point (saturated) so that there is maximum (latent) heat held in a semi-gaseous state. The steam makes contact with the load in the chamber and releases the heat, thus resulting in sterilization. The time that the steam is in contact with the devices is crucial and is known as the "holding time".

Types of autoclaves

- The *pre-vacuum* steam sterilizer is the most widely-used sterilizer and is suitable for the sterilization of wrapped clean instruments, gowns, drapes, towelling and other dry materials required for surgery. Air removal is part of the cycle and thus it is suitable for medical devices with lumens and porous loads.
- *Downward (gravity) displacement* sterilizers are designed for sterilizing bio-hazardous waste, solutions and instruments. They are now obsolete and have many drawbacks as sterility cannot be assured and they are less reliable than pre-vacuum sterilizers. They are not the best option for wrapped packs or porous materials. Air removal is by gravity displacement and they

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are also not suitable for medical devices with lumens.

- *Non-vacuum steam sterilizers*: self-contained (benchtop) sterilizers are sometimes used, but they are only suitable for relatively few or simple items. Table top sterilizers may be used in outpatient departments, dental surgeries and some family planning clinics, but they should not be considered for use in ORs and they are also not suitable for medical devices with lumens.

Sterilization by chemical (low temperature) automatic methods

Chemical gas (low temperature) sterilization is used to sterilize heat- and moisture-sensitive devices. It should be noted that these methods are expensive to install and to run. The mechanics are complex and well-trained staff should be employed if this method is used. Manual chemical sterilization is not recommended because the process cannot be controlled and may lead to occupational health issues.

Use of chemicals, such as chlorine, ortho-phthalaldehyde or glutaraldehyde, is not recommended for sterilization. Although they have sporicidal activity, it is difficult to control the process and there is a risk of contamination during the rinse to removal residual chemicals before patient use. In addition, items cannot be packed and stored, but must be used immediately after rinsing.

Sterilization with gaseous chemical methods should be carried out in chambers with automated cycles that provide safety for the user and guarantee the process. Medical device compatibility will vary with each low temperature sterilization method. Low temperature (gas) sterilization can be achieved using a number of different chemicals for example, ethylene oxide, hydrogen peroxide gas/plasma, ozone, low temperature and steam formaldehyde.

Immediate use sterilization system or "flash" sterilization

An Immediate use sterilization sysstem or "flash" sterilization is a common term that describes the fast sterilization of non-porous and/or non-cannulated surgical instruments in an unwrapped condition in downward displacement steam instrument sterilizers located close to the point where the instruments will be used immediately. In the past, "flash"sterilization was the main means of providing sterile instruments for surgery. Special high-speed sterilizers are usually located in the OR in order to process unwrapped instruments and instruments for urgent use. For example, the only available hand piece is dropped on the floor in the middle of the procedure and this single instrument needs to be sterilized in a rush. These sterilizers operate at 134° C for 3-10 minutes. "Flash" sterilization delivers the instruments wet and very hot into the OR environment. Of note, "flash" sterilization should never replace the lack of material or instruments for a programmed surgical procedure.

If an immediate use sterilization system must be used, it should be used only after all of the following conditions have been met:

- Work practices should ensure proper cleaning, inspection and arrangement of instruments before sterilization.
- The physical layout of the area ensures direct delivery of sterilized items to the point of use.
- Procedures are developed, followed and audited to ensure aseptic handling and staff safety during transfer of the sterilized items from the sterilizer to the point of use.

Validation

In sterile services, it is the process and not the procedure, which is usually tested and validated to ensure high quality assurance and the reliability of the process. There are both simple and complex methods to check that the surgical package has been through the correct decontamination process. Validation of the sterilization process has to take place at every step and can be quite confusing for the sterile services department staff. For details, please refer to the WHO/PAHO decontamination and reprocessing manual for health care facilities *(13)*.

Loan instruments

It is common practice for expensive medical devices used for operations, such as instruments for orthopaedics, neurology or implants and transplants, to be rented ("loaned") from supply companies and brought to the OR. Often the companies deliver the sets directly to the OR and recuperate them directly, thus bypassing the sterile services department. These medical devices are used between several hospitals and the greatest concern is that often there is no control of correct reprocessing of these devices. In LMICs, many

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companies supplying loan instruments do not have facilities to reprocess medical devices and they are often moved from one health care facility to another without adequate reprocessing. In these circumstances, there is often very little documentation about where or how the medical devices have been used. In a very comprehensive document published by the UK Institute of Decontamination Sciences, which outlines the relationship between the OR, the supply company and the sterile services department, it is clear that the ultimate responsibility for patient safety and quality of sterilization lies with the sterile services department in the health care facility and not the supply company *(14)*. Therefore, it is vital that all medical devices destined for the OR must transit via the sterile services department of that health care facility and are validated as safe to use.

Storage of sterile packs

After sterilization, the packs are removed and allowed to cool. If there is an adequate supply of surgical trays and equipment, appropriate storage in the sterile services department has to be provided before the packs are dispatched to the OR. The proper storage of sterile instruments and equipment is essential to ensure that the product maintains its level of sterilization or disinfection. The storage area for sterile packs has specific requirements.

- Store in a clean, dry environment (that is, far from moisture sources) that is protected from any damage. It is recommended that the storage containers should not be made of absorbent material, such as wood.
- The area must be bright, light and airy with good air circulation. The temperature must be moderate without wide fluctuations during the day.
- The storage area should have an adequate level of lighting and the walls should be smooth and easy to clean.
- Access to the area should be restricted.
- The packs should be placed on open racks rather than closed shelves in a single layer to prevent moisture from accumulating between the packs.
- The labels must be visible and clear.
- The pack inspection register should be clearly visible. The racks must be at least 10 cm off the ground and from the ceiling.
- Before use, packages should be inspected in order to verify that they meet the requirements of a sterile product.

User sterility check

It is the duty of the sterile services manager or the person in charge of the sterile services department to ensure that a medical device does not leave the unit unless it is completely safe to use on a human. When there is a lack of equipment in the OR, it is frequent that medical devices are taken for use in the knowledge that the reprocessing cycle has not been completed. However, it is also the responsibility of each health care worker not to allow the use of an unsafe device on a patient. Therefore, all staff should be trained in the checks to be made before a medical device may be used.

Use of sterile instruments in the operating room

1. Role of the nurse who lays out the sterile surgical instruments on the operating trolley in the operating room

The nurse who prepares the operating trolley should check that:

- the preparation area is quiet, clean and undisturbed;
- the packs are not wet (no moisture);
- the packaging of the pack is intact, not torn or opened;
- there are no water marks from condensation indicating non-sterility;
- the chemical indicator strip is present and has a uniform change of colour;
- the internal indicator shows sterilization;
- the devices are clean;
- the surfaces of the devices are intact;
- the devices are fit for use.

2. Role of the scrub nurse

The scrub nurse should check to ensure that:

- the devices are ready and fit for use;
- the devices are not dirty or broken;
- there are an adequate number of devices for the procedure (to avoid opening several packs or resorting to an immediate use sterilization system);
- the pack indicators are placed in the patient notes;
- the surgeon is aware of any shortage of equipment or devices.

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3. Role of the surgeon and surgical team

The surgeon should ensure that before making an incision:

- the operating field is sterile and clearly defined;
- the devices are visibly clean;
- the devices are fit for purpose;
- all the necessary equipment is available;
- there is no unnecessary delay on the operating table because of a lack of instruments;
- the pack indicators are in the patient notes and are satisfactory.

On completion of the surgical procedure, OR staff should:

- check that all instruments are present before returning to the sterile services department;
- rinse the instruments as per the standard operating protocol;
- ensure that items are securely contained in a leak-proof container before transportation to the sterile services department;
- inform the sterile services department of any issues with the surgical instruments, for example, a broken device.

Decontamination of endoscopes

An increasing number of diagnostic and therapeutic procedures are now being carried out using rigid or flexible endoscopes *(16)*. Effective decontamination will protect the patient from infection, ensure the quality of diagnostic procedures and samples and prolong the life of the equipment *(17)* (Table 3.3.4). The source of infection may be due to:

- the previous patient or inadequate decontamination of the endoscope before reuse;
- endogenous skin, bowel or mucosal flora;
- contaminated lubricants, dyes, irrigation fluid or rinse water;
- inadequate decontamination of the reprocessing equipment.

Staff should be aware of the complexities of the endoscopes they are processing to ensure that the construction of the endoscope is fully understood. Failures in decontamination, particularly for flexible endoscopes, have been reported due to failure to access all channels of the endoscope. Irrespective of the method of disinfection or sterilization, cleaning is an essential stage in the decontamination procedure and the manufacturers' instructions should be followed at all times. An endorsement of compatibility of the endoscope with the decontamination process is essential.

Rigid endoscopes are relatively easy to clean, disinfect and sterilize as they do not have the sophistication of functionality, construction and channel configuration and compatibility issues that exist with flexible endoscopes. Where possible, all reprocessing of autoclavable endoscopes and their accessories should take place in a sterile services department or dedicated decontamination unit as the process controls and validation are already in place. It should never take place in the clinical area *(17)*.

Flexible endoscopes are heat-sensitive and require chemical disinfection (or low temperature disinfection) *(18)*. Decontamination of flexible endoscopes should take place in a dedicated well-ventilated room (up to 12 air changes per hour) away from the procedure room. There should be adequate ventilation to remove potentially harmful disinfectant vapour. The room should be equipped with a sink with sufficient capacity to accommodate the largest endoscopes and a dedicated wash hand basin equipped with soap and disposable paper towels.

There should be a workflow direction within the room from dirty to clean to avoid the possibility of recontamination of decontaminated endoscopes from those just used on a patient. Systems should be in place to indicate which endoscopes are ready for patient use and recorded either manually or by an automated endoscope reprocessor. Modern units will have a 2-room system with pass-through washer disinfectors to separate the clean and dirty areas. Storage of endoscopes should be organized to avoid any recontamination of processed endoscopes. There should be sufficient storage for the consumables used during the decontamination procedure, for example, personal protective equipment, chemicals, cleaning brushes and sufficient capacity for waste disposal.

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Table 3.3.4. **Types of endoscopic procedures**

Types of endoscopes	Rigid endoscope example	Flexible endoscope example	Level of decontamination
Invasive: passed into normally sterile body cavities or introduced into the body through a break in the skin or mucous membrane	Arthroscope Laparoscope Cystoscope	Nephroscope Angioscope Choledochoscope	Sterilization by steam or a low temperature method, for example, gas plasma.
Non-invasive: in contact with intact mucous membrane, but does not enter sterile cavities	Bronchoscope	Gastroscope Colonoscope Bronchoscope	High-level disinfection, for example, immersion in glutaraldehyde, peracetic acid, chlorine dioxide.

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4. EVIDENCE-BASED RECOMMENDATIONS ON MEASURES FOR THE PREVENTION OF SURGICAL SITE INFECTION

PREOPERATIVE MEASURES

4.1 Preoperative bathing

Recommendations

It is good clinical practice for patients to bathe or shower prior to surgery.

The panel suggests that either a plain or antimicrobial soap may be used for this purpose.
(Conditional recommendation, moderate quality of evidence)

The panel decided not to formulate a recommendation on the use of chlorhexidine gluconate (CHG)-impregnated cloths for the purpose of reducing SSI due to the limited and very low quality evidence.

Rationale for the recommendation

- The GDG considers it good clinical practice to bathe or shower before surgery to ensure that the skin is as clean as possible and to reduce the bacterial load, especially at the site of incision. Moderate quality evidence shows that preoperative bathing with antimicrobial soap containing CHG has neither benefit nor harm compared to plain soap in reducing the SSI rate. As no study was available using antimicrobial agents other than CHG, the GDG unanimously agreed that either plain or antimicrobial soap may be used.
- Evaluation of the evidence from 3 observational studies showed that preoperative bathing with 2% CHG-impregnated cloths may have some benefit in reducing the SSI rate when compared to bathing with CHG soap or no preoperative bathing. However, in 2 of these studies, the comparison group was inadequate as it included patients who did not comply with instructions to use the cloths preoperatively. This limited and very low quality evidence was considered as insufficient to make any recommendation regarding the use of CHG cloths. All GDG members agreed not to formulate a recommendation on this topic, apart from one member who would have preferred to have a recommendation discouraging the use of CHG-impregnated cloths due to concerns about the waste of resources if these products are purchased, especially in developing countries.

Remarks

- Although no study including paediatric patients was retrieved, the GDG believes that the good practice statement on the importance of patient bathing applies also to paediatric patients. However, if performed with antimicrobial soap, the manufacturer's instructions should be followed regarding the suitability for this age category.
- The GDG identified possible harm associated with the use of CHG-containing solutions, although it was stressed that this is a rare occurrence. Two studies *(1, 2)* found that CHG solutions may cause skin irritation, delayed reactions, such as contact dermatitis and photosensitivity, and hypersensitivity reactions in very rare cases, such as anaphylactic shock. Some of these potential adverse events may be induced also by ingredients of regular soap, such as fragrances. A concern of the GDG was the possible development of reduced susceptibility to CHG, particularly when using CHG-impregnated cloths *(3)*.
- The GDG also expressed concern about the cost of CHG-impregnated cloths, in particular in settings with limited resources where other interventions may have a higher priority.

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Background

Preoperative whole-body bathing or showering is considered good clinical practice to make the skin as clean as possible prior to surgery in order to reduce the bacterial load, especially at the site of incision. This is generally done with an antimicrobial soap (usually CHG 4% combined with a detergent or in a triclosan preparation) in settings where this is available and affordable *(4, 5)*.

Preoperative showering with antiseptic agents is a well-accepted procedure for reducing skin microflora *(6-8)*, but it is less clear whether this procedure leads to a lower incidence of SSI *(7, 8)*. Although rare, patient hypersensitivity and allergic reactions to CHG can occur *(1)*.

When considering the available evidence, the most relevant question is whether preoperative bathing or showering with an antimicrobial soap is more effective than plain soap to reduce SSI. The GDG also considered it relevant to investigate whether using CHG-impregnated cloths rather than bathing with CHG soap is more effective.

Several organizations have issued recommendations regarding preoperative bathing (Table 4.1.1). Most recommend bathing with soap the day of the operation or the day before. Only the US Institute of Healthcare Improvement bundle for hip and knee arthroplasty recommends CHG soap for preoperative bathing. Others state that the use of an antimicrobial soap instead of plain soap is an unresolved issue.

Table 4.1.1. **Recommendations on preoperative bathing according to available guidelines**

Guidelines (year issued)	Recommendations on preoperative bathing and related time of administration
SHEA/IDSA practice recommendation (2014) *(9)*	Unresolved issue.
NICE (2008 and 2013 update) *(10, 11)*	Bathing is recommended to reduce the microbial load, but not necessarily SSI. Soap should be used. The use of antiseptic soap to prevent SSI is inconclusive.
Health Protection Scotland bundle (2013) *(12)*	Ensure that the patient has showered (or bathed/washed if unable to shower) using plain soap on day of or day before surgery.
The Royal College of Physicians of Ireland (2012) *(13)*	Bathing with soap is recommended on the day of or before the procedure.
US Institute of Healthcare Improvement bundle for hip and knee arthroplasty (2012) *(14)*	Preoperative bathing with CHG soap is recommended for at least 3 days before surgery.
UK High impact intervention bundle (2011) *(15)*	Patient showering (or bathing/washing if unable to shower) is recommended preoperatively using soap.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; UK: United Kingdom.

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Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG members decided to conduct a systematic review to assess the effectiveness of preoperative bathing or showering with antimicrobial soap (including CHG-impregnated cloths) compared to plain soap and to determine if the former should be recommended for surgical patients to prevent SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 2) was to evaluate whether preoperative bathing using an antimicrobial soap is more effective in reducing the risk of SSI than bathing with plain soap. The review evaluated also whether preoperative bathing with CHG-impregnated cloths is more effective than using an antimicrobial soap. The target population included patients of all ages undergoing a surgical procedure. The primary outcome was occurrence of SSI and SSI-attributable mortality.

A total of 9 studies (7 RCTs and 2 observational studies) including a total of 17 087 adult patients *(2, 16-23)* investigated preoperative bathing or showering with an antimicrobial soap compared to plain soap.

There is a moderate quality of evidence that bathing with CHG soap does not significantly reduce SSI rates compared to bathing with plain soap (OR: 0.92; 95% CI: 0.80–1.04).

Three observational studies *(24-26)* examined the effectiveness of bathing with CHG-impregnated cloths on SSI rates. One prospective cohort study *(24)* compared bathing with CHG 2% cloths vs. CHG 4% antiseptic soap. Two other prospective studies *(25, 26)* compared bathing twice preoperatively with CHG 2%-impregnated cloths to no preoperative bathing among orthopaedic surgery patients. In the latter studies, the comparison group was inadequate as it comprised patients who did not comply with instructions to use the cloths preoperatively (and therefore most likely did not bathe). No RCTs meeting the specified inclusion criteria were identified.

There is only very low quality evidence that preoperative bathing with CHG-impregnated cloths may reduce SSI rates when compared to either bathing with CHG soap or no bathing. The body of retrieved evidence focused on adult patients and no studies were available in the paediatric population. No studies reported SSI-attributable mortality rates.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG acknowledged that most people with access to water would bathe prior to surgery. It was highlighted that patients wish to be informed of best clinical practice and they will tend to carry out the procedures that they were told to do by the professional health care worker. Some GDG members highlighted that patients may value CHG-impregnated cloths if access to clean water is limited. However, others emphasized that the evidence on the use of CHG-impregnated cloths is very low quality and their use could contribute to CHG resistance.

Resource use

The GDG pointed out that the availability of and access to clean water can be a problem in rural areas in LMICs and preoperative bathing may be neglected. In addition, antimicrobial soap will place an additional financial burden on the health care facility and/or patients in many of these countries. Similarly, CHG-impregnated cloths will pose an additional important financial burden and availability might be very limited in LMICs. Plain soap is more widely available and cheaper than antimicrobial soap.

A cost-effectiveness study *(16)* found that preoperative whole-body washing with a CHG solution is not a cost-effective intervention for reducing SSI. However, it is important to note that this study predominantly consisted of clean surgical procedures for which the risk of SSI is low. Findings from 2 additional studies suggested that the use of CHG-impregnated cloths could lead to reducing health care costs, mainly by decreasing the incidence of SSI *(27, 28)*.

Research gaps

GDG members highlighted that the available evidence compared only CHG as the antiseptic agent to bathing with plain soap. Further research is needed to compare different antiseptic agents to each other and to plain soap for preoperative bathing. Well-designed RCTs and cost-effectiveness analyses are also needed to examine the timing and duration of bathing and its importance in the context of different types of surgery and wound classes, especially in LMICs. In addition, microbiological studies of contamination levels could be of interest. Finally, well-designed RCTs are needed to produce better quality results on

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the effectiveness of CHG-impregnated cloths to reduce SSI and their cost implications, in particular in low-resource settings. The long-term impact of the use of CHG on the possible induction of CHG resistance should also be studied, particularly CHG-impregnated cloths. Further research is also needed to clarify the effect of soap or antiseptics on the skin microbiome.

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4.2 Decolonization with mupirocin ointment with or without chlorhexidine gluconate body wash for the prevention of *Staphylococcus aureus* infection in nasal carriers undergoing surgery

Recommendations

1. **The panel recommends that patients undergoing cardiothoracic and orthopaedic surgery with known nasal carriage of *S. aureus* should receive perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash.**
   (Strong recommendation, moderate quality of evidence)

2. **The panel suggests considering to treat also patients with known nasal carriage of *S. aureus* undergoing other types of surgery with perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash.**
   (Conditional recommendation, moderate quality of evidence)

Rationale for the recommendation

- Moderate quality evidence shows that the use of mupirocin 2% ointment with or without a combination of CHG body wash in surgical patients with *S. aureus* nasal carriage has significant benefit when compared to placebo/no treatment in reducing the *S. aureus* SSI rate, as well as the overall *S. aureus* HAI rate.
- The GDG carefully considered this evidence and the additional subgroup analysis conducted by the systematic review team. The GDG concluded that the evidence is most solid for the cardiothoracic and orthopaedic patient population and that recommending the intervention with the same strength for all surgical patients would pose cost and feasibility constraints, including diagnostic implications to identify carriers among all surgical patients.
- As a result, the GDG agreed to recommend that cardiothoracic and orthopaedic surgical patients with known nasal carriage of *S. aureus* should receive perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash. The strength of this recommendation was considered to be strong. Although the risk and consequences of postoperative *S. aureus* infection are more relevant in cardiothoracic and orthopaedic surgery, the GDG noted that the data from the meta-analysis and meta-regression show that patients with known *S. aureus* nasal carriage undergoing other types of surgery might also benefit from perioperative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash. The strength of this recommendation was considered to be conditional and the GDG proposed to use the terminology "The panel suggests considering..." to highlight the need for careful local evaluation about whether and how to apply this recommendation, in particular regarding feasibility of carriers' identification in a broader surgical patient population and cost effectiveness.
- In patients undergoing other types of surgery to be targeted with this intervention, it is advisable to take other factors into account, such as the local rates of *S. aureus* and methicillin-resistant *S. aureus* (MRSA) and patient-related factors. Among the latter, the most important are past *S. aureus* infection, known carrier status of community-acquired MRSA, and patients colonized by *S. aureus* in sites other than the nose.
- The GDG emphasized that the recommendation to use mupirocin with or without a combination of CHG body wash is derived from the available evidence as CHG 4% soap was used for full body wash in combination with mupirocin nasal ointment in 2 of the included 6 studies. Moreover, in one study CHG 2% soap body wash was used as standard preoperative clinical practice.
- The GDG highlighted that the studies identified as the evidence base for these recommendations did not assess screening for *S. aureus* as part of the intervention. Consequently, no recommendation can be formulated on the role of screening in this context or the surgical patient population that should undergo screening for *S. aureus* carriage. The GDG noted also that standard operating procedures should be agreed upon according to national recommendations and the decision based

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on the local epidemiology, the patient's risk factors for *S. aureus* acquisition, the microbiological capacity and financial resources available at the health care facility. The GDG emphasized that this recommendation applies to facilities where screening for *S. aureus* is feasible. The GDG strongly believes also that decolonization with mupirocin ointment with or without a combination of CHG body wash should be performed on known *S. aureus* carriers only in order to avoid unnecessary treatment and the spread of resistance.

Remarks

- Included studies were performed in adult patients undergoing cardiac, orthopaedic, general, gynaecological, neurological, Mohs micrographic, vascular and gastrointestinal surgery. Based on this evidence, this recommendation is not applicable to paediatric patients.
- The available evidence focused on the nasal carriage of *S. aureus*. Other body sites of frequent and/or known colonization could be considered for decolonization. However, due to the lack of substantial evidence, no recommendation can be made in this direction.
- Studies were performed mostly in high-income countries.
- Mupirocin nasal ointment at a concentration of 2% was used in all included studies. In 2 of the included 6 studies *(1, 2)* CHG 4% soap was used for full body wash in combination with the mupirocin nasal ointment. In one study *(3)* CHG 2% soap body wash was used as standard preoperative clinical practice.
- The application of mupirocin varied from 2 times a day for 5 days *(2, 4, 5)* to 7 days *(3)* before surgery or from the day of hospital admission until the day of surgery *(6)*. Daily administration was continued after surgery for a total of 5 days only in one trial *(1)*. In all studies, at least one administration took place in the immediate preoperative period. Given the variability of treatment protocols, the GDG was unable to give specific instructions about the frequency and duration of mupirocin administration.
- The GDG identified AMR as an important possible harm associated with the use of mupirocin *(7)*. It was emphasized that an approach to treat all patients, regardless of their carriage status, instead of carriers only increases the likelihood of resistance to mupirocin *(8, 9)*. Consequently, monitoring of AMR is recommended in facilities where mupirocin is used *(10-12)*. The available evidence *(3, 5, 6)* and additional studies *(13, 14)* showed no trend towards an increasing prevalence of mupirocin resistance following its short-term use in surgical patients. However, there is evidence that the increased short-term use of mupirocin leads to an increase of resistance to mupirocin and other antibiotics *(15)*. Moreover, in settings known to have a high prevalence of mupirocin resistance, the recommendation to use perioperative intranasal mupirocin ointment may not apply.
- Potential allergic reactions to mupirocin should be accounted for.
- One recent study *(16)* showed a reduction in mortality at one year in patients receiving mupirocin compared to patients receiving placebo. The present review of the evidence based on 3 studies *(1, 3, 5)* did not find an effect on short-term mortality (up to 8 weeks follow-up).
- The GDG identified a possible harm associated with the use of CHG-containing solutions, although it was stressed that this is a rare occurrence. Two studies *(17, 18)* found that CHG solutions may cause skin irritation, delayed reactions (such as contact dermatitis and photosensitivity) and hypersensitivity reactions in very rare cases, such as anaphylactic shock. Some of these potential adverse events may be induced also by ingredients of regular soap, such as fragrances. A concern of the GDG was the possible development of reduced susceptibility to CHG *(19)*.

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Background

S. aureus is the leading health care-associated pathogen in hospitals worldwide. These infections are associated with substantial morbidity and mortality and this trend is increasing due to the widespread dissemination of MRSA *(20)*.

Staphylococcal infections occur regularly in hospitalized patients and can have severe consequences, including postoperative wound infections, nosocomial pneumonia and catheter-related bacteraemia *(21-25)*. A recent study of over 7 million hospital admissions in the USA estimated that the annual national impact was 2.7 million additional days in hospital, US$ 9.5 billion excess costs and at least 12 000 in-patient deaths *(26)*. Given the high burden of these infections for the patient and the health system, effective prevention strategies are essential.

Traditionally, the control of *S. aureus* has been focused on preventing cross-transmission between patients *(27)*. However, it has been shown repeatedly that a large proportion (approximately 80% after surgery) of HAI due to *S. aureus* originate from the patients' own flora *(23, 28, 29)*. Nasal carriage of *S. aureus* is now considered a well-defined risk factor for subsequent infection in various patient groups *(22, 30)*.

Mupirocin nasal ointment (usually applied to the nose 2 times daily for 5 days) is an effective, safe and relatively cheap treatment for the eradication of carriage. Mupirocin can be used for the eradication of both methicillin-sensitive *S. aureus* (MSSA) and MRSA, although mupirocin resistance has been reported *(31)*. Several interventional studies have attempted to reduce infection rates by eradicating nasal carriage *(22)*. Recently, rapid molecular diagnostics with the capacity to detect *S. aureus* nasal carriage within hours rather than days have become available *(32, 33)*, thus enabling the prompt pre-emptive treatment of carriers when appropriate.

The SSI prevention guideline published by SHEA/IDSA) *(34)* recommends screening for *S. aureus* and decolonizing surgical patients for high-risk procedures. Some SSI prevention bundles, such as the one issued by the US-based Institute for Healthcare Improvement *(35)* recommend to screen for *S. aureus* and decolonize prior to surgery, if positive (Table 4.2.1). However, these recommendations are not based upon systematic reviews of the literature and meta-analysis or a rigorous evaluation of the quality of the available evidence.

Table 4.2.1. **Recommendations on screening and decolonization of *S. aureus* according to available guidelines and bundles**

Guidelines (year issued)	Recommendations on screening and decolonizations of S. aureus
SHEA/IDSA (2014) *(34)*	Screen for *S. aureus* (**MSSA and MRSA**) and decolonize surgical patients for high-risk procedures, including some orthopaedic and cardiothoracic procedures.
NICE (2008) *(36)*	Do not use nasal decontamination with topical antimicrobial agents aimed at eliminating *S. aureus* routinely to reduce the risk of SSI.
Institute for Healthcare Improvement: hip and knee arthroplasty (2012) *(35)*	Screen for *S. aureus*. If positive, decolonize 3 days before surgery with nasal mupirocin and CHG soap for 5 days in total for both **MSSA and MRSA**.
Health Protection Scotland bundle (2013) *(37)*	Screen for **MRSA** based on clinical risk assessment.
UK High impact intervention bundle (2011) *(38)*	Screen for **MRSA**: follow local guideline. Screen and decolonize prior to surgery, if found positive.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; SSI: surgical site infection; MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*; CHG: chlorhexidine gluconate.

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Following the in-depth analysis of the sources and strength of evidence in available guidelines, the GDG members decided to conduct a systematic review to assess the available evidence on the effectiveness of decolonization with mupirocin nasal ointment for the reduction of the *S. aureus* infection rate, including SSI, in patients undergoing surgery with known *S. aureus* nasal carriage.

Summary of the evidence

The purpose of the evidence review (web Appendix 3) was to determine whether decolonization with intranasal mupirocin ointment with or without a combination with CHG soap body wash reduces *S. aureus* overall infection rates, including SSI. The target population included patients of all ages with known *S. aureus* nasal carriage undergoing a surgical procedure. The primary outcomes were the occurrence of SSI and SSI-attributable mortality.

Six RCTs *(1-6)* including 2385 patients comparing mupirocin nasal ointment combined with or without CHG soap body wash to placebo or no treatment were identified. Five trials described surgical patients (cardiac, orthopaedic, general, gynaecological, neurological or Mohs micrographic surgery) and one *(1)* included both surgical (cardiac, vascular, orthopaedic, gastrointestinal or general surgery) and non-surgical patients (internal medicine). According to the selected studies, the following comparisons were evaluated:

1. mupirocin vs. placebo/no treatment with the following outcomes:
    a. all HAI caused by *S. aureus*;
    b. health care-associated SSI caused by *S. aureus*.

Overall, a moderate quality of evidence shows that the use of mupirocin 2% ointment combined with or without CHG soap body wash has a significant benefit for the reduction of the SSI rate caused by *S. aureus* in surgical patients with nasal carriage when compared to placebo/no treatment (OR: 0.46; 95% CI: 0.31–0.69), including the overall health care-associated *S. aureus* infection rate (OR: 0.48; 95% CI: 0.32–0.71). It should be noted that most studies included patients undergoing cardiothoracic and orthopaedic surgery, but 2 trials included also other types of procedures. Indeed, in meta-regression analysis, there was no evidence to suggest that the effect on the *S. aureus* infection rate differed between different types of surgery (*P*=0.986).

The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG is confident that patients with nasal *S. aureus* colonization would prefer to be treated with mupirocin ointment nasally with or without a combination of CHG body wash in order to reduce the risk of SSI. Conversely, patients could be concerned about the emergence of AMR, as well as the possible development of reduced susceptibility to antiseptics, such as CHG.

Resource use

The use of mupirocin, including screening for *S. aureus* ("screen-and-treat" strategy), was shown to be cost-effective in 2 studies *(1, 39)*. On average, hospital costs were € 1911 lower per patient treated with mupirocin and CHG soap (n=210) than the costs of care in the placebo arm (n=205; € 8602 vs. € 10 513; *P*=0.01). A subgroup analysis showed that cardiothoracic patients with *S. aureus* nasal carriage treated with mupirocin and CHG cost € 2841 less (n=280; € 9628 vs. €12 469; *P*=0.006) and orthopaedic patients € 955 less than non-treated patients (n=135; € 6097 vs. € 7052; *P*=0.05). Furthermore, based on a nasal *S. aureus* carriage rate of 20%, the authors estimated a saving of approximately € 400 000 per 1000 surgical patients *(39)*.

The GDG highlighted that the access to and availability of nasal mupirocin ointment could be limited for LMICs and pose a financial burden, including also to patients. In addition, antimicrobial soap will pose an additional financial burden to the health care facility and/or patients in many LMICs. The same applies to the technical laboratory capacity and financial burden for the screening process.

Research gaps

Most GDG members emphasized that no further studies are needed on mupirocin. However, given the variability in the timing and duration of mupirocin administration and bathing with CHG across the trials included in this review, additional

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well-designed RCTs are needed to clarify this issue in surgical patients. GDG members highlighted that other agents for the decolonization of nasal *S. aureus* carriers scheduled for surgery should be investigated in well-designed double-blind RCTs. It was underlined that the development and implementation of an inexpensive screening process for *S. aureus* is highly desirable for LMICs. In addition, there is a need for effectiveness and cost-effectiveness studies in these settings.

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4.3 Screening for extended-spectrum beta-lactamase colonization and the impact on surgical antibiotic prophylaxis

Recommendation

The panel decided not to formulate a recommendation due to the lack of evidence.

Rationale for the recommendation

The literature search did not identify any relevant studies comparing the tailored modification of SAP for the prevention of SSI in areas with a high prevalence of extended spectrum beta-lactamase (ESBL)-producing Enterobacteriacae (including patients with rectal colonization of ESBL) to no modification of standard antibiotic prophylaxis. Furthermore, no studies comparing routine screening for ESBL (irrespective of ESBL prevalence prior to surgery) with no screening that could inform a recommendation for this question were identified.

Remarks

- The prevalence of ESBL-producing Enterobacteriacae was considered to be high when demonstrating a prevalence of >10% on the total number of all samples submitted to the laboratory for investigation, including both infection and/or colonization.
- The GDG believes that routine screening for ESBL prior to surgery might increase the widespread use of broad-spectrum antibiotics (particularly carbapenems) pre-surgery in ESBL-colonized patients. This practice may be harmful as it is likely to further increase the emergence of resistance in gram-negative bacteria, especially carbapenem-resistant Enterobacteriacae. The WHO global surveillance report on AMR has already highlighted concerns about the emergence of antibiotic-resistant bacteria due to the inappropriate use of antimicrobial agents. Importantly, the options for the treatment of infections are now extremely limited due to the lack of development of a new class of antimicrobial agents over the past decades *(1)*.

Background

In recent years, the prevalence of patients colonized with ESBL-producing bacteria has increased globally both in health care facilities and in the community. Similar to most gram-negative bacteria, ESBL resides in the gastrointestinal tract and decolonization is very difficult to achieve. The most frequent infections caused by ESBL concern the urinary tract and, to a lesser extent, bloodstream infections. Current SSI prevention guidelines do not address the screening, decolonization and modification of SAP in patients who are colonized with these organisms prior to surgery or the effect of these procedures for the prevention of SSI. The GDG decided to conduct a systematic review to assess the effectiveness of these measures.

Summary of the evidence

The purpose of the evidence review (web Appendix 4) was to evaluate whether the tailored modification of SAP in areas with a high prevalence of ESBL-producing Enterobacteriaceae (>10%), including patients known to be colonized with ESBL, is more effective in reducing the risk of SSI than no modification of prophylaxis. A further objective was to investigate whether routine screening for ESBL in both low and high ESBL prevalence areas has an impact on reducing the risk of SSI compared to no screening. The target population included patients of all ages undergoing a surgical operation. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

The literature search did not identify any studies comparing the tailored modification of SAP for the prevention of SSI in areas with a high prevalence of ESBL-producing Enterobacteriaceae (including patients with rectal colonization of ESBL) to no modification of standard prophylaxis. Similarly, no studies were identified comparing routine patient screening for ESBL with no screening as a preventive measure prior to surgery.

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Additional factors considered

Resource use

In the absence of evidence, the implementation of routine screening for ESBL to detect faecal colonization prior to surgery would have major cost implications, especially in LMICs. For example, this would include clinical staff who have to take a swab and competent microbiology laboratory services to detect ESBL, perform antibiotic susceptibility tests and then communicate the results to the surgical team in a timely manner. This may be difficult as most laboratories are under-resourced and may lack good quality control programmes, particularly in LMICs. In addition, when the screening swab is positive for ESBL, it is very tempting for a clinical team to use carbapenems on colonized patients. This generates additional costs as they have to be given by the intravenous route, which is costly and time-consuming, notably in settings with low resources where there are already a shortage of nursing and medical power.

Research gaps

The GDG members highlighted that although there is an increase in the emergence of ESBL-producing Enterobacteriacae worldwide, no controlled trials or good quality observational studies have been published to answer the questions of this review, even in countries where ESBL-producing Enterobacteriaceae are endemic. Well-designed, RCTs and good quality observational studies are urgently needed to give guidance to the surgical team and prevent the inappropriate use of broad-spectrum antibiotics and the emergence of multidrug-resistant organisms on a global basis. As a priority, these studies should investigate whether the tailored modification of SAP in areas with a high prevalence of ESBL-producing Enterobacteriacae, including patients known to be colonized with ESBL, is more effective in reducing the risk of SSI than no modification of the standard prophylaxis.

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4.4 Optimal timing for preoperative surgical antibiotic prophylaxis

Recommendations

The panel recommends the administration of SAP prior to the surgical incision when indicated (depending on the type of operation).
(Strong recommendation, low quality of evidence)

The panel recommends the administration of SAP within 120 minutes before incision, while considering the half-life of the antibiotic.
(Strong recommendation, moderate quality of evidence)

Rationale for the recommendations

1. Overall low quality evidence shows that the administration of SAP after the incision causes harm with a significant increase of the SSI risk compared with administration of SAP prior to incision. Adequate tissue concentrations of the antibiotic should be present at the time of incision and throughout the procedure for SAP to be effective. This necessitates administration prior to incision. Further evidence shows that a low tissue concentration of antibiotics at the time of wound closure is associated with higher SSI rates *(1, 2)*. As a result, the GDG unanimously agreed to recommend the administration of SAP prior to incision and decided that the strength of this recommendation should be strong, although the overall quality of evidence is low. It is unlikely that higher quality evidence will be available in the future and indeed it would be unethical to perform a study where SAP is only administered post-incision because of the risk to cause significant harm.

2. A moderate quality of evidence comparing different time intervals prior to incision shows significant harm when SAP is administered before 120 minutes compared to within 120 minutes pre-incision. Given the significant increase of SSI with SAP administration more than 120 minutes before incision, the GDG decided to recommend SAP administration within 120 minutes pre-incision. A further analysis of data from studies assessing the effect of SAP administration on SSI at different time intervals within the 120-minute pre-incision period was performed, that is, 120-60 minutes vs. 60-0 minutes and 60-30 minutes vs. 30-0 minutes. No significant difference was found. Therefore, based on the available evidence, it is not possible to establish more precisely the optimal timing within the 120-minute interval.

   Several GDG members expressed concern that serum and tissue concentrations of antibiotics with a short half-life may be less effective than administration closer to the time of incision if given early in this time interval. For this reason, the GDG recommends to take into account the half-life of the administered antibiotics in order to establish the exact time of administration within 120 minutes pre-incision (for example, administration closer to the incision time [<60 minutes] for antibiotics with a short half-life, such as cefazolin, cefoxitin and penicillins in general).The same attention should be paid to the single antibiotic half-life when considering re-dosing during prolonged surgery. Concerns about antibiotic protein binding may arise when choosing highly-bound antimicrobials, such as ceftriaxone, teicoplanin or ertapenem. Under particular pathophysiological conditions (for example, patients with a low level of serum proteins, such as the critically ill or very elderly individuals), such drug disposition may indeed be affected. In addition, malnourishment, obesity, cachexia or renal disease with protein loss may result in suboptimal antibiotic exposure through increased antibiotic clearance in the presence of normal or augmented renal function, including overexposure and potential toxic effects in the presence of severely impaired renal function.

Remarks

- It is not within the scope of these guidelines to provide recommendations on what type of operations require SAP and the antibiotics, doses and intraoperative redosing rules that should be used. Separate specific guidelines will be made available by WHO on this topic. Examples of procedures that do not require SAP are clean orthopaedic operations not involving implantation of foreign materials or low-risk elective laparoscopic procedures.

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- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. However, the GDG considers this recommendation valid also for paediatric patients.
- In the included studies, the information was generally unclear regarding the duration of the procedure, re-dosing protocol, exact timing of the administration, infusion time and whether the half-life of the administered antibiotics was taken into account.
- Studies on caesarean section were not included in this review as they compared pre-incisional administration of SAP vs. administration after cord clamping. A recent systematic review on caesarean section indicated that SAP should be administered prior to incision in order to reduce maternal infectious morbidities *(3)*. This aligns with the recommendations in other surgical procedures where SAP is indicated.
- The guidelines of the American Society of Health-System Pharmacists (ASHSP) *(4)* recommend that intraoperative re-dosing is needed if the duration of the procedure exceeds 2 half-lives of the drug or if there is excessive blood loss during the procedure. While the benefit of this approach seems reasonable from a drug pharmacokinetic aspect, the reviewed studies have not addressed in SAP protocols the duration of surgical procedures or re-dosing in relation to SSI. No recommendation could be concluded on the benefit or harm of this approach.
- Some guidelines distinguish that some antibiotics require administration over 1-2 hours, such as fluoroquinolones and vancomycin. Therefore, the administration of these agents should begin within 120 minutes before the surgical incision. The literature search has not identified studies with SSI as an outcome that differentiate between the timing of administration of antibiotics requiring a longer period and those with a shorter administration timing. Clinicians should consider the half-life and protein binding as the most important pharmacokinetic parameters of any single SAP agent in order to ensure adequate serum and tissue concentration at the time of incision and during the entire surgical procedure.

Background

SAP refers to the prevention of infectious complications by administering an effective antimicrobial agent prior to exposure to contamination during surgery *(4)*. Successful SAP requires delivery of the antimicrobial agent in effective concentrations to the operative site before contamination occurs *(5)*. Microbial contamination of the wound during the procedure can be of exogenous or endogenous origin. The benefit of the routine use of SAP prior to non-clean and implant surgery to prevent SSI has long been recognized. Further evidence of its benefit for other clean procedures where the consequences of an infection would be devastating (for example, cardiac and neurosurgery) is also an important research topic. Of note, the effect of SAP does not concern the prevention of SSI caused by postoperative contamination. Within these guidelines, the recommendations have been developed with a focus on the optimal timing of SAP administration and the indication and type of SAP depending on the type of surgery is outside the scope of the document. Some experimental and clinical studies have demonstrated an effect of SAP timing on SSI *(6, 7)*, but the optimal timing is still under debate.

The administration of SAP prior to surgery has been specified in many clinical practice guidelines issued by professional societies or national authorities (Table 4.4.1). Several of these guidelines, such as those published by the ASHP *(4)*, SHEA/ IDSA) *(8)*, the Royal College of Physicians of Ireland *(9)* or Health Protection Scotland *(10)*, recommend administration within 60 minutes prior to incision (120 minutes for vancomycin and fluoroquinolones due to prolonged infusion times) *(3)*. However, these recommendations are not based on systematic reviews of the literature and meta-analysis or a rigorous evaluation of the quality of the available evidence.

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Table 4.4.1. **Recommendations on SAP according to available guidelines**

Guidelines (date issued)	Recommendations on SAP and the related time of administration
SHEA/IDSA (2014) *(8)*	Administer only when indicated, within 1 hour before incision with superior efficiency between 0 and 30 minutes prior to incision compared with administration between 30 and 60 minutes.
NICE (2013) *(11).*	Single dose of antibiotic intravenously on starting anaesthesia. Prophylaxis should be given earlier for operations in which a tourniquet is used, that is, *after* rather than before tourniquet inflation.
ASHSP (2013) *(4)*	Administration of the first dose of the antimicrobial beginning within 60 minutes before surgical incision is recommended. Administration of vancomycin and fluoroquinolones should begin within 120 minutes before surgical incision because of the prolonged infusion times required for these drugs.
The Royal College of Physicians of Ireland (2012) *(9)*	At induction (within 60 minutes prior to incision surgery). If a *tourniquet* is to be applied, a 15-minute period is required between the end of antibiotic administration and tourniquet application. Single dose, except if blood loss (>1.5 L in adults or 25 mL/kg in children) and prolonged surgical procedures (4 hours).
USA Institute of Health Improvement: surgical site infection (2012) *(12)*	Within 60 minutes prior to incision. Discontinue within 24 hours (48 hours for cardiac patients).
Health Protection Scotland bundle (2013) *(10)*	Within 60 minutes prior to incision. Follow SIGN104 guideline.
UK High impact intervention care bundle (2011) *(13)*	Appropriate antibiotics administered within 60 minutes prior to incision and only repeated if there is excessive blood loss, a prolonged surgical procedure or during prosthetic surgery.

SAP: Surgical antibiotic prophylaxis; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; ASHSP: American Society of Health-Care Pharmacists.

Following the in-depth analysis of the sources and strength of evidence in current guidelines, the GDG members decided to conduct a systematic review to assess the available evidence on the correct timing of SAP administration.

Summary of the evidence

The purpose of the evidence review (web Appendix 5) was to compare the effect of different timings of SAP administration on the risk of SSI and to identify the optimal timing to effectively prevent SSI.

The target population were patients of all ages undergoing surgical interventions where SAP was indicated. The primary outcomes were the occurrence of SSI and SSI-attributable mortality.

A total of 13 observational studies *(7, 14-25)* including a total of 53 975 adult patients were identified; 2 were from multiple centres. No RCTs were identified. The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. The literature search did not identify any studies that reported on SSI-attributable mortality. Despite substantial heterogeneity in reporting time intervals between the selected studies, separate meta-analyses were performed to evaluate the following comparisons of SAP timing administration: pre- vs. post-incision within 120 minutes vs. more than 120 minutes prior to incision; more than 60 minutes vs. within 60 minutes prior to incision; and 30-60 minutes vs. 0-30 minutes.

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Moderate quality evidence shows that SAP administration before 120 minutes pre-incision is associated with a significantly higher risk of SSI when compared to administration within 120 minutes (OR: 5.26; 95% CI: 3.29–8.39). Furthermore, there is low quality evidence that administration of SAP after incision is associated with a significantly higher risk of SSI compared to administration prior to incision (OR: 1.89; 95% CI: 1.05–3.4). In addition, low quality evidence shows that administration within 60 minutes prior to incision has neither benefit nor harm for the reduction of SSI rates compared to administration between 60 to 120 minutes prior to incision. Similarly, SAP administration within 30 to 0 minutes prior to incision has neither benefit nor harm for the reduction of SSI rates when compared to administration within 60 to 30 minutes prior to incision.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG concluded that all patients, health care providers and policy-makers will favour the intervention for both recommendations. Due to logistic and practical considerations, anaesthesiologists tend to administer SAP in the operating room. This is often close to the start of incision, but it still lies within the 120-minute interval recommended by the GDG.

Resource use

There are no extra costs related to an optimized timing interval for SAP. However, the GDG believes that it is important to define responsibility for timely SAP administration and organizational resources may be required. In-service training including best practices for SAP administration should be provided. Feasibility and equity are not identified as significant issues for both recommendations.

Research gaps

The GDG highlighted the limited evidence available on optimal SAP timing to prevent SSI and the need for further studies on this topic. In particular and as a high priority, RCTs comparing the effect of different time intervals within the 120 minutes prior to incision are needed, that is, 120-60 minutes vs. 60-0 minutes and 60-30 minutes vs. 30-0 minutes. These should clearly state the duration of the procedure, the re-dosing protocol according to the drug chosen, as well as the infusion time and best exact timing of administration, while taking into account the half-lives of the antibiotics. Research is warranted also to identify the best timing according to specific types of surgical procedures. Furthermore, well-designed RCTs are necessary to investigate the relation between the pharmacokinetic and pharmacodynamic parameters of the antimicrobial agents used for SAP, including tissue levels at the incision site and SSI rates. The GDG noted that there are no high quality data examining the effect of dose adjustments or intraoperative re-dosing on SSI rates. Thus, it would be important to conduct RCTs comparing optimal doses of antibiotics and re-dosing protocols.

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4.5 Mechanical bowel preparation and the use of oral antibiotics

Recommendations

1. **The panel suggests that preoperative oral antibiotics combined with mechanical bowel preparation (MBP) should be used to reduce the risk of SSI in adult patients undergoing elective colorectal surgery.**
   (Conditional recommendation, moderate quality evidence)
2. **The panel recommends that MBP alone (without administration of oral antibiotics) should not be used for the purpose of reducing SSI in adult patients undergoing elective colorectal surgery.**
   (Strong recommendation, moderate quality evidence)

Rationale for the recommendations

1. Overall moderate quality evidence shows that preoperative oral antibiotics combined with MBP reduce the SSI rate compared to MBP alone. Of note, none of the included studies investigated the effect of oral antibiotics alone, that is, without combining their administration with MBP. All studies also applied standard intravenous antibiotic prophylaxis. Furthermore, the available evidence shows that there is no difference between the intervention and control groups in the occurrence of anastomotic leakage. This result is important because concerns can be raised about the possible higher frequency of leakage if MBP is not performed. Considering the moderate quality of the evidence and the demonstrated effect, the GDG decided to suggest that preoperative oral antibiotics in combination with MBP should be used to reduce the risk of SSI in addition to routine standard intravenous antibiotic prophylaxis, when appropriate.
2. A moderate quality of evidence shows that preoperative MBP alone has no benefit in reducing the SSI rate when compared to performing no MBP. Moreover, the meta-analysis indicates that no MBP has a non-significant beneficial effect in reducing the risk of SSI. In addition, the available evidence shows that there is no difference in the occurrence of anastomotic leakage with or without MBP. Therefore, the GDG unanimously agreed to recommend that MBP alone, without administration of oral antibiotics, should not be used for the purpose of reducing SSI in elective colorectal surgery.

Remarks

- MBP refers to the preoperative administration of substances to induce voiding of the intestinal and colonic contents. Polyethylene glycol and/or sodium phosphate were the agents of choice for MBP in most studies. However, the protocols differed between the trials in terms of dosage, timing of the application and fasting. It was emphasized that suboptimal cleaning of the colon may be more problematic than no bowel preparation at all.
- All studies included adult patients undergoing colorectal surgical procedures; therefore, the effectiveness of these interventions is not proven for paediatric patients.
- Apart from the MBP regimen, the oral antibiotics and the drug of choice for intravenous antibiotic prophylaxis varied across the studies. In 8 trials, oral aminoglycosides were combined with anaerobic coverage (metronidazole *(1-5)* or erythromycin *(6-8)*) and 3 studies *(9-11)* applied a gram-negative coverage only.
- The GDG acknowledges that is difficult to provide a universal statement on the choice of drugs for oral antibiotics to be used for MBP. The combination of the drugs used should guarantee an activity against both facultative gram-negative and anaerobic bacteria. The choice of antimicrobials should be made ideally according to local drug availability, updated resistance data within institutions and the volume of surgical activity.
- The GDG identified possible harms of the intervention of MBP with varying levels of severity. These include patient discomfort, electrolyte abnormalities and potentially severe dehydration at the time of anaesthesia and incision.

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- The GDG pointed out that there is an alert issued by the US Food and Drug Administration highlighting that acute phosphate nephropathy (a type of acute renal failure) is a rare but serious adverse event associated with oral sodium phosphate bowel cleansing *(12)*.
- Concerns were also raised with regard to the potential adverse effects of the oral antibiotics used (for example, high risk of idiosyncratic reaction with erythromycin). A further concern was AMR as a potential unintended consequence of this intervention. The effectiveness of oral antibiotics may decrease due to their widespread use, thus triggering the emergence of resistant strains. The GDG noted that there was a widespread belief that non-absorbable antibiotics should be preferably used. In the corresponding comparisons, a combination of non-absorbable and absorbable antibiotics was administered in 8 of 11 RCTs *(1-8)*. Two studies *(9, 10)* applied non-absorbable and one study *(11)* absorbable antibiotics only.
- The GDG emphasized that the intervention of oral antibiotics with MBP is for preoperative use only and should not be continued postoperatively. This intervention should not be referred to as "selective digestive decontamination" (SDD) in order to avoid any confusion with SDD used for the prevention of ventilator-associated pneumonia in the intensive care setting.

Background

The optimal preparation of the bowel of patients undergoing colorectal surgery has been a subject of debate for many years. The main focus has been on whether or not mechanical cleansing of the bowel should be part of the standard preoperative regimen. MBP involves the preoperative administration of substances to induce voiding of the intestinal and colonic contents. The most commonly used cathartics for MPB are polyethylene glycol and sodium phosphate. It was assumed that cleaning the colon of its contents was necessary for a safe operation and could lower the risk of SSI by decreasing the intraluminal faecal mass and theoretically decreasing the bacterial load in the intestinal lumen. Furthermore, it was believed that it could prevent the possible mechanical disruption of a constructed anastomosis by the passage of hard faeces. Finally, MBP was perceived to improve handling of the bowel intraoperatively.

Another aspect of preoperative bowel preparation that has evolved over the last decades concerns the administration of oral antibiotics. Since the 1930s, orally administered antibiotics have been used with the aim to decrease the intraluminal bacterial load. However, these drugs had typically poor absorption, achieved high intraluminal concentrations and had activity against (anaerobic and aerobic) species within the colon. The addition of oral antibiotics that selectively target potentially pathogenic microorganisms in the digestive tract, predominantly gram-negative bacteria, *S. aureus* and yeasts, is known also as "selective digestive decontamination". This term originates from intensive care medicine and usually refers to a regime of tobramycin, amphotericin and polymyxin combined with a course of an intravenous antibiotic, often cefotaxime. Originating from the belief that oral antibiotics would work only when the bowel had been cleansed of its content, a regime of oral antibiotics was frequently combined with MBP.

A few organizations have issued recommendations regarding preoperative MBP and the administration of oral antimicrobials (Table 4.5.1). For example, SHEA/IDSA recommend to use MBP for colorectal procedures, but only combined with oral antibiotics. However, these recommendations are not based on systematic reviews of the literature and meta-analysis or a rigorous evaluation of the quality of the available evidence.

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Table 4.5.1. **Recommendations on MBP and the administration of oral antimicrobials according to available guidelines**

Guidelines (year issued)	Recommendations on MBP and the administration of oral antimicrobials
SHEA/IDSA practice recommendation (2014) *(13)*	Use a combination of parenteral antimicrobial agents and oral antimicrobials to reduce the risk of SSI following colorectal procedures. (i) The additional SSI reduction achieved with MBP has not been studied, but the data supporting the use of oral antimicrobials have all been generated in combination with MBP. (ii) MBP preparation without oral antimicrobials does not decrease the risk of SSI.
NICE (2008) *(14)*	Do not use MBP routinely to reduce the risk of SSI.

MBP: mechanical bowel preparation; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; SSI: surgical site infection; NICE: National Institute for Health and Care Excellence.

Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG decided to conduct a systematic review to assess the available evidence on the effectiveness of preoperative oral antibiotics and MBP for the prevention of SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 6) was to evaluate whether preoperative MBP is more effective in reducing the risk of SSI than no MBP at all. The review evaluated also whether combining the preoperative administration of oral antibiotics with MBP in addition to the standard preoperative intravenous antibiotic prophylaxis is more effective than MBP alone. The population targeted were patients of any age undergoing elective colorectal surgery. The primary outcome was the occurrence of SSI and SSI-attributable mortality. Data on anastomotic leakage were analysed separately as a secondary outcome. The body of retrieved evidence focused on adult patients and no study was available in the paediatric population.

A total of 24 RCTs *(1-11, 15-27)* were identified. They compared either MBP with no MBP or the combined intervention of MBP and oral antibiotics with MBP and no oral antibiotics.

A total of 11 RCTs *(1-11)* including a total of 2416 patients and comparing preoperative MBP combined with the administration of oral antibiotics vs. MBP and no oral antibiotics were identified. Moderate quality evidence shows that preoperative MBP combined with oral antibiotics reduces the SSI rate when compared to MBP only (OR: 0.56; 95% CI: 0.37–0.83). Using this intervention, there is neither benefit nor harm in the occurrence of anastomotic leakage (OR: 0.64; 95% CI: 0.33–1.22).

A total of 13 RCTs *(15-27)* including a total of 4869 patients and comparing MBP with no MBP were identified. Moderate quality evidence shows that preoperative MBP has neither benefit nor harm for the reduction of SSI rates when compared to no MBP at all (OR: 1.31; 95% CI: 1.00–1.72). The available evidence shows also that there is no difference in the occurrence of anastomotic leakage with or without MBP (OR: 1.03; 95% CI: 0.73–1.44).

Among the studies comparing MBP combined with oral antibiotics vs. MBP alone, only 2 *(8, 11)* reported specifically on SSI-attributable mortality. Both studies reported a lower mortality rate when oral antibiotics were administered, although they failed to report any test for statistical significance. Of the 13 trials comparing MBP with no MBP, 3 reported specifically on SSI-attributable mortality *(18, 23, 27)*, but they did not find any statistical difference in the mortality rate.

None of the identified RCTs specifically evaluated the role of oral antibiotics without a MBP regimen, but some observational studies *(28-30)* using registry databases suggested that oral antibiotics may be effective in reducing the risk of SSI, irrespective of being combined with MBP. In addition, a prospective, randomized study *(31)*

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strongly supports the use of oral antibiotics as part of a bundled intervention, but in combination with MBP. In this study, the combination of the preoperative administration of oral antibiotics and MBP was omitted in one group and compared with a standard regimen of oral antibiotics and MBP, while both arms received intravenous antibiotics prior to the surgical incision.

Additional factors considered when formulating the recommendation

Values and preferences

One study *(9)* found a higher incidence of diarrhoea when oral antibiotics were administered. Another study *(1)* assessed patient tolerance with 3 different oral antibiotic regimes. Patients reported more gastrointestinal symptoms (that is nausea and vomiting) at the time of preoperative preparation when given 3 doses of oral antibiotics compared to no oral antibiotics or one dose only. Among the studies comparing MBP with no MBP, 4 reported on patient discomfort. Berrera and colleagues *(15)* reported that half of all patients (50%) receiving MBP reported fair or poor tolerance. The main causes were nausea (56%), vomiting (23%) and cramping abdominal pain (15%). In another study *(16)* including 89 patients with MBP, 17-28% complained of similar disorders which led to a stop of preoperative MBP in 11% of cases. In one study *(17)*, MBP was associated with discomfort in 22% of patients, including difficulty in drinking the preparation, nausea, vomiting and abdominal pain. Zmora and colleagues *(27)* found that diarrhoea in the early postoperative period was more common in the MBP than the non-MBP group and reached statistical significance. The GDG acknowledged that some patients, for example, the elderly or disabled, might prefer not to undergo MBP, regardless of the outcome.

Resource use

It was acknowledged that MBP, including the administration of oral antibiotics, involves an additional workload as this intervention requires organizational resources to ensure its appropriate administration (for example, clear written instructions to patients and staff education). Furthermore, the initial cost is higher compared to not undertaking this intervention, but none of the included studies reported on costs and cost-effectiveness. However, the GDG concluded that the benefits of administering oral antibiotics outweigh these aspects. The antibiotics commonly used for the intervention (erythromycin, metronidazole and an aminoglycoside) are generally inexpensive and readily available, including in LMICs.

Research gaps

The GDG highlighted that there is enough evidence available on MBP alone. However, further research is needed on the effects of using oral antibiotics without MBP for the prevention of SSI. In particular, well-designed RCTs are needed to compare oral antibiotics and adequate intravenous prophylactic antibiotics vs. adequate intravenous prophylactic antibiotics only. The GDG noted also that there is limited evidence on the role of these interventions for patients undergoing laparoscopic procedures. However, some observational studies of mixed populations who underwent open and laparoscopic procedures suggested benefits for MBP across all groups. A RCT was recently published on this topic and showed a significant reduction of SSI in laparoscopic patients receiving oral antibiotics in addition to MBP and standard intravenous antibiotic prophylaxis *(32)*. However, this study could not be included in the systematic review due to the time limits determined for study inclusion.

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4.6 Hair removal

Recommendation

The panel recommends that in patients undergoing any surgical procedure, hair should either not be removed or, if absolutely necessary, it should be removed only with a clipper. Shaving is strongly discouraged at all times, whether preoperatively or in the operating room (OR).
(Strong recommendation, moderate quality of evidence)

Rationale for the recommendation

- For the formulation of the recommendation, the GDG considered the meta-analysis comparing clipping and no hair removal vs. shaving to be the most relevant. Moderate quality evidence shows a clear benefit of either no hair removal or clipping when compared to shaving with a significant decrease of the SSI risk.
- As a result, the GDG unanimously agreed to recommend that hair should either not be removed or, if absolutely necessary, it should be removed only with a clipper and the strength of this recommendation should be strong.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. However, the GDG considers this recommendation valid also for paediatric patients.
- When analysed separately, there was no significant difference between clipping and shaving compared to no hair removal, but clipping was found to be significantly beneficial when compared to shaving. The GDG decided that no hair removal and clipping should be compared to shaving in the same group as they are both similar in nature.
- It was noted that only one study *(1)* compared different times of hair removal (night before vs. day of surgery for both shaving and clipping). This study showed no clear evidence favouring any of the times for either method. Therefore, the GDG agreed that no recommendation regarding the timing of hair removal could be given. However, it was acknowledged that if hair is removed, removal shortly before surgery could be the most practical and safest approach.
- No studies were identified evaluating the effect of settings where hair removal is performed (OR vs. ward or home) with the outcome of SSI. Thus, the GDG agreed that no recommendation could be developed regarding the location of hair removal with clippers when this is necessary.
- The GDG did not identify any possible harm associated with no hair removal or using clippers.

Background

Removal of hair from the intended site of surgical incision has traditionally been part of the routine preoperative preparation of patients undergoing surgery. Hair removal may be necessary to facilitate adequate exposure and preoperative skin marking. Furthermore, suturing and the application of wound dressings can be complicated by the presence of hair. Apart from these practical issues, hair has been associated with a lack of cleanliness and the potential to cause SSI. There is also the belief that hair removal inversely increases the risk of SSI by causing microscopic trauma of the skin. To minimize the potential of skin trauma, the use of clippers instead of razors has been proposed for preoperative hair removal. In contrast to razors that involve a sharp blade drawn directly over the skin, clippers cut the hair close to the skin without actually touching it. A third method for hair removal is the application of depilatory creams containing chemicals. Drawbacks of the use of these creams are the necessity to leave them in place for approximately 15-20 minutes for the hair to be dissolved and the potential for allergic reactions. A Cochrane review published in 2009 and updated in 2011 found no statistically significant difference in SSI rates between hair removal and no hair removal interventions.

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However, a significant harm was observed when hair removal with razors was compared with clipping *(2)*.

Among available guidelines, 4 explicitly recommend to avoid routine hair removal as a part of preoperative measures to prevent SSI *(3-6)*.

All other guidelines recommend not using razors. If electric clippers are used, a single-use head should be used (Table 4.6.1). Only a few guidelines provide an evaluation of the quality of the evidence.

Table 4.6.1. **Recommendations on hair removal according to available guidelines**

Guidelines (date issued)	Recommendations on hair removal
SHEA/IDSA (2014) *(6)*	Hair should not be removed at the operative site unless the presence of hair will interfere with the operation. Do not use razors. If hair removal is necessary, remove hair outside the operating room using clippers or a depilatory agent.
NICE (2013) *(7)*	Evidence for preoperative hair removal in reducing SSI rates is insufficient. Razors should not be used for hair removal because they increase the risk of SSI. If hair has to be removed, use electric clippers with a single-use head on the day of surgery as clipping may be associated with a reduced rate of SSI.
The Royal College of Physicians of Ireland (2012) *(4)*	Avoid hair removal. If hair must be removed, then use single-patient use clippers and not razors.
USA Institute for Healthcare Improvement: surgical site infection (2012) *(5)*	Avoid hair removal. If removal is necessary, remove outside the operating room using a single-patient use clipper.
Health Protection Scotland bundle (2013) *(3)*	Avoid hair removal. If removal is necessary, use a single-patient use clipper.
UK High impact intervention bundle (2011) *(8)*	If hair removal is required, use clippers with a disposable head and timed as close as possible to the operating procedure.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; SSI: surgical site infection; NICE: National Institute for Health and Care Excellence; UK: United Kingdom.

Following the in-depth analysis of the sources and strength of evidence in current guidelines, the GDG members decided to conduct a systematic review to assess the available evidence on the need and correct method for hair removal.

Summary of the evidence

The purpose of the evidence review (web Appendix 7) was to investigate whether the method and timing of hair removal (using clippers, depilatory cream or shaving with razors) or no hair removal affect the incidence of SSI. The target population was patients of all ages undergoing a surgical procedure. The primary outcomes were the occurrence of SSI and SSI-attributable mortality.

A total of 15 RCTs or quasi-randomized trials *(1, 9-22)* comparing the effect of preoperative hair removal vs. no hair removal or different methods of hair removal (shaving, clipping and depilatory

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cream) were identified. Meta-analyses were performed to evaluate the following comparisons: shaving, clipping and depilatory cream individually vs. no hair removal, shaving vs. clipping and shaving vs. depilatory cream. As no hair removal and clipping are similar in terms of reduced potential to cause microscopic skin trauma, an additional analysis was performed combining no hair removal and clipping *vs.* shaving.

A low to very low quality of evidence shows that shaving, clipping or the use of depilatory cream has neither benefit nor harm related to the reduction of the SSI rate when compared to no hair removal (OR: 1.78; 95% CI: 0.96-3.29; OR: 1.00;95% CI: 0.06-16.34; and OR: 1.02; 95% CI: 0.42-2.49, respectively).

However, when hair is removed, there is a low quality of evidence showing that clipping has a significant benefit in reducing the SSI rate compared to shaving (OR: 0.51; 95% CI: 0.29-0.91). A very low quality of evidence shows that the use of depilatory cream has neither benefit nor harm when compared to shaving for the prevention of SSI (OR: 2.78; 95% CI: 0.86-9.03). When clipping and no hair removal were combined in the meta-analysis, a moderate quality of evidence showed that both are associated with a significantly lower risk of SSI when compared to shaving (OR: 0.51; 95% CI: 0.34-0.78).

A moderate quality of evidence shows that hair removal the day before surgery does not affect the SSI rate compared to hair removal on the day of surgery (OR: 1.22; 95% CI: 0.44-3.42).

The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

Studies evaluating surgeon or patient preferences for hair removal show variable results. Ilankovan and colleagues investigated patient and surgeon preferences before maxillofacial surgery and showed that patients prefer no hair removal over shaving, while the surgeons' assessment of the difficulty of wound closure did not differ between the two methods *(18)*.

The GDG acknowledged that the preferences of both patients and surgeons may differ according to the body area. Some members expressed the following opinions.

- Surgeons may be hesitant to use clippers in the male genitalia area.
- Women may prefer shaving for surgery in the genital area or even come to the hospital already shaved because of cultural norms.
- Surgeons may prefer to remove hair because of concerns that long hair would interfere with surgery and stick to the drapes.

While acknowledging this variability of approaches and cultural issues, the GDG emphasized that these preferences could be changed with an awareness-raising campaign to highlight the benefits of the recommendation and the harms of shaving practices, together with strong implementation strategies. Furthermore, the GDG was confident that the typical values of the target population regarding the SSI outcome would most probably favour the intervention.

Resource use

The GDG observed that avoiding hair removal has no cost and puts no burden on staff. Clippers are expensive and it might be difficult to procure them in LMICs. It is generally advisable to use single-use clippers/clipper heads, which may again be difficult to procure in LMICs. Of note, when reused, clipper heads can be very difficult to clean and decontaminate. When required for reuse, the GDG suggests that local infection prevention procedures are followed for clipper/clipper head decontamination, taking into account the following basic instructions for the general process: carefully disassemble the blades; clean with soap and water using a cloth and wearing appropriate personal protective equipment; dry with a fresh cloth and wipe with alcohol, again using a fresh cloth. Following the procedure, dispose of cloths and personal protective equipment, cleanse hands and store the clipper in a clean, covered dry storage space to avoid contamination.

Research gaps

Although the evidence to support the recommendation appears to be sufficient, the GDG provided the following directions for additional research on this topic. Studies are needed to evaluate the optimal timing and the most appropriate setting (ward vs. home) for the hair removal procedure when it is considered necessary by the surgeon. It would be important also to conduct surveys on the acceptability of patients

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and surgeons regarding hair removal (or not) prior to surgery, particularly for body areas where preferences may vary, for example, genitalia for females and the maxillofacial area for males. The best and most acceptable methods of hair removal in settings with limited resources need to be investigated, including low-cost solutions. In particular, studies with a focus on the use of clippers in LMICs are needed to stimulate research on the design and production of an affordable clipper for these settings, including a cost-effectiveness analysis. For all settings, research is required to develop and test evidence-based procedures on how to decontaminate clippers.

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4.7 Surgical site preparation

Recommendation

The panel recommends alcohol-based antiseptic solutions based on CHG for surgical site skin preparation in patients undergoing surgical procedures.
(Strong recommendation, low to moderate quality of evidence)

Rationale for the recommendation

- Moderate quality evidence shows that the use of alcohol-based antiseptic solutions for surgical site skin preparation is more effective compared to aqueous solutions in reducing SSI. A meta-analysis of available studies (low quality of evidence) showed that alcohol-based CHG is beneficial in reducing SSI rates compared to alcohol-based povidone-iodine (PVP-I). As a result, the GDG agreed to recommend the use of an alcohol-based antiseptic solution preferably based on CHG for surgical site preparation on intact skin. The strength of this recommendation was considered to be strong.
- The GDG discussed whether to formulate the recommendation for adult patients only or to make a recommendation for all patients. The body of evidence focused on adult patients. The paediatric population was not represented as most commercially-available products have no indications for use in these patients due to the lack of studies in this population. By contrast, the GDG emphasized that it is unlikely that high quality evidence will be available in the future on paediatric patients, mainly due to ethical reasons.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. Therefore, the effectiveness of this intervention is not proven for paediatric patients.
- Although the systematic review time limits for inclusion were set to a publication date between 1 January 1960 and 15 August 2014, a relevant trial published on 4 February 2016 was exceptionally included after discussion with the WHO Guidelines Review Committee and the GDG. The GDG was confident that no additional relevant trial had been published since the systematic review set date and therefore the search was not fully updated.
- According to the available studies, a sub-analysis of the comparison of alcohol-based antiseptic solutions vs. aqueous solutions was performed. A significant benefit in reducing the risk of SSI was observed with CHG in an alcohol-based solution compared to PVP-I in an aqueous solution. No significant difference was found between alcohol-based vs. aqueous PVP-I solutions. Most of the included studies used isopropyl alcohol at a concentration of 70-74%. Concentrations of the iodophor compound ranged from 0.7-10% and from 0.5-4% for CHG. Due to this heterogeneity and the lack of data to confirm any one direction, the GDG did not feel comfortable to include a statement about the concentration of the antiseptic compound in the recommendation.
- Washing the patient's skin with detergents or antiseptics is dealt with in chapter 4.1 and should be performed separately outside of the OR, whereas surgical site skin preparation is done prior to surgery within the OR.
- The GDG identified possible harms associated with the use of alcohol-based solutions and it was highlighted that they should not be used on neonates or be in contact with mucosa or eyes. CHG solutions must not be allowed to come into contact with the brain, meninges, eye or middle ear. As alcohol is highly flammable, alcohol-based antiseptic preparations may ignite if used in the presence of diathermy and they must be allowed to dry by evaporation. Therefore, it is advisable to ensure that the drapes are not saturated with alcohol or that the alcohol-based solution has not formed a pool underneath the patient before operating. While possible allergies should be accounted for (for example, to PVP-I), it should be noted that CHG has a potential risk of causing skin irritation. OR staff should be trained and informed about the potential harms associated with the solutions used for surgical site preparation.

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Background

Surgical site preparation refers to the preoperative treatment of the intact skin of the patient within the OR. Preparation includes not only the immediate site of the intended surgical incision, but also a broader area of the patient's skin. The aim of this procedure is to reduce the microbial load on the patient's skin as much as possible before incision of the skin barrier. The most widely used agents include CHG and PVP-I in alcohol-based solutions, which are effective against a wide range of bacteria, fungi and viruses. However, aqueous solutions, particularly those containing iodophors, are also widely used, notably in developing countries.

Application techniques for preoperative surgical site preparation are also a topic of interest. However, 3 trials investigating the effect of the application technique with comparable antiseptic compounds showed no difference in surgical site infection (SSI) rates *(1-3)*. Despite current knowledge of the antimicrobial activity of many antiseptic agents and application techniques, it remains unclear what is the best approach to surgical site preparation *(4, 5)*.

Several guidelines, such as those published by SHEA/IDSA) *(6)*, NICE *(7)* or the Royal College of Physicians of Ireland *(8)*, recommend the use of an alcohol-based solution for surgical site preparation (Table 4.7.1). However, these recommendations are not based upon systematic reviews of the literature and meta-analysis or a rigorous evaluation of the quality of the available evidence.

Table 4.7.1. **Recommendations on surgical site skin preparation according to available guidelines**

Guidelines (date issued)	Recommendations on surgical site skin preparation
SHEA/IDSA (2014) *(6)*	Wash and clean skin around the incision site. Use a dual agent skin preparation containing alcohol, unless contraindications exist.
NICE (2013) *(7)*	PVP-I or CHG, although alcohol-based solutions may be more effective than aqueous solutions. The most effective antiseptic for skin preparation before surgical incision remains uncertain.
The Royal College of Physicians of Ireland (2012) *(8)*	CHG 2% in isopropyl 70% alcohol solution; PVP-I with alcohol for patients who are allergic to CHG.
USA Institute for Healthcare Improvement: hip and knee arthroplasty (2012) *(9)*	Combining either an iodophor or CHG with alcohol is better than PVP-I alone.
Health Protection Scotland bundle (October 2013) *(10)*	CHG 2% in isopropyl 70% alcohol solution; PVP-I with alcohol for patients who are allergic to CHG.
UK High impact intervention bundle (2011) *(11)*	CHG 2% in isopropyl 70% alcohol solution; PVP-I with alcohol for patients who are allergic to CHG.

PVP-I: povidone-iodine; CHG: chlorhexidine gluconate; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence.

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Following the in-depth analysis of the sources and strength of evidence in available guidelines, the GDG decided to conduct a systematic review to assess the available evidence on the efficacy of solutions and antiseptic agents used for surgical site skin preparation.

Summary of the evidence

The purpose of the evidence review (web Appendix 8) was to compare the effect of different solutions (alcohol-based vs. aqueous preparations) and antiseptic agents (CHG vs. PVP-I) used for surgical site skin preparation in order to prevent SSI. The target population included patients of all ages undergoing a surgical procedure. The primary outcomes were the occurrence of SSI and SSI-attributable mortality.

A total of 17 RCTs *(2, 12-27)* comparing antiseptic agents (PVP-I and CHG) in aqueous or alcohol-based solutions were identified. According to the selected studies, the following comparisons were evaluated:

1. Alcohol-based antiseptic solutions vs. aqueous solutions
   a) CHG in an alcohol-based solution vs. PVP-I in an aqueous solution
   b) PVP-I in an alcohol-based solution vs. PVP-I in an aqueous solution

2. CHG vs. PVP-I - both in alcohol-based solutions

Moderate quality evidence shows that alcohol-based antiseptic solutions are overall more effective compared to aqueous solutions in reducing the risk of SSI (OR: 0.60; 95% CI: 0.45–0.78). More specifically, a low quality of evidence shows a significant reduction of the SSI risk with the use of alcohol-based CHG compared to PVP-I in alcohol-based solutions (OR: 0.58; 95% CI: 0.42–0.80). Moderate quality evidence shows also a significant benefit in using CHG alcohol-based solutions compared to aqueous PVP-I for the reduction of SSI rates (OR 0.65; 95% CI: 0.47–0.90). However, very low quality evidence suggests that there is no significant difference between PVP-I alcohol-based solutions and PVP-I aqueous solutions (OR 0.61; 95% CI: 0.19–1.92).

The literature search did not identify any studies that used aqueous CHG for surgical site skin preparation. The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. Furthermore, most commercially available products have no indications for use in paediatric patients due to the lack of studies in this population. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patients' values and preferences with regards to this intervention. The GDG concluded that most patients wish to receive this intervention in order to reduce the risk of SSI.

However, the use of alcohol might be refused by patients and/or health care workers because of religious reasons. This issue was addressed as part of the WHO *Clean Care is Safer Care* programme of work and a chapter on this topic is included in the WHO *guidelines on hand hygiene in health care (28)*, which recommends the preferred use of alcohol-based handrub (ABHR) for hand cleansing. The engagement of cultural and religious leaders (for example, in the hand hygiene campaign in health care facilities) proved useful to overcome such barriers and positive solutions were found. Indeed, an encouraging example is the statement issued by the Muslim Scholars' Board of the Muslim World League during the Islamic High Council's meeting held in Mecca, Saudi Arabia, in January 2002: "It is allowed to use medicines that contain alcohol in any percentage that may be necessary for manufacturing if it cannot be substituted. Alcohol may be used as an external wound cleanser, to kill germs, and in external creams and ointments." There may be a necessity to resume the discussion with religious leaders and individual patients with regards to the recommendation to use alcohol-based solutions for surgical site skin preparation.

Resource use

The GDG highlighted that the availability of alcohol-based solutions is limited in LMICs, particularly when combined with an antiseptic compound. These commercial products may represent a financial burden to health care facilities and patients if they are required to provide care supplies. The GDG discussed the implementation of this recommendation in LMICs and argued that local production may be a more affordable and feasible option in these settings, provided that adequate quality control is put in place. As an example, in

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the context of the Surgical Unit-based Safety Programme, instructions for the local production of an alcohol- and CHG-based preparation were produced and implemented by WHO in 5 African hospitals *(29)*. A cost-effectiveness study *(30)* found that although CHG is more expensive, its effectiveness to reduce SSI makes it up to 36% more cost-effective than PVP-I.

Research gaps

GDG members highlighted that the use of alcohol-based solutions in surgical site skin preparation per se is no longer a research topic. There is a need for well-designed RCTs comparing specific preparations containing CHG, PVP-I and other antiseptics in alcohol-based and other solutions, taking into consideration their effectiveness, toxicity and costs. The GDG remarked that studies should focus on SSI as the critical endpoint and defined according to the CDC criteria. Furthermore, there is a need to compare commercial products with locally-produced solutions in health facilities in LMICs in effectiveness and cost-effectiveness studies. As there are no studies investigating the use of these solutions in paediatric patients, studies in this population would be particularly welcome. Currently, a few alcohol-based or aqueous solutions with antiseptic compounds contain colouring agents. Adding these agents to preparations can be helpful to indicate where surgical site preparation products have been applied on the patient's skin, but further studies would be needed if new colouring agents are proposed in order to ascertain effectiveness and tolerability.

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4.8 Antimicrobial skin sealants

Recommendation

The panel suggests that antimicrobial sealants should not be used after surgical site skin preparation for the purpose of reducing SSI.
(Conditional recommendation, very low quality of evidence)

Rationale for the recommendation

- Overall very low quality evidence from eight RCTs and one quasi-randomized trial shows that the preoperative application of antimicrobial skin sealants, in addition to standard surgical site skin preparation, produces neither benefit nor harm in reducing the SSI rate. The GDG unanimously agreed that there is no advantage in using antimicrobial sealants and suggested not using them. Given the quality of the evidence, the GDG decided that the strength of this recommendation should be conditional.

Remarks

- The body of retrieved evidence mainly focused on adult patients, but one study also included children. This recommendation is valid for both patient populations.
- The GDG observed that most studies investigating cyanoacrylate-based antimicrobial sealants were funded by manufacturers of commercial sealants.
- All included studies investigated the use of antimicrobial sealants on the skin of the surgical site before incision.
- Although the type and concentration of the antiseptics used for skin preparation varied among the included studies, the GDG underlined that the intervention and control groups in each of the studies received the same skin preparation technique, while antimicrobial sealants were added in the intervention group.
- The GDG identified skin irritation and allergic reactions as possible harms associated with the use of antimicrobial sealants.

Background

The endogenous bacteria on a patient's skin is believed to be the main source of pathogens that contribute to SSI *(1)*. Surgical site skin preparation commonly includes scrubbing or applying alcohol-based preparations containing antiseptic agents prior to incision, such as CHG or iodine solutions. Additional technologies are being researched and developed to reduce the rate of contamination at the surgical site and subsequent SSI.

Antimicrobial skin sealants are sterile, film-forming cyanoacrylate-based sealants commonly applied as an additional antiseptic measure after standard skin preparation of the surgical site and prior to skin incision. The sealant is intended to remain in place and block the migration of flora from the surrounding skin into the surgical site by dissolving over several days postoperatively. As an antimicrobial substance, sealants have been shown to reduce bacterial counts on the skin of the operative site *(2)*. However, most studies reported only changes in bacterial colonization and did not investigate SSI rates. Therefore, the use of antimicrobial sealants for the purpose of preventing SSIs is still under debate.

Currently available SSI prevention guidelines do not address the use of antimicrobial skin sealants and their effect to prevent SSI. The GDG decided to conduct a systematic review to assess the effectiveness of their use.

Summary of the evidence

The purpose of the evidence review (web Appendix 9) was to evaluate whether the use of antimicrobial skin sealants in addition to standard surgical site skin preparation is more effective in reducing the risk of SSI than standard surgical site skin preparation only. The target population were patients of all ages undergoing a surgical procedure. The primary outcome

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was the occurrence of SSI and SSI-attributable mortality.

A total of nine studies including a total of 1974 patients and comprising 8 RCTs *(3-10)* and one prospective quasi-randomized trial *(11)* were identified. The studies compared the effect of the addition of antimicrobial skin sealants to standard skin preparation in the intervention group vs. standard skin preparation only in the control group.

Very low quality evidence shows no benefit or harm for the reduction of SSI rates when using the addition of antimicrobial sealants compared to standard surgical site skin preparation only (OR: 0.69; 95% CI: 0.38–1.25).

The body of retrieved evidence mainly focused on adult patients, but one study also included children. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was retrieved on patient values and preferences with regards to this intervention. However, the GDG observed that some studies *(8, 12)* reported that patients may suffer skin irritation due to the antimicrobial sealants as they remain on the skin for some time. Therefore, patients may prefer not to experience skin irritation, particularly when there is no evidence of benefit in using antimicrobial sealants to prevent SSI.

Resource use

The GDG pointed out that the availability of antimicrobial sealants may be limited in LMICs and their cost was a potential major resource concern. Lipp and colleagues observed that no studies included in a meta-analysis reported the cost of cyanoacrylate sealants as a preoperative preparation of the surgical site and no benefit was shown in preventing SSI *(13)*.

In addition to economic concerns, the availability of these commercial products may be an added barrier in LMICs. Furthermore, training in the proper technique and resources for their use would need to be available for surgical staff.

Research gaps

GDG members highlighted that many of the available RCTs have a high risk of bias and potential conflicts of interest. Several studies were excluded because they reported only bacterial colonization and not SSI as the primary outcome. Further studies are needed to identify evidence associated with important outcomes, including SSI rates (rather than microbial data), length of stay, cost-effectiveness and adverse effects on skin.

Most of the included studies investigated the use of cyanoacrylate-based sealants in contaminated procedures and the use of these agents may be more or less effective in other procedures. Importantly, the protocol for standard surgical site skin preparation with antiseptics varied across studies, thus making it difficult to discern the actual effect of the sealant alone. The GDG considers that more well-designed RCTs with adequate power are needed. These should focus on SSI as the primary outcome, rather than a reduction in the microbial load. Conducting trials with a more diverse surgical patient population will also further support evidence-based guidance on the use of antimicrobial sealants. For example, more evidence is needed in paediatric surgical patients.

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4.9 Surgical hand preparation

Recommendation

The panel recommends that surgical hand preparation be performed either by scrubbing with a suitable antimicrobial soap and water or using a suitable ABHR before donning sterile gloves.
(Strong recommendation, moderate quality of evidence)

Rationale for the recommendation

- The GDG noted that surgical hand preparation is vitally important to maintain the lowest possible contamination of the surgical field, especially in the event of sterile glove puncture during the procedure. Appropriate surgical hand preparation is recommended in the WHO *guidelines on hand hygiene in health care (1)* issued in 2009 and in all other existing national and international guidelines on the prevention of SSI.
- Moderate quality evidence shows the equivalence of handrubbing with an ABHR and handscrubbing with antimicrobial soap and water for surgical hand preparation for the prevention of SSI.

Remarks

- The available evidence on SSI as an outcome is limited to three RCTs. The trials compared handrubbing (with alcohol-based preparations) vs. handscrubbing (with PVP-I, CHG or plain soap) for surgical hand preparation and showed no significant difference between the two methods.
- Evidence from additional studies using the bacterial load on participants' hands as the outcome demonstrated that some ABHR formulations are more effective to reduce colony-forming units than scrubbing with water and antimicrobial or plain soap. The relevance of this outcome to the risk of SSI remains uncertain and the GDG considered this as indirect evidence and concluded that the recommendation could not be developed based on this surrogate outcome. Only evidence from RCTs with an SSI outcome was taken into account for the recommendation development.
- The WHO hand hygiene guidelines recommend preferably using "a product ensuring sustained activity". It was assumed that the sustained activity ensured by certain products (for example, CHG) was desirable, but there was no evidence that these products were more effective in directly reducing the risk of SSI. In the absence of such evidence, the GDG decided not to make any recommendations on specific products with or without a sustained effect and it emphasized the need to define what is considered a "suitable" product.
- The hands of the surgical team should be clean upon entering the OR by washing with a non-medicated soap. Once in the operating area, repeating handrubbing or scrubbing without an additional prior handwash is recommended before switching to the next procedure.
- It should be kept in mind that the activity of ABHRs may be impaired if hands are not completely dried before applying the product or by the handwashing itself. Hence, surgical handscrub and surgical handrub with alcohol-based products should not be combined sequentially *(1)*.
- When choosing ABHR, health care facilities should regularly procure products with proven efficacy (that is, complying with European norms or those of the American Society for Testing and Materials or equivalent international standards) to implement this recommendation and position no-touch or elbow-operated dispensers in surgical scrub rooms. Alternatively, antimicrobial soap, clean running water and disposable or clean towels for each health care worker should be available in the scrub room.
- In LMICs where ABHR availability is limited, WHO strongly encourages facilities to undertake the local production of an alcohol-based formulation according to WHO guidance, which has been demonstrated to be a feasible and low-cost solution *(1, 2)*.
- Skin irritation, dryness, dermatitis and some rare allergic reactions are adverse events that can occur following frequent scrubbing for surgical hand preparation. Although these are less frequent with

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ABHRs and more frequent with iodophors, even well-tolerated ABHRs containing emollients may cause a transient stinging sensation at any site of broken skin (cuts, abrasions). Allergic contact dermatitis or contact urticaria syndrome caused by hypersensitivity to alcohol or to various additives present in some ABHRs are rare occurrences. ABHR preparations with strong fragrances may be poorly tolerated by a few health care workers with respiratory allergies. Studies of surgeon preferences indicate a primary preference for ABHRs with a higher tolerability and acceptability, due mostly to the shorter application time required and fewer skin reactions.

- Care must be taken to avoid contact with the eyes when using preparations with CHG 1% or greater as it may cause conjunctivitis or serious corneal damage. Ototoxicity precludes its use in surgery involving the inner or middle ear. Direct contact with brain tissue and the meninges should be avoided. The frequency of skin irritation is concentration-dependent, with products containing 4% most likely to cause dermatitis when used frequently for antiseptic handwashing. True allergic reactions to CHG are very uncommon *(1)*.
- Alcohols are flammable and health care workers handling alcohol-based preparations should respect safety standards.

Background

The purpose of routine hand hygiene in patient care is to remove dirt, organic material and reduce microbial contamination from transient flora. In contrast to hygienic hand hygiene through handwash or handrub, surgical hand preparation must eliminate the transient flora and reduce the resident flora. In addition, it should inhibit the growth of bacteria under the gloved hand *(1)*. Despite the limited scientific evidence on the effect of surgical hand preparation (usually called "handscrubbing") in reducing SSIs, the aim of this preventive measure is to reduce the release of skin bacteria from the hands of the surgical team to the open wound for the duration of the procedure, particularly in the case of an unnoticed puncture of the surgical glove. A rapid multiplication of skin bacteria occurs under surgical gloves if hands are washed with a non-antimicrobial soap, whereas it occurs more slowly following preoperative scrubbing with a medicated soap. The skin flora, mainly coagulase-negative staphylococci, *Propionibacterium* spp. and *Corynebacteria* spp., are rarely responsible for SSI, but in the presence of a foreign body or necrotic tissue, even inocula as low as 100 colony-forming units can trigger such infections *(3)*.

The spectrum of antimicrobial activity for surgical hand preparation should be as broad as possible against bacteria and fungi. Viruses are rarely involved in SSI and are not part of test procedures for licensing in any country. Similarly, activity against spore-producing bacteria is not part of international testing procedures. According to the European Committee for Standardization *(4, 5)* and the American Society for Testing and Materials *(6)*, antiseptic preparations intended for use as surgical hand preparations are evaluated for their ability to reduce the number of bacteria released from hands for immediate and persistent activity, thus targeting both transient and resident flora. Therefore, to be considered efficacious, antiseptic preparations should comply with either the European norm 12791 *(7)* or the American Society for Testing and Materials E-1115 standards *(8)*.

The WHO *guidelines on hand hygiene in health care (1)* (Table 4.9.1) recommend to keeping nails short and to remove all jewellery, artificial nails or nail polish before surgical hand preparation. If hands are visibly soiled, the guidelines recommend to wash hands and remove debris from underneath fingernails using a nail cleaner (not brushes), preferably under running water (sinks should be designed to reduce the risk of splashes). Surgical hand antisepsis should be performed using either (but not combined) a suitable antimicrobial soap or ABHR, preferably with a product ensuring sustained activity, before donning sterile gloves. Hands and forearms should be scrubbed with antimicrobial soap for the length of time recommended by the manufacturer, usually 2–5 minutes. The guidelines stipulate that if the quality of water is not assured in the OR, surgical hand antisepsis using ABHR is recommended. A sufficient amount of ABHR should be applied to *dry* hands and forearms for the length of time recommended by the manufacturer, typically 1.5 minutes, and hands and forearms allowed to dry before donning sterile gloves. Several organizations have issued recommendations regarding surgical hand preparation and these are summarized in Table 4.9.1.

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Table 4.9.1. **Summary of recommendations on surgical hand preparation according to available guidelines**

Guidelines (date issued)	Recommendations on surgical hand preparation
WHO *Guidelines on hand hygiene in health care* (2009) *(1)*	• Surgical hand antisepsis should be performed using either a suitable antimicrobial soap or suitable ABHR, preferably with a product ensuring sustained activity, before donning sterile gloves. • If the quality of water is not assured in the OR, surgical hand antisepsis using an ABHR is recommended before donning sterile gloves when performing surgical procedures. • When performing surgical hand antisepsis using an antimicrobial soap, scrub hands and forearms for the length of time recommended by the manufacturer, typically 2–5 minutes. Long scrub times (for example, 10 minutes) are not necessary. • When using an alcohol-based surgical handrub product with sustained activity, follow the manufacturer's instructions for application times. Apply the product to dry hands only. Do not combine surgical handscrub and surgical handrub with alcohol-based products sequentially. • When using an ABHR, use a sufficient amount of the product to keep hands and forearms wet with the handrub throughout the surgical hand preparation procedure. • After application of the ABHR as recommended, allow hands and forearms to dry thoroughly before donning sterile gloves.
SHEA/IDSA (2014) *(9)*	• Use an appropriate antiseptic agent to perform preoperative surgical scrub, scrubbing the hands and forearms for 2–5 minutes for most products.
NICE (2008 and 2013) *(10,11)*	• The operating team should wash their hands prior to the first operation on the list using an aqueous antiseptic surgical solution and ensure that hands and nails are visibly clean, with a single-use brush or pick for the nails. • Before subsequent operations, hands should be washed using either using an ABHR or an antiseptic surgical solution. • If hands are soiled, they should be washed again with an antiseptic surgical solution. • The revised version of this guideline published in 2013 repeats the same surgical hand preparation recommendation with the addition of ensuring the removal of any hand jewellery, artificial nails and nail polish before starting surgical hand decontamination.

OR: operating room; ABHR: alcohol-based handrub; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence.

A Cochrane systematic review was published in 2008 *(12)* and very recently updated in 2016 *(13)*. The update included 14 RCTs; four trials reported rates of SSIs as the primary outcome, while the other studies measured the numbers of colony-forming units on participants' hands. The main finding was that that there is no firm evidence that one type of hand antisepsis (either ABHRs or aqueous scrubs) is better than another in reducing SSIs, but the quality of the evidence was considered low to very low. However, moderate or very low quality evidence showed that ABHRs with additional antiseptic ingredients may be more effective to reduce colony-forming units compared with aqueous scrubs *(12, 13)*.

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Following an in-depth analysis of the sources and strength of the evidence in current guidelines, which are not based on systematic reviews and GRADE methodology, the GDG decided to address the issue of what type of products and scrubbing technique should be used for surgical hand preparation.

Summary of the evidence

The purpose of the evidence review (web Appendix 10) was to compare the effect of different techniques (that is, handrubbing vs. handscrubbing), products (that is, different ABHR formulations and plain or medicated soap) and application times for the same product. The primary outcome was the occurrence of SSI and SSI-attributable mortality. The target population included patients of all ages undergoing a surgical procedure.

Only six studies comprising 3 RCTs *(14-16)* and three observational studies *(17-19)* were identified with SSI as the primary outcome. All studies compared handrubbing to handscrubbing for surgical hand preparation. Handrubbing was performed by using either Sterilium® (Bode Chemie GmbH, Hamburg-Stellingen, Germany; 75% aqueous alcohol solution containing propanol-1, propanol-2 and mecetronium), the WHO-recommended formulation II (75% (volume/volume [v/v]) isopropyl alcohol, 1.45% (v/v) glycerol, 0.125% (v/v) hydrogen peroxide), Avagard® (3M, Maplewood, MN, USA; 61% ethanol plus CHG 1% solution) or Purell® (Gojo Industries Inc., Akron, OH, USA; 62% ethyl alcohol as an active ingredient; water, aminomethyl propanol, isopropyl myristate, propylene glycol, glycerine, tocopheryl acetate, carbomer and fragrance as an inactive ingredient). Handscrubbing products contained either CHG or PVP-I and/or plain soap. Five studies compared ABHR to handscrubbing with an antimicrobial soap containing either PVP-I 4% or CHG 4% and showed no significant difference in SSI. The same result was found in a cluster randomized cross-over trial comparing ABHR to handscrubbing with plain soap *(15)*. It was not possible to perform any meta-analysis of these data as the products used for handrubbing and/or handscrubbing were different.

The systematic review also identified 58 studies conducted either in laboratory or hospital settings, which evaluated participants' hand microbial colonization following surgical hand preparation with different products and techniques. There was a high variability in the study setting, microbiological methods used, type of product and time of sampling. The GDG decided not to take this indirect evidence into consideration to formulate the recommendation. Evidence from RCTs with only a SSI outcome was taken into account for the development of the recommendation, which is rated as moderate due to inconsistency. The overall evidence shows no difference between handrubbing and handscrubbing in reducing SSI.

The systematic review did not identify any studies comparing different durations of the technique for the same product with an SSI outcome. Only studies assessing the bacterial load on hands were found. After evaluation of this indirect evidence, the GDG decided not to develop any recommendation on the duration of surgical hand preparation and to continue to recommend following the manufacturer's instructions for each product.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. Given that surgical hand preparation has been considered to be best clinical practice since almost 200 years and is recommended in all surgical guidelines, the GDG is confident that the typical values and preferences of the target population regarding the outcome would favour the intervention.

Studies of surgeon preferences indicate a primary preference for ABHR. In general, studies show that ABHRs are more acceptable by surgeons compared to handscrubbing, due mainly to the reduced time required for surgical hand preparation and fewer skin reactions. The included studies provided some data on acceptability and tolerability of the products. According to a user survey in a study conducted in Kenya *(15)*, OR staff showed a preference for ABHR as it was faster to use, independent of the water supply and quality and did not require drying hands with towels. No skin reactions were reported with either ABHR or plain soap and water. Parienti and colleagues *(14)* assessed 77 staff for skin tolerance and found that skin dryness and irritation was significantly better in the handrubbing periods of the study. Although Al-Naami and colleagues *(16)* failed to show a significant difference, a survey of OR staff in a Canadian surgical hand preparation intervention

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study *(18)* showed that 97% of responders approved of the switch to handrubbing and four persons even noted an improvement in their skin condition. All studies reported fewer (one or none) episodes of substantial dermatitis with ABHR compared to handscrubbing. In one study, some surgeons noted the occasional reversible bleaching of the forearm hair after the repeated use of handrub *(15)*.

Resource use

Observational studies with SSI outcome show a significant cost benefit of handrubbing. A Canadian study *(18)* showed that the standard handscrub-related costs of direct supplies were evaluated to be around Can$ 6000 per year for 2000 surgical procedures, not including the cost of cleaning and sterilizing surgical towels. The actual expenses incurred after a full year of handrub use were Can$ 2531 for an annual saving of approximately Can$ 3500. A dramatic decrease in surgical towel use (an average of 300 fewer towels per week) added to the savings. Two other studies *(17, 19)* from the USA and Cote d'Ivoire showed lower costs with Avagard® and Sterilium® when compared to the use of antiseptic-impregnated hand brushes and a PVP-I product, respectively. One RCT *(15)* also supported these findings and showed that the approximate total weekly cost of locally-produced ABHR according to the modified WHO formula was just slightly higher than plain soap and water (€ 4.60 compared with € 3.30; cost ratio: 1:1.4).

Despite this evidence on the cost-effectiveness of ABHRs, they may still have a high cost and limited availability in LMICs, even if local production is promoted. The barriers to local production may include the difficulty to identify staff with adequate skills, the need for staff training, constraints related to ingredient and dispenser procurement and the lack of adequate quality control. However, the GDG strongly emphasized that local production still remains a promising option in these circumstances. A WHO survey *(20)* of 39 facilities from 29 countries demonstrated that the WHO ABHR formulations can be easily produced locally at low cost and are very well tolerated and accepted by health care workers. Although the contamination of alcohol-based solutions has seldom been reported, the GDG emphasized the concern that top-up dispensers, which are more readily available, impose a risk for microbial contamination, especially in LMICs. According to the survey, the reuse of dispensers at several sites helped to overcome difficulties caused by local shortages and the relatively high costs of new dispensers. However, such reuse may lead to handrub contamination, particularly when empty dispensers are reprocessed by simple washing before being refilled, and the "empty, clean, dry, then refill" strategy to avoid this risk may require extra resources.

The feasibility and costs related to the standard quality control of locally-produced products is another consideration. In the WHO survey *(20)*, 11/24 assessed sites could not perform quality controls locally due to lack of equipment and costs. However, most sites were able to perform basic quality control with locally-purchased alcoholmeters. The use of soap and water will require disposable towels, which adds to the cost. Towel reuse is not recommended in the health care setting and towels should be changed between health care workers, thus resulting in resource implications.

Research gaps

The GDG noted that there are major research gaps and heterogeneity in the literature regarding comparisons of product efficacy, technique and duration of the scrubbing methods with SSI as the primary outcome. In particular, it would be useful to conduct RCTs in clinical settings to compare the effectiveness of various antiseptic products with sustained activity to reduce SSI vs. ABHR or antimicrobial soap with no sustained effect. Well-designed studies on the cost-effectiveness and tolerability/acceptability of locally-produced formulations in LMICs would be also helpful. Furthermore, research is needed to assess the interaction between products used for surgical hand preparation and the different types of surgical gloves, in relation to SSI outcome.

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Surgical Handrubbing Technique

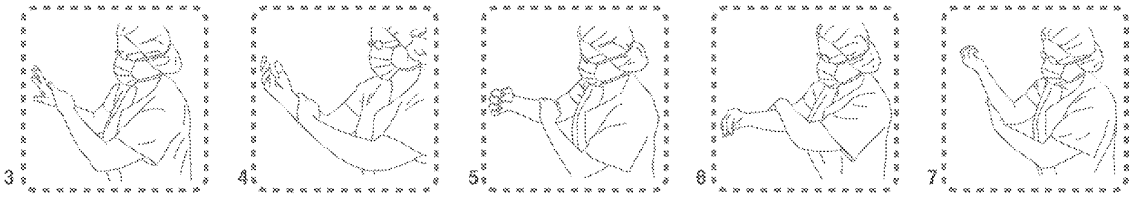
- Handwash with soap and water on arrival to OR, after having donned theatre clothing (cap/hat/bonnet and mask).
- Use an alcohol-based handrub (ABHR) product for surgical hand preparation, by carefully following the technique illustrated in Images 1 to 17, before every surgical procedure.
- If any residual talc or biological fluids are present when gloves are removed following the operation, handwash with soap and water.



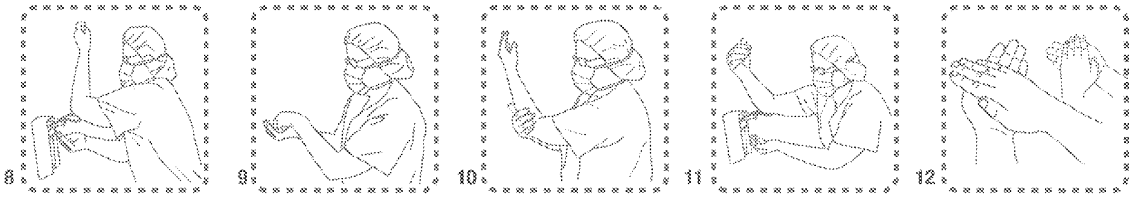
Put approximately 5ml (3 doses) of ABHR in the palm of your left hand, using the elbow of your other arm to operate the dispenser.



Dip the fingertips of your right hand in the handrub to decontaminate under the nails (5 seconds).



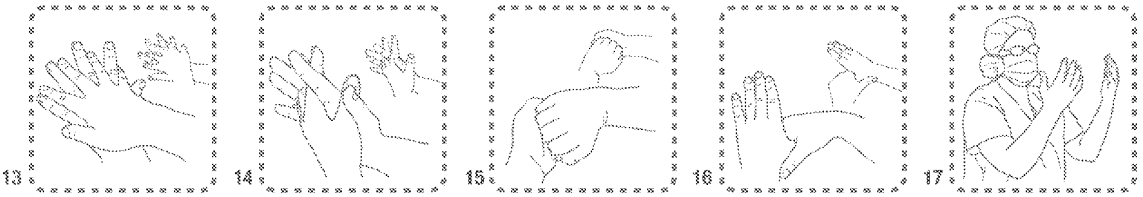
Images 3-7: Smear the handrub on the right forearm up to the elbow. Ensure that the whole skin area is covered by using circular movements around the forearm until the handrub has fully evaporated (10-15 seconds).



Images 8-10: Now repeat steps 1-7 for the left hand and forearm.

Put approximately 5ml (3 doses) of ABHR in the palm of your left hand as illustrated, to rub both hands at the same time up to the wrists, following all steps in images 12-17 (20-30 seconds).

Cover the whole surface of the hands up to the wrist with ABHR, rubbing palm against palm with a rotating movement.



Rub the back of the left hand, including the wrist, moving the right palm back and forth, and vice-versa.

Rub palm against palm back and forth with fingers interlinked.

Rub the back of the fingers by holding them in the palm of the other hand with a sideways back and forth movement.

Rub the thumb of the left hand by rotating it in the clasped palm of the right hand and vice versa.

When the hands are dry, sterile surgical clothing and gloves can be donned.

Repeat this sequence (average 60 sec) the number of times that adds up to the total duration recommended by the ABHR manufacturer's instructions. This could be two or even three times.

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PREOPERATIVE AND/OR INTRAOPERATIVE MEASURES

4.10 Enhanced nutritional support

Recommendation

The panel suggests considering the administration of oral or enteral multiple nutrient-enhanced nutritional formulas for the purpose of preventing SSI in underweight patients who undergo major surgical operations.

(Conditional recommendation, very low quality of evidence)

Rationale for the recommendation

- Multiple nutrient-enhanced nutritional formulas contain any combination of arginine, glutamine, omega-3 fatty acids and nucleotides.
- After careful appraisal of the included studies, the research team and the GDG decided to perform meta-analysis comparisons including only studies in which the oral and enteral routes were used and excluding those where the parenteral route was used. The main reason was that the parenteral route is very different and the experts considered it inappropriate to administer enhanced nutritional formulas only for the purpose of preventing SSI when considering the infectious risk related to intravenous access.
- Overall very low quality evidence from eight RCTs and two observational studies shows that multiple nutrient-enhanced formulas demonstrate a benefit in reducing the risk of SSI compared to standard nutritional support. The population studied were adult patients undergoing major surgical procedures (mainly cancer and cardiac patients).
- Overall low quality evidence from five RCTs and one observational study (very low quality) shows that a single nutrient-enhanced formula (containing either arginine or glycine or omega-3 fatty acids) produces neither benefit nor harm when compared to standard nutritional support in reducing the risk of SSI.
- As a result of these evaluations and comparisons, the GDG agreed to suggest that underweight patients who are undergoing major surgical operations (particularly oncology and cardiovascular procedures) may benefit from the administration of oral or enteral multiple nutrient-enhanced nutritional formulas for the purpose of preventing SSI. Given the very low quality of the evidence, the strength of this recommendation was considered to be conditional and the GDG proposed to use the terminology "The panel suggests considering..." to highlight the need for careful local and patient-by-patient evaluation about whether and how to apply this recommendation, in particular depending on the availability of nutritional formulas and costs.
  Note: "underweight" is a term describing a person whose body weight is considered too low to be healthy. The definition usually refers to people with a body mass index of under 18.5 or a weight 15-20% below the norm for their age and height group.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. Therefore, the effectiveness of the intervention is not proven for paediatric patients and is valid for adult patients only.
- There is little evidence as to whether the timing of administration of multiple nutrient-enhanced nutritional formulas modifies the effect on the prevention of SSI. Therefore, the GDG was unable to identify an optimal timing and duration of the administration of these formulas.
- The GDG emphasized that most patients included in the studies were receiving enteral feeding through a tube for other reasons than the prevention of SSI. When inserting a feeding tube solely to administer multiple nutrient-enhanced nutritional formulas for the purpose of SSI prevention, it is important to be aware of the possible discomfort and harm ranging from mucosal irritation and the development of sinusitis to perforation. The GDG does not encourage the insertion of a feeding tube for the sole purpose of preventing SSI. In particular, it considers that improving nutritional status should not in any way lead to a delay in surgery.

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- The GDG identified contaminated preparations as a potential harm, especially due to contaminated water and/or a break in the aseptic technique during preparation. This risk is increased when the feeding takes place at the patient's home. It is good practice to follow clinical and IPC guidelines and aseptic precautions when preparing nutritional formulas.

Background

Malnutrition, including protein-energy and micronutrient deficiencies, continues to be a major public health problem, particularly in developing countries. It affects also the rapidly growing elderly population in high-income countries *(1, 2)*. Nutritional status can have a profound impact on the immune system *(3)* as documented by some studies *(2-4)*. These alterations in host immunity may make patients more susceptible to postoperative infections and malnutrition was reported as a threat to surgical outcome, such as delayed recovery, higher rates of morbidity and mortality, prolonged hospital stay, increased health care costs and a higher early readmission rate *(2-7)*.

Some studies showed that early nutritional support can improve the outcome following major surgery and decrease the incidence of infectious complications in selected malnourished or severely injured patients. The hypothesis is that the immune system may be modulated by the use of specific types of nutritional support *(2, 3, 6, 8)*.

Surgery also induces an altered metabolism of protein, marked by a negative nitrogen balance and changes in amino acid patterns in blood. In addition, inflammation is integral to the recovery after stress, such as a surgical procedure. Therefore, nutritional support is being used more and more as a means to increase protein and caloric intake during the perioperative period, particularly by using formulas high in specific amino acids, antioxidants and anti-inflammatory nutrients *(9, 10)*.

Given the role of nutrition in the host response to surgery, many researchers believe that nutritional interventions would reduce SSI and the related morbidity. However, an epidemiological association between incisional SSI and malnutrition has been difficult to demonstrate consistently for all surgical subspecialties. There is very little consensus on the optimal timing and dosage of multiple nutrient-enhanced nutrition, especially for the prevention of SSI.

At present, there are no formal recommendations for nutrition supplementation for SSI prevention. Recent recommendations from SHEA/IDSA state that the preoperative administration of parenteral nutrition should not delay surgery *(11)*. Following an in-depth analysis of the resources and limited recommendations from other guidelines, the GDG members decided to conduct a systematic review on the effectiveness of nutrition supplementation for SSI prevention.

Summary of the evidence

The purpose of the evidence review (web Appendix 11) was to evaluate the effect of enhanced nutritional support compared to standard nutrition for the prevention of SSI. The population targeted were patients of all ages undergoing surgical procedures. The primary outcomes were the occurrence of SSI and SSI-attributable mortality.

A total of 23 studies comprising 19 RCTs *(12-30)* and four observational studies *(31-34)* were identified with SSI as a reported outcome. Studies included adult patients undergoing cardiac surgical procedures (one study) or undergoing elective surgical procedures for head and neck, gastrointestinal, colorectal or gynaecological cancer. No study was available in the paediatric population. There was a substantial variation in the route of administration, nutritional formulas used and the definition of SSI. After careful appraisal of the included studies, the research team and the GDG decided to perform meta-analysis comparisons including only studies in which the oral and enteral routes were used and excluded those using the parenteral route.

Despite the above-mentioned heterogeneity, two meta-analyses were performed to evaluate the following comparisons: a multiple nutrient-enhanced nutritional formula vs. standard nutrition and a single nutrient-enhanced nutritional formula vs. standard nutrition, administered through either oral or enteral routes.

A total of 10 studies were identified. They comprised

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eight RCTs *(15, 19-21, 23, 26, 28, 29)* and two observational studies *(31, 33)* including a total of 1434 patients and comparing the use of multiple nutrient-enhanced nutritional formulas (containing any combination of arginine, glutamine, omega-3 fatty acids and nucleotides) to standard nutrition. One study *(19)* involved data from multiple centres. Very low quality evidence shows that a multiple nutrient-enhanced nutritional formula has a significant benefit when compared to a standard nutritional formula in reducing the risk of SSI. The combined OR was 0.53 (95% CI: 0.30–0.91) for the RCTs and 0.07 (95% CI; 0.01–0.53) for the observational studies.

Furthermore, six studies including 397 patients and comprising of five RCTs *(14, 16-18, 29)* and one observational study *(32)* compared the use of nutritional supplements enhanced with a single nutrient (either arginine, glycine or branched chain amino acids) to standard nutrition. These studies included adult patients undergoing elective surgical procedures with head and neck cancer, hepatocellular carcinoma and cardiac disease. Low quality evidence shows that a single nutrient-enhanced formula has neither benefit nor harm for the reduction of SSI when compared to standard nutrition (RCTs: OR: 0.61; 95% CI: 0.13–2.79; observational study: OR: 0.29; 95% CI: 0.06–1.39).

The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. It was acknowledged that although patients may value measures to prevent SSI, they do not wish to be exposed to discomfort or possible harm due to a feeding tube inserted solely for that purpose. The GDG is confident that patients would very likely accept the administration of multiple nutrient-enhanced nutritional formulas if they are already receiving enteral feeding. Moreover, if oral feeding is possible, this would be an alternative likely welcomed by most patients. Some of the formulas were dairy-based, which may represent a problem for individuals who avoid dairy products for dietary, ethical or cultural reasons.

Resource use

No cost-effectiveness studies were identified. However, the use of enhanced nutrition support is expensive and requires additional work for clinical staff. In facilities where these formulas are used, there is a special need for dieticians and pharmacists, including the training of staff on their appropriate use and preparation. It is essential that all oral feeds be prepared in a clean dedicated area using an aseptic technique. Furthermore, the availability of enhanced nutrition formulas may be limited, particularly in LMICs, including the availability of ingredients for the preparation of the formulas (for example, clean drinking water). IPC measures for the preparation of the formulas need to be implemented. Given the very low quality of evidence for a benefit, the GDG was uncertain whether the benefits outweigh the costs of multiple nutrient-enhanced nutritional formulas.

Research gaps

The GDG highlighted that the few trials studying the efficacy of enhanced nutritional support for the prevention of SSI are small and generally of low quality. In addition, they are often conducted in populations that are at a high risk of malnutrition (for example, gastrointestinal cancer), which limits their generalizability. Many studies were funded by manufacturers of proprietary formulas and this could increase the potential for bias.
Future well-designed RCTs should be independent of manufacturers and performed in larger populations of individuals undergoing a variety of general surgical procedures. The impact of nutritional support should be investigated further in LMICs. Studies should investigate the benefit of other nutritional elements (for example, iron, zinc) and vitamins. Finally, the optimal timing and duration of the administration of nutritional support in relation to the time of surgery should be further assessed by well-designed RCTs.

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4.11 Perioperative discontinuation of immunosuppressive agents

Recommendation

The panel suggests not discontinuing immunosuppressive medication prior to surgery for the purpose of preventing SSI.
(Conditional recommendation, very low quality of evidence)

Rationale for the recommendation

- Very low quality evidence shows that the perioperative discontinuation of methotrexate (MTX) might be harmful or have no effect on the risk of SSI compared to its continuation. Furthermore, very low quality evidence from two observational studies showed that the perioperative discontinuation of tumour necrosis factor (TNF) inhibitors (anti-TNF) might have a benefit for the reduction of the SSI rate when compared to the continuation of anti-TNF. Taking into consideration (1) the very limited evidence (for anti-TNF) or lack of evidence and even potential harm (for MTX) to support a discontinuation of treatment, and (2) the risk associated with the discontinuation of treatment on the patient's underlying disease/s, the GDG unanimously agreed to suggest that immunosuppressive medication should not be discontinued for the purpose of preventing SSI.

Remarks

- The GDG emphasized that the decision to discontinue immunosuppressive medication may be made on an individual basis, involving the prescribing physician, the patient and the surgeon.
- No relevant evidence was found on the perioperative discontinuation of long-term corticosteroid therapy.
- The population investigated in the studies on MTX included patients with rheumatoid arthritis *(1-5)* and Crohn's disease *(6)*. Studies on anti-TNF investigated a population with rheumatoid arthritis *(7)* and other inflammatory rheumatic diseases *(8)*.
- The time point and time interval of discontinuation of the immunosuppressive agent were very heterogeneous across studies or not specified.
- The GDG identified the occurrence of a flare-up of the underlying disease as a potential harm associated with discontinuation of immunosuppressive therapy. The risk of major adverse events associated with discontinuation is high in patients taking immunosuppressive therapy after organ transplantation or for rheumatoid arthritis, whereas it might be lower in those taking immunosuppressive agents for inflammatory bowel disease *(4, 5, 9-14)*.

Background

Immunosuppressive agents are drugs that inhibit or prevent activation of the immune system. They are commonly prescribed to prevent rejection of transplanted organs or for the treatment of inflammatory diseases, such as rheumatoid arthritis or inflammatory bowel disease. Some observational studies indicate that the immunosuppressive effect of the drugs could lead to impaired wound healing and increased risk of infection in patients treated with these agents *(8)*. Conversely, the discontinuation of immunosuppressive treatment could induce flares of disease activity and long-term interruptions of therapy might induce the formation of anti-drug antibodies and subsequently decrease the effect of the immunosuppressives *(15)*.

To date, only one SSI prevention guideline has issued a recommendation regarding the administration of immunosuppressive agents in the perioperative period. This guideline was published by SHEA/IDSA and recommends avoiding the use of immunosuppressive agents in the perioperative period if possible *(16)*. However, this recommendation is not based on systematic reviews of the literature and meta-analyses or a rigorous evaluation of the quality of the available evidence. Of note, several other SSI prevention guidelines do not address this topic.

Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG decided to conduct a systematic review to assess the influence of immunosuppressive agents on the

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incidence of SSI and whether a discontinuation of immunosuppressive medication in the perioperative period is effective to prevent SSI in surgical patients.

Summary of the evidence

The purpose of the evidence review (web Appendix 12) was to evaluate whether a discontinuation of immunosuppressive medication in the perioperative period is more effective in reducing the risk of SSI than continuation of the medication. The target population was patients of all ages taking immunosuppressive agents and undergoing a surgical procedure. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

A total of eight studies comparing the perioperative discontinuation of immunosuppressive medication vs. continuation were identified and included a total of 2461 patients. They comprised one RCT *(5)*, one quasi-RCT *(3)* and six observational studies *(1, 2, 4, 6-8)*. Six studies comprising one RCT *(5)*, one quasi-RCT *(3)* and four observational *(1, 2, 4, 6)* investigated MTX and two observational studies *(7, 8)* investigated anti-TNF. The time point and time interval of discontinuation of the immunosuppressive agent were as follows: seven days before surgery *(5)*; one week prior to surgery and the week of surgery *(2)*; two weeks before surgery until two weeks after surgery *(3)*; within four weeks prior to surgery *(6)*; four weeks before surgery *(1)*; and one, four or eight weeks before and reintroduced one week after surgery *(8)*. The remaining two studies gave a rather unspecific description of the time point and time interval of discontinuation, that is, more than four times the half-life of the agent *(7)* or more than one week during the perioperative period *(4)*.

According to the selected studies the following comparisons were evaluated:

Discontinuation vs. continuation of:

a. MTX
b. anti-TNF.

Very low quality evidence shows that the perioperative discontinuation of MTX might be harmful or have no effect on the risk of SSI when compared to continuation of MTX. The combined OR was 7.75 (95% CI: 1.66–36.24) for the controlled trials and 0.37 (95% CI: 0.07–1.89) for the observational studies. Furthermore, there is very low quality evidence from two observational studies *(7, 8)* that the perioperative discontinuation of anti-TNF might have a benefit in reducing the SSI rate compared to the continuation of anti-TNF (OR: 0.59; 95% CI: 0.37–0.95).

The body of retrieved evidence focused mainly on adult patients, although a few studies also included a paediatric population *(6, 8)*. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG is confident that most patients value the prevention of SSI, but they also do not want to be exposed to the risk of flare-ups or progression of their underlying disease due to the discontinuation of immunosuppressive therapy. Furthermore, most patients would like to be fully informed about the consequences of these decisions and to be involved in the decision making process.

Resource use

No cost-effectiveness data are available on the continuation or discontinuation of immunosuppressive therapy. The GDG pointed out that when making any decision on discontinuation, the physician treating the underlying disease or another senior physician will have to be involved, which may generate additional costs.

Research gaps

GDG members highlighted that well-designed RCTs are urgently needed to clarify this issue. Trials should examine also the optimal time between discontinuation of immunosuppressive agent(s) and time of surgery. In addition, the importance of the optimal dose of the various immunosuppressive therapy agents with regards to the SSI rate should be investigated. Studies should take into account new immunosuppressive agents. The GDG pointed out that surveillance and registry data are very likely to contribute also to the evidence in this field of research.

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4.12 Perioperative oxygenation

Recommendation

The panel suggests that adult patients undergoing general anaesthesia with tracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen (FiO_2) intraoperatively and, if feasible, in the immediate postoperative period for 2-6 hours to reduce the risk of SSI.
(*Conditional recommendation, moderate quality of evidence*)

Rationale for the recommendation

- A moderate quality of evidence shows that providing high FiO_2 (80%) is beneficial in adult surgical patients under general anaesthesia with tracheal intubation and results in a significant decrease of the risk of SSI compared to 30-35% FiO_2.
- There is low quality of evidence regarding no increased risk of major adverse events such as atelectasis, cardiovascular events, ICU admission, and death during the study period, associated with using high FiO_2 in adult surgical patients under general anaesthesia with tracheal intubation. As a result, the GDG suggests that patients undergoing surgical procedures under general anaesthesia with tracheal intubation should receive 80% FiO_2 intraoperatively and in the immediate postoperative period for 2-6 hours, if feasible, and that the strength of this recommendation should be conditional.
- This recommendation is based on FiO_2 administered, rather than on arterial partial pressure of oxygen (PaO_2) or arterial oxygen saturation measured by pulse oximeter, as the clinical trials that led to the recommendation development provided results based only on FiO_2 administered.

Remarks

- This recommendation has been updated in 2018 after the initial guideline publication in 2016 (see section 2 of Methods) *(1, 2)*. The systematic review on the evidence of effectiveness of the use of high FiO_2 previously used for the 2016 WHO recommendation was updated to April 2018 and an independent systematic review on adverse effects associated with the recommended intervention has been conducted *(3, 4)*.
- In the updated review, the evidence for a beneficial effect has become weaker, despite an increased number of patients. In the 2018 update, the exclusion of two studies by Schietroma M and colleagues included in the previous systematic review due to disputed credibility and the net addition of four new trials testing the effectiveness of the use of high FiO_2 did not strengthen the evidence for effect modification found in the original review or for a benefit in patients undergoing general anaesthesia with tracheal intubation that led to the strong recommendation in the WHO guidelines.
- An independent systematic review on safety shows no substantive evidence to discourage the use of high FiO_2 in this population. However, adverse events were not the primary focus of the original studies and the evidence is thus limited.
- Further high-quality RCTs are urgently needed.
- The body of retrieved evidence focused on adult patients and no study specifically performed in a paediatric population was identified. Therefore, the effectiveness of this intervention is not proven for paediatric patients.
- After careful appraisal of the included studies, the research team and the GDG decided to perform meta-analysis comparisons including only patients under general anaesthesia with tracheal intubation and mechanical ventilation. Studies using neuraxial anaesthesia with a facemask or nasal cannula were excluded. Indeed, according to a meta-regression analysis introducing general anaesthesia with tracheal intubation as a significant covariate, the type of anaesthesia proved to independently modify the effect of hyperoxygenation. In neuraxial anaesthesia with a nasal cannula or facemask, the control of ventilation (and thereby control of the actual administration of high FiO_2 to the lungs) is limited and was therefore considered as different from an intervention with mechanical ventilation.
- The benefit of hyperoxygenation tended to be greater in open colorectal surgery than in other types of surgery, but no significant association was found between the type of surgery and the effect of hyperoxygenation.

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- The GDG emphasized that reduced SSI was found only in studies of patients intubated for general anaesthesia who received 80% FiO_2 during surgery and continued to receive the higher oxygen concentration through a high flux mask in the immediate postoperative period. This should be considered as part of the intervention.
- Other potential sources of heterogeneity were discussed, including the age of the population (older patients may benefit more) and duration of surgery. It is known that colorectal surgery has a higher risk for SSI compared to other surgical procedures and hyperoxygenation may be beneficial in this group of patients due to the predominance of anaerobic flora in the colonic flora.
- There was a considerable variation in the exclusion criteria for underlying lung disease, especially chronic obstructive pulmonary disease.
- The GDG highlighted that the benefits of hyperoxygenation would likely be maximized when normothermia and normovolemia are maintained (see chapters 4.13 and 4.15 for the recommendations on normothermia and normovolemia).
- The GDG acknowledged also that the studies were performed in high-income countries only.
- In settings where medical oxygen is scarce, policy-makers may not consider this recommendation as a priority.
- The GDG pointed out that FiO_2 is not the ideal parameter to be measured; PaO_2 better reflects the amount of O_2 possibly delivered to the tissues and thus could influence the SSI risk more directly.
- Although monitoring oxygen saturation does not directly reflect the effect of this intervention, it is recommended as good practice, primarily to detect hypoxia in all patients undergoing general anesthesia during surgery and in the postoperative period, regardless of the concentration of inspired oxygen the patient receives.
- This recommendation is limited to the use of high FiO_2 in the perioperative period for the prevention of SSI and does not cover administration of high FiO_2 and its effects in other settings and populations.

Background

There is evidence that an optimized blood flow to the surgical incision reduces SSI rates through the avoidance of hypothermia and hypoxia *(12-14)*. Since 2000, several trials have been published on the use of high FiO_2 concentrations during the perioperative period and the potential association with lower rates of SSI (*see Summary of the evidence*). These studies include RCTs, meta-analyses and the long-term survival follow-up of original cohorts.

The intervention consists of providing patients with 80% FiO_2 compared to the usual administration of 30% FiO_2. Patients are routinely given 100% FiO_2 for 30 seconds to 2 minutes prior to intubation and then maintained on either "normoxia", defined as 30% or 35% FiO_2, or "hyperoxia", defined as oxygen at 80% FiO_2.

The arguments for providing oxygen levels beyond the standard 30% are largely based on two notions *(15)*. The first is that the surgical incision may not be adequately perfused and therefore might receive substantially higher oxygen if there is a higher partial pressure of oxygen in the blood *(16)*. The other notion is that the host defence systems might be further improved by higher oxygen partial pressures, particularly by enhancing neutrophil oxidative killing *(17)*.

Perioperative oxygenation has been specified in clinical practice guidelines issued by professional societies or national authorities (Table 4.12.1). SSI prevention bundles from both NHS England's High impact intervention approach and Health Protection Scotland, as well as guidelines from the Royal College of Physicians of Ireland and the UK-based NICE, recommend maintaining a haemoglobin oxygen saturation of at least 95% *(6, 8, 9, 18)*. The SSI prevention guidelines of SHEA/IDSA recommend optimizing tissue oxygenation by administering supplemental oxygen during and immediately following surgical procedures involving mechanical ventilation *(5)*. Following an in-depth analysis of the sources and strength of the evidence in current guidelines, GDG members decided to conduct a systematic review to assess the available evidence on optimal perioperative oxygenation.

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Table 4.12.1. **Recommendations on oxygenation preparation according to available guidelines on oxygenation preparation according to available guidelines**

Guidelines (date issued)	Recommendations on oxygenation preparation
SHEA/IDSA (2014) *(5)*	Optimize tissue oxygenation by administering supplemental oxygen during and immediately following surgical procedures involving mechanical ventilation.
NICE (2008) *(6)*	Sufficient oxygen to maintain a haemoglobin saturation of more than 95%.
Royal College of Physicians of Ireland (2012) *(7)*	Haemoglobin saturation is maintained above 95% (or greater if there is underlying respiratory insufficiency).
Health Protection Scotland [bundle] (2013) *(8)*	Haemoglobin saturation is maintained above 95% (or greater if there is underlying respiratory insufficiency).
NHS Engalnd [High impact intervention bundle] (2011) *(9)*	Haemoglobin saturation is maintained above 95% (or greater if there is underlying respiratory insufficiency) both during the intra- and postoperative stages (recovery room).
American College of Surgeons/ Surgical Infection Society (2016) *(10)*	The administration of supplemental oxygen (80%) is recommended in the immediate postoperative period following surgery performed under general anaesthesia.
USA CDC (2017) *(11)*	For patients with normal pulmonary function undergoing general anaesthesia with endotracheal intubation, administer increased FiO_2 during surgery and after extubation in the immediate postoperative period. To optimize tissue oxygen delivery, maintain perioperative normothermia and adequate volume replacement. (Category IA–strong recommendation; moderate-quality evidence.)

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; England; USA: United States of America; CDC: Centers for Disease Control and Prevention.

A 2015 systematic review assessed the same PICO question as these guidelines *(7)*. However, the conclusions by Wetterslev and colleagues differ substantially from those presented here. The authors did not conduct a subgroup analysis based on the type of anaesthesia (that is, general anaesthesia with tracheal intubation vs. neuraxial with facemask or nasal cannula) as was done here, following the strong suggestion of the GDG. General anaesthesia was therefore not identified as a significant covariate and, consequently, it was not taken into account in the final analysis, thus resulting in a different outcome. The GDG strongly believes that the approach chosen here is superior and that the difference in outcomes is of critical importance for the presented recommendation.

In a recent systematic review *(19)*, Chu and colleagues investigated the effects of liberal oxygen therapy on morbidity and mortality in critically ill patients. Liberal oxygen therapy was defined as any oxygen target higher than that of a more conservative control group. Interventions ranged from 30% up to 100% FiO_2, but most did not exceed 30%. Intended exposure duration ranged from one up to 166 hours, but typically exceeded 12 hours. The study population included mostly patients with critical illness, stroke, myocardial infarction or cardiac arrest. Only one trial (0.9% of patients in the meta-analysis) included surgical patients receiving 80% FiO_2 perioperatively and showed no increase in mortality *(20)*. Importantly, the intervention and population differed substantially from those targeted in the WHO recommendation. The authors found high quality evidence that liberal oxygen therapy increases mortality in critically ill patients. Although important for the care of critically

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ill patients, these findings appear to have little relevance to the perioperative use of 80% FiO_2 in patients undergoing surgery.

Summary of the evidence

The purpose of the evidence review *(3, 4)* was to compare the effect of increased (80%) FiO_2 with standard (30-35%) FiO_2 on the occurrence of SSI, SSI attributable mortality, and other adverse events. The target population included patients of all ages undergoing a surgical procedure. Two systematic reviews were conducted. One on the effectiveness of this intervention, which is an update of the original review performed for the 2016 WHO guidelines, and one on the safety of the use of high FiO_2 in surgical patients for the purpose of reducing the risk of SSI. Pre-specified safety outcomes of interest were: 1) mortality; 2) ischaemic vascular events affecting coronary and cerebral circulation; 3) respiratory adverse effects (for example, respiratory failure, acute respiratory distress syndrome, number of ventilator days, and lung complications, such as pneumonia or atelectasis, re-intubation or prolonged intubation); and 4) length of hospital stay. In addition, a hypothesis-generating/scoping approach was used to capture any new or unexpected serious adverse effects that may have been reported in this patient population. The pre-specified effectiveness outcomes were the occurrence of SSI and SSI-attributable mortality.

Both reviews included 17 moderate-good quality RCTs *(14, 21-35)*; the safety review also included two non-randomized studies *(36, 37)*. All studies administered 80% FiO_2 in the intervention group; 16 studies administered 30% FiO_2 in the control group and one study used 35% oxygen. Four RCTs used a gas mixture with nitrous oxide. The other studies used room air or nitrogen (N_2). Patients were under general anaesthesia with endotracheal intubation and mechanical ventilation in 12 studies. In the remaining five, patients were anaesthetised, but awake and breathed spontaneously with the allocated gas mixture delivered via a facemask or nasal cannula. Surgical procedures ranged from surgery of the gastrointestinal tract, including five studies on colorectal surgery, to caesarean sections and trauma surgery. In addition to the RCTs, two non-randomized studies with serious-critical risk of bias were included in the safety review.

Effectiveness

Meta-analysis of the included trials showed little evidence of a benefit of perioperative administration of high (80%) FiO_2 on the prevention of SSI compared to standard (30-35%) FiO_2: Relative risk (RR): 0.89; 95% CI: 0.73-1.07 (Table 2). There was evidence of heterogeneity (tau^2=0.055; Chi^2 test for heterogeneity: *P*=0.025; I^2 =45.4%). After careful appraisal of the included studies, the research team and the GDG noted that the method of delivery of the intervention (that is, under general anaesthesia with endotracheal intubation and mechanical ventilation vs. oxygen administration via a facemask or nasal cannula without intubation) and the type of procedure could be potential effect modifiers. Meta-regression indicated that the method of oxygen administration modified the effect of the administration of high FiO_2 on the incidence of SSI (test of interaction, *P*=0.048; proportion variance explained, 27%). In patients under general anaesthesia with endotracheal intubation and mechanical ventilation, 80% FiO_2 reduced the incidence of SSI (RR: 0.80: 95% CI 0.64-0.99; tau^2=0.051; Chi^2 test for heterogeneity, *P*=0.043; I^2=46.7%). By contrast, if patients were awake and breathing spontaneously via a facemask or nasal cannula, there was no evidence of a benefit of the intervention (RR: 1.20; 95% CI: 0.91-1.58; tau^2=0.000; Chi^2 test for heterogeneity, *P*=0.482; I^2=0.0 %). The type of procedure did not affect the effect estimate (test of interaction, *P*=0.110). Similarly, there was no evidence that the use of nitrous oxide in the gas mixture influenced the effect (test of interaction, *P*=0.945).

Safety

No evidence of harm with high FiO_2 was found for major adverse effects in the meta-analysis of randomized trials: atelectasis RR; 0.91 (95% CI: 0.59–1.42); cardiovascular events RR: 0.90 (95% CI: 0.32–2.54); intensive care admission RR: 0.93 (95% CI: 0.7 –1.12); death during the trial RR: 0.49 (95% CI: 0.17–1.37). One non-randomized study reported that high FiO_2 was associated with major respiratory adverse effects (RR: 1.99 [95% CI: 1.72-2.31]).

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG concluded that all patients, health care providers and policy-makers will likely favour the intervention. The GDG acknowledged that oxygen administration with a mask might be quite

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uncomfortable for patients in the postoperative period when they are extubated and waking up from anaesthesia. More research is needed on the use of high FiO_2, including qualitative research on patient values and preferences.

Resource use

In LMICs, oxygen availability (procurement and distribution) and the related costs are a problem and a burden on available resources. Nevertheless, the implementation of this recommendation and the need for oxygen for other critical clinical uses should drive an increased access to oxygen, including its local production in hospitals, which should be encouraged. However, it was pointed out that even when it is implemented, the equipment for both the concentration and production of oxygen (that is, oxygen generation tanks/pumps) may not be cost effective or readily available. Lack of quality control (for example, contamination of the tanks with bacteria and fungi can occur, especially during condensation), incorrectly labelled tanks, maintenance of production and infrastructure challenges (for example, electricity) are other considerations in resource-limited settings. It was noted also that a high flux mask would be needed to maintain high-flow oxygen in the postoperative period in extubated patients, which would be an additional cost. Furthermore, as it may be uncomfortable for patients to wear a mask for 2-6 hours after surgery, it could be an additional burden on staff.

Research gaps

The GDG members highlighted the limited evidence available in some areas. More research from high quality RCTs is needed on the effectiveness and safety of the perioperative use of high FiO_2, in particular to provide more details on research aspects as follows. New trials should account for the values of PaO_2 obtained when high FiO_2 is applied, that is, they should standardize (normalize) lung conditions through the application of an optimal perioperative ventilatory management. They should also account for other factors related to delivery of oxygen at the cellular level, such as haemodynamics, fluid management, temperature and anaesthetic agents, and have a more diverse geographical representation that includes settings with limited resources and different surgical interventions, while ensuring that basic IPC measures are in place.

Adverse events should be reliably defined, monitored or reported as the study primary outcome. SSI should be defined according to standardized criteria (for example, CDC or ECDC criteria) and sub-specified as superficial, deep and organ/ space occupying.

Research is also needed to investigate the benefit of post-extubation hyperoxemia, including different durations, concentrations and oxygen administration routes. As the underlying mechanism of the effect of hyperoxygenation on the incidence of SSI is not entirely understood, translational research investigating these mechanisms is needed. The possible incidence of "awareness" under general anaesthesia with endotracheal intubation and the use of muscle relaxants was not investigated as a potential adverse event with the use of high FiO_2, as well as the consequences of the use of a higher concentration of narcotics, hypnotics or inhalational agents. More research is needed on the use of high FiO_2, including qualitative research on patient values and preferences. Studies including children are needed as none included the paediatric population so far.

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4.13 Maintaining normal body temperature (normothermia)

Recommendation

The panel suggests the use of warming devices in the operating room and during the surgical procedure for patient body warming with the purpose of reducing SSI.
(Conditional recommendation, moderate quality of evidence)

Rationale for the recommendation

- Overall moderate quality evidence from two RCTs shows that the maintenance of normothermia has a significant benefit in reducing the risk of SSI when compared to non-warming standard care. The GDG unanimously agreed that warming devices should be used to avoid patient hypothermia in the operating room and during the surgical procedure in order to reduce the risk of SSI and, more importantly, other complications associated with surgery (see below). Considering the quality of the evidence (moderate, but relying only on 2 small RCTs), the GDG did not reach full consensus about the strength of this recommendation and most members (11 vs. 4) voted for a conditional recommendation. The GDG appraised that the available evidence supporting this recommendation is limited. It was noted also that no observational studies investigating body warming with a SSI outcome were identified.
- However, the GDG emphasized that there are additional relevant benefits of warming strategies, such as a decrease in myocardial events, blood loss and transfusion requirements.
- The GDG agreed that the evidence was insufficient to identify a target temperature to be reached and maintained or an optimal device for warming the patient (for example, fluid warmers or simple blankets). The generally accepted target is core temperature >36°C, considering that "hypothermia" (or low body temperature) is defined as a core temperature below 36°C and is common during and after major surgical procedures lasting more than two hours. However, it was not possible to reach an agreement regarding the optimal pre- and postoperative time for warming.

Remarks

- Included studies were conducted in high-income countries and in adult patient populations. However, the GDG considers this recommendation valid also for paediatric patients.
- The systematic review team and the GDG decided to exclude the study by Wong and colleagues *(1)* because the PICO question asks for a comparison of warming vs. non-warming, whereas the study by Wong applies warming procedures in both groups. Nevertheless, the GDG acknowledged that the study showed a tendency towards reduced SSI in the intervention group, which employed more intensive warming.
- The GDG identified a potential harm of skin burns, depending on the warming device (possible with conductive warming mattresses).
- It was mentioned also that the increased temperature within the work environment may be a concern for surgical staff. Of note, raising the room temperature is not an option to warm the patient as it causes thermal discomfort for the surgical staff, with an increased risk of dripping sweat onto the surgical site.

Background

Hypothermia (or low body temperature) is defined as a core temperature below 36°C and is common during and after major surgical procedures lasting more than two hours. The human body has a central compartment comprising the major organs where temperature is tightly regulated and a peripheral compartment where temperature varies widely *(2)*. Heat loss is compensated by reducing blood flow through the skin and by increasing heat production, mainly by inducing muscular activity (shivering) and increasing the basal metabolic rate. Typically, the periphery compartment may be 2-4°C cooler than the core compartment *(2)*.

Exposure to a cold operating room environment and anaesthetic-induced impairment of thermoregulatory control are the most common

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events leading to hypothermia *(3, 4)*. Skin surface exposure during the perioperative period can increase heat loss. Furthermore, cool intravenous and irrigation fluids directly cool patients. Sedatives and anaesthetic agents inhibit the normal response to cold, resulting in improved blood flow to the periphery and increased heat loss *(3, 4)*. During the early period of anaesthesia, these effects are observed as a rapid decrease in core temperature caused by redistribution of heat from the central to the peripheral compartment. This early decrease is followed by a more gradual decline, reflecting ongoing heat loss. With epidural or spinal analgesia, the peripheral blockade of vasoconstriction below the level of the nerve block results in vasodilatation and greater ongoing heat loss.

For the above reasons, inadvertent non-therapeutic hypothermia is considered to be an adverse effect of general and regional anaesthesia *(5)*. Published research has correlated unplanned perioperative hypothermia with impaired wound healing, adverse cardiac events, altered drug metabolism and coagulopathies *(5-7)*.

It is unclear how the maintenance of normothermia in the core body compartment might reduce the incidence of SSI. All available studies measure core and not peripheral temperature. However, it is highly likely that the reported lower core temperatures result in reduced cutaneous temperature at the operative site. Nonetheless, incisional warming has not been shown to decrease SSI rates *(8)*. A recent Cochrane review of the effect of warmed intravenous fluids found no statistically significant differences in core body temperature or shivering between individuals given warmed and room temperature irrigation fluids *(9)*, but SSI was not the primary outcome. Another Cochrane review of interventions used for treating inadvertent postoperative hypothermia concluded that active warming reduces the time to achieve normothermia. Several warming devices have been studied, including forced-air warming, circulating hot water devices, radiant blankets, radiant warmers and electric blankets. Again, SSI was not among the primary outcomes of the review *(10)*. Temperature monitoring can be performed non-invasively either orally or by infrared ear temperature measurement, which is inaccurate. Intraoperatively, acceptable semi-invasive temperature monitoring sites are the nasopharynx, oesophagus and urinary bladder *(11)*.

Some of the current health care bundles and guidelines recommend that body temperature be maintained above 35.5-36°C during the perioperative period, although there is no consensus among these recommendations for the lower limit or optimal timing for normothermia (Table 4.13.1).

Table 4.13.1. **Recommendations on body temperature control (normothermia) according to available guidelines**

Guidelines (date issued)	Recommendations on body temperature control (normothermia)
SHEA/IDSA (2014) *(12)*	Maintain normothermia (temperature of 35.5°C or more) during the perioperative period in surgical patients who have an anaesthesia duration of at least 60 minutes.
Royal College of Physicians of Ireland (2012) *(13)*	Body temperature maintained above 36° C in the perioperative period (excludes cardiac patients).
Health Protection Scotland bundle (2013) *(14)*	Body temperature maintained above 36° C in the perioperative period (excludes cardiac patients).
UK High impact intervention bundle (2011) *(15)*	Body temperature maintained above 36° C in the perioperative period.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; England

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Following an in-depth analysis of the sources and strength of evidence in available guidelines, the GDG decided to conduct a systematic review to assess the effectiveness of body warming on the prevention of SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 14) was to assess whether perioperative body warming vs. no warming is more effective in reducing the risk of SSI. The target population was patients of all ages undergoing a surgical procedure. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Two RCTs *(16, 17)* including a total of 478 patients were identified (one was a multicentre study). Both studies compared the effect of body warming in the intervention group vs. no warming in the control group. Both studies addressed pre- and intraoperative warming; no studies were identified that assessed the effect of postoperative warming on SSI. The population studied were adult patients undergoing elective colorectal, hernia repair, vascular and breast surgical procedures. No study was available in the paediatric population. No observational study with SSI as the primary outcome was identified. The literature search did not identify any studies that reported on SSI-attributable mortality.

Moderate quality evidence shows that body warming has a significant benefit when compared to no warming in reducing the risk of SSI (OR: 0.33; 95% CI: 0.17–0.62).

Additional factors considered when formulating the recommendation

Values and preferences

No study was retrieved on patient values and preferences with regards to this intervention. The GDG emphasized that pain, nausea and shivering are among the most frequently reported adverse events following cooling down of the body temperature in the OR. Therefore, the GDG acknowledged that patients may prefer being kept warm during the surgical procedure and would also favour the intervention in order to reduce the risk of SSI. By contrast, the GDG is confident that patients wish to be protected from skin burns due to temperature and contact pressure (for example, conductive warming mattress).

Resource use

The GDG highlighted that the use of warming devices, such as forced-air warming devices or radiant blankets, increases the space and energy needed to store and run the equipment. The equipment and maintenance costs represent also a substantial financial burden, especially for LMICs. Availability and procurement are additional issues in LMICs. It was pointed out that the use of warming devices may decrease the risk of adverse outcomes and overall hospital costs *(18-20)*.

The GDG observed that given the lack of evidence to identify the optimal warming devices, it is arguable that simple blankets might function as efficiently as electrically-run devices in warming the patient, particularly in low-resource settings,

Research gaps

The GDG highlighted that well-designed RCTs are needed to identify the target temperature, the optimal devices (fluid warmers, mattresses, simple blankets, etc.) and the proper timing and duration of warming (pre-/intra-/postoperative). Trials should focus on SSI as the primary outcome and ideally address the cost-effectiveness of the intervention. It was emphasized also that there is no evidence from LMICs or in the paediatric population, which represent important research areas.

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4.14 Use of protocols for intensive perioperative blood glucose control

Recommendation

The panel suggests the use of protocols for intensive perioperative blood glucose control for both diabetic and non-diabetic adult patients undergoing surgical procedures to reduce the risk of SSI.
(Conditional recommendation, low quality of evidence)

Rationale for the recommendation

- Overall low quality evidence shows that a protocol with more strict blood glucose target levels has a significant benefit in reducing SSI rates when compared to a conventional protocol. There was evidence that the effect was smaller in studies that used intensive blood glucose controls intraoperatively only compared to studies that used an intensive protocol postoperatively or both intra- and postoperatively. Among the intensive protocols, the effect was similar in studies with a target blood glucose level of ≤110 mg/dL (6.1 mmol/L) and an upper limit target level of 110-150 mg/dL (6.1-8.3 mmol/L). Similar to meta-regression analysis, there was no evidence that the effect of intensive blood glucose control differed between studies of diabetic and non-diabetic patients. Thus, the GDG unanimously agreed that the recommendation to use protocols for intensive perioperative blood glucose control should apply to both diabetics and non-diabetics. However, the GDG decided that the available evidence did not allow the definition of an optimal target level of blood glucose. The strength of this recommendation was considered to be conditional.

Remarks

- The GDG observed that most studies were done in intensive care settings, with no studies in paediatric populations. Therefore, the effectiveness of this intervention is not proven for paediatric patients.
- In general, blood glucose target levels in the intensive protocol group were ≤150 mg/dL (8.3 mmol/L), whereas blood glucose target levels in the conventional protocol group were all <220 mg/dL (12.2 mmol/L).
- Intravenous insulin administration was performed in the intensive protocol group in all studies and in the conventional protocol group in most studies. Three trials *(1-3)* used subcutaneous administration in the conventional group. Some studies used continuous insulin administration, whereas others used intermittent. One study *(4)* administered a fixed high dose of intravenous insulin with dextrose 20% infused separately to maintain a blood glucose level between 70 and 110 mg/dL ("insulin clamp").
- Duration and timing of glucose control differed between studies. The definitions of postoperative glucose control varied from 18 hours and "until enteral nutrition" to a maximum of 14 days.
- Five trials *(1-3, 5, 6)* studied diabetic patients, 8 studies *(4, 7-13)* included both diabetic and non-diabetic individuals, and 2 studies *(14, 15)* concerned only non-diabetic patients. The most frequent surgical procedures were cardiac surgery. Some studies focused on patients undergoing other major surgical procedures, including abdominal surgery.
- The GDG emphasized that hypoglycaemia is a possible harm associated with protocols with strict blood glucose target levels. Hypoglycaemia has a serious risk of life-threatening complications, such as cardiac events. Different definitions for hypoglycaemic events were used in the studies and varied from blood glucose levels ≤40 mg/dL (2.2 mmol/L) to ≤80 mg/dL (4.4 mmol/L).
- Data from the available evidence showed no difference in the risk of death and stroke with the use of an intensive protocol compared to a conventional protocol.

Background

Blood glucose levels rise during and after surgery due to surgical stress. Surgery causes a stress response that results in a release of catabolic hormones and the inhibition of insulin. Moreover, surgical stress influences pancreatic beta-cell function, which results in lower plasma insulin levels. Taken together, this relative

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hypoinsulinaemia, insulin resistance and excessive catabolism from the action of counter-regulatory hormones make surgical patients at high risk for hyperglycaemia, even non-diabetic individuals *(16)*.

Several observational studies *(17-20)* showed that hyperglycaemia is associated with an increased risk of SSI and therefore an increased risk of morbidity, mortality and higher health care costs in both diabetic and non-diabetic patients and in different types of surgery. Conflicting results have been reported regarding the different treatment options to control hyperglycaemia in diabetic and non-diabetic patients, the optimal target levels of blood glucose and the ideal timing for glucose control (intra- and/or postoperative). Moreover, some studies targeting relatively low perioperative glucose levels have highlighted the risk of adverse effects associated with intensive protocols as they may cause hypoglycaemia *(21-24)*.

Several organizations have issued recommendations regarding perioperative blood glucose control (Table 4.14.1). While most recommendations focus on the diabetic patient only, those issued by SHEA/IDSA *(25)* and the American College of Physicians *(26)* apply to all surgical patients. They recommend either target levels between 140-200 mg/dL (7.8-11.1 mmol/L) or upper limits of 180 mg/dL (10mmol/L) or 198 mg/dL (11mmol/L). Due to the risk of hypoglycaemia, targeting lower levels should be avoided *(26, 27)*.

Table 4.14.1. **Recommendations on perioperative blood glucose control according to available guidelines**

Guidelines (year issued)	Recommendations on perioperative blood glucose control
SHEA/IDSA practice recommendation (2014) *(25)*	Control blood glucose during the immediate postoperative period for cardiac and non-cardiac surgery patients. a) Maintain postoperative blood glucose at 180 mg/dL or lower. b) Intensive postoperative glucose control (targeting levels less than 110 mg/dL) has not been shown to reduce the risk of SSI and may actually lead to higher rates of adverse outcomes, including stroke and death.
NICE (2008) *(28)*	Do not give insulin routinely to patients who do not have diabetes to optimize blood glucose postoperatively as a means of reducing the risk of SSI.
Health Protection Scotland bundle (2013) *(29)*	Ensure that the diabetic patient's glucose level is kept at <11 mmol/L throughout the operation.
The Royal College of Physicians of Ireland (2012) *(30)*	Ensure that if the patient is diabetic that the glucose level is kept at <11 mmol/L throughout the operation.
UK High impact intervention bundle (2011) *(31)*	A glucose level of <11 mmol/L has to be maintained in diabetic patients.
The Society of Thoracic Surgeons practice guideline series (2009) *(27)*	All patients with diabetes undergoing cardiac surgical procedures should receive an insulin infusion in the operating room and for at least 24 hours postoperatively to maintain serum glucose levels ≤180 mg/dL.
American College of Physicians: clinical practice guideline (2011) *(26)*	Do not use intensive insulin therapy (4.4 to 6.1 mmol/L [80 to 110 mg/dL]) to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus. A target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) is recommended if insulin therapy is used in SICU/MICU patients.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; SICU: surgical intensive care unit; MICU: medical intensive care unit.

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Following an in-depth analysis of the sources and strength of the evidence in current guidelines, the GDG members decided to conduct a systematic review to assess the impact of perioperative blood glucose levels on the risk of SSI and to determine the optimal perioperative target levels in diabetic and non-diabetic surgical patients to prevent SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 15) was to evaluate whether the use of protocols for intensive perioperative blood glucose control is more effective in reducing the risk of SSI than conventional protocols with less stringent blood glucose target levels. The population studied were patients of all ages, both diabetic and non-diabetic, and undergoing several types of surgical procedures. The primary outcome was the occurrence of SSI and SSI-attributable mortality. A total of 15 RCTs *(1-15)* including a total of 2836 patients and comparing intensive perioperative blood glucose protocols vs. conventional protocols with less stringent blood glucose target levels were identified. Eight studies were performed in adult patients undergoing cardiac surgery *(1, 2, 4, 6, 9-11, 15)*, 6 in patients undergoing abdominal or major non-cardiac surgery *(3, 5, 7, 12-14)*, and one other study in patients undergoing emergency cerebral aneurysm clipping *(8)*. No study was available in a paediatric population. In 2 studies *(4, 7)*, glucose control was performed intraoperatively only. Eight studies *(1, 2, 6, 8, 9, 11, 13, 15)* investigated intra- and postoperative glucose control and 5 studies *(3, 5, 10, 12, 14)* focused on postoperative glucose control.

None of the studies had SSI as their primary outcome. Most studies had a combined outcome of postoperative complications. The definition of SSI was also different in most studies.

There was substantial heterogeneity among the selected studies in the population, notably regarding the timing when intensive blood glucose protocols were applied in the perioperative period and intensive blood glucose target levels. For this reason, separate meta-analyses were performed to evaluate intensive protocols vs. conventional protocols in different settings (that is, in diabetic, non-diabetic and a mixed population) with intraoperative, intra- and postoperative glucose control, and in trials with intensive blood glucose upper limit target levels of ≤110 mg/dL (6.1 mmol/L) and 110-150 mg/dL (6.1-8.3 mmol/L) (web Appendix 15).

Overall, there is low quality evidence that a protocol with more strict blood glucose target levels has a significant benefit in reducing SSI rates when compared to a conventional protocol (OR: 0.43; 95% CI; 0.29–0.64). In addition, there was no evidence in meta-regression analyses that the effect of intensive blood glucose control differed between studies of diabetic and non-diabetic patients (P=0.590). There was evidence that the effect was smaller in studies that used intensive blood glucose control intraoperatively only (OR: 0.88; 95% CI: 0.45-1.74) compared to studies that used controls postoperatively or both intra- and postoperatively (OR: 0.47; 95% CI: 0.25-0.55; P=0.049 for the difference between ORs). Among the intensive protocols, the effect was similar in studies with upper limit target blood glucose levels of ≤110 mg/dL (6.1 mmol/L) and 110-150 mg/dL (6.1-8.3 mmol/L) (P=0.328).

Data from the available evidence showed no difference in the risk of postoperative death and stroke with the use of an intensive protocol compared to a conventional protocol (OR: 0.74; 95% CI: 0.45-1.23 and OR: 1.37; 95% CI: 0.26-7.20, respectively). The study by Ghandi and colleagues was the only one that reported more strokes and deaths in the intensive group *(11)*. This study had comparable 24-hour achieved blood glucose levels in the intensive care unit in both groups, although they were significantly lower in the intensive group intraoperatively and at baseline. Other studies showed equal or even less strokes and/or deaths in the intensive group, but these findings were not significant. In meta-regression analyses, there is no evidence for a difference in risk between studies with an upper limit target blood glucose level of ≤110 mg/dL (6.1 mmol/L) and an upper limit level of 110-150 mg/dL (6.1-8.3 mmol/L) (P=0.484 for mortality and P=0.511 for stroke).

Meta-analysis of hypoglycaemic events in the 8 RCTs with a blood glucose upper limit target level of ≤110 mg/dL (6.1 mmol/L) showed an increased risk of hypoglycaemic events with the use of an intensive protocol over a conventional protocol (OR: 4.18; 95% CI: 1.79–9.79). However, 2 of the 8 studies included in this analysis had no hypoglycaemic events *(4, 13)* and only 3 studies *(3, 7, 14)* found significantly more hypoglycaemic events with the use of the intensive protocol. A meta-analysis of 4 studies *(1, 2, 6, 10)* showed an increased risk of hypoglycaemic events with the use of a strict protocol with a blood glucose upper

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limit target level of 110-150 mg/dL (6.1-8.3 mmol/L) compared to a conventional protocol (OR: 9.87; 95% CI: 1.41–69.20). Two studies included in this analysis had no hypoglycaemic events *(1, 2)*. Among the studies that could not be included in the meta-analysis due to missing data, 2 reported significantly more hypoglycaemic events in the intensive group *(8, 12)*, while no difference in risk was observed in another study *(9)*. Overall, there is an increased risk for hypoglycaemic events with the use of either intensive protocol for blood glucose control (OR: 5.55; 95% CI: 2.58–11.96). In meta-regression analyses, there is no evidence for a difference in the risk of hypoglycaemia between studies with a target blood glucose level of ≤110 mg/dL (6.1 mmol/L) and an upper limit target level of 110-150 mg/dL (6.1-8.3 mmol/L) (P=0.413).

The GDG underlined that there are many observational studies showing a reduction in SSI with intensive blood glucose control in non-diabetic populations. However, after discussion, the GDG agreed not to include the data from the observational studies.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG is confident that most patients wish to receive this intervention in order to reduce the risk of SSI. Patients are concerned about hypoglycaemic events, as well as being monitored for the blood glucose target level on a regular (sometimes a few times daily) basis, which might be associated with frequent needle pricks.

Resource use

The GDG members emphasized that apart from in intensive care settings, patients are more likely to receive a conventional protocol because of concerns regarding resources and the ability to monitor blood glucose adequately. The GDG highlighted that the purchase and storage (refrigerator) of insulin is a financial burden in LMICs and the availability of insulin is a concern. The equipment for the application of frequent glucose control is also expensive and may be limited in availability in such settings. In addition, the medical staff has to be carefully trained to correctly monitor the blood glucose level and treat hypoglycaemic events. There are no data available to determine the cost-effectiveness of different protocols.

Research gaps

GDG members highlighted that the available evidence mostly consists of intensive care and cardiac surgery populations. There is a need for studies in the paediatric setting, as well as in non-ICU surgical patients and those undergoing different types of surgical procedures. Adequately-powered RCTs should be performed to compare different blood glucose target levels in order to better define the optimal level for the purpose of SSI prevention, but with only a very limited risk of hypoglycaemia. For a given target level, there should be studies investigating the optimal route of insulin administration, as well as studies on the duration of continued postoperative glucose control. In particular, the GDG noted that research on cost-effectiveness and studies from LMICs are needed.

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4.15 Maintenance of adequate circulating volume control/normovolemia

Recommendation

The panel suggests the use of goal-directed fluid therapy (GDFT) intraoperatively to reduce the risk of SSI.
(Conditional recommendation, low quality of evidence)

Rationale for the recommendation

- Overall low quality evidence shows that intraoperative GDFT has significant benefit in reducing the SSI rate compared to standard fluid management. This effect is shown also for GDFT in the postoperative period.
- Considering that both fluid overload and hypovolemia are likely to affect other clinical outcomes, the GDG agreed to emphasize that specific fluid management strategies, such as GDFT or restrictive fluid management, may be used during surgery for purposes other than the reduction of SSI, for example, to support cardiovascular and renal functions.
- Considering the low quality evidence, as well as the above-mentioned factors, the GDG agreed to suggest the use of GDFT intraoperatively and decided that the strength of this recommendation should be conditional.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. Therefore, this effectiveness of this intervention is not proven for paediatric patients.
- GDFT refers to a haemodynamic treatment based on the titration of fluid and inotropic drugs according to cardiac output or similar parameters.
- Restrictive fluid management refers to the administration of a regimen with a reduced volume of fluids in the bolus and/or over time compared to local standard fluid maintenance.
- Standard fluid maintenance in the control group refers to the administration of fluid regimens at the discretion of the treating medical team or according to the local standard.
- Most trials among the included studies compared the efficacy of specific fluid management strategies with standard fluid regimens in the intraoperative period. Fourteen RCTs investigated GDFT *(1-14)* and 5 RCTs focused on restrictive fluid management *(15-19)*. As the PICO question focused on fluid management during surgery, these comparisons were used to formulate the recommendation.
- Further trials compared specific fluid management strategies vs. standard fluid management in the preoperative *(20)* and/or postoperative period *(21-24)*.
- It was discussed that the actual physiological effect of administered fluids may also differ, depending on several other factors, such as surgical stress, normothermia and tissue oxygenation.
- The GDG argued that both fluid overload and hypovolemia are likely to increase mortality and morbidity *(25)*.
- Although the optimal strategy for GDFT cannot be identified from the published data due to the heterogeneity of the protocols used in the included studies, the panel suggests administering haemodynamic therapy based on a goal-directed approach during the entire surgical procedure. Optimization is preferably based on dynamic pre-load parameters (that is, pulse pressure variation, systolic pressure variation) derived from arterial catheter measurements (when an arterial line is indicated) or minimal invasive alternatives.
- The GDG felt that using an algorithm is helpful, while taking into account that local resources and expertise may vary and limit possibilities for the optimal strategy. Indeed, the variety of effective algorithms on a multitude of outcomes indicates that having an algorithm for a specific goal is the most important factor, more than any particular algorithm associated with the effect of GDFT.

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Background

Wound healing and resistance to infection is dependent on tissue oxygen tension. In addition, sufficient tissue oxygenation is essential for collagen synthesis and wound repair *(17)* and is improved by adequate arterial oxygenation. Ideally, perioperative fluid therapy prevents tissue hypoxia by maximizing the cardiac output and thus improving arterial oxygenation. However, the optimal perioperative fluid strategy remains a subject of debate. A large variability exists between regimens in daily practice and both fluid overload (hypervolemia) and hypovolemia have been associated with increased mortality and morbidity. Fluid overload leads to a decrease in muscular oxygen tension. Due to surgical trauma, a systemic inflammatory response arises, which leads to a fluid shift to the extravascular space. Following a large fluid shift, generalized oedema may occur, which decreases tissue oxygenation and impedes tissue healing. By contrast, hypovolemia leads to arterial and tissue hypoxia due to a decrease in cardiac output.

The optimal fluid (colloid or crystalloid) or strategy of fluid management (GDFT, liberal or restricted) remains a subject of controversy. GDFT uses cardiac output or similar parameters to guide intravenous fluid and inotropic administration, but the disadvantage of this strategy is the difficulty to adequately assess normovolemia. Liberal and restrictive fluid strategies use standard fluid regimens not based on cardiac output. Nevertheless, an adequate assessment of normovolemia in these strategies remains complicated. In addition, the physiological effects of any given volume of fluid may differ, depending on the magnitude of the surgical stress response and not solely on the volume of fluids administered. At present, there is no universal definition of normovolemia or a standardized method for its assessment. Some studies assess normovolemia by urinary output or serum markers, whereas others use more invasive techniques, such as cardiac output or cardiac index.

Few organizations have issued recommendations regarding the maintenance of normovolemia (Table 4.15.1). The UK-based NICE recommends maintaining adequate perfusion during surgery *(26)*. Based on an evidence update in 2013, it is stated that haemodynamic GDFT appears to reduce SSI rates *(27)*. The SHEA/IDSA guidelines do not formulate a specific recommendation on the maintenance of normovolemia for SSI prevention. However, in a statement on oxygen therapy, it is indirectly recommended to maintain an appropriate volume replacement *(28)*.

Table 4.15.1. **Recommendations for the maintenance of normovolemia according to available guidelines**

Guidelines (year issued)	Recommendations for the maintenance of normovolemia
SHEA/IDSA practice recommendation (2014) *(28)*	No specific recommendation on the maintenance of normovolemia for SSI prevention. Indirect recommendation: "Supplemental oxygen is most effective when combined with additional strategies to improve tissue oxygenation, including maintenance of normothermia and **appropriate volume replacement**".
NICE (2008) *(26)*	Maintain adequate perfusion during surgery.
NICE (2013 update) *(27)*	Haemodynamic goal-directed therapy (titration of fluid and inotropic drugs to reach normal or supraoptimal physiological endpoints, such as cardiac output and oxygen delivery) appears to reduce SSI rates.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; SSI: surgical site infection; NICE: National Institute for Health and Care Excellence;

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Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG members decided to conduct a systematic review to assess the effectiveness of specific fluid management strategies compared with standard fluid regimens and to determine if certain fluid management strategies during surgery might be beneficial to prevent SSI in surgical patients.

Summary of the evidence

The purpose of the evidence review (web Appendix 16) was to evaluate whether specific fluid management strategies for the maintenance of normovolemia are more effective in reducing the risk of SSI than standard fluid regimens administered during surgery. The target population included patients of all ages undergoing a surgical operation. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Twenty-four RCTs *(1-24)* including a total of 4031 patients and comparing specific strategies of fluid management with standard fluid management were identified. Types of surgical procedures included were colorectal, abdominal, general, urology, gynaecological, cardiothoracic, vascular, orthopaedic and other surgery.

Due to heterogeneity among the selected studies in the type of specific fluid management strategy used throughout the perioperative period, separate meta-analyses were performed for GDFT or restrictive fluid regimens vs. standard fluid regimens in the pre-, intra- and postoperative periods.

Overall, there is low quality evidence that intraoperative GDFT has a significant benefit in reducing the SSI rate compared to standard fluid management (OR: 0.56; 95% CI: 0.35–0.88). By contrast, very low quality evidence indicated that intraoperative restrictive fluid management has neither benefit nor harm compared to standard intraoperative fluid management in reducing the SSI rate (OR: 0.73; 95% CI: 0.41–1.28).

One study *(20)* compared GDFT vs. standard fluid management preoperatively and demonstrated no benefit in reducing the risk of SSI (OR: 0.47; 95% CI: 0.13–1.72), whereas a meta-analysis of 2 RCTs *(22, 23)* comparing GDFT vs. standard fluid management in the postoperative period showed a decrease of the risk of SSI in the GDFT group (OR: 0.24; 95% CI: 0.11–0.52). One study *(24)* comparing restrictive vs. standard fluid management postoperatively showed no difference in risk (OR: 6.20; 95% CI: 0.68–56.56). Similarly, one RCT *(21)* compared GDFT vs. standard fluid management pre- and postoperatively combined and demonstrated no benefit (OR: 0.75; 95% CI: 0.16–3.52).

The retrieved evidence focused on adult patients only. No study was available in a paediatric population. Five RCTs reported that either fluid overload or hypovolemia seem to be associated with increased mortality and morbidity *(15, 18, 19, 23, 24)*.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG pointed out that patients are seldom informed about fluid management.

Resource use

The GDG underlined that there are no studies on the costs or cost-effectiveness of different fluid management strategies during surgery. However, the GDG noted that GDFT might require more resources, including the fact that the medical staff needs to be specifically trained. It was noted that in low-resource settings, anaesthesia is often provided by non-specialized professionals and there may also be a limitation in the type of intravenous fluids available.

Research gaps

The GDG highlighted that a widely-accepted definition for normovolemia is needed. Future studies including large well-designed RCTs with clear definitions should aim at identifying the most accurate and least invasive method of measuring normovolemia and assess its influence with regard to tissue oxygenation and normothermia. In particular, studies should be conducted in LMICs. More research is required to investigate the effectiveness of different fluid management strategies in paediatric populations.

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4.16 Drapes and gowns

Recommendations

1. **The panel suggests that either sterile, disposable, non-woven or sterile, reusable woven drapes and surgical gowns can be used during surgical operations for the purpose of preventing SSI.**
   (Conditional recommendation, moderate to very low quality of evidence)

2. **The panel suggests not to use plastic adhesive incise drapes with or without antimicrobial properties for the purpose of preventing SSI.**
   (Conditional recommendation, low to very low quality of evidence)

Rationale for the recommendations

- It is good clinical practice to use sterile drapes and gowns for surgery. To determine what type of surgical drapes and gowns are the most effective for the purpose of preventing SSI, the GDG decided to focus on disposable non-woven and reusable woven drapes, including plastic adhesive incise drapes with or without antimicrobial properties. Non-woven and woven drapes and gowns with antimicrobial properties were not considered a priority and no relevant evidence was found.
- Available evidence from one RCT, one quasi-RCT and 2 observational studies (moderate quality for RCTs and very low for observational) shows that the use of sterile disposable non-woven drapes and sterile surgical gowns has neither benefit nor harm when compared to sterile reusable woven drapes and surgical gowns in reducing the SSI rate. Considering the quality of the evidence, the GDG unanimously agreed to suggest that either sterile disposable non-woven or sterile reusable woven drapes and surgical gowns can be used. The strength of this recommendation was considered to be conditional.
- The GDG pointed out that there is no evidence for the potential effect of the timing or usefulness of changing surgical drapes or gowns in the course of a surgical operation for the purpose of preventing SSI.
- Evidence available from one RCT, one quasi-RCT and 2 observational studies (overall very low quality for both RCTs and observational) shows that the use of adhesive iodophor-impregnated incise drapes has neither benefit nor harm when compared to no adhesive incise drapes in reducing the SSI rate.
- Available evidence from 2 RCTs (overall low quality) shows that the use of plastic, adhesive, non-impregnated incise drapes has neither benefit nor harm when compared to no adhesive incise drapes in reducing the SSI rate.
- Considering the lack of evidence that plastic adhesive incise drapes (with or without antimicrobial properties) prevent SSI, the GDG unanimously agreed that they should not be used. Given the quality of the evidence (moderate to very low), the strength of this recommendation was considered to be conditional.

Remarks

- The GDG highlighted that if the material of the disposable and reusable surgical drapes and gowns is permeable to liquids, it can expose health care workers to body fluids and also represents a risk for patients. Ideally, the material should be impermeable to prevent the migration of microorganisms. The GDG remarked that both reusable and disposable drapes and gowns commercially available are in permeable or impermeable forms.
- The GDG identified possible harms associated with the use of disposable drapes in that the adhesive bands of single-use drapes may provoke skin rash or eczema and devices may be dislodged when removing adhesive drapes after the surgical procedure *(1)*.
- Regarding plastic, adhesive incise drapes, the GDG identified allergic reactions as a possible harm associated with the use of iodophor-impregnated incise drapes *(2)*. The GDG noted also that a further possible harm could be that pieces of the adhesive film might remain in the wound.

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Background

Sterile surgical drapes are used during surgery to prevent contact with unprepared surfaces and maintain the sterility of environmental surfaces, equipment and the patient's surroundings. Similarly, sterile surgical gowns are worn over the scrub suit of the operating team during surgical procedures to maintain a sterile surgical field and reduce the risk of the transmission of pathogens to both patients and staff *(3)*.

Surgical gowns and drapes are fabricated from either multiple- or single-use materials. In addition, there is a considerable variation in design and performance characteristics within each of these two broad categories, which reflects the necessary trade-offs in economy, comfort and degree of protection required for particular surgical procedures *(4)*.

During surgical procedures, the risk of pathogen transmission increases if the barrier materials become wet. Consequently, the multiple- or single-use materials of the drapes and gowns used in a surgical procedure should prevent the penetration of liquids. Reusable materials are typically composed of different tightly woven textiles and/or knitted cotton or other fabrics possibly blended with polyester and/or chemically treated. These products have to be durable and provide protection after many cycles of processing and treatment. Disposable surgical drapes and gowns are typically composed of non-woven material of synthetic and/or natural origin, possibly combined with chemical treatment *(3)*.

Adhesive plastic incise drapes, either plain or impregnated with an antimicrobial agent (mostly an iodophor), are used on the patient's skin after completion of the surgical site preparation. The film adheres to the skin and the surgeon cuts through the skin and the drape itself *(5)*. Such a drape is theoretically believed to represent a mechanical and/or microbial barrier to prevent the migration of microorganisms from the skin to the operative site *(6)*. However, some reports have shown an increased recolonization of the skin following antiseptic preparation underneath adhesive drapes compared to the use of no drapes *(7)*.

A Cochrane review *(8)* and its updates *(5, 9)* of the effect of adhesive incise drapes to prevent SSI found that there is no evidence that plastic adhesive drapes reduce SSI. No recommendation is available on the use of sterile disposable or reusable drapes and surgical gowns for the purpose of SSI prevention.

This topic is addressed in a few of the recent available guidelines, but with conflicting recommendations. The recent SHEA/IDSA guidelines issued in 2014 recommend that plastic adhesive drapes with or without antimicrobial properties should not be used routinely as a strategy to prevent SSI *(10)*. However, the UK-based NICE issued a guideline in 2008 recommending that an iodophor-impregnated drape should be used if a plastic adhesive drape is required *(11)*.

Following an in-depth analysis of the available resources and given the limited recommendations from other guidelines, the GDG decided to conduct a systematic review to assess the effect of the use of sterile disposable or reusable drapes and surgical gowns, including plastic adhesive incise drapes, for the purpose of SSI prevention.

Summary of the evidence

The purpose of the evidence review (web Appendix 17) was to evaluate 3 important questions: (1) whether sterile disposable non-woven drapes and gowns or sterile reusable woven drapes and gowns should be used to prevent SSI; (2) whether changing drapes during operations affect the risk of SSI; and (3) whether sterile, disposable, adhesive incise drapes should be used to reduce the risk of SSI. The target population included patients of all ages undergoing a surgical procedure, with the presence of postoperative drainage. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

A total of 11 studies *(1, 12-21)* related to these topics with SSI as the primary outcome were identified and included 4 RCTs *(12, 17, 20, 21)*.

Regarding the first question, five studies including a total of 6079 patients and comprising one RCT *(12)*, one quasi-RCT *(13)* and three observational *(1, 14, 15)* were identified. Studies included clean and clean-contaminated (for example, general, cardiothoracic, orthopaedic, neurosurgery and plastic surgery) procedures. Four studies *(1, 12, 13, 15)* compared the use of sterile, disposable non-woven drapes and gowns vs. sterile, reusable woven drapes and gowns. One study *(14)* compared the use of sterile, disposable fenestrated drapes designed originally for cardiac catheterization with traditional draping that involved the use of multiple

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reusable cloth drapes. There was a substantial variation among studies in the definition of SSI and the type and material of the single-use and reusable drapes and gowns.

After careful appraisal of the retrieved studies, a meta-analysis including the studies evaluating sterile, disposable non-woven vs. sterile, reusable woven drapes and gowns was performed. A moderate (RCTs) and very low (observational studies) quality of evidence showed that the use of sterile disposable non-woven drapes and gowns has neither benefit nor harm compared to sterile reusable woven items (OR: 0.85; 95% CI: 0.66–1.09 for RCTs; OR: 1.56; 95% CI: 0.89–2.72 for observational studies).

Regarding the second question, no studies assessing whether changing drapes during operations affects the risk of SSI were identified.

Regarding the third question, 6 studies (3 RCTs *(17, 20, 21)*, one quasi-RCT *(16)* and 2 observational *(18, 19)*) including a total of 1717 adult patients with SSI as an outcome were identified. Studies included clean and clean-contaminated (for example, cardiac, hip fracture fixation, open appendectomy, hernia repair and liver resection for hepatocellular carcinoma) surgical procedures. There was a substantial variation in the definition of SSI among studies.

Two separate meta-analysis comparisons were performed to evaluate sterile, disposable, antimicrobial-impregnated adhesive incise drapes vs. sterile non-adhesive incise drapes, and sterile, non-antimicrobial-impregnated adhesive incise drapes vs. sterile non-adhesive incise drapes. There is a very low quality of evidence suggesting that the use of sterile, disposable, antimicrobial-impregnated adhesive incise drapes has neither benefit nor harm compared to sterile non-adhesive incise drapes in reducing the risk of SSI (OR: 2.62; 95% CI: 0.68–10.04 for RCTs; OR: 0.49; 95% CI: 0.16–1.49 for observational studies). There is a low quality of evidence from 2 RCTs that the use of sterile, disposable non-antimicrobial-impregnated adhesive incise drapes has neither benefit nor harm compared to sterile non-adhesive incise drapes in reducing the risk of SSI (OR: 1.10; 95% CI: 0.68–1.78).

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to the interventions addressed in the recommendations. The GDG is confident that most patients would not want to be involved in the decision of whether to use disposable or reusable drapes and surgical gowns as long as the risk of SSI is minimized. It was acknowledged also that although patients may value measures to prevent SSI, they do not wish to be exposed to discomfort or possible harm due to skin irritation or allergic reactions to drapes (for example, associated with some adhesive disposable drapes or adhesive incise drapes).

Resource use

The GDG acknowledged that many different aspects need to be taken into account when evaluating the resource implications for the use of sterile disposable vs. sterile reusable drapes and surgical gowns. These include (but are not limited to) direct purchase costs and costs related to laundry and sterilization, labour required for reprocessing and waste disposal *(22)*. Two studies *(23, 24)* showed lower costs associated with the use of disposable drapes and gowns, whereas a cost-benefit analysis *(22)* found costs for sterile disposable drapes and gowns to be relatively higher compared with reusable ones. Other authors reported that costs were similar for disposable and reusable items *(25, 26)*. The heterogeneous findings of the available data on resource implications suggest that disposable and reusable surgical drapes and gowns are probably similar in costs.

In LMICs, the availability of disposable drapes and gowns and adhesive incise drapes may be limited and costs may represent a high financial burden, whereas labour costs for reprocessing reusable items may be less of an issue. The disposal of single-use drapes and gowns and the ecological impact should be considered as their use generates additional clinical waste. Taking into account the lack of evidence of any benefit for the prevention of SSI, the additional cost for plastic adhesive incise drapes is not justified, irrespective of the setting.

Research gaps

The GDG highlighted that the available evidence regarding the interventions addressed in the recommendations is limited and comes mainly

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from high-income countries. More well-designed RCTs investigating the use of sterile disposable compared to sterile reusable drapes and surgical gowns in terms of SSI prevention are needed, particularly in LMICs. A cost-effectiveness analysis is highly recommended, especially in low-resource settings. Further research should focus also on different types of materials (including permeable and impermeable materials) and address environmental concerns (water, energy, laundry, waste, etc.). Another research priority is to investigate whether drapes should be changed during the operation and if this measure has an effect on SSI rates. The GDG highlighted that the use of adhesive incise drapes is not considered a high priority topic in the field of SSI prevention research. Nevertheless, well-designed RCTs should be encouraged to further investigate the potential benefits of these products, which are aggressively promoted by the manufacturing companies.

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4.17 Wound protector devices

Recommendation

The panel suggests considering the use of wound protector (WP) devices in clean-contaminated, contaminated and dirty abdominal surgical procedures for the purpose of reducing the rate of SSI. *(Conditional recommendation, very low quality of evidence)*

Rationale for the recommendation

- Overall very low quality evidence shows that a single- or double-ring WP device has benefit in reducing the rate of SSI compared with regular wound protection. Meta-regression analysis showed no strong evidence for a difference in the effect between single- and double-ring WPs. There was also no evidence that the effect differed between clean-contaminated or contaminated or dirty surgery and other surgery.
- The GDG agreed to suggest the use of either WP device in abdominal surgery with laparotomy for the purpose of reducing SSI. Given the very low quality evidence, the strength of the recommendation was considered to be conditional and the GDG proposed to use the terminology "The panel suggests considering..." to highlight the need for careful local evaluation about whether and how to apply this recommendation, in particular regarding the availability of these devices and associated costs.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. Therefore, the effectiveness of this intervention is not proven for paediatric patients.
- Two differently designed types of commercially-available WP devices have been used as an intervention in the included studies, that is, single- *(1-6)* and double-ring WPs *(7-11)*.
- With regard to the degree of wound contamination in abdominal surgery, 5 studies included clean-contaminated *(3-7)*, 5 studies included contaminated *(2-6)* and 6 studies investigated dirty procedures *(2-6, 9)*.
- The GDG identified possible harms associated with the use of WP devices, particularly in patients with abdominal adhesions. In these cases, the insertion of a WP device may be difficult and lead to the need to enlarge the incision, to injuries to the small bowel and to the prolongation of the procedure. A further concern is the limited space to access the surgical field after insertion of the WP.
- Although poorly assessed by the studies included, no serious adverse effects have been reported.
- The GDG emphasized that the operating surgeon needs to be familiar with handling a WP device during placement, in the operative phase and upon removal to avoid wound contamination at these critical time points, particularly when WP is used in patients with a high intra-abdominal bacterial load, such as diffuse peritonitis.
- The GDG highlighted that these are single-use devices that must not be reused.

Background

Although surgeons have progressively paid more attention to the control of operative wound contamination during surgical procedures, incisional SSI is still a frequent postoperative adverse event jeopardizing patient safety and increasing health care costs.

Conventional surgical drapes are commonly used by surgeons to limit the aseptic surgical area and to cover the freshly-made wound edges. Nevertheless, this non-fixed mechanical barrier may become dislodged or potentially contaminated.

To better reinforce the aspects related to wound edge isolation, surgical WP devices have been fabricated and marketed, unlike new developed drugs that need different controlled studies before approval by regulatory bodies. These new surgical devices comprise a non-adhesive plastic sheath attached to a single or double rubber ring that firmly secures the sheath to the wound edges. The device is intended to facilitate the retraction of the incision during surgery without the need for additional mechanical retractors and cloths. Theoretically, commercially-available WPs are intended to reduce wound edge contamination to

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a minimum during abdominal surgical procedures, including contamination from outside (clean surgery) and inside the peritoneal cavity (clean-contaminated, contaminated and dirty surgery). Although these surgical devices are already on the market, their real usefulness and cost-effectiveness warrants additional evidence-based analysis.

Few organizations have issued recommendations regarding the use of WP devices (Table 4.17.1).

The UK-based NICE states that wound edge protection devices may reduce SSI rates after open abdominal surgery, but no recommendation is given due to the lack of further high quality evidence *(12)*. However, SHEA/IDSA guidelines recommend the use of impervious plastic WPs for gastrointestinal and biliary tract surgery *(13)*.

Table 4.17.1. **Recommendations on the use of WP devices according to available guidelines**

Guidelines (year issued)	Recommendations on the use of WP devices
SHEA/IDSA practice recommendation (2014) *(13)*	Use impervious plastic WPs for gastrointestinal and biliary tract surgery.
NICE (2013 update) *(12)*	Wound edge protection devices may reduce the SSI rate after open abdominal surgery, but the current lack of high quality studies implies that more research is needed.

WP: wound protector; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence.

Following the in-depth analysis of the sources and strength of evidence in current guidelines, the GDG decided to conduct a systematic review to assess the effectiveness of WP devices compared with standard wound edge protection and to determine if they might be beneficial to prevent SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 18) was to evaluate whether the use of a WP device is more effective in reducing the risk of SSI than conventional wound protection, which is mainly through placing wet towels between the wound edge in combination with steel retractors. The target population included patients of all ages undergoing either elective or urgent abdominal surgery through conventional open access. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Eleven trials comparing the use of a WP device with conventional wound protection in abdominal surgical procedures with laparotomy were identified. These included a total of 2949 patients and comprised 10 RCTs *(1, 3-11)* and one prospective controlled trial *(2)*. There is very low quality evidence for the benefit of either a single- or double-ring WP device in reducing the SSI rate when compared with standard wound protection (OR: 0.42; 95% CI: 0.28–0.62).

This beneficial effect was observed both for single- (OR: 0.51; 95% CI; 0.34–0.76) and double-ring WPs (OR: 0.25; 95% CI: 0.13–0.50). Similarly, meta-regression analysis showed no strong evidence for a difference in the effect between single- and double-ring WPs (P=0.107). There was also no evidence that the effect differed between clean-contaminated (P=0.244), contaminated (P=0.305) or dirty (P=0.675) surgery and other surgery. The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG is confident that most patients wish to receive this intervention in order to reduce the risk of SSI. Patients will prefer also to be treated by

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surgeons who are familiar with the use of WP devices in order to reduce the risk of complications.

Resource use

In LMICs, the availability of WP devices may be limited and represent a high financial burden. The GDG pointed out that this intervention may not be prioritized in resource-limited settings compared to other interventions to reduce SSI. It was highlighted that there is a need for staff training, irrespective of the setting. Few studies addressed the cost-effectiveness of the intervention. Two small studies found the use of WP to be cost-effective *(6, 9)*, while one larger trial did not *(14)*.

Research gaps

The GDG highlighted that the available evidence consists mainly of low quality small studies. There is a need for properly designed multicentre RCTs. The SSI outcome should be defined according to the CDC criteria and sub-specified as superficial, deep and organ/space occupying infections. Specific and relevant surgical procedures should be reported regarding the level of wound contamination and the rate of incisional SSI (for example, colorectal surgery and laparotomy for peritonitis). Investigators should consider comparing single- with double-ring WP devices. Trials should report adverse events related to the intervention. Finally, cost-effectiveness studies are also needed.

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4.18 Incisional wound irrigation

Recommendations

The panel considers that there is insufficient evidence to recommend for or against saline irrigation of incisional wounds before closure for the purpose of preventing SSI.

The panel suggests considering the use of irrigation of the incisional wound with an aqueous PVP-I solution before closure for the purpose of preventing SSI, particularly in clean and clean-contaminated wounds.

The panel suggests that antibiotic incisional wound irrigation before closure should not be used for the purpose of preventing SSI.
(Conditional recommendations/low quality of evidence)

Rationale for the recommendation

- RCTs comparing wound irrigation vs. no wound irrigation or wound irrigation using different solutions with SSI as an outcome were evaluated. Evidence was available on intraperitoneal, incisional wound and mediastinal irrigation in patients undergoing various surgical procedures.
- Considering the substantial heterogeneity in the available evidence, the GDG decided to focus only on incisional wound irrigation. In particular, the GDG agreed not to consider intraperitoneal irrigation for the formulation of recommendations as the identified studies described contaminated and dirty intra-abdominal procedures (for example, peritonitis). Therefore, wound irrigation was likely to represent a therapeutic intervention, rather than a prophylactic measure.
- Very low quality evidence shows that incisional wound irrigation with saline solution has neither benefit nor harm compared to no irrigation.
- Low quality evidence shows that the irrigation of the incisional wound with an aqueous PVP-I solution is beneficial with a significant decrease of the risk of SSI when compared to irrigation with a saline solution.
- Very low quality evidence shows that the irrigation of the incisional wound with antibiotic solutions has neither benefit nor harm compared to irrigation with a saline solution or no irrigation.
- The GDG agreed that there is insufficient evidence to issue a recommendation for or against the saline solution irrigation of incisional wounds for the purpose of preventing SSI. The GDG also decided to suggest considering the use of irrigation of the incisional wound with an aqueous PVP-I solution. The term "considering" was proposed to highlight that a decision-making process is needed, especially focusing on clean and clean-contaminated wounds. Finally, the GDG agreed to suggest that antibiotic incisional wound irrigation should not be used for the purpose of preventing SSI. The strength of these recommendations should be conditional due to the low quality of the evidence.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. Therefore, the effectiveness of irrigation of the incisional wound with an aqueous PVP-I solution is not proven for paediatric patients.
- The available evidence from 7 RCTs *(1-7)* (10 estimates) showed that irrigation of the incisional wound with an aqueous PVP-I solution was beneficial in reducing the risk of SSI when compared to irrigation with a saline solution. Stratification of the evidence by contamination showed that the effect was attributable to incisional wound irrigation in clean and clean-contaminated procedures rated as wound classes I and II according to the CDC system *(8)*.
- The evidence on irrigation of incisional wounds with aqueous PVP-I is available from studies investigating PVP-I 10% in open abdominal surgery (CDC wound classes I-IV; 3 RCTs), PVP-I 1% in appendectomies (CDC wound classes II-IV; one RCT) and PVP-I 0.35% in orthopaedic spine surgery (CDC wound class I; 3 RCTs). There was no evidence for a dose-response effect with regard to the concentration of the PVP-I solution used.

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- Two RCTs showed that the pulse pressure irrigation of incisional wounds with a normal saline solution was beneficial in reducing the risk of SSI in CDC wound classes I and II-III compared to normal irrigation with a saline solution. One RCT showed that irrigation with a normal saline solution applied with pressure to the incisional wound was beneficial compared to no irrigation. Nevertheless, the GDG considered that there is insufficient evidence to issue a recommendation for or against the saline solution irrigation of incisional wounds as one RCT investigating regular irrigation with a saline solution showed neither benefit nor harm when compared to no irrigation. When saline solution irrigation is used, the use of pulse pressure irrigation may be considered.
- The available evidence from 5 RCTs shows that the antibiotic irrigation of the incisional wound has neither benefit nor harm in reducing SSI when compared to no or saline solution irrigation.
- Of the included studies, 3 RCTs *(5, 9, 10)* described sterility of the irrigation fluid. The other studies did not report whether the irrigation fluid was sterile or not.
- The GDG discussed allergic reactions and metabolic adverse events as potential harms of iodine uptake. However, clinical signs of iodine toxicity were not reported in the included studies *(5)*. In the case of known or presumed allergy to iodine, other products (for example, chlorhexidine) should be used if incisional wound irrigation is performed. PVP-I must not be allowed to come into contact with exposed meninges and neural tissues, such as the brain or spinal cord *(11)*. Based on in vitro studies *(12, 13)*, the GDG also raised concerns about the potential toxic effects of PVP-I on fibroblasts, the mesothelium and the healing of tissue. No study assessed undesirable outcomes for pulse pressure irrigation.
- The GDG highlighted the risk of emergence of AMR associated with the use of antibiotics for wound irrigation. Considering that the evidence shows that this procedure has no benefit with regard to SSI prevention, the GDG strongly emphasized that this practice is associated with an unnecessary risk of contributing to AMR. Furthermore, the GDG underlined that there is no standardized procedure to prepare an antibiotic solution for wound irrigation and no certainty of target attainment by using this method.

Background

Intraoperative wound irrigation is the flow of a solution across the surface of an open wound to achieve wound hydration and it is widely practised to help prevent SSI *(14-16)*. It is intended to act as a physical cleaner by removing cellular debris, surface bacteria and body fluids, to have a diluting effect on possible contamination, and to function as a local antibacterial agent when an antiseptic or antibiotic agent is used. Up to 97% of surgeons state that they use intraoperative irrigation *(14)*.

However, practices vary depending on the patient population, the surface of application and solutions used. Similar variations in methodology and results can be observed in studies investigating the effect of wound irrigation *(17)*. Some experimental studies have also raised concerns about the cytotoxicity of some bactericidal additives, but the clinical relevance of these findings is unclear. Moreover, most of the literature investigating wound irrigation dates from an era when infection prevention measures were incomparable to practice today.

Two clinical practice guidelines issued by professional societies and a national authority have included contradictory recommendations regarding intraoperative wound irrigation (Table 4.18.1). The SHEA/IDSA guideline recommends performing intraoperative antiseptic wound lavage (grade II level of evidence) *(18)*. The UK-based NICE guideline states that there is only limited evidence suggesting a benefit for intraoperative wound irrigation with PVP-I. However, although wound irrigation with PVP-I may reduce SSI, PVP-I is not licensed for open wounds by the US Food and Drug Administration *(19)*. Therefore, the NICE guideline recommends that wound irrigation should not be used to reduce the risk of SSI *(20)* .

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Table 4.18.1. **Recommendations on wound irrigation according to available guidelines**

Guidelines (date issued)	Recommendations on wound irrigation to reduce the risk of SSI
SHEA/IDSA (2014) *(18)*	Perform antiseptic wound lavage (for example, with diluted PVP-I).
NICE (2008) *(20)*	Do not use wound irrigation to reduce the risk of SSI.

SSI: surgical site infection; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence.

Following the in-depth analysis of the sources and strength of evidence in current guidelines, the GDG members decided to conduct a systematic review to assess the available evidence on wound irrigation.

Summary of the evidence

The purpose of the evidence review (web Appendix 19) was to investigate whether intraoperative wound irrigation (with or without active agents or pressured application) affects the incidence of SSI. The population studied were adult patients undergoing a surgical procedure. The primary outcome was the occurrence of SSI and SSI-attributable mortality. Only studies investigating wound irrigation (flow of solution across the surface of an open wound, with or without active additives) were included. Studies investigating the topical application of antibiotics or antiseptics (powder, gels, sponges, etc.) other than intraoperative wound irrigation were not included. To ensure that only evidence relevant to the current standard of infection prevention measures was included in our analyses, studies where SAP was not administered appropriately (that is, preoperatively and intravenous) were excluded. In addition, studies where wound irrigation represented a therapeutic intervention for a pre-existent infection rather than a prophylactic measure were also excluded.

A total of 21 RCTs comparing (active) wound irrigation vs. no (active) wound irrigation in patients undergoing various surgical procedures were identified with SSI as the outcome (web Appendix 19). There was substantial heterogeneity in the available evidence. The main differences were related to the irrigated surface, the composition of the irrigation fluid and the surgical procedure with the associated wound contamination level. After careful appraisal of the included studies, the research team and the GDG decided to restrict the recommendation to incisional wound irrigation as too little (and heterogeneous) evidence was available to address other applications of irrigation (that is, intraperitoneal or mediastinal irrigation). In particular, the GDG agreed not to consider intraperitoneal irrigation for the formulation of recommendations as the identified studies described contaminated and dirty intra-abdominal procedures (for example, peritonitis). Therefore, wound irrigation was likely to represent a therapeutic intervention, rather than a prophylactic measure.

Meta-analyses were performed to evaluate the following comparisons in incisional wound irrigation: saline solution vs. no irrigation; syringe pressure irrigation with saline solution vs. no irrigation; pulse pressure irrigation with saline solution vs. normal saline solution; aqueous PVP-I vs. saline solution; and antibiotic vs. saline solution or no irrigation.

One study *(21)* compared irrigation of the incisional wound with normal saline solution to no irrigation in women undergoing a caesarean section (CDC wound class II). The study demonstrated no significant difference between wound irrigation and no irrigation on the incidence of incisional wound infection (OR: 1.09; 95% CI: 0.44-2.69; *P*=0.85). The quality of evidence was very low due to risk of bias and imprecision. When different methods of irrigation were compared, a low quality of evidence from 2 studies *(22, 23)* demonstrated a significant benefit for pulse pressure irrigation in preventing SSI compared to normal irrigation with a saline solution (OR: 0.30; 95% CI: 0.08-0.86; *P*=0.0003). A moderate quality of evidence from another study *(24)* demonstrated a significant benefit for irrigation with a normal saline solution applied with force compared to no irrigation (OR: 0.35; 95% CI: 0.19-0.65; *P*=0.0009).

Seven RCTs *(1-7)* compared irrigation of the incisional wound with aqueous PVP-I solutions in

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different concentrations to irrigation with a saline solution. Meta-analysis of these studies demonstrated a significant benefit for incisional wound irrigation with an aqueous PVP-I solution (OR: 0.31; 95% CI: 0.13-0.73; *P*=0.007). However, the quality of evidence was low due to risk of bias and imprecision. Stratification for wound contamination and PVP-I solution showed that the effect was attributable to incisional wound irrigation in clean and clean-contaminated procedures with PVP-I 10% and PVP-I 0.35%.

Five studies *(25-29)* compared irrigation of the incisional wound with an antibiotic solution to irrigation with a normal saline solution or no irrigation in CDC wound classes I-IV. A meta-analysis of the 5 RCTs demonstrated no significant difference between antibiotic irrigation of the incisional wound and no irrigation or only with a saline solution (OR: 1.16; 95% CI: 0.64-2.12; P=0.63). The quality of evidence was very low due to risk of bias and imprecision.

Factors considered when formulating the recommendation

Values and preferences

Patient values and preferences were not assessed by the studies, but the GDG argued that the recommendation was in line with the values and preferences of most patients.

Resource use

The GDG pointed out that there is a lack of data on costs or the cost-effectiveness of interventions using wound irrigation. Although the GDG recognized that saline and PVP-I solutions are usually readily available in most settings, the availability of sterile products may be limited in LMICs. In many settings, the availability and costs of pulse pressure devices, including their purchase, waste disposal, procurement, energy and machine maintenance, represent a high financial burden, especially in LMICs. Moreover, the use of pressure devices introduces the need for staff protection, such as gowns and face shields.

Research gaps

The GDG highlighted that the available evidence comes from old studies mainly conducted in the 1980s. This represents a serious limitation as IPC measures have changed significantly since that period. New well-designed RCTs using standard of care protocols for SAP are needed to evaluate and compare the most commonly-used irrigation practices with a special emphasis on the agent used and a focus on the prevention of SSI in different surgical procedures. In particular, it is unclear as to what is the best alternative agent to PVP-I in the case of an adverse event with this solution. These studies should be conducted in both high-income and LMICs. In addition, trials should address also the cost-effectiveness of the intervention and the harm associated with irrigation and the agents used for irrigation.

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4.19 Prophylactic negative pressure wound therapy

Recommendation

The panel suggests the use of prophylactic negative pressure wound therapy (pNPWT) in adult patients on primarily closed surgical incisions in high-risk wounds, for the purpose of the prevention of SSI, while taking resources into account.
(Conditional recommendation, low quality of evidence)

Rationale for the recommendation

- Overall low quality evidence shows that pNPWT has a benefit in reducing the risk of SSI in patients with a primarily closed surgical incision following high-risk wounds (for example, in case of poor tissue perfusion due to surrounding soft tissue/skin damage, decreased blood flow, bleeding/hematoma, dead space, intraoperative contamination) when compared to conventional postoperative wound dressings.
- The GDG emphasized that the devices used for pNPWT are expensive and may not be available in low-resource settings. Thus, the prioritization of this intervention should be carefully considered according to resources available and other priority measures for the prevention of SSI.
- It was also noted that there were no trials comparing different levels of negative pressure or different durations of applying negative pressure to the wound. In addition, studies did not report subgroup analyses by type of surgery or the degree of wound contamination. In stratified meta-analyses, there was little evidence that the effects differed by type of surgery, wound class or the level and duration of applying negative pressure. The GDG concluded that the effect appears to be independent of these factors and that no recommendations can be made on the optimal level of pressure or duration of application.
- As a result of the low quality evidence and the other above-mentioned factors, the majority of GDG members agreed to suggest the use of pNPWT on primarily closed surgical incisions in high-risk procedures, but taking resources into account. One GDG member disagreed with the recommendation because he considered the evidence insufficient to support it. The GDG decided that the strength of this recommendation should be conditional.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. Therefore, this recommendation is not proven for paediatric patients. The GDG pointed out that all RCTs were performed in clean surgery (4 in orthopaedic and trauma surgery), apart from one study that also included abdominal procedures. By contrast, the included observational studies were performed in clean, clean-contaminated, contaminated and dirty procedures. As pNPWT devices are commonly used in abdominal surgery, the GDG considered that observational studies should be included.
- Negative pressure devices were set between 75 mm Hg and 125 mm Hg with the postoperative duration ranging from 24 hours up to 7 days. The control group used sterile dry gauze, tape, occlusive or absorbent dressings.
- The overall quality of evidence was low for the RCTs due to risk of bias and imprecision and low for the observational studies.
- The GDG discussed potential mechanisms for the observed benefit of pNPWT, including less wound dehiscence, better removal of fluids and protection against microorganisms entering the wound from the surrounding environment.
- The GDG identified the appearance of blisters *(1)* or maceration as possible harms associated with the use of use of negative pressure devices. No other relevant adverse event was identified through the available evidence.

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Background

Negative Pressure Wound Therapy consists of a closed sealed system connected to a vacuum pump, which maintains negative pressure on the wound surface. pNPWT is used on primarily closed surgical incisions to prevent SSI. Although negative pressure wound therapy has been used since the late 1990s for several purposes, such as open bone fractures *(2)*, diabetic ulcers *(3)* and management of open abdomen wounds *(4)*, its use for the prevention of SSI is relatively new. After the first report of its use in orthopaedic surgery in 2006 *(5)*, several studies have followed.

Current SSI prevention guidelines do not offer a recommendation on the use of pNPWT. Only the UK-based NICE addresses this topic in a recent evidence update of its guidelines, but without formulating a recommendation. These guidelines state that "NPWT appears to reduce SSI rates after the invasive treatment of lower limb trauma, but may be less effective in other patient groups, such as those with multiple comorbidities. Further research is needed." *(6)*.

Following discussion about the interest in this topic and the lack of recommendations in other guidelines, the GDG decided to conduct a systematic review to assess the effectiveness of the use of pNPWT to prevent SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 20), was to evaluate whether the use of pNPWT is more effective in reducing the risk of SSI than the use of conventional wound dressings without negative pressure therapy. The target population included patients of all ages undergoing a surgical procedure. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Nineteen articles describing 21 studies that compared the use of pNPWT with conventional wound dressings were identified. These included a total of 6122 patients and comprised six RCTs *(1, 5, 7-9)* and 15 observational studies *(10-23)* (RCTs, 562; observational studies, 5560). One article *(5)* described two separate studies and another article assessed and analysed separately two different patient populations (breast and colorectal) *(20)*.

Due to heterogeneity among the selected studies regarding the type of surgical procedure or wound contamination class, as well as the level and duration of applying negative pressure, additional separate meta-analyses were performed. These concerned the type of surgical procedure, wounds classified as clean and clean-contaminated, the duration of pNPWT for <5 days vs. >5 days and a pressure level of <100 mmHg vs. >100 mmHg (web Appendix 20).

Overall, there is low quality evidence from RCTs and observational studies that pNPWT has a significant benefit in reducing the risk of SSI in patients with a primarily closed surgical incision when compared to conventional postoperative wound dressings (RCTs: OR: 0.56; 95% CI: 0.32–0.96; observational studies: OR: 0.30; 95% CI: 0.22–0.42). When stratified by the type of surgery (web Appendix 20), the most relevant meta-analyses results showed no statistically significant benefit in the reduction of the risk of SSI in orthopaedic and/or trauma surgery. By contrast, a significant benefit was observed in reducing SSI rates with the use of pNPWT compared to conventional wound dressings in abdominal (9 observational studies; OR: 0.31; 95% CI: 0.19–0.49) and cardiac surgery (2 observational studies; OR: 0.29; 95% CI: 0.12–0.69).

In the stratification by wound contamination class (web Appendix 20), the most relevant meta-analyses results showed a significant benefit in reducing SSI rates with the use of pNPWT compared to conventional wound dressings in clean surgery (8 observational studies; OR: 0.27; 95% CI: 0.17–0.42) and in clean-contaminated surgery (8 observational studies; OR: 0.29; 95% CI: 0.17–0.50).

When considering different durations of pNPWT (for either < or ≥ 5 days) and a pressure level (of either < or ≥ 100 mmHg), the significant benefit observed with the use of pNPWT remained unchanged (web Appendix 20).

The body of retrieved evidence focused on adult patients only. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG is confident that most patients would

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wish to receive this intervention in order to reduce the risk of SSI. However, there are concerns about comfort and convenience as some devices can be noisy and may disturb sleep. The GDG pointed out that the use of pNPWT may prolong hospital stay, but this could be prevented by the use of portable suction systems.

Resource use

The availability and costs of these devices and the potential extension of hospital stay are major concerns, mainly in LMICs, but also in high-resource settings. The GDG remarked that patients are generally more likely to receive a conventional dressing instead of pNPWT due to lack of material and evidence of cost-effectiveness. However, studies in gynaecological patients showed that the intervention may be cost-effective *(24-26)*. The GDG acknowledged that it may be possible to construct a non-portable, locally-made device at low cost for LMICs. It was highlighted also that there is a need to train staff in handling these devices, regardless of the setting.

Research gaps

The GDG highlighted that additional well-designed RCTs investigating the use of pNPWT for SSI prevention are needed, especially in LMICs. Future research is likely to have an important impact on our confidence in the estimate of effect. The main research priority is to identify the groups of patients in whom this intervention is cost-effective, including those undergoing contaminated and dirty procedures. Further research is also needed to identify the optimal level of negative pressure and duration of application.

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4.20 Use of surgical gloves

Recommendation

The panel decided not to formulate a recommendation due to the lack of evidence to assess whether double-gloving or changing of gloves during the operation or using specific types of gloves is more effective in reducing the risk of SSI.

Remarks

- Gloving refers to the use of sterile gloves by the surgical team during the operation.
- During the operation, glove decontamination with alcohol or other products for the purpose of reuse should never be performed.
- Sterile surgical gloves (as well as medical examination gloves) are single-use items and should not be reused.
- The literature search failed to identify relevant studies on the following topics of interest that ultimately could inform a recommendation for these questions with regard to the prevention of SSI: a comparison of double-gloving vs. using a single pair of gloves; the intraoperative changing of gloves vs. retaining gloves; and latex gloves vs. other types of gloves.
- The GDG emphasized that most surgeons prefer to double-glove because it is plausible that bacterial contamination of the surgical field may occur in the event of glove perforation. Moreover, most surgeons prefer to wear double gloves for their own protection against injury from sharps and/or bloodborne infections. In the case of double-gloving, a routine change of the outer gloves during long surgeries is often recommended by health care practitioners. However, no evidence was found to support these practices.

Background

The invasive nature of surgery introduces a high risk for the transfer of pathogens that may cause bloodborne infections in patients and/or the surgical team, as well as SSI. This risk may be reduced by implementing protective barriers, such as wearing surgical gloves.

A Cochrane review *(1)* published in 2009 investigated whether additional glove protection reduces the number of SSIs or bloodborne infections in patients or the surgical team and the number of perforations to the innermost pair of surgical gloves. There was no direct evidence that additional glove protection worn by the surgical team reduces SSI in patients. However, the review had insufficient power for this outcome as only two trials were found with the primary outcome of SSI, both of which reported no infections. No trials were found with transmitted bloodborne infections as an outcome in surgical patients or the surgical team in relation to the gloving method. Thirty-one RCTs were identified with the outcome of glove perforation, leading to the result that the use of a second pair of surgical gloves, triple gloving, knitted outer gloves and glove liners significantly reduces perforations to the innermost gloves.

Few organizations have issued recommendations regarding the use of gloves (Table 4.20.1). The latest WHO *guidelines for safe surgery* published in 2009 *(2)* recommend that the operating team should cover their hair and wear sterile gowns and sterile gloves during the operation, but without any indication on single or double-gloving. The SHEA/IDSA guidelines *(3)* recommend that all members of the operative team should double-glove and change gloves when perforation is observed. However, the modalities and frequency of changing gloves have not been included in any guidelines or recommendations *(2-4)*.

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Table 4.20.1. **Recommendations on gloving according to available guidelines**

Guidelines (year issued)	Recommendations on the use of gloves
WHO guidelines for safe surgery (2009) *(2)*	The operating team should cover their hair and wear sterile gowns and sterile gloves during the operation.
SHEA/IDSA practice recommendation (2014) *(3)*	All members of the operative team should double-glove and change gloves when perforation is observed.

WHO: World Health Organization; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America.

Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG decided to conduct a systematic review to assess the effectiveness of double-gloving and the changing of gloves at a specific time during the operation to reduce SSI. The question of whether a specific type of gloving is beneficial in reducing the risk of SSI was also addressed.

Summary of the evidence

The purpose of the evidence review (web Appendix 21) was to evaluate whether double-gloving or the changing of gloves during the operation is more effective in reducing the risk of SSI than single-glove use or no change of gloves. In a third approach, it was evaluated whether specific types of gloving (that is, glove liners, coloured perforation indicator systems, cloth/steel outer gloves, triple gloves) are more effective in reducing the risk of SSI than the use of latex gloves.
The target population included patients of all ages undergoing a surgical operation. The primary outcome was the occurrence of SSI and SSI-attributable mortality. Bacterial contamination of the gloves was considered as a surrogate outcome.

Ten studies comprising 8 RCTs *(5-12)* and 2 observational studies *(13, 14)* were identified. Among these, one observational study compared the efficacy of double-gloving with the use of a single pair of gloves with an SSI outcome *(13)* and another (observational) with a cerebrospinal fluid shunt infection outcome *(14)*. Six studies compared the changing of gloves during the operation with the retaining of gloves (3 RCTs with an SSI outcome *(6, 7, 10)*, 2 RCTs *(5, 11)* focusing on bacterial contamination and one RCT *(12)* reporting on both). Two RCTs with an SSI outcome compared specific types of gloving with the use of latex gloves *(8, 9)*. Types of surgery included were neurosurgery, hernia repair, caesarean section, orthopaedic and vascular surgery.

Due to heterogeneity among the selected studies regarding comparison, design and outcome, quantitative meta-analyses were not performed.

Whereas one observational study *(14)* showed that the cerebrospinal fluid shunt infection rate was significantly higher in the single-glove group compared to the double-glove group, another observational study *(13)* found no difference in the risk of SSI between double- vs. single-gloving in patients undergoing hernia repair. Three RCTs *(6, 7, 10)* showed no difference in risk for post-caesarean SSI or endometritis when comparing changing of gloves or removal of the external second pair of gloves after delivery of the placenta or fetus to retaining the gloves during the entire procedure. One RCT *(12)* reported a reduction of superficial SSI when changing of gloves was performed vs. no change of gloves before the first contact with the vascular prosthesis in synthetic vascular graft surgery. Three RCTs *(5, 11, 12)* and one additional non-comparative observational study *(15)* showed that changing of the external second pair of gloves in the course of the operation significantly decreases the incidence of bacterial contamination of the gloves. Two RCTs *(8, 9)* showed no difference in SSI when comparing different types of gloves (double-gloving) in orthopaedic surgery.

The methodological quality of most of the selected studies was poor as most trials did not provide sufficient details of their process of randomization, allocation, sample size calculation and blinding. SSI

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definitions varied across the studies. There were few studies with SSI as the primary outcome. Included studies with bacterial contamination as a surrogate outcome showed a great heterogeneity in the setting, design and outcome measures. There is no direct evidence demonstrating the link between bacterial contamination and SSI rates.

The body of retrieved evidence focused on adult patients and no study was available in a paediatric population. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered

Resource use

The availability of surgical gloves could be limited in LMICs, particularly specific types, such as glove liners, coloured perforation indicator systems, cloth steel outer gloves. In limited resource settings, an acceptable quality of gloves needs to be ascertained as patients are often asked to purchase surgical gloves themselves, which could be of substandard quality.

Research gaps

GDG members highlighted that well-designed RCTs investigating the effectiveness of double-gloving compared to the use of a single pair of gloves would be welcome, especially in LMICs. In addition, RCTs evaluating whether a change of gloves during the operation is more effective in reducing the risk of SSI than no change of gloves are needed, including an assessment of the criteria for changing gloves during the surgical procedure. It would be interesting also to compare different types of gloving to address the question of the optimal type of gloves to be used. All studies should focus on SSI as the primary outcome and be defined according to the CDC criteria and sub-specified as superficial, deep and organ space-occupying.

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4.21 Changing of surgical instruments

Recommendation

The panel decided not to formulate a recommendation on this topic due to the lack of evidence.

Remarks

- Surgical instruments are tools or devices that perform functions such as cutting, dissecting, grasping, holding, retracting or suturing. Most surgical instruments are made from stainless steel.
- The literature search failed to identify relevant studies comparing wound closure using new, sterile surgical instruments with wound closure with previously-used instruments in contaminated surgery for the purpose of preventing SSI.
- The GDG believes that changing instruments for wound closure in contaminated surgery is common practice. A change of instruments prior to wound closure after contaminated surgical procedures seems logical, particularly after colorectal surgery or in patients operated on for diffuse peritonitis. Nevertheless, there is no evidence to support this practice.

Background

SSI is caused by microorganisms either from the patient's own skin flora or from the environment surrounding the patient. In both cases, there is a potential for microorganisms to adhere to surgical instruments and consequently contaminate the incisional wound, particularly during contaminated surgical procedures. Therefore, it is common practice to exchange surgical instruments used in contaminated surgical procedures for a new sterile set of surgical instruments before wound closure.

Current SSI prevention guidelines do not address the exchange of surgical instruments prior to wound closure and its effect to prevent SSI. The GDG decided to conduct a systematic review to assess the effectiveness of this practice.

Summary of the evidence

The purpose of the evidence review (web Appendix 22) was to evaluate whether wound closure employing new, clean surgical instruments is more effective in reducing the risk of SSI than wound closure with previously-used surgical instruments. The target population included patients of all ages undergoing contaminated surgical operations. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

The literature search did not identify any studies comparing wound closure using new, sterile surgical instruments and wound closure with previously-used surgical instruments in contaminated surgery.

Two studies, one RCT *(1)* and one observational study *(2)*, investigated the change of instruments in colorectal surgery in combination with other interventions performed before wound closure, including the change of drapes, gowns and gloves, wound lavage and rescrubbing (not homogeneous in terms of interventions). Both studies showed no benefit for the prevention of SSI.

Research gaps

The GDG highlighted that well-designed RCTs investigating the change of instruments prior to wound closure would be welcome. SSI outcome should be defined according to CDC criteria and studies should be conducted in LMICs and high-income countries and include different surgical procedures. However, several GDG members pointed out that such trials are unlikely to be done. In the future, it is more likely that further studies of combined interventions will be conducted.

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4.22 Antimicrobial-coated sutures

Recommendation

The panel suggests the use of triclosan-coated sutures for the purpose of reducing the risk of SSI, independent of the type of surgery.
(Conditional recommendation, moderate quality of evidence)

Rationale for the recommendation

Overall low to moderate quality evidence shows that antimicrobial-coated sutures have significant benefits in reducing SSI rates in patients undergoing surgical procedures when compared to non-coated sutures. The effect seems to be independent of the type of suture, procedure or wound contamination classification. In meta-regression analysis, there was no evidence that the effect of antimicrobial-coated sutures differed between braided and monofilament sutures, clean, cardiac or abdominal surgery, and other surgeries. However, the GDG highlighted that the available trials examined triclosan-coated, absorbable sutures only. There were no studies identified that investigated other antimicrobial agents. Considering the low to moderate quality of the evidence and the low quality of comparisons in the subgroups of the RCTs included in the meta-regression analyses, the GDG agreed that the strength of the recommendation should be conditional.

Remarks

- The body of retrieved evidence mostly focused on adult patients and only one study was available in a paediatric population. This recommendation can be applied to paediatric patients, but the manufacturer's instructions should be checked to evaluate any contraindication for paediatric patients.
- The GDG discussed the available evidence and agreed to consider only studies comparing the same type of suture in order to prevent confounding by type of suture (monofilament or braided).
- The overall quality of evidence was moderate for the RCTs due to risk of bias and low for the observational studies. The GDG discussed whether or not to consider indirectness for the overall comparison of antimicrobial-coated vs. non-coated sutures. The agreement was that indirectness does not apply because the PICO question is very broad.
- Included studies were performed in high- and middle-income countries.
- Types of surgical procedures included were colorectal, abdominal, breast, head and neck, lower limb, spinal, cardiac, vascular and other surgery.
- The types of sutures investigated in the included studies were triclosan-coated polydioxanone suture vs. polydioxanone suture featuring a monofilament suture construction (3 RCTs *(1-3)*); triclosan-coated polyglactin 910 suture vs. polyglactin 910 suture featuring a braided (multifilament) suture construction (7 RCTs *(4-10)* and 4 observational studies *(11-14)*); and polyglactin 910 and poliglecaprone 25 (both triclosan-coated) sutures vs. polyglactin 910 and poliglecaprone 25 sutures featuring a braided (polyglactin 910) and a monofilament (poliglecaprone 25) suture construction (3 RCTs *(15-17)* and one observational study *(18)*).
- No adverse events have been associated in the included studies with the use of antimicrobial-coated sutures. However, the GDG pointed out that there is limited evidence that triclosan may have negative effects on wound healing *(19)* or lead to contact allergy *(20)*. Although the development of resistance is mentioned as a concern, the daily absorption of triclosan from consumer products (for example, commercially-available hand soap) is higher than a single triclosan suture *(21-23)*.

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Background

Surgical suture material is used to adequately adapt the wound edges and thus it is in direct contact with the wound itself. To prevent microbial colonization of the suture material in operative incisions, sutures with antibacterial activity have been developed. Triclosan (5-chloro-2-[2.4-dichlorophenoxy] phenol) is a broad-spectrum bactericidal agent that has been used for more than 40 years in various products, such as toothpaste and soaps. Higher concentrations of triclosan work as a bactericide by attacking different structures in the bacterial cytoplasm and cell membrane *(24)*. At lower concentrations, triclosan acts as a bacteriostatic agent binding to enoyl-acyl reductase, a product of the Fab I gene and thus inhibiting fatty acid synthesis *(25, 26)*.

Several trials have shown that the use of triclosan-coated sutures leads to a reduction of the number of bacteria in vitro and also of wound infections in animal and clinical studies *(27-29)*. Of note, this effect is not confined to any particular tissue or organ system *(23)*. Apart from triclosan, several novel antimicrobial coatings are now becoming available *(30, 31)*, but there are still no reported clinical studies comparing the efficacy of novel antibacterial sutures with non-coated ones. Triclosan-coated polyglactin 910, triclosan-coated polydioxanone, and triclosan-coated poliglecaprone 25 are commercially-available sutures with antimicrobial properties. Commonly-used non-coated sutures are polyglactin 910, polydioxanone, poliglecaprone 25, polyglycolic acid and polyglyconate sutures.

Few organizations have issued recommendations regarding the use of antimicrobial-coated sutures (Table 4.22.1). The UK-based NICE suggests that antimicrobial-coated sutures may reduce the SSI risk compared to non-coated sutures, although this effect may be specific to particular types of surgery, such as abdominal procedures *(32)*. The SHEA/IDSA guidelines indicate that antiseptic-impregnated sutures should not be used routinely as a strategy to prevent SSI *(33)*.

Table 4.22.1. **Recommendations on the use of antimicrobial-coated sutures according to available guidelines**

Guidelines (year issued)	Recommendations on the use of antimicrobial-coated sutures
SHEA/IDSA practice recommendation (2014) *(33)*	Do not routinely use antiseptic-impregnated sutures as a strategy to prevent SSI.
NICE (2013 update) *(32)*	Antimicrobial-coated sutures may reduce the SSI risk compared to uncoated sutures, although this effect may be specific to particular types of surgery, such as abdominal procedures.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; SSI: surgical site infection.

Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG decided to conduct a systematic review to assess if the use of antimicrobial-coated sutures might be beneficial for surgical patients to prevent SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 23) was to evaluate whether the use of antimicrobial-coated sutures is more effective in reducing the risk of SSI than the use of non-coated sutures. The target population included patients of all ages undergoing a surgical procedure. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Eighteen studies (13 RCTs *(1-10, 15-17)* and five cohort studies *(11-14, 18)*) including a total of 7458 patients (RCTs, 5346; observational studies, 2112) and comparing the use of antimicrobial- with non-coated sutures were identified.

Seven studies compared the efficacy of antimicrobial-coated sutures with non-coated sutures in mixed wounds (5 RCTs *(2-5, 8)* and 2 observational studies *(12, 14)*). A further 7 studies (5 RCTs *(6, 10, 15-17)*

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and 2 observational studies *(11, 18)*) made the same comparison in clean wounds, mainly cardiac and breast cancer surgery, and 4 studies (3 RCTs *(1, 7, 9)* and one observational study *(13)*) concerned clean-contaminated wounds in abdominal surgery.

Due to heterogeneity among the selected studies regarding the type of suture used, type of surgical procedure or wound contamination class, additional separate meta-analyses were performed for triclosan-coated polydioxanone suture vs. polydioxanone suture, triclosan-coated polyglactin 910 suture vs. polyglactin 910 suture, and polyglactin 910 and poliglecaprone 25 (both triclosan-coated) sutures vs. polyglactin 910 and poliglecaprone 25 sutures, as well as in clean, clean-contaminated and mixed types of wounds (web Appendix 23).

Overall, there is moderate to low quality evidence that antimicrobial-coated sutures have significant benefit in reducing SSI rates in patients undergoing surgical procedures when compared to non-coated sutures (moderate quality for RCTs: OR: 0.72; 95% CI: 0.59–0.88; low quality for observational studies: OR: 0.58; 95% CI: 0.40–0.83).
In meta-regression analysis, there was no evidence that the effect of antimicrobial-coated sutures differed between braided and monofilament sutures (P=0.380), or between clean (P=0.69), cardiac (P=0.900) or abdominal (P=0.832) and other types of surgery. According to these analyses, the effect seems to be independent of the type of suture, procedure or wound contamination classification.

Regarding the comparisons of specific types of sutures (web Appendix 23), only the meta-analyses of the studies comparing triclosan-coated polyglactin 910 suture vs. polyglactin 910 suture featuring a braided suture construction showed that the use of antimicrobial-coated sutures has significant benefit compared to non-coated sutures in reducing SSI rates (OR: 0.62; 95% CI: 0.44–0.88 for RCTs; OR: 0.58; 95% CI: 0.37–0.92 for observational studies).

Some limitations of the included studies should be noted. The quality of the included RCTs was moderate to low. Indeed, some studies had an unclear or high risk of blinding of participants, care-providers and outcome assessors, and/or a high risk of incomplete outcome data. Furthermore, some studies had industrial sponsorship or conflicts of interest with a commercial company.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG is confident that most patients wish to receive this intervention in order to reduce the risk of SSI, but patients must be informed about the small and unconfirmed risk of allergy to triclosan. The GDG emphasized that patients would like to be part of the process by being involved and informed.

Resource use

The GDG emphasized that sutures are expensive in general. Moreover, the availability of antimicrobial-coated sutures is limited in LMICs. In settings where patients have to pay for the material themselves, an increase in costs would represent an additional personal financial burden. At the time of formulating this recommendation, the GDG noted that manufacturers sold the antimicrobial-coated and non-coated sutures for approximately the same price. However, the GDG is not aware of the future pricing policy of manufacturers. The use of antimicrobial-coated sutures could increase the cost per patient, but it might reduce the mean length of hospital stay and reduce potential costs to the health care system due to the avoidance of the risk of SSI *(5, 8, 34)*.

The body of retrieved evidence mostly focused on adult patients and only one study *(4)* was available in a paediatric population. The literature search did not identify any studies that reported on SSI attributable-mortality.

Research gaps

The GDG highlighted the limited evidence available in some areas and the need for further research on the effects of antimicrobial-coated sutures in reducing SSI rates. In particular, studies should be conducted in LMICs and include different surgical procedures. Comparisons between antimicrobial-coated and non-coated sutures should be performed with the same type of suture material, including non-absorbable sutures. In particular, comparisons with an alternative antimicrobial agent to triclosan would be welcome. More research is required to investigate the effectiveness of antimicrobial-coated sutures in the paediatric population and in various types of settings. All studies should be designed as a RCT with the SSI outcome defined according to CDC criteria and sub-specified as superficial, deep and organ space

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occupying. Adverse events related to the intervention should be clearly reported, including the need to assess the risk of allergy. Importantly, possible emerging AMR to the antimicrobial agent should be monitored. Moreover, cost-effectiveness studies are also needed. Of note, research investigating the effectiveness of antimicrobial-coated sutures should be independently funded with a limited influence of industry sponsorship.

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4.23 Laminar airflow ventilation systems in the context of operating room ventilation

Recommendation

The panel suggests that laminar airflow ventilation systems should not be used to reduce the risk of SSI for patients undergoing total arthroplasty surgery.
(Conditional recommendation, low to very low quality of evidence)

Rationale for the recommendation

Very low quality evidence shows that in both total hip (THA) and knee (TKA) arthroplasty, laminar airflow ventilation has no benefit when compared to conventional ventilation in reducing the SSI rate. In THA, conventional ventilation had a non-significant beneficial effect in reducing the risk of SSI. Therefore, the GDG unanimously agreed that laminar airflow ventilation systems should not be used as a preventive measure to reduce the risk of SSI for total arthroplasty surgery. The strength of this recommendation was considered to be conditional, considering the very low quality of the supporting evidence. For other types of procedures, the available evidence consisted of single observational studies only and the GDG considered this body of evidence to be insufficient to lead to any specific recommendation. Moreover, laminar airflow ventilation has been of interest mainly as a preventive measure in orthopaedic arthroplasty surgery.

Remarks

- Conventional ventilation systems pass air with a mixed or turbulent flow into the OR. These systems aim to homogenize the fresh air and the air, aerosols and particles within the room. This leads to an accelerated dilution of the air volume and an irregular movement of the particles. Conventional turbulent ventilation systems are used for any type of surgery. Systems with laminar airflow are frequently used in an environment where a contamination with particles is a highly adverse event, for example, in orthopaedic implant surgery. The goal of laminar airflow is to pass the fresh air unidirectionally with a steady velocity and approximately parallel streamlines to create a zone where the air, aerosols and particles within the room are being driven out.
- No possible harms associated with the recommendation were identified. However, the cooling effect of the fresh air from a laminar airflow system on the surgical wound and the patient may lead to lower intraoperative tissue temperatures in the surgical wound or systemic hypothermia if the temperature is not monitored intraoperatively *(1)*.
- The GDG underlined that most data are from national surveillance databases or registries. Although these studies have a large sample size, they are not designed specifically for this comparison. Indeed, comparisons were between hospitals with laminar flow and those with conventional ventilation, rather than comparisons within the same hospital. This may lead to major confounding by factors such as differences in hospital/surgeon volume, characteristics of admitted patients and/or the extent of implementation of other SSI prevention measures.
- The systematic review investigated also the use of fans or cooling devices and natural ventilation in the operating room compared to conventional ventilation with regards to the risk of SSI. However, the literature search did not identify studies that evaluated these interventions. One observational study *(2)* that evaluated natural ventilation in the operating room compared to conventional ventilation following THA and TKA found no difference in the SSI risk.
- Given the very limited evidence on natural ventilation and fans/cooling systems, the GDG decided not to develop a recommendation on these topics. Nevertheless, it is advisable to ensure a proper ventilation rate of the operating room and an adequate maintenance of the components of the installed ventilation system *(3)*.

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Background

The ventilation system in the operating room is designed to provide certain functions, primarily to create thermal comfort for the patient and staff and to maintain constant air quality by eliminating aerosols and particles within the room. It serves also to maintain certain air pressure requirements between communicating rooms. Special ventilation systems supplying filtered air at positive pressure are required in the operating room. Ideally, around 20 air changes per hour are necessary to dilute microorganisms generated in the operating room and to exclude ingress from surrounding areas *(3)*.

There are various systems used to ventilate an operating room. Natural ventilation is the most basic way and refers to airflow by natural forces. WHO provides the following definition *(4)*: "use of natural forces to introduce and distribute outdoor air into or out of a building. These natural forces can be wind pressures or pressure generated by the density difference between indoor and outdoor air". Exploiting natural ventilation may be a suitable solution for settings with limited resources and it is considered as an option for IPC by WHO. However, there is no evidence available for its use in operating rooms *(4)*.

A well-designed ventilation system that takes advantage of natural air movements is still complex to achieve and is limited to a benign local climate *(4)*. If natural ventilation alone is not sufficient to fulfil the desired functions mentioned above, fans and cooling or warming devices are commonly installed, mostly to maintain the air temperature and humidity at a comfortable level. Limitations of these devices might be an inadequate rate of air changes per hour and control of the direction of airflow in the operating room and the spread of particles and dust, thus resulting in an insufficient elimination of aerosols and particles.

In most LMICs, operating rooms do not have a full mechanical ventilation system and the air conditioning used is a recirculating cooling device. If such a system is used, it should be wall-mounted rather than floor standing, and should be maintained regularly, including filters checked, cleaned or changed. The use of fans in the operating room is not recommended and should be used only as a last resort if the lack of air circulation affects the surgeon's performance. Any fans in the operating room or preparation room should be cleaned on a regular basis.

In well-resourced environments, conventional ventilation systems that pass air with a mixed or turbulent flow into the operating room are the most widely installed. These systems aim to homogenize the fresh air and the air, aerosols and particles within the room. This leads to an accelerated dilution of the air volume and an irregular movement of the particles. Conventional turbulent ventilation systems are used for all types of surgery. Systems with laminar airflow are frequently used in an environment where contamination with particles is a highly adverse event, for example, orthopaedic implant surgery. The goal of passing the fresh air unidirectionally with a steady velocity and approximately parallel streamlines is to create a zone where the air, aerosols and particles within the room are being driven out. Limitations to this principle are all forces disrupting the parallel airflow.

In many countries, the use of high efficiency particulate air filters (at least 99.97% efficient in removing particles ≥0.3 µm in diameter) in the operating room ventilation system is mandatory by law. Of note, the utmost importance must be paid to the maintenance of any kind of ventilation system and its components. The operating room ventilation system should be regularly checked and filters changed (the need for this is assessed by monitoring the pressure differential across the filters) according to local standard operating procedures, which should be based on the manufacturer's instructions and international guidelines.

A systematic review *(5)* published in 2012 on the influence of laminar airflow on prosthetic joint infections found laminar airflow ventilation to be a risk factor for the development of a severe SSI.

Some guidelines have issued recommendations regarding the ventilation systems in the operating room (Table 4.23.1), but several other SSI prevention guidelines do not address this topic. These range from a technical advice for proper air handling in the operating room *(6)* to leaving this question as an unresolved issue *(3)*. However, these recommendations are not based on systematic reviews of the literature and meta-analysis or a rigorous evaluation of the quality of the available evidence.

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Table 4.23.1. **Recommendations on ventilation systems in the operating room according to available guidelines**

Guidelines (year issued)	Recommendations on ventilation systems in the operating room
SHEA/IDSA practice recommendation (2014) *(6)*	Follow the American Institute of Architects' recommendations for proper air handling in the operating room.
CDC/HICPAC Guidelines for environmental infection control in health-care facilities (2003) *(3)*	No recommendation for orthopaedic implant operations in rooms supplied with laminar airflow.

SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; CDC: Centers for Disease Control and Prevention; HICPAC: Healthcare Infection Control Practices Advisory Committee.

Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG decided to conduct a systematic review to assess the effectiveness of ventilation systems in the operating room for the prevention of SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 24) was to evaluate whether a laminar airflow ventilation system is more effective in reducing the risk of SSI than a conventional ventilation system. The review investigated also whether fans or cooling devices and natural ventilation are acceptable alternatives to conventional ventilation for the prevention of SSI. The target population was patients of all ages undergoing a surgical procedure. The primary outcome was the occurrence of SSI and SSI-attributable mortality. Definitions in included studies that related to severe SSI, periprosthetic infection and deep infections requiring revision were considered as deep SSI.

Twelve observational studies *(2, 7-17)* comparing laminar airflow with conventional ventilation were identified. No RCTs were identified. Most data were obtained from national surveillance systems and registries. Of note, although these sources had a large sample size, the databases were not specifically designed for this comparison. Most studies focused on THA (33 0146 procedures) and TKA (134 368 procedures). Only single studies were available for other types of surgery (appendectomy *(7)*, cholecystectomy *(7)*, colon surgery *(7)*, herniorrhaphy *(7)*, gastric *(8)* and vascular surgery *(9)*). The population studied were mostly adult patients. According to the selected studies, the following comparisons were evaluated.

1. Laminar airflow ventilation vs. conventional ventilation
    a. in THA
    b. in TKA.

Very low quality evidence shows that laminar airflow ventilation has no benefit when compared to conventional ventilation in reducing the SSI rate in THA (OR: 1.29; 95% CI: 0.98–1.71) or TKA (OR: 1.08; 95% CI: 0.77–1.52).

In single observational studies, laminar flow was found to be associated with an increased overall risk of SSI in patients undergoing appendectomy; no significant association was shown in colon surgery, cholecystectomy and herniorraphy.
In gastric and open vascular surgery, the absence of laminar flow was found to increase the risk of SSI.

The search did not identify data that evaluated the use of fans or cooling devices in the operating room and their impact on the risk of SSI compared to a normal/conventional ventilation system.
One observational study *(2)* that evaluated natural ventilation in the operating room compared with conventional ventilation and its impact on the risk of SSI following THA and TKA found no difference in the risk of SSI.

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The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention. The GDG is confident that the typical values and preferences of the target population regarding the outcome would not favour the intervention and therefore would agree with the recommendation. The GDG believes also that patients would not have an opinion about a hospital ventilation system, as long as other aspects are being taken into account to prevent infections.

Resource use

Cost-effectiveness analyses found laminar airflow to be more expensive compared to a conventional ventilation system. An Italian study *(18)* evaluated an increase of 24% in building costs and an increase of 36% in annual operating costs. A model calculation study from Australia *(19)* evaluated additional costs of AUD$ 4.59 million per 30 000 THAs performed. Additional costs of € 3.24 procedure (1000 procedures per year for 15 years) were calculated by a German study group *(20)*. The GDG highlighted that the implementation of laminar airflow is difficult in low-income settings due to the lack of resources, technical expertise and infrastructure.

Research gaps

The GDG highlighted the very low quality evidence available on the topic and the need for further research on the effects of laminar flow in reducing the SSI rate, particularly well-designed clinical trials in the field of endoprosthetic surgery. The GDG acknowledged that RCTs may not be reasonable as they would require a massive investment with a high sample size to have enough power to see a difference. In addition, cluster trials could be problematic as it would be almost impossible to control for confounding factors, such as different surgeons operating in the same operating room. Nationwide databases may provide the best affordable information, but adherence to international definitions and more information about confounders need to be obtained from country surveillance systems and registries. The lack of evidence on the impact of fans/cooling devices and natural ventilation on the SSI rate compared to conventional ventilation emphasizes the need for further research in this field in order to evaluate whether these systems might be an alternative in resource-limited countries when properly designed and maintained.

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POSTOPERATIVE MEASURES

4.24 Surgical antibiotic prophylaxis prolongation

Recommendation

The panel recommends against the prolongation of SAP administration after completion of the operation for the purpose of preventing SSI.
(Strong recommendation/moderate quality of evidence)

Rationale for the recommendation

- Moderate quality evidence from a high number of RCTs (44 studies included in the overall meta-analysis) shows that prolonged SAP postoperatively has no benefit in reducing SSI after surgery when compared to a single dose. However, there was some evidence (low to very low quality) that a prolonged postoperative administration of antibiotics may be beneficial to reduce the risk of SSI in cardiac, vascular and orthognathic surgery when compared to single-dose prophylaxis. Considering this limited and low to very low quality evidence in support of SAP prolongation in the above-mentioned procedures, as well as the possible harm associated with the prolonged duration of antibiotic administration, the GDG agreed to recommend against the prolongation of antibiotic administration after completion of the operation for the purpose of preventing SSI.
- Considering the possible adverse events, the risk of generating AMR linked to SAP prolongation and the high number of available studies of moderate quality showing no benefit, the strength of the recommendation was decided to be strong.

Remarks

- In the included studies, "single dose" usually refers to a preoperative dose with or without intraoperative re-dosing, depending on the duration of the operation and the half-life of the drug. The included studies always compared the same antibiotic agent in the same dose per administration.
- The guidelines of the American Society of Health-System Pharmacists *(1)* recommend that intraoperative re-dosing is needed if the duration of the procedure exceeds 2 half-lives of the drug or if there is excessive blood loss during the procedure. While the benefit of this approach seems reasonable from a drug pharmacokinetic aspect, the reviewed studies have not addressed the duration of surgical procedures or re-dosing in relation to SSI in standard antibiotic prophylaxis protocols. No recommendation could be concluded on the benefit or harm of this approach.
- For cardiac (2 RCTs *(2, 3)*) and orthognathic surgery (3 RCTs *(4-6)*), there was some evidence that prolonging antibiotic administration after completion of the operation may be beneficial in reducing the risk of SSI when compared to single-dose prophylaxis. By contrast, other RCTs *(7-13)* showed no benefit of prolonging antibiotic prophylaxis beyond 24 hours compared to prophylaxis for up to 24 hours in these types of surgery.
- In vascular surgery, there was some evidence from one RCT *(14)* that prolonging antibiotic prophylaxis until intravenous lines and tubes are removed may be beneficial in reducing the risk of SSI when compared to single-dose prophylaxis.
- The GDG highlighted the risk of promoting AMR if antibiotics are prolonged in the postoperative period, both in the individual patient and at the health care facility level. In addition, this practice might negatively affect the patient microbiome and lead to short- and long-term gastrointestinal complications. A relevant harm possibly linked to prolonged SAP is the intestinal spread of *C. difficile* with a higher risk of a clinical manifestation of infection.

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Background

The preventive effect of the routine use of SAP prior to non-clean and implant surgery has long been recognized. However, the benefit of continuing SAP after completion of the procedure is unclear. While current guidelines recommend a maximum postoperative SAP duration of 24 hours, increasing evidence shows that there may be non-inferiority of a single preoperative dose (and possible additional intraoperative doses according to the duration of the operation). Despite this, surgeons still have a tendency to routinely continue SAP up to several days after surgery *(15, 16)*.

The use and duration of postoperative prophylaxis have been specified in clinical practice guidelines issued by professional societies or national authorities (Table 4.24.1). Several guidelines, such as those published by SHEA/IDSA *(17)* and the American Society of Health-System Pharmacists *(1)*, recommend discontinuing SAP within 24 hours after surgery. The 2012 SSI prevention bundle from the US Institute of Healthcare Improvement *(18)* recommends discontinuing SAP within 24 hours in general and within 48 hours in cardiac surgery. Other guidelines published by the UK-based NICE *(19)*, the Scottish Intercollegiate Guidelines Network (SIGN) *(20)*, the Royal College of Physicians of Ireland *(21)* and the UK Department of Health *(22)*, recommend a single dose of preoperative SAP and no postoperative continuation with or without exceptions for specific surgical procedures.

Table 4.24.1. **Recommendations on SAP according to available guidelines**

Guidelines (date issued)	Recommendations on SAP duration
SHEA/IDSA (2014) *(17)*	Stop agent within 24 hours after the procedure for all procedures.
American Society of Health-System Pharmacists *(1)*	Discontinue antibiotic prophylaxis within 24 hours after surgery.
NICE (2008) *(19)*	Consider giving a single dose of antibiotic prophylaxis intravenously on starting anaesthesia.
The Royal College of Physicians of Ireland (2012) *(21)*	With the exception of a small number of surgical indications (see below), the duration of surgical prophylaxis should be a single dose. Duration of prophylaxis involving more than a single dose, but not for more than 24 hours: open reduction and internal fixation of compound mandibular fractures, orthognathic surgery, complex septorhinoplasty (including grafts), head and neck surgery. Duration for more than 24 hours, but not for more than 48 hours: open heart surgery.
USA Institute for Healthcare Improvement: surgical site infection (2012) *(18)*	Discontinue antibiotic prophylaxis within 24 hours and 48 hours for cardiac patients.
SIGN: Antibiotic prophylaxis in surgery (2014) *(20)*	A single dose of antibiotic with a long enough half-life to achieve activity throughout the operation is recommended. Up to 24 hours of antibiotic prophylaxis should be considered for arthroplasty.
UK High impact intervention bundle (2011) *(22)*	Appropriate antibiotics were administered within 60 minutes prior to incision and only repeated if there was excessive blood loss, a prolonged operation or during prosthetic surgery.

SAP: surgical antibiotic prophylaxis; SHEA: Society for Healthcare Epidemiology of America; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; SIGN: Scottish Intercollegiate Guidelines Network.

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Following an in-depth analysis of the sources and strength of evidence in current guidelines, the GDG members decided to conduct a systematic review to assess the available evidence on the effectiveness of prolonged antibiotic prophylaxis to prevent SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 25) was to investigate whether prolonged SAP in the postoperative period is more effective in reducing the risk of SSI than perioperative prophylaxis (single dose before incision and possible intraoperative additional dose/s according to the duration of the operation). The target population included patients of all ages undergoing a surgical procedure for which SAP is indicated. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Sixty-nine RCTs *(2-9, 11-14, 23-79)* including a total of 21 243 patients and investigating the optimal duration of antibiotic prophylaxis in a variety of surgical procedures were identified: appendectomy *(23-27)*; colorectal surgery *(28-30, 60-64, 75)*; upper gastrointestinal tract surgery *(31-34)*; cholecystectomy *(35, 65)*; hepatobiliary surgery *(76, 80)*; mixed general surgery *(37-42, 79)*; caesarean section *(43-45)*; gynaecological surgery *(46, 47, 74)*; orthopaedic and trauma surgery *(48, 49)*; spine surgery *(50, 66)*; cardiac surgery *(2, 3, 7, 8, 77)*; thoracic surgery *(51)*; vascular surgery *(14)*; transplantation surgery *(52)*; head and neck surgery *(53, 67-69, 78, 81)*; ear, nose and throat surgery *(55, 70)*; maxillofacial surgery *(56-59, 71)*; orthognathic surgery *(4-6, 9, 11-13, 72)*; and others *(73)*. Both intervention and control groups received the same preoperative regimen in all included studies and they only differed in the postoperative continuation of antibiotic prophylaxis. There were variations in the antibiotic regimens and in the duration of SAP prolongation. The first dose of the antibiotic prophylaxis was always administered preoperatively.

Considering the heterogeneity among the selected studies regarding the duration of SAP prolongation postoperatively and the type of surgical procedure, several separate meta-analyses were performed according to the following comparisons (web Appendix 25).

1. Any prolonged regimen vs. no postoperative dose (44 RCTs).
2. A prolonged regimen less than 24 hours postoperatively vs. a single postoperative dose (one RCT).
3. A prolonged regimen more than 24 hours postoperatively vs. a prolonged regimen less than 24 hours postoperatively (23 RCTs).
4. A prolonged regimen more than 48 hours postoperatively vs. a prolonged regimen less than 48 hours postoperatively (3 RCTs).
5. Type of procedure with a prolonged antibiotic regimen:
   a. cardiac surgery
   b. vascular surgery
   c. orthognathic surgery.

Overall, there is a moderate quality of evidence that prolonged postoperative antibiotic prophylaxis has no benefit in reducing the SSI rate when compared to a single dose of antibiotic prophylaxis (OR: 0.89; 95% CI: 0.77–1.03).

In cardiac *(2, 3)* and orthognathic surgery *(4-6)*, there is some low quality evidence that SAP continuation after completion of the operation may be beneficial in reducing SSI when compared to a single dose of prophylaxis (OR: 0.43; 95% CI: 0.25–0.76 and OR: 0.30; 95% CI: 0.10–0.88, respectively). Conversely, other RCTs *(7-13)* showed no benefit in SSI prevention by prolonging SAP beyond 24 hours compared to SAP for up to 24 hours in both cardiac *(7, 8)* (OR: 0.74; 95% CI: 0.32–1.73; very low quality of evidence) and orthognathic surgery *(9-13)* (OR: 0.34; 95% CI: 0.08–1.44; very low quality of evidence). In vascular surgery, there was some evidence from one RCT *(14)* that prolonging antibiotic prophylaxis until intravenous lines and tubes are removed may be beneficial in reducing the risk of SSI when compared to a single dose (OR: 0.50; 95% CI: 0.25–0.98).

The retrieved evidence focused mostly on adult patients. Only 2 studies *(27, 61)* addressed specifically the paediatric population. Fifteen studies *(4, 6, 11-13, 25, 26, 37, 39, 41, 42, 57, 70, 82, 83)* included some paediatric patients, but with a majority of adult patients. Among the 69 included studies, 14 *(4, 6, 9, 11, 13, 26, 38, 43-45, 56, 57, 70, 77)* were conducted in LMICs.
The literature search did not identify any studies that reported on SSI-attributable mortality.

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Additional factors considered when formulating the recommendation

Values and preferences

Patient values and preferences were not assessed by the studies. The GDG argued that the recommendation was likely to be similar to the values and preferences of most patients. The GDG pointed out that some patients feel reassured by receiving prolonged antibiotic prophylaxis, while others would prefer to receive the lowest number of drugs possible and, in particular, to discontinue antibiotics as soon as possible.

Resource use

Studies addressing cost-effectiveness reported a cost reduction associated with shorter antibiotic prophylaxis regimens. This varied from US$ 36.90 to US$ 1664 and was attributable to the lower number of antibiotic doses administered and a reduced treatment of side-effects and duration of hospitalization *(24, 47, 52, 55, 74, 84)*.
The GDG emphasized that the recommendation may generate cost savings due to reduced expenses in drugs and materials, staff time and reduced costs due to the prevention of adverse events associated with prolonged antibiotic prophylaxis. The GDG highlighted that there is a need to raise awareness and provide education on the rational use of antibiotics and antibiotic stewardship among both health care workers (surgeons in particular, with reference to this recommendation) and patients.

Research gaps

The GDG highlighted that there is a need for further well-designed RCTs in cardiac and vascular surgery, as well as in in the paediatric population. Importantly, it would be crucial that studies include the selection of the most appropriate antibiotic according to the surgical procedure. Future trials should investigate the effect of prolonged antibiotic prophylaxis on the microbiome.

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4.25 Advanced dressings

Recommendation

The panel suggests not using any type of advanced dressing over a standard dressing on primarily closed surgical wounds for the purpose of preventing SSI.
(Conditional recommendation/low quality of evidence)

Rationale for the recommendation

- Advanced dressings used in the included studies were of the following types: hydrocolloid; hydroactive; silver-containing (metallic or ionic); and polyhexamethylene biguanide (PHMB) dressings. Standard dressings were dry absorbent dressings.
- Low quality evidence from 10 RCTs shows that advanced dressings applied on primarily closed incisional wounds do not significantly reduce SSI rates compared to standard wound dressings. The GDG unanimously agreed that advanced dressings should not be used as a preventive measure to reduce the risk of SSI. Given the low quality of the evidence, the GDG decided that the strength of this recommendation should be conditional.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. However, the GDG considered this recommendation valid also for paediatric patients.
- The GDG identified possible harms associated with the use of silver-containing dressings. Allergic reactions or skin irritations may develop in some patients *(1)*.
- Regarding ionic silver dressings, the GDG was concerned about the possible exposure of patients and health care workers to nanoparticles. It was also pointed out that microbial resistance to silver and PHMB may develop.
- The GDG also highlighted that the availability of advanced dressings may be limited in LMICs and their purchase might represent a financial burden.
- The GDG emphasized that dressings used on primarily closed surgical wounds should be sterile and should be applied with an aseptic technique.
- The studies included did not investigate negative pressure dressings. pNPWT is dealt with in chapter 4.19 of these guidelines.

Background

The term "surgical wound" used in this document refers to a wound created when an incision is made with a scalpel or other sharp cutting device and then closed in the operating room by suture, staple, adhesive tape, or glue and resulting in close approximation to the skin edges. It is common practice to cover such wounds with a dressing. The dressing acts as a physical barrier to protect the wound from contamination from the external environment until the wound becomes impermeable to microorganisms. The dressing can also serve to absorb exudate from the wound and keep it dry.

A wide variety of wound dressings are available (web Appendix 26). Advanced dressings are mainly hydrocolloid or hydrogels or fibrous hydrocolloid or polyurethane matrix hydrocolloid dressings and vapour-permeable films.

A Cochrane review *(2)* and its update *(3)* of the effect of dressings for the prevention of SSI found no evidence to suggest that one dressing type was better than any others.

The UK-based NICE issued a clinical guideline for SSI prevention and treatment in 2008 which recommended covering surgical incisions with an appropriate interactive dressing at the end of the procedure *(4)*. The 2013 evidence update of these guidelines suggests that no particular type of dressing emerges as the most effective in reducing the risk of SSI, although silver nylon dressings may be more effective than gauze.

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The update recommends further research to confirm the effectiveness of modern types of dressing *(5)*. Postoperative care bundles recommend that surgical dressings be kept undisturbed for a minimum of 48 hours after surgery unless leakage occurs. However, there are currently no specific recommendations or guidelines regarding the type of surgical dressing *(6-8)*.

Following an in-depth analysis of the sources and strength of evidence in current guidelines and reviews, the GDG members decided to conduct a systematic review to assess the effectiveness of advanced dressings compared to standard surgical wound dressings for the prevention of SSI.

Summary of the evidence

The purpose of the evidence review (web Appendix 26) was to evaluate whether the use of advanced dressings is more effective in reducing the risk of SSI than standard wound dressings. The target population included patients of all ages undergoing a surgical procedures. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Ten RCTs *(1, 9-17)*, including a total of 2628 patients, evaluated advanced dressings compared to standard dressings. Patients were adults undergoing sternotomy and elective orthopaedic, cardiac, vascular, plastic, abdominal and colorectal cancer surgical procedures. There were variations in the interventions as some studies used hydrocolloid, hydroactive and silver- or PHMB-impregnated dressings. In addition, there were variations in the definition of SSI and the duration of postoperative follow-up.

Despite the heterogeneity of the types of advanced dressings used in the selected studies, separate meta-analyses were performed to evaluate (1) an overall comparison of advanced vs. standard dressings, and (2) hydrocolloid or silver-impregnated or hydroactive or PHMB dressings vs. standard dressings.

Overall, there is low quality evidence that advanced dressings do not significantly reduce SSI rates compared to standard dressings (OR: 0.80; 95% CI: 0.52–1.23). In particular, compared to standard dressings, very low quality evidence showed neither benefit nor harm for hydrocolloid dressings (OR: 1.08; 95% CI: 0.51–2.28), silver-impregnated dressings (OR: 0.67; 95% CI: 0.34–1.30) and hydroactive dressings (OR: 1.63; 95% CI: 0.57–4.66). There is also low evidence for PHMB-containing dressings (OR: 0.20; 95% CI: 0.02–1.76).

The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. In addition, no studies reported SSI-attributable mortality rates.

Additional factors considered when formulating the recommendation

Values and preferences

There are many factors that may contribute to the preferences of surgeons and/or patients with regard to the use of particular dressings. Although no difference in SSI prevention was shown in the meta-analysis of 10 RCTs, other outcomes were reported in some studies. Two RCTs included in these analyses assessed patient comfort and reported that hydrocolloid dressings were more comfortable than standard dressings *(16, 17)*. Another study reported better cosmetic results in patients whose incisions were dressed with hydrocolloid dressings compared to incisions covered with standard dressings, despite no SSI events in either group *(13)*. It was acknowledged that patients may prefer a low frequency of dressing change.

Resource use

The cost and availability of advanced dressings may be a limitation, particularly in LMICs. The added cost of using hydrogel, hydrocolloid or silver-containing dressings has been investigated by several studies included in this review. Two studies reported fewer dressing changes for hydrogel dressings compared to standard dressings *(10, 16)*. Although the hydrogel dressings were associated with a cost 2 to 5 times higher than standard dressings, they may be beneficial for patients unable to change dressings or requiring a return to hospital for subsequent dressing changes *(16)*. One study attributed increased nursing time with standard dressings, which is a consideration for hospitals with a small nursing staff. Another study reported higher costs for hydrocolloid compared to standard dressings *(17)*. In addition to cost, it may be difficult for some LMICs to acquire and properly use moist or metallic dressings. However, one study reported that hydrocolloid dressings were less complicated to apply *(15)*.

Research gaps

It was emphasized that there are very few large, high-quality trials investigating different types of dressings with SSI prevention as a primary outcome.

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Future clinical studies should focus on generating a large sample size and include blind outcome assessment. Well-designed studies conducted in LMICs are needed, as well as in the paediatric population. The GDG highlighted a special interest in investigating the use of silver-containing dressings in orthopaedic and cardiac surgery with regard to SSI prevention. Assessment of adverse events should be considered in the trials, including the possible effects of silver nanoparticles. In addition, it would be interesting to explore the comparison of opaque dressings with transparent ones in terms of postoperative visual examination and the duration of keeping the primary dressing in place, ultimately with regard to SSI prevention.

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4.26 Antimicrobial prophylaxis in the presence of a drain and optimal timing for wound drain removal

Recommendations

1. **The panel suggests that perioperative antibiotic prophylaxis should not be continued to the presence of a wound drain for the purpose of preventing SSI.**
   (Conditional recommendation, low quality of evidence)

2. **The panel suggests removing the wound drain when clinically indicated. No evidence was found to recommend an optimal timing of wound drain removal for the purpose of preventing SSI.**
   (Conditional recommendation, very low quality of evidence)

Rationale for the recommendation

- Overall low quality evidence (from 7 RCTs) indicates that prolonged antibiotic prophylaxis in the presence of a wound drain has neither benefit nor harm in reducing SSI when compared to perioperative prophylaxis alone (single dose before incision and possible intraoperative additional dose/s according to the duration of the operation). Considering the lack of evidence that prolonged antibiotic prophylaxis prevents SSI and the possible associated harms (see below), the GDG unanimously agreed that antibiotic prophylaxis should not be continued in the presence of a wound drain. Given the low quality of the evidence, the strength of this recommendation was considered to be conditional.
- Very low quality evidence (from 11 RCTs) shows that the early removal of wound drains has neither benefit nor harm in reducing the SSI rate when compared to late removal of drains (at postoperative day 6 or later). In particular, no benefit was shown when comparing early removal (from postoperative days 1 to 5) with removal on or after postoperative day 6. Results were also similar when comparing early removal with removal determined according to the volume of drainage. Considering the very low quality evidence and the finding that the body of evidence does not identify an optimal time point for wound drain removal with regard to the prevention of SSI, the GDG decided to suggest that the wound drain should be removed when clinically indicated. Given the very low quality of evidence, the strength of this recommendation was considered to be conditional.

Remarks

- The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. However, the GDG considers this recommendation valid also for paediatric patients.
- The GDG emphasized that the body of evidence does not identify an optimal time point of wound drain removal with regard to the reduction of SSI. Definitions for the early removal of drains varied across the studies from 12 hours to 5 days postoperatively. In addition, the definitions for the late removal of drains varied from removal when the drainage volume became minimal (that is, <30 or <50 mL/day) or at specific time points, such as postoperative days 2 to 10.
- The GDG pointed out that the evidence on the optimal time for drain removal consists of studies that were done with closed wound drains. Therefore, the related recommendation refers to the use of closed wound drainage systems.
- The available evidence on the optimal time for drain removal was limited to studies conducted in breast and orthopaedic surgery.
- It was noted that the great majority of available studies on the topics of these recommendations were conducted in high- and middle-income countries; only one study is available from a low-income country.
- The GDG identified possible harms associated with the prolonged duration of antibiotic administration, such as the selection and emergence of resistant bacteria, the risk of fungal superinfections and *Clostridium difficile* infection and side effects of antibiotics. Furthermore, early removal of the wound drain may be associated with possible postoperative complications, such as an increase of the occurrence of seroma and haematoma requiring treatment *(1)*.
- The GDG highlighted that wound drains are single-use devices and must not be reused.

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Background

The use of drainage tubes in surgical wounds has a long history *(2)*. Prophylactic placement postoperatively has been widely practiced since the mid-1800s with the dictum of Lawson Tait, the 19th century British surgeon, "When in doubt, drain", well known to all surgical trainees. However, some studies have called into question the benefits of routine drainage *(3, 4)*. It is even argued that drains might adversely affect surgical outcomes, for example, affecting anastomotic healing by causing infection in the anastomotic area and the abdominal wound *(5, 6)*. Thirty-four systematic reviews investigating the effect of drains compared to no wound drainage in terms of the related infection risk in surgical patients have been published so far. A meta-review summarizing these reviews (web Appendix 27) demonstrated that most meta-analyses showed a tendency towards a beneficial effect of not using a wound drain with regard to a reduced risk of wound infection, but no significant differences were achieved.

The aim of drainage tubes is to remove any fluid or blood that may collect in the wounds and cavities created by the surgical procedure and thus may cause complications. When used, the optimal time for drain removal after surgery is still unknown. Drains are usually left in place until the amount of fluid draining out of them in a 24-hour period has reduced to a certain volume (typically less than 30 mL to 100 mL). However, some surgeons will remove the drains at a particular time point after surgery, which may vary from hours to more than a week. In most cases, antibiotic prophylaxis is continued postoperatively when a drain is used, but this practice is not evidence based.

With the presence of drainage tubes, the need for perioperative antibiotic prophylaxis and the optimal regimen requires further assessment and investigation given the dramatic increase in AMR worldwide. In recognition of the fact that AMR is now considered a major health problem, the implementation of global and national programmes to optimize the use of antibiotic agents in humans has been strongly urged by WHO *(7)*.

There are currently no formal recommendations for antimicrobial prophylaxis in the presence of a drain or regarding wound drain removal for the prevention of SSI. Following an in-depth analysis of the resources and lack of recommendations from other guidelines, the GDG decided to conduct a systematic literature review on these topics.

Summary of the evidence

The purpose of the evidence review (web Appendix 27) was to evaluate whether prolonged antibiotic prophylaxis in the presence of a wound drain is more effective in reducing the risk of SSI than perioperative prophylaxis alone (single dose before incision and possible intraoperative additional dose/s according to the duration of the operation). The review evaluated also whether the early removal of wound drains is more effective than late removal to prevent SSI. The target population included patients of all ages undergoing a surgical operation with the presence of postoperative drainage. The primary outcome was the occurrence of SSI and SSI-attributable mortality.

Seven RCTs *(8-14)* were identified. They included a total of 1670 patients and investigated whether antibiotics should be administered preoperatively as a single dose and possibly re-dosed according to the duration of the operation, or if their administration should be extended to the postoperative period.

Three studies reported a prolonged antibiotic administration until the wound drain was removed *(8, 9, 11)*. In the remaining 4 trials, patients received a 3-day *(10, 14)* or 5-day intravenous course *(13)*. Patients enrolled in the studies underwent general surgery *(8-10, 14)*, kidney transplantation *(11)* and pilonidal sinus surgery *(13)*. One trial *(12)* determined whether prolonged antibiotic prophylaxis reduced the risk of infectious complications for patients undergoing elective thoracic surgery with tube thoracostomy. The antibiotic was continued for 48 hours after the procedure or until all thoracostomy tubes were removed, whichever came first.

There is low quality evidence that prolonged antibiotic prophylaxis in the presence of a wound drain has neither benefit nor harm in reducing SSI when compared to perioperative prophylaxis alone (OR: 0.79; 95% CI: 0.53–1.20).

Eleven RCTs *(1, 15-24)* including a total of 1051 patients and comparing early vs. late removal of drainage were identified. Nine studies investigated the duration of drains in patients undergoing mastectomy *(1, 15-22)* and 2 studies after hip or knee arthroplasty *(23, 24)*. Study definitions

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for early drain removal varied from removal at 12 hours, 24 hours and 48 hours to 3, 4 or 5 days postoperatively. Late removal was either defined as removal when the drainage volume became minimal (that is, <30 mL/day or <50 mL/day) or as specific time points, such as postoperative days 2, 6, 8 and 10. One trial *(24)* compared 3 different time points of drain removal (12 hours, 24 hours and 48 hours).

Despite this heterogeneity, two subgroup analyses were performed based on two main classifications for the indication of late wound drain removal, that is, specific time points with drain removal at postoperative day 6 or later (3 studies *(17, 19, 22)*) and drainage volume (6 studies *(1, 15, 16, 18, 20, 21)*). Early removal was considered to be from postoperative days 1 to 5. Therefore, 2 studies that compared drain removal at postoperative day 1 vs. postoperative day 2 *(23)* and 12 hours/24 hours vs. postoperative day 2 *(24)* were not included in the subgroup comparisons.

There is very low quality evidence that the early removal of wound drains has neither benefit nor harm in reducing the SSI rate when compared to late removal (OR: 0.86; 95% CI: 0.49–1.50). When this comparison was sub-classified by late removal at specific time points (postoperative day 6 or later) and drainage volume, the results remained unchanged (OR: 0.63; 95% CI: 0.07–5.70 and OR: 0.93; 95% CI: 0.51–1.70, respectively).

The body of retrieved evidence focused on adult patients and no study was available in the paediatric population. The literature search did not identify any studies that reported on SSI-attributable mortality.

Additional factors considered when formulating the recommendation

Values and preferences

The GDG is confident that most patients do not wish to receive prolonged antibiotic prophylaxis to reduce SSI in the absence of good evidence for a benefit, including the possibility of potential harms, such as the development of AMR, antimicrobial-related adverse events and *C. difficile* infection.

The GDG acknowledged that wound drains are uncomfortable and inconvenient for patients. One survey showed that patients prefer early wound drain removal *(15)*. Even patients who developed seromas requiring aspiration indicated their preference for early removal with a return to hospital for further aspiration if necessary. In one trial on mastectomy, Barton and colleagues *(1)* reported that early drain removal increased the occurrence of seromas requiring treatment and this trial was even halted because of the significantly higher rate of adverse events in the early removal group.

Resource use

The GDG noted that the availability of antibiotics might be limited, particularly in LMICs. The additional costs of prolonged antibiotic prophylaxis in the presence of a wound drain, including the acquisition of wound drains, may represent not only a financial burden to the health system/ medical centre in low-resource settings, but also to the patients themselves. The GDG emphasized that there is a need to raise awareness and education on the rational use of antibiotics and antibiotic stewardship among both health care workers (surgeons in particular, with reference to this recommendation) and patients. Early removal of drains may shorten hospital length of stay and therefore lead to cost savings *(22)*.

Research gaps

GDG members highlighted that the available evidence on the time point of wound drain removal is limited to the fields of breast and orthopaedic surgery only. The GDG observed that the number of studies evaluating specific time points is very limited and there is therefore a need for RCTs to focus on specific time points for drain removal, rather than on drainage volume. All future studies should use SSI as the outcome, defined according to CDC criteria, and report any adverse events related to the time of drain removal. There is a need also for well-designed RCTs, especially in orthopaedic joint replacement and cardiac surgery. All included studies were in adult patients and more research is required to investigate the benefit of early drain removal in paediatric populations and among neonates. The great majority of the available evidence comes from high- and middle-income countries and more studies in low-income countries are required.

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5. DISSEMINATION AND IMPLEMENTATION OF THE GUIDELINES

The overall aim of this guideline is to improve the quality of care and outcome of patients undergoing surgical procedures through the prevention of SSI.

Uptake of the guidelines by all players included in the target audience is essential. In particular, adoption of the recommendations within national and local IPC and safe surgery guidelines and policies is a key element. Their translation into practice in surgical services and operating rooms is the ultimate and most important goal to achieve a reduction of harm due to SSI through the continuum of the patient's surgical journey. The dissemination and implementation of these guidelines are crucial steps that should be undertaken by the international community, as well as by national and local health services.

Guidelines implementation

The IPC team of the WHO Service Delivery and Safety Department worked with experts and colleagues at country level to develop an implementation strategy and resources to facilitate adoption and adaptation of the WHO recommendations. This work is based on a systematic literature review aimed at identifying successful strategies and protocols for the implementation of SSI prevention measures *(1)*, included those recommended by these guidelines.

Furthermore, the implementation of the Surgical Unit-based Safety Programme in hospitals in the WHO African Region and the USA which was supported by the WHO IPC team and the Johns Hopkins Armstrong Institute for Patient Safety and Quality (Baltimore, MD), provided insightful lessons learned and results. This was a quasi-experimental before/after study implementing a range of SSI prevention measures, together with infection surveillance, combined with an improvement of the patient safety culture.

The quantitative results *(2)* have shown a significant reduction of SSI and improvement of the patient safety climate, while qualitative evaluations have provided insightful lessons learned on barriers and facilitating factors for implementation. As demonstrated by the Surgical Unit-based Safety Programme and other projects, IPC guidelines are most successfully implemented when embedded in an enabling environment supportive of a patient safety culture. Following expert consultation and collection of country stories and implementation examples, two main implementation documents were produced. One document describes a range of evidence-based approaches to achieve successful SSI prevention implementation, including in the context of a broader surgical safety climate *(3)*. This document also provides key considerations and lessons learned from the dissemination and adoption of the WHO safe surgery checklist. The second document is an operational manual which proposes a practical approach to implement the SSI prevention recommendations using the WHO hand hygiene and infection prevention and control multimodal strategy *(4)*. Furthermore, a package of additional implementation tools has been developed by WHO according to the multimodal strategy for SSI prevention (https://www.who.int/infection-prevention/tools/surgical/en/)

Guidelines dissemination and evaluation

The recommendations in these guidelines are being disseminated through a broad network of international technical partners and stakeholders in the field of IPC, surgery and patient safety, including professional societies and patient organizations. More specifically, the WHO Global Infection Prevention and Control network and the Global Initiative for Emergency and Essential Surgical Care forum have been targeted. Other WHO teams working on IPC projects, WHO

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country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies and nongovernmental organizations have been targeted through specific communications and support and collaboration is provided for dissemination and implementation as appropriate. Dissemination has been done also through all facilities participating in the WHO *Save Lives: Clean Your Hands* and *Safe Surgery Saves Lives* global campaigns. Plans are being developed to conduct pilot implementation in some countries and regions. All these activities are supported by specific communication messages and, importantly, by the implementation strategy document and tool package planned to be issued shortly after publication of the guidelines.

Dissemination through the scientific literature is considered crucial for the successful uptake and adoption of the recommendations and WHO and members of the Systematic Reviews Expert Group have already submitted some papers for publication in peer-reviewed journals.

The WHO IPC team will continue to work with all stakeholders and implementers to identify and assess the priorities, barriers and facilitators to guideline implementation. The team will support also the efforts of stakeholders to develop guideline adaptation and implementation strategies tailored to the local context. The recommendations contained in the present guideline should be adapted into locally appropriate documents that are able to meet the specific needs of each country and its health service. Modifications to the recommendations, where necessary, should be limited to conditional recommendations and justifications for any changes should be made in an explicit and transparent manner.

To assess and follow-up the implementation of these guidelines, an evaluation framework will be developed by the WHO IPC team and colleagues from regional offices. This work will also be based on already available tools from Surgical Unit-based Safety Programme and other IPC projects.

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6. ANNEXES

6.1 Guidelines Development Group

Professor Hanan H Balkhy
WHO Collaborating Centre and GCC Center for Infection Control
Infection Prevention and Control Department
King Saud Bin Abdulaziz University for Health Sciences
PO Box 22490
Riyadh 11426, Kingdom of Saudi Arabia
BalkhyH@ngha.med.sa

Professor F. Javier Belda
University of Valencia
Department of Anesthesia
Valencia, Spain
Fco.javier.belda@uv.es

Professor Sean Berenholtz
Armstrong Institute for Patient Safety and Quality
Johns Hopkins Medicine
Baltimore, MD, USA
sberenho@jhmi.edu

Professor Marja A Boermeester
Department of Surgery
Amsterdam Gastroenterology and Metabolism
Amsterdam Infection and Immunity
Amsterdam UMC
University of Amsterdam
Meibergdreef 9
1105AZ Amsterdam, the Netherlands
m.a.boermeester@amc.uva.nl

Dr Nizam Damani
Craigavon Area Hospital
Portadown, Craigavon, Co Armagh, UK
nizdamani@aol.com

Professor E. Patchen Dellinger
University of Washington
Box 356410 Room BB 441
1959 N.E. Pacific Street
Seattle, WA 98195-6410, USA
patch@u.washington.edu

Dr Mazen Ferwana
National & Gulf Centre for Evidence Based Health Practice
King Saud Bin Abdulaziz University for Health Sciences MNGHA
Riyadh, Kingdom of Saudi Arabia
ferwanam@ngha.med.sa

Professor Petra Gastmeier
Institute of Hygiene and Environmental Medicine
Charité-University Medicine Berlin
Hindenburgdamm 27
12203 Berlin, Germany
petra.gastmeier@charite.de

Professor Robert Greif
Department of Anesthesiology and Pain Therapy
Bern University Hospital
University of Bern
Bern, Switzerland
robert.greif@insel.ch

Dr Xavier Guirao
Endocrine & Head and Neck Surgery
Corporació Sanitaria del Parc Taulí de Sabadell
University Hospital Sabadell
Barcelona, Spain
xguirao@gmail.com

Ms Regina Namata Kamoga
Community Health and Information Network (CHAIN)
Kampala, Uganda
namata.kamoga@gmail.com

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Dr Asad Latif
Armstrong Institute for Patient Safety and Quality
Johns Hopkins Medicine
Baltimore, MD, USA
aaltif1@jhmi.edu

Professor Nordiah Awang Jalil
Department of Medical Microbiology &
Immunology and Head of Infection Control Unit
Universiti Kebangsaan Malaysia Medical Centre
Jalan Yaacob Latif, Bandar Tun Razak 56000 Cheras
Kuala Lumpur, Malaysia
nordiah@ppukm.ukm.edu.my

Professor Fauzia Khan
Aga Khan University
Karachi, Pakistan
Fauzia.khan@aku.edu

Ms Robinah Kaitiritimba
Uganda National Health Consumers' Organisation
Plot 744 Namuli Road, Bukoto, P.O Box 70095
Kampala Uganda
rkitungi@yahoo.com

Ms Claire Kilpatrick
KS Healthcare Consulting
London, UK
clairekilpatrick.ck@googlemail.com

Dr Janet Martin
World Federation of Societies of Anaesthesiologists
(WFSA)
Anesthesia and Perioperative Medicine
Schulich School of Medicine & Dentistry
Western University
London, Ontario, Canada
janet.martin@lhsc.on.ca

Professor Shaheen Mehtar
Tygerberg Hospital & Stellenbosch University
Tygerberg 7505
Cape Town, Republic of South Africa
smehtar@sun.ac.za

Dr Babacar Ndoye
Infection Control Africa Network
Dakar, Senegal
basendoye2@yahoo.fr

Dr Peter M Nthumba
Plastic, Reconstructive and Hand Surgery Unit
Medical Education and Research Unit
AIC Kijabe Hospital
Kijabe, Kenya
nthumba@gmail.com

Dr Jannicke Mellin-Olsen
WFSA
London, United Kingdom
mellinolsen@gmail.com

Professor Bisola Onajin Obembe
WFSA
Department of Anaesthesiology
College of Health Sciences
University of Port Harcourt
Rivers State, Nigeria
bisolaobembe@yahoo.co.uk

Professor Akca Ozan
Department of Anaesthesiology and Perioperative
Medecine
University of Louisville, USA
ozan.akca@louisville.edu

Dr Leonardo Pagani
Infectious Diseases Unit
Bolzano Central Hospital
Via L. Boehler, 5
39100 Bolzano, Italy
lpagani.id@gmail.com

Professor Didier Pittet
Infection Control Programme and
WHO Collaborating Centre on Patient Safety
University of Geneva Hospitals and Faculty of
Medicine
4 Rue Gabrielle-Perret-Gentil
1211 Geneva 14, Switzerland
Didier.Pittet@hcuge.ch

Professor Jianan Ren
Research Institute of General Surgery
Jinling Hospital
Medical School of Nanjing University
Nanjing, 210002, People's Republic of China
jan@medmail.com.cn

Professor Joseph S Solomkin
University of Cincinnati College of Medicine
231 Albert B. Sabin Way
Cincinnati OH 45267-0558, USA /
CEO, OASIS Global, 6005 Given Road
Cincinnati, OH 45243, USA
solomkjs@ucmail.uc.edu

Ms Akeau Unahalekhaka
Faculty of Nursing
Chiang Mai University
A Muang
Chiang Mai, 50200 Thailand
akeau@hotmail.com

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Professor Dr Andreas Widmer
Division of Infectious Diseases & Hospital Epidemiology and Infection Control
University of Basel Hospital and Clinics
4031 Basel, Switzerland
Andreas.Widmer@usb.ch

Professor Matthias Egger
Methodologist
Institute of Social and Preventive Medicine
University of Bern
Finkenhubelweg 11
3012 Bern, Switzerland
egger@ispm.unibe.ch

6.2 WHO Steering Group

Dr Benedetta Allegranzi
Infection Prevention and Control Global Unit
Department of Service Delivery and Safety
allegranzib@who.int

Dr Edward Kelley
Department of Service Delivery and Safety
kelleye@who.int

Dr Walter Johnson
Department of Service Delivery and Safety
johnsonw@who.int

Dr Bassim Zayed
Department of Service Delivery and Safety
baszayed99@yahoo.com

Dr Sergey Eremin
Department of Pandemic and Epidemic Diseases
eremins@who.int

Dr Valeska Stempliuk
Regional Office for the Americas
stempliv@paho.org

6.3 Systematic Reviews Expert Group

Dr Benedetta Allegranzi
Infection Prevention and Control Global Unit
Service Delivery and Safety, HIS
WHO
20 Avenue Appia
1211 Geneva 27, Switzerland
allegranzib@who.int

Dr Jasper Atema
Department of Surgery (G4-142)
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105AZ Amsterdam, the Netherlands
j.j.atema@amc.nl

Professor Sean Berenholtz
Armstrong Institute for Patient Safety and Quality
Johns Hopkins Medicine
Baltimore, MD, USA
sberenho@jhmi.edu

Dr Peter Bischoff
Institute of Hygiene and Environmental Medicine,
Charité-University Medicine Berlin
Hindenburgdamm 27
12203, Berlin, Germany
peter.bischoff@charite.de

Professor Marja A. Boermeester
Department of Surgery (G4-132.1)
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105AZ Amsterdam, the Netherlands
m.a.boermeester@amc.uva.nl

Ms Quirine Boldingh
Department of Surgery (G4-132.1)
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105AZ Amsterdam, the Netherlands
j.q.boldingh@amc.uva.nl

Dr Sarah Gans
University of Amsterdam
Meibergdreef 9
1105AZ Amsterdam, the Netherlands
s.l.gans@amc.uva.nl

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Professor Petra Gastmeier
Institute of Hygiene and Environmental Medicine
Charité-University Medicine Berlin
Hindenburgdamm 27
12203 Berlin, Germany
petra.gastmeier@charite.de

Dr Stacey Gomez
OASIS Global
6005 Given Road
Cincinnati OH 45243, USA
gomes.stacey@gmail.com

Dr Xavier Guirao
Unit of Endocrine & Head and Neck Surgery
Unit of Surgical Infection Support
Assistant Professor in Surgery, UAB
Hospital Universitari Parc Tauli, Sabadell
Barcelona, Spain
xguirao@gmail.com

Dr Stijn de Jonge
Department of Surgery (G4-129)
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105AZ Amsterdam, the Netherlands
s.w.dejonge@amc.uva.nl

Professor Jan Kluytmans
Amphia Hospital Breda
Laboratory for Microbiology and Infection Control
4800 RK Breda, the Netherlands
jankluytmans@gmail.com

Dr Zeynep Kubilay
Infection Prevention & Control Global Unit,
Service Delivery and Safety, HIS
WHO
20 Avenue Appia
1211 Geneva 27, Switzerland
zepella@hotmail.com

Ms Caroline Landelle
Infection Control Programme and WHO
Collaborating Centre on Patient Safety
University of Geneva Hospitals
4 Rue Gabrielle-Perret-Gentil
1211 Geneva 14, Switzerland
caroline.landelle@gmail.com

Dr Asad Latif
Armstrong Institute for Patient Safety and Quality
Johns Hopkins Medicine
Baltimore, MD, USA
alatif1@jhmi.edu

Professor Yoon K Loke
Norwich Medical School, University of East Anglia
Norwich, UK
Y.Loke@uea.ac.uk

Mr. Adam Peel
Norwich Medical School, University of East Anglia
Norwich, UK
a.peel@uea.ac.uk

Dr Katharina Mattishent
Norwich Medical School, University of East Anglia
Norwich, UK
k.mattishent@uea.ac.uk

Ms Sandra Pequeno
Iberoamerican Cochrane Center
Biomedical Institute, IIB-Sant Pau-CIBERESP
Barcelona, Spain

Professor Didier Pittet
Infection Control Programme and WHO
Collaborating Centre on Patient Safety
University of Geneva Hospitals and Faculty
of Medicine
4 Rue Gabrielle-Perret-Gentil
1211 Geneva 14, Switzerland
Didier.Pittet@hcuge.ch

Professor Jianan Ren
Research Institute of General Surgery
Jinling Hospital, Medical School of Nanjing
University
305 East Zhongshan Rd
Nanjing 210002, People's Republic of China
jan@medmail.com.cn

Dr Miranda van Rijen
Amphia Ziekenhuis, Molengracht
PO Box 90158
4800 RK Breda, the Netherlands
mvanrijen@amphia.nl

Dr. Ashnish Sinha
Norwich Medical School, University of East Anglia
Norwich, UK
ashnish@doctors.org.uk

Professor Joseph S. Solomkin
University of Cincinnati College of Medicine
231 Albert B. Sabin Way
Cincinnati, OH 45267-0558, USA
CEO, OASIS Global
6005 Given Road
Cincinnati, OH 45243, USA
solomkjs@ucmail.uc.edu

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Dr. Menaka Thavarajah
Norwich Medical School, University of East Anglia
Norwich, UK
menakathavarajah@yahoo.co.uk

Dr Fleur de Vries
Department of Surgery (G4-133)
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam, the Netherlands
f.e.devries@amc.uva.nl

Dr Xiuwen Wu
Department of Surgery
Jinling Hospital, Medical School of Nanjing University
305 East Zhongshan Road
Nanjing 210002, People's Republic of China
xiuwenwoo@gmail.com

Dr Bassim Zayed
Antimicrobial Resistance and Infection Prevention and Control Team
WHO Eastern Mediterranean Regional Office
Cairo, Egypt

6.4 External Peer Review Group

Professor Emmanuel A. Ameh
Department of Surgery
Ahmadu Bello University & Ahmadu Bello University Teaching Hospital
Zaria, Nigeria
eaameh@yahoo.co.uk

Professor Valerie Robertson
Zimbabwe Infection Prevention and Control Project
Department of Medical Microbiology,
University of Zimbabwe
Harare, Zimbabwe
robertson@uz-ucsf.co.zw

Dr Fernando Otaíza
IPC Unit
Departamento de Calidad y Seguridad del Paciente
Subsecretaría de Redes Asistenciales
Ministerio de Salud
Santiago, Chile
fotaiza@minsal.cl

Professor Kamal Itani
General Surgery
VA Boston Healthcare System & Boston University School of Medicine
Boston, USA
Kamal.Itani@va.gov

Dr Ilker Uçkay
Infectious Diseases and Orthopaedic Surgery,
University of Geneva Hospitals
4 Rue Gabrielle Perret-Gentil
1211 Geneva 14, Switzerland.
Ilker.Uckay@hcuge.ch

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World Health Organization

20 Avenue Appia
CH-1211 Geneva 27
Switzerland
Tel.: +41 22 791 5060

Email: savelives@who.int
Please visit us at:
www.who.int/gpsc/en

World Health Organization

9 789241 550475

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AVERY DENNISON | Medical

Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road
Longford, N39 RC80, Ireland
Phone: +353 43 33 49586
Fax: +353 43 3349566

AINN Hold Letter for K230645

FDA/CDRH/DCC
SEP 25 2023
RECEIVED

K230645/S001

22 September 2023

U.S. Food and Drug Administration
Centre for Devices and Radiological Health
10903 New Hampshire Avenue
Document Control Center WO66-G609
Silver Spring, MD 20993-0002

Subject: Avery Dennison Response to AINN Hold Letter for K230645, the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Dear Madam or Sir:

Pursuant to Section 745(b) of the FD&C Act per section 1136 of FDASIA, Avery Dennison Medical Ltd. is submitting an e-copy of this response to the Hold Letter for K230645 for your review. Additionally, the e-copy is accompanied with the original signed cover letter. Thank you.

Regards,

(b)(6)

Elizabeth Gallantine, PhD
Project Manager Europe
Avery Dennison
Phone: + 353 43 331 1341
E-mail: elizabeth.gallantine@eu.averydennison.com

Classification: Avery Dennison - Secret

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DO NOT DATE THIS DOCUMENT

K230645
Avery Dennison Medical Ltd.
Trade/Device Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Contact Name: Lisa Bartakovics

This document is being communicated via e-mail as an attachment. The date on which FDA sent this e-mail is the official date of this correspondence.

We have reviewed your submission K230645 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number K230645 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please refer to the eCopy guidance at https://www.fda.gov/media/83522/download for current information on eCopy requirements.

Your response is due within 180 days from the date of this request, which is the hold date plus 180 days. If a complete response is not received in CDRH's Document Control Center by this date, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

This request for additional information has undergone supervisory review to ensure that the deficiencies cited are least burdensome and relevant to the marketing decision. Please see the revised guidance "Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions" issued

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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on September 29, 2017 (https://www.fda.gov/media/71735/download) for clarification regarding major and minor deficiencies.

MAJOR DEFICIENCY LIST

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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FDA is offering a teleconference within 10 calendar days from the date on this letter to address any clarification questions you may have pertaining to the deficiencies. If you are interested in a teleconference, please provide (1) proposed dates and (2) a list of your clarification questions via email at least 48 hours before the teleconference to the lead reviewer assigned to your submission. We would like to emphasize that the purpose of the meeting is to address specific clarification questions. Please note that if the specific clarification questions are not received at least 48 hours before the teleconference, the review team might not

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be able to provide feedback. The teleconference is not intended for review of new information, test methods or data; these types of questions could be better addressed via a Submission Issue Q-Submission (Q-Sub). For additional information regarding Q-Subs, please refer to the Guidance for Industry and FDA Staff on Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions at https://www.fda.gov/media/114034/download.

Least Burdensome (LB) Flag

The LB flag is an approach to allow submitters the opportunity for the informal review by or on behalf of Division management of an issue raised in an FDA request for additional information (i.e., a deficiency letter). The goal of the LB flag is to quickly address FDA requests that submitters do not believe are least burdensome or when submitters believe they are being held to a different standard than their legally marketed predicate device. The LB flag is not intended to clarify deficiencies, is not an appeal under 21 CFR 10.75, and is not intended to provide a review of a proposed response to deficiencies.

If you would like to throw the LB flag, FDA has several criteria that should be met before you submit your request:

- You should have tried to address your concern by discussing it with Division management before attempting to throw the LB flag. This discussion with Division management may take place as part of a teleconference (such as the voluntary teleconference held within 10 days following transmission of an Additional Information letter to clarify deficiencies), email, or a Q-Submission Submission Issue Request.
- Your flag should generally be limited to two topic areas. Topic areas are common premarket review deficiency categories that apply to many device types across multiple reviewing Divisions. Examples of topic areas include biocompatibility, sterility, reprocessing, software, electromagnetic compatibility, wireless, electrical safety, clinical, and non-clinical performance testing.
- If you would like to discuss issues pertaining to more than two topic areas, you should contact OPEQSubmissionSupport@fda.hhs.gov for more information.
- You should throw the LB flag within 60 calendar days of the date that FDA sent the deficiency letter.

Upon meeting the criteria, you should send a short email (e.g., 1-2 page) that includes: 1) a summary of the deficiencies under disagreement, 2) a summary of relevant communications with Division management, and 3) a proposed path forward. The LB flag should be sent to the lead reviewer and their Assistant Director. You should also copy OPEQSubmissionSupport@fda.hhs.gov on your LB flag email request. Within two business days of your email, your request will be acknowledged by the reviewing Division. If you do not meet the criteria for the LB flag, you will be notified in this acknowledgement email.

Your LB flag should contain sufficient information to determine whether the deficiency letter was not least burdensome, or you are being held to a different standard than your predicate device. FDA may request a phone call with you to discuss your concern further and intends to communicate feedback from Division management on LB flags through email no later than 21 calendar days of their receipt. Please note that the LB flag does not change the deadline for your response to the Document Control Center. If you have any questions, please contact OPEQSubmissionSupport@fda.hhs.gov.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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U.S. FOOD & DRUG ADMINISTRATION

eConsult Cover Sheet

Consult Number:	CON239422
Document Number:	K230645
Applicant:	Avery Dennison Medical Ltd.
Trade Name:	BeneHold Surgical Incise Drape with CHG antimicrobial II
Consult Type:	Toxicology and Chemical Risk Assessment
Requestor:	Yongqing Chen [CHENYO] yongqing.chen@fda.hhs.gov
Requestor Home:	CDRH\ OHT4\ DHT4B\ THT4B2
Requested Consultant:	Angela Burke -S (Affiliate) Digitally signed by Angela Burke -S (Affiliate) Date: 2023.04.29 17:27:38 -05'00'
Gatekeeper / Consultant:	Angela Burke [ANGELA.BURKE] angela.burke@fda.hhs.gov ; 479-579-8521
Consultant Home:	CDRH\ OPEQ
Date Requested:	April 14, 2023
Due Date:	May 1, 2023
Instructions:	Thank you so much for willing to help us. Please review the TRA within the attachment 15.9. Please let me know if you have any questions/comments. Best, --Yongqing

For each of the specific issues identified in the recommended requests to the applicant above, I provided a statement of bases for the request(s); and cite as part of it an available, applicable, and relevant final rule, statue, final guidance, or FDA-recognized consensus standard for each.

Reviewer Sign-Off: Angela Burke -S (Affiliate)
Digitally signed by Angela Burke -S (Affiliate)
Date: 2023.04.29 17:28:03 -05'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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March 23, 2023</br></br>

Acceptance Review Notification - Accepted

An administrative acceptance review was conducted on your submission K230645, and it was found to contain all of the necessary elements and information needed to proceed with the substantive review. We will contact you should we require any additional information during the course of the substantive review.

The lead reviewer assigned to your submission is me, Yongqing Chen. The file is being reviewed in Office of Health Technology 4, Division of Health Technology 4 B. The first line supervisor is the Assistant Director, Personal Protective Equipment, Reprocessing and Disinfection Devices. You may contact me at any point during the review if you have questions or concerns. You can provide valuable support for CDRH to continue to improve our programs by raising to the attention of management relevant issues that arise during the course of this review. If you feel there is an unresolved issue or a matter that requires additional attention, you should contact the Assistant Director. If your concern or issue is not addressed by the Assistant Director, you should contact the Division Director or OHT Director. The contact information for each management level can be found in the CDRH Management Directory.

We will contact you should we require any additional information during the course of the substantive review. FDA aims to apply the least burdensome principles when requesting additional information.

If you have general questions about the review process for your submission, you should contact OPEQSubmissionSupport@fda.hhs.gov.

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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For record.

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Sent: Tuesday, October 31, 2023 7:54 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Subject: [EXTERNAL] Re: K230645/S001 Review Complete

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Yongqing

Thank you for your email and for sharing this news.

We have made the requested changes to our (b)(4) and I have a copy available today to share with you.

Thanks again for all your assistance with this submission.

Best regards to you.

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)

elaine.minagh@eu.averydennison.com<mailto:firstname.lastname@eu.averydennison.com> | medical.averydennison.com<https://medical.averydennison.com/en/home.html>

[Image removed by sender.]

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Wed, 25 Oct 2023 at 20:28, Yongqing Chen [CHENYO] <yongqing.chen@fda.hhs.gov<mailto:yongqing.chen@fda.hhs.gov>> wrote:

October 25, 2023

We have completed our review. Please refer to the attached letter for details.

If you have any questions, please contact the lead reviewer assigned to your submission, Yongqing Chen.

*** This is a system-generated email notification ***

The information transmitted is intended only for the person or entity to which it is addressed and may contain confidential and/or privileged material. Any review, retransmission, dissemination or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is prohibited. If you received this in error, please contact the sender and delete the material from any device.

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For details about the personal information we process and why, please see our Privacy Notice<https://www.averydennison.com/en/home/legal-and-privacy-notices.html>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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October 25, 2023</br></br> We have completed our review. Please refer to the attached letter for details.

If you have any questions, please contact the lead reviewer assigned to your submission, Yongqing Chen.

 *** This is a system-generated email notification ***

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

BIOCOMPATIBILITY REVIEW OF K230645, AVERY DENNISON MEDICAL LTD.

To:	Yongqing Chen, CDRH\OHT4\DHT4B\THT4B2
From:	Sojan Abraham, CDRH\OHT4\DHT4B\THT4B1
Through:	Clarence Murray III, Assistant Director, CDRH\OHT4\DHT4B\THT4B1
Consult Type:	Biocompatibility
Consult:	CON237401
Submission:	K230645
Device Name:	BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Sponsor:	Avery Dennison Medical Ltd.
Date:	04/24/2023

(b)(5)

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Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Digital Signature Concurrence Table (Doc ID: 04504.03.05)	
For each of the specific issues identified in the recommended requests to the applicant above, I contributing consulting reviewer, have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability for requests.	
Reviewer Sign-Off	Sojan Abraham -S Digitally signed by Sojan Abraham -S Date: 2023.04.25 23:01:35 -04'00'

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Major Deficiency - Question 7

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This document expires upon the next approved and released revision by Avery Dennison.
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Project Number: (b)(4)
Version

CONFIDENTIAL

Biological Risk Assessment

Device Name: BeneHold CHG Surgical Incise Drape (b)(4)

Prepared for:

Avery Dennison Medical
(b)(4)
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

Prepared by:

(b)(4)

(b)(4)

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Question 4

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

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Minor Deficiency - Question 1

(b)(4)

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Minor Deficiency - Question 3

(b)(4)

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(b)(4) (b)(4)

Process Validation Report

Ethylene Oxide Sterilization Process - ISO 11135, Overkill Approach

Date: 20-Feb-2023

Customer: Avery Dennison

Report Number and Revision: (b)(4)

Title: Product Adoption Qualification Summary Report – Avery Dennison - (b)(4) (b)(4)

Prepared By: (b)(4)

Study Lead:

(b)(4)

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"Classification: Avery Dennison - Confidential"

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AVERY DENNISON | Medical

Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road
Longford, N39 RC80, Ireland
Phone: +353 43 33 49586
Fax: +353 43 3349566

AINN Hold Letter for K230645

22 September 2023

U.S. Food and Drug Administration
Centre for Devices and Radiological Health
10903 New Hampshire Avenue
Document Control Center WO66-G609
Silver Spring, MD 20993-0002

Subject: Avery Dennison Response to AINN Hold Letter for K230645, the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Dear Madam or Sir:

Pursuant to Section 745(b) of the FD&C Act per section 1136 of FDASIA, Avery Dennison Medical Ltd. is submitting an e-copy of this response to the Hold Letter for K230645 for your review. Additionally, the e-copy is accompanied with the original signed cover letter. Thank you.

Regards,

(b)(6)

Elizabeth Gallantine, PhD
Project Manager Europe
Avery Dennison
Phone: + 353 43 331 1341
E-mail: elizabeth.gallantine@eu.averydennison.com

Classification: Avery Dennison - Secret

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

FDA/CDRH/DCC
MAR 0 8 2023
RECEIVED

AVERY DENNISON | Medical

Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road
Longford, N39 RC80, Ireland
Phone: +353 43 33 49586
Fax: +353 43 3349566

K230645

Traditional 510(k) Notification

15 February 2023

U.S. Food and Drug Administration
Centre for Devices and Radiological Health
10903 New Hampshire Avenue
Document Control Center WO66-G609
Silver Spring, MD 20993-0002

Subject: 510(k) Notification for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Dear Madam or Sir:

Pursuant to Section 745(b) of the FD&C Act per section 1136 of FDASIA, Avery Dennison Medical Ltd. is submitting an e-copy of this Traditional 510(k) for your review. Additionally, the e-copy is accompanied with the original signed cover letter. Thank you.

Regards,

(b)(6)

Lisa Bartakovics
Sr. Global Director, Regulatory Affairs and Quality Assurance
Avery Dennison
Phone: (b)(6)
E-mail: regulatoryaffairs@eu.averydennison.com

Classification: Avery Dennison - Secret

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Dear Ms. Minagh,

Thank you for your prompt response and help! I will let you know if we have any further questions for you.

Best regards,
Yongqing

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Sent: Wednesday, October 25, 2023 6:45 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <kelsey.kaht@averydennison.com>; Annelies Luyts <annelies.luyts@eu.averydennison.com>; Shan Perkin <shan.perkin@eu.averydennison.com>; Sarah Suy <sarah.suy@eu.averydennison.com>; K230645@docs.fda.gov
Subject: Re: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr Chen

(b)(4)

I want to thank you for your guidance throughout this entire process.
I look forward to hearing from you soon.

Best Regards

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel (b)(6) (Mobile)
elaine.minagh@eu.averydennison.com | medical.averydennison.com

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https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Tue, 24 Oct 2023 at 21:28, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Ms. Callantine,
>
> Thank you again for working with us on this submission. (b)(4)
>
> (b)(4)

Please let me know if you have other questions.

Best regards,
Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Tuesday, October 24, 2023 11:26 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <kelsey.kaht@averydennison.com>; Annelies Luyts <annelies.luyts@eu.averydennison.com>; Shan Perkin <shan.perkin@eu.averydennison.com>; Sarah Suy <sarah.suy@eu.averydennison.com>
Subject: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

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Dear Mr. Chen

Please find in attachment our responses to your comments with the supporting documentation.

Thank you once again for your support with this submission. Please let us know if you have any further questions.

Kind Regards,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

Image removed by sender.

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For details about the personal information we process and why, please see our Privacy Notice
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DrÂ

Yongqing
 It is a pleasure to work with you on this submission. We have receivedÂ your query and are working very hard to formulate a response that will satisfy you. However, I fearÂ that we do not have enough time to coordinate this to a satisfactory level. Â Is it possible that we could receiveÂ an extension until Monday the 23rd of October?
 Many thanks and best regardsÂ
 ElaineÂ Â <br clear="all"> <div dir="ltr

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the COB of this Thursday (October 19, 2023).<u></u><u></u>

(b)(4)

<u></u>Â <u></u>

Please contact me if you have any questions.<u></u><u></u>

<u></u>Â <u></u>

Best regards,<u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Yongqing<u></u><u></u>

<u></u>Â <u></u>

<u></u>Â <u></u>

From: Chen, Yongqing

Sent: Tuesday, October 10, 2023 8:11 AM

To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Subject: RE: [EXTERNAL] K230645 Update<u></u><u></u>

<u></u>Â <u></u>

Dear Dr. Gallantine,<u></u><u></u>

<u></u>Â <u></u>

Thank you for letting me know this contact change. Good luck for your new move!<u></u><u></u>

<u></u>Â <u></u>

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for you.<u></u><u></u>

<u></u>Â <u></u>

Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

<u></u>Â <u></u>

<u></u>Â <u></u>

<u></u>Â <u></u>

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Sent: Tuesday, October 10, 2023 7:43 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p class="MsoNormal" style="line-height:12pt;background:rgb(255,235,156)"><span
style="font-size:10pt;color:rgb(156,101,0)">CAUTION:</span><span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
click links or open attachments

unless you recognize the sender and know the content is safe.<u></u><u></u></span></p>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<p class="MsoNormal">Dear Mr. Chen,Â  <u></u><u></u></p>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<p class="MsoNormal">I hope you are well!<u></u><u></u></p>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<p class="MsoNormal">IÂ am writing to inform you that I am leaving Avery Dennison at
the end of this month and will therefore no longer be the point of contact for the
current submission K230645.<u></u><u></u></p>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<p class="MsoNormal">My colleague Elaine Minagh, copied on this message, will become
the point of contact for future correspondence regarding the Avery Dennison submission.
I have provided Elaine&amp;#39;s contact information below:<u></u><u></u></p>

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<p class="MsoNormal">Elaine Minagh, Regulatory Affairs Manager<u></u><u></u></p>

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<p class="MsoNormal">Avery Dennison Medical Ltd.<u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-serif;color:rgb(41,41,41)">IDA
Business Park, Ballinalee Road, Longford, County Longford, N39 DX73,
Ireland</span><u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-
serif;color:rgb(41,41,41)">Telephone: 00Â </span><span style="font-family:Arial,sans-
serif;letter-spacing:0.15pt">      (b)(6)      ?</span><u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-serif;color:rgb(41,41,41)">e-
mail:Â <a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com</a></span><u></u><u></u></p>

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<p class="MsoNormal">Thank you for your support on this submission.<u></u><u></u></p>

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<p class="MsoNormal">Please let me know if you have any questions.<u></u><u></u></p>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<p class="MsoNormal">Best Wishes,<u></u><u></u></p>

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<p class="MsoNormal">Lizzie<u></u><u></u></p>

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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+ (b)(6)
(b)(6) <br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><span style="font-
family:Arial,sans-serif"><u></u><u></u></span></p>

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height="82" style="width:2.5555in;height:0.8541in" id="m_-3733366803405760289m_-
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alt="Image removed by sender."></span></a><u></u><u></u></p>

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href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Product Selector</a></span><u></u><u></u></p>

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<p class="MsoNormal">On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;
wrote:<u></u><u></u></p>

</div>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

<div>

<p class="MsoNormal">Thank you for the update Mr Chen! <u></u><u></u></p>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<div>

<p class="MsoNormal">Have a great day,Â <u></u><u></u></p>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<p class="MsoNormal">Lizzie<br clear="all">

<u></u><u></u></p>
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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+ (b)(6)
(b)(6) <br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><span style="font-
family:Arial,sans-serif"><u></u><u></u></span></p>

<p style="margin:0in"><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-serif;border:1pt
none windowtext;padding:0in;text-decoration:none"><img border="0" width="245"
height="82" style="width:2.5555in;height:0.8541in" id="m_-3733366803405760289m_-
1891516952761364032m_8099847791546314356Picture_x0020_2" src="cid:18b481133a34ce8e91"
alt="Image removed by sender."></span></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
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</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
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href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
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</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/13p-
IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tC
spI55uupICUMOIuUIw8Rwd-DL-
JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html" target="_blank">
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Product Selector</a></span><u></u><u></u></p>

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<p class="MsoNormal">On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

</div>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Dear Dr. Gallantine,<u></u><u></u></p>

<p class="MsoNormal">The supplement has been received on Monday and the team review has
been starting on Monday (09/25/2023).<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Respectfully,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> Chen, Yongqing

<br>
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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Sent: Tuesday, September 26, 2023 8:27 AM

To: ELIZABETH GALLANTINE <<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com>

Cc: Elaine Minagh <<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com>

Subject: RE: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

Dear Dr. Gallantine,<u></u><u></u>

Thank you for the update. It might take one or more days for DCC
to notify the appropriate Center/Office. I will let you know when the supplement has
been assigned to me.<u></u><u></u>

Â <u></u><u></u>

Respectfully,<u></u><u></u>

Yongqing<u></u><u></u>

Â <u></u><u></u>

<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

From: ELIZABETH GALLANTINE <<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com>

Sent: Tuesday, September 26, 2023 8:16 AM

To: Chen, Yongqing <<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov>

Cc: Elaine Minagh <<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com>

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

CAUTION:<span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
click links or open attachments unless you recognize the sender and know the content is
safe.<u></u><u></u>

Â <u></u><u></u>

Good Morning Mr Chen,Â

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p class="MsoNormal">The USB file has now arrived in Silver Creek. Could you let us
know when you have received it, please?<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Thank you,Â <u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Lizzie<br clear="all">

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Lizzie Gallantine, Ph.DÂ | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â Tel: +353 43 33 49586Â |Â Direct Line: + 353 43 331 1341Â

Mobile:Â + (b)(6) (b)(6)

elizabeth.gallantine@eu.averydennison.comÂ |Â medical.averydennison.com<u></u><u></u>

Error! Filename not specified.<u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
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</span><span style="font-size:7.5pt;font-family:Arial,sans-
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href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |

</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/13p-
IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tC
spI55uupICUMOIuUIw8Rwd-DL-
JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

<p style="margin:0in">Â <u></u><u></u></p>

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<p style="margin-right:1.25in;margin-bottom:0in;margin-left:0in">

<span style="font-size:9.5pt">Â </span><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

</div>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Dear Dr. Gallantine,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you for letting us know and look forward to working with you
on this submission.<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Best regards,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;

<br>

<b>Sent:</b> Monday, September 25, 2023 5:31 AM<br>

<b>To:</b> Chen, Yongqing &lt;<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt;<br>

<b>Cc:</b> Elaine Minagh &lt;<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com</a>&gt;<br>

<b>Subject:</b> Re: [EXTERNAL] K230645 Update<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

<div style="border:1pt solid rgb(156,101,0);padding:2pt">

<p class="MsoNormal" style="line-height:12pt;background:rgb(255,235,156)">

<span style="font-size:10pt;color:rgb(156,101,0)">CAUTION:</span><span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
click links or open attachments unless you recognize the sender and know the content is
safe.</span><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Dear Mr Chen,Â

<u></u><u></u></p>
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Â <u></u><u></u>

We have completed our response to the hold letter for K230645. TheÂ documents on a USB file were shippedÂ on Friday 22 September and are currentlyÂ in transit (b)(4).<u></u><u></u>

Â <u></u><u></u>

We have separatedÂ each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if

you have any questions.<u></u><u></u>

Â <u></u><u></u>

Best Wishes,Â <u></u><u></u>

Â <u></u><u></u>

Lizzie<u></u><u></u>

Â <u></u><u></u>

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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+ (b)(6)
(b)(6)Â <br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><u></u><u></u></p>

<p style="margin:0in"><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;border:1pt
none windowtext;padding:0in;text-decoration:none">Error! Filename not
specified.</span></b></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
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</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/13p-
IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tC
spI55uupICUMOIuUIw8Rwd-DL-
JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

<p style="margin:0in">Â <u></u><u></u></p>

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<p style="margin-right:1.25in;margin-bottom:0in;margin-left:0in">

<span style="font-size:9.5pt">Â </span><u></u><u></u></p>

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<p class="MsoNormal">On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

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<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Good morning Ms. Bartakovics,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you for keeping us updated on your submission. I think your
approach is reasonable for your purpose. We would appreciate, in your response
document/letter, if you can guide

us the location of your (b)(4) this will help us to
quickly find them without missing any important information.<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Best regards,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> Lisa Bartakovics &lt;<a
href="mailto:lisa.bartakovics@averydennison.com"
target="_blank">lisa.bartakovics@averydennison.com</a>&gt;

<br>

<b>Sent:</b> Tuesday, August 29, 2023 10:16 AM<br>

<b>To:</b> Chen, Yongqing &lt;<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt;<br>

<b>Cc:</b> ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;<br>
```

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.<u></u><u></u>

Â <u></u><u></u>

Good Morning Mr. Chen-<u></u><u></u>

Â <u></u><u></u>

I am winding down my time with Avery Dennison and therefore met with the team this morning to discuss our response to the hold letter for K230645. I just wanted to confirm that

the response needs to be submitted as an e-copy that has been verified through the e-submitter tool. Since there are additional reports and documents to submit, we plan to add those documents into folders as attachments to our response. There are quite a few

questions to address so it seemed as though a folder approach made the most sense for organizational purposes. If there is a better approach, please let me know so we may adopt that template.<u></u><u></u>

Â <u></u><u></u>

Much appreciated.<u></u><u></u>

Â <u></u><u></u>

Have a nice day.<u></u><u></u>

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Regards,<u></u><u></u></p>

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<p class="MsoNormal"><br clear="all">

<u></u><u></u></p>

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<p style="margin:0in"><b><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Lisa Bartakovics</span></b><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Senior Director Global Regulatory Affairs and Quality<br>

Avery Dennison Medical</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">m: (b)(6) k</span><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">7100 Lindsay Dr. Mentor, OH 44060</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin:0in"><span style="font-size:9pt;font-family:Arial,sans-
serif;color:black;border:1pt none windowtext;padding:0in">Error! Filename not
specified.</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin-bottom:0in"><a
href="https://www.facebook.com/AveryDennisonCorporation" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Facebook</span></a><span style="font-size:10pt;font-
family:Arial,sans-serif;color:rgb(67,67,67)">

Â  </span><a href="https://twitter.com/AveryDennison" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-serif;color:black">Twitter</span></a><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(67,67,67)"> Â

</span><a href="https://www.linkedin.com/company/avery-dennison/" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-
serif;color:black">LinkedIn</span></a><u></u><u></u></p>

<p class="MsoNormal"><br>

<a href="https://www.averydennison.com/" target="_blank"><span style="font-
size:10pt;font-family:Arial,sans-
serif;color:black">averydennison.com</span></a><b><span style="font-size:10pt;font-
family:Arial,sans-serif;color:black"> Â

</span></b><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">medical.averydennison.com</span></a><u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">On Mon, Aug 21, 2023 at 9:02â€¯AM Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

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<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Hi Lizzie,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you very much for sending me your contact info. Look forward
to working with you on this submission.<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Best regards,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;

<br>

<b>Sent:</b> Monday, August 21, 2023 9:15 AM<br>

<b>To:</b> Chen, Yongqing &lt;<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt;<br>

<b>Cc:</b> Elaine Minagh &lt;<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com</a>&gt;; Lisa Bartakovics &lt;<a
href="mailto:lisa.bartakovics@averydennison.com"
target="_blank">lisa.bartakovics@averydennison.com</a>&gt;<br>

<b>Subject:</b> Re: [EXTERNAL] K230645 Update<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

<div style="border:1pt solid rgb(156,101,0);padding:2pt">

<p class="MsoNormal" style="line-height:12pt;background:rgb(255,235,156)">
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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.<u></u><u></u>

Â <u></u><u></u>

Hi Yongqing

<u></u><u></u>

Â <u></u><u></u>

I hope you're well! My contact information is:<u></u><u></u>

Â <u></u><u></u>

Lizzie Gallantine, PhD., Project Manager Europe<u></u><u></u>

Avery Dennison Medical Ltd.<u></u><u></u>

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland<u></u><u></u>

Telephone: (b)(6) <u></u><u></u>

e-mail:

elizabeth.gallantine@eu.averydennison.com<u></u><u></u>

Â <u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p class="MsoNormal"><span style="font-family:Arial,sans-
serif;color:rgb(41,41,41)">Thank you!</span><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-
serif;color:rgb(41,41,41)">Lizzie</span><u></u><u></u></p>

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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+(b)(6)
(b)(6) <br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><u></u><u></u></p>

<p style="margin:0in"><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;border:1pt
none windowtext;padding:0in;text-decoration:none">Error! Filename not
specified.</span></b></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |

</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/171Rs-7v4aDq7dEhkA8m-xeEroyziv0B9-
2ORcBfvLsuvmZOn2dWHkRKeP7p7o3Yv9mIvflpWjh15YlsvCtg5aiAMWGB3MtKV6aietR8j4kIOQ77xCR7u8z8-
ddPIQjqUyaHxnRQFK6_b6JLfpRKnNnPczsUAmE6awMgovHe3UD56sOtHpvlEHIsZ69MbkJGvgJyg6nY-
rniQIjnIE-s-
wiLZSCf7zuctgeWyXwcXM90/https%3A%2F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-
selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

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<p style="margin-right:1.25in;margin-bottom:0in;margin-left:0in">

<span style="font-size:9.5pt">Â </span><u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p class="MsoNormal">On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

</div>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Dear Ms. Gallantine,<u></u><u></u>

Â <u></u><u></u>

Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our

system? Thank you!<u></u><u></u>

Â <u></u><u></u>

Error! Filename not specified.<u></u><u></u>

Please let me know if you have any questions.<u></u><u></u>

Â <u></u><u></u>

Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

Â <u></u><u></u>

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com>

Sent: Friday, August 18, 2023 4:24 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Elaine Minagh <elaine.minagh@eu.averydennison.com>

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.<u></u><u></u>

Â <u></u><u></u>

Dear Mr. Chen-<u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Â <u></u><u></u>

I hope you have had an enjoyable summer and this email finds you well.<u></u><u></u>

Â <u></u><u></u>

I am writing to inform you that I am leaving Avery Dennison at the end of the month and will therefore no longer be the point of contact for submission K230645.<u></u><u></u>

Â <u></u><u></u>

Elizabeth Gallantine, copied on this message, will serve as the point of contact for future correspondence regarding the Avery Dennison submission. She will provide updates regarding

the response to the hold letter and coordinate all future correspondence.<u></u><u></u>

Â <u></u><u></u>

It has been a pleasure working with you and I hope to work with you again in the future.<u></u><u></u>

Â <u></u><u></u>

Please let me know if you have any questions.<u></u><u></u>

Â <u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p class="MsoNormal">Regards,<u></u><u></u></p>

</div>

<div>

<p class="MsoNormal">Lisa Bartakovics<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

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<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Dear Ms. Bartakovics,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you for keeping me updated and please let me know if you
have any questions for us.<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Best regards,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> Lisa Bartakovics &lt;<a
href="mailto:lisa.bartakovics@averydennison.com"
target="_blank">lisa.bartakovics@averydennison.com</a>&gt;

<br>

<b>Sent:</b> Thursday, June 1, 2023 12:20 PM<br>

<b>To:</b> Chen, Yongqing &lt;<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt;<br>

<b>Cc:</b> regulatoryaffairs regulatoryaffairs &lt;<a
href="mailto:regulatoryaffairs@eu.averydennison.com"
target="_blank">regulatoryaffairs@eu.averydennison.com</a>&gt;<br>

<b>Subject:</b> [EXTERNAL] K230645 Update<u></u><u></u></p>
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<p class="MsoNormal">Â <u></u><u></u></p>

<div style="border:1pt solid rgb(156,101,0);padding:2pt">

<p class="MsoNormal" style="line-height:12pt;background:rgb(255,235,156)">

<span style="font-size:10pt;color:rgb(156,101,0)">CAUTION:</span><span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
click links or open attachments unless you recognize the sender and know the content is
safe.</span><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Dear Mr. Chen-<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Thank you again for the teleconference, we greatly appreciate your
time and that of the team.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Therefore, Avery Dennison plans to respond to all of the points
within theÂ Hold Letter for K230645 in early September. I wanted to provide an update
so that you are aware we are

working on the items identified in the Hold Letter and will respond back to you as soon
as (b)(4) is completed.<u></u><u></u></p>

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Â <u></u><u></u>

Please let me know if you have any furtherÂ questions.Â
<u></u><u></u>

Â <u></u><u></u>

Thank you and have a nice day.<u></u><u></u>

Â <u></u><u></u>

Â <u></u><u></u>

Regards,<u></u><u></u>

<br clear="all">

<u></u><u></u>

<span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Lisa Bartakovics<u></u><u></u>

<span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical<u></u><u></u>

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serif;color:black"><a
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amp;source=g" target="_blank">7100 Lindsay Dr. Mentor, OH
44060<u></u><u></u>

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LinkedIn<u></u><u></u>

averydennison.com Â

medical.averydennison.com<u></u><u></u>

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<p style="margin:0in"><b><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Lisa Bartakovics</span></b><u></u><u></u></p>

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serif;color:black">7100 Lindsay Dr. Mentor, OH 44060</span><u></u><u></u></p>

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Major Deficiency - Question 2

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

(b)(4)

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Major Deficiency - Question 13

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Revision: (b)(4)

Study #: (b)(4)

July 12th, 2022

Antimicrobial Performance of Avery Dennison's CHG Incise Drape (b)(4)

(b)(4)

PART I

FINAL REPORT

(b)(4)

Customer:
(b)(4)
Research and Development Engineer
Avery Dennison Medical
7070 Spinach Dr.
Mentor, Ohio 44060
Phone: (b)(4)
Email: (b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRHFOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Revision: (b)(4)

Study #: (b)(4)

October 7th, 2021

Recovery Validation of CHG Loaded Incise (b)(4)

(b)(4)

FINAL REPORT

(b)(4)

Customer:

(b)(6)

Research and Development Engineer
Avery Dennison Medical
7070 Spinach Dr.
Mentor, Ohio 44060
M: (b)(6)

(b)(6)

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Study #: (b)(4)

October 7th, 2021

Neutralization of the Antimicrobial Coating Used on CHG Loaded Incise Drape (b)(4)

FINAL REPORT

(b)(4)

Customer:

(b)(6)
Research and Development Engineer
Avery Dennison Medical
7070 Spinach Dr.
Mentor, Ohio 44060
M: (b)(6)

Approved:

Revision #	Date	Comments

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U.S. FOOD & DRUG ADMINISTRATION

K230645
Avery Dennison Medical Ltd.
Trade/Device Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Contact Name: Lisa Bartakovics

This document is being communicated via e-mail as an attachment. The date on which FDA sent this e-mail is the official date of this correspondence.

We have reviewed your submission K230645 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number K230645 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please refer to the eCopy guidance at https://www.fda.gov/media/83522/download for current information on eCopy requirements.

Your response is due within 180 days from the date of this request, which is the hold date plus 180 days. If a complete response is not received in CDRH's Document Control Center by this date, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

This request for additional information has undergone supervisory review to ensure that the deficiencies cited are least burdensome and relevant to the marketing decision. Please see the revised guidance "Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions" issued on September 29, 2017 (https://www.fda.gov/media/71735/download) for clarification regarding major and minor deficiencies.

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FDA is offering a teleconference within 10 calendar days from the date on this letter to address any clarification questions you may have pertaining to the deficiencies. If you are interested in a teleconference, please provide (1) proposed dates and (2) a list of your clarification questions via email at least 48 hours before the teleconference to the lead reviewer assigned to your submission. We would like to emphasize that the purpose of the meeting is to address specific clarification questions. Please note that if the specific clarification questions are not received at least 48 hours before the teleconference, the review team might not be able to provide feedback. The teleconference is not intended for review of new information, test methods or data; these types of questions could be better addressed via a Submission Issue Q-Submission (Q-Sub). For additional information regarding Q-Subs, please refer to the Guidance for Industry and FDA Staff on Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions at https://www.fda.gov/media/114034/download.

Least Burdensome (LB) Flag

The LB flag is an approach to allow submitters the opportunity for the informal review by or on behalf of Division management of an issue raised in an FDA request for additional information (i.e., a deficiency letter). The goal of the LB flag is to quickly address FDA requests that submitters do not believe are least burdensome or when submitters believe they are being held to a different standard than their legally marketed predicate device. The LB flag is not intended to clarify deficiencies, is not an appeal under 21 CFR 10.75, and is not intended to provide a review of a proposed response to deficiencies.

If you would like to throw the LB flag, FDA has several criteria that should be met before you submit your request:

- You should have tried to address your concern by discussing it with Division management before attempting to throw the LB flag. This discussion with Division management may take place as part of a teleconference (such as the voluntary teleconference held within 10 days following transmission of an Additional Information letter to clarify deficiencies), email, or a Q-Submission Submission Issue Request.
- Your flag should generally be limited to two topic areas. Topic areas are common premarket review deficiency categories that apply to many device types across multiple reviewing Divisions. Examples of topic areas include biocompatibility, sterility, reprocessing, software, electromagnetic compatibility, wireless, electrical safety, clinical, and non-clinical performance testing.
- If you would like to discuss issues pertaining to more than two topic areas, you should contact OPEQSubmissionSupport@fda.hhs.gov for more information.
- You should throw the LB flag within 60 calendar days of the date that FDA sent the deficiency letter.

Upon meeting the criteria, you should send a short email (e.g., 1-2 page) that includes: 1) a summary of the deficiencies under disagreement, 2) a summary of relevant communications with Division management, and 3) a proposed path forward. The LB flag should be sent to the lead reviewer and their Assistant Director. You should also copy OPEQSubmissionSupport@fda.hhs.gov on your LB flag email request. Within two

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business days of your email, your request will be acknowledged by the reviewing Division. If you do not meet the criteria for the LB flag, you will be notified in this acknowledgement email.

Your LB flag should contain sufficient information to determine whether the deficiency letter was not least burdensome, or you are being held to a different standard than your predicate device. FDA may request a phone call with you to discuss your concern further and intends to communicate feedback from Division management on LB flags through email no later than 21 calendar days of their receipt. Please note that the LB flag does not change the deadline for your response to the Document Control Center. If you have any questions, please contact OPEQSubmissionSupport@fda.hhs.gov.

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Minor Deficiency - Question 4

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BeneHold Surgical Incise Drape with CHG (b)(4) Formulation Stability Protocol

(b)(4)

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Stability Report
BeneHold Surgical Incise Drape with CHG Antimicrobial II (b)(4)

The following signatures will be captured electronically via the electronic document control system. Below is a list of required approvers and associated titles.

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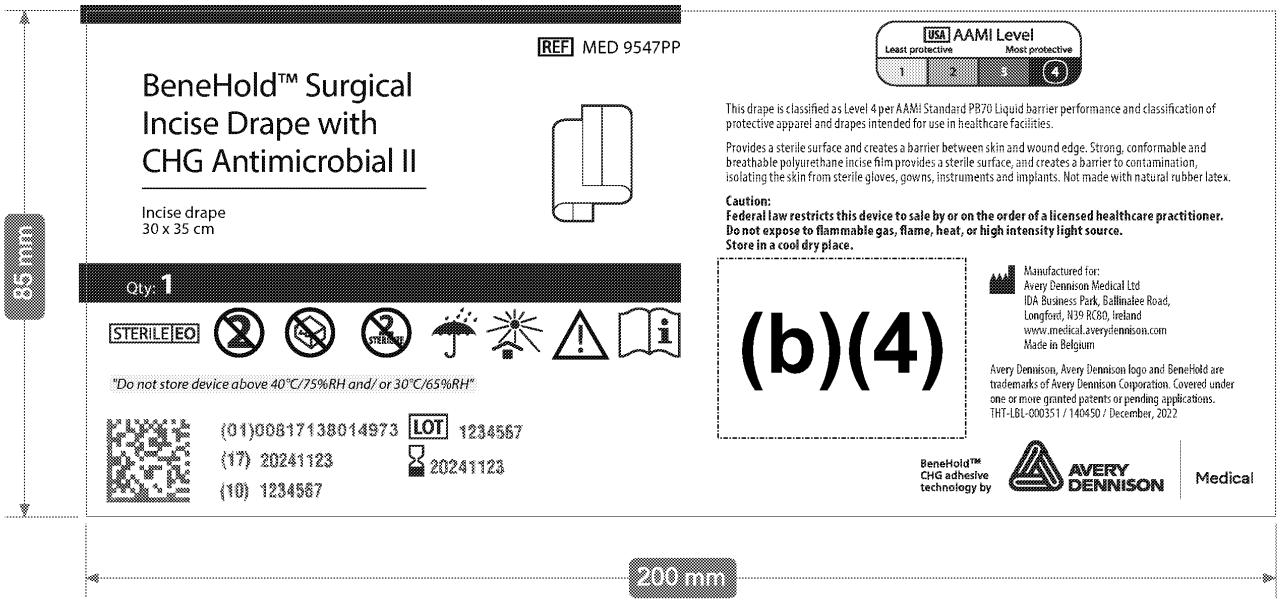
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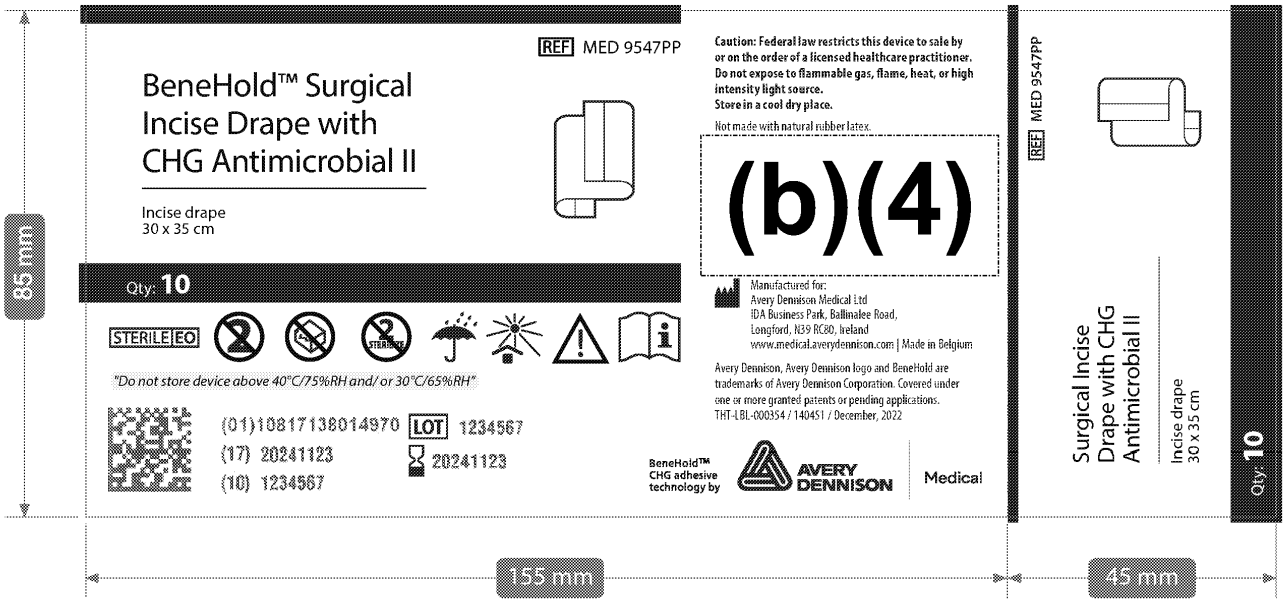


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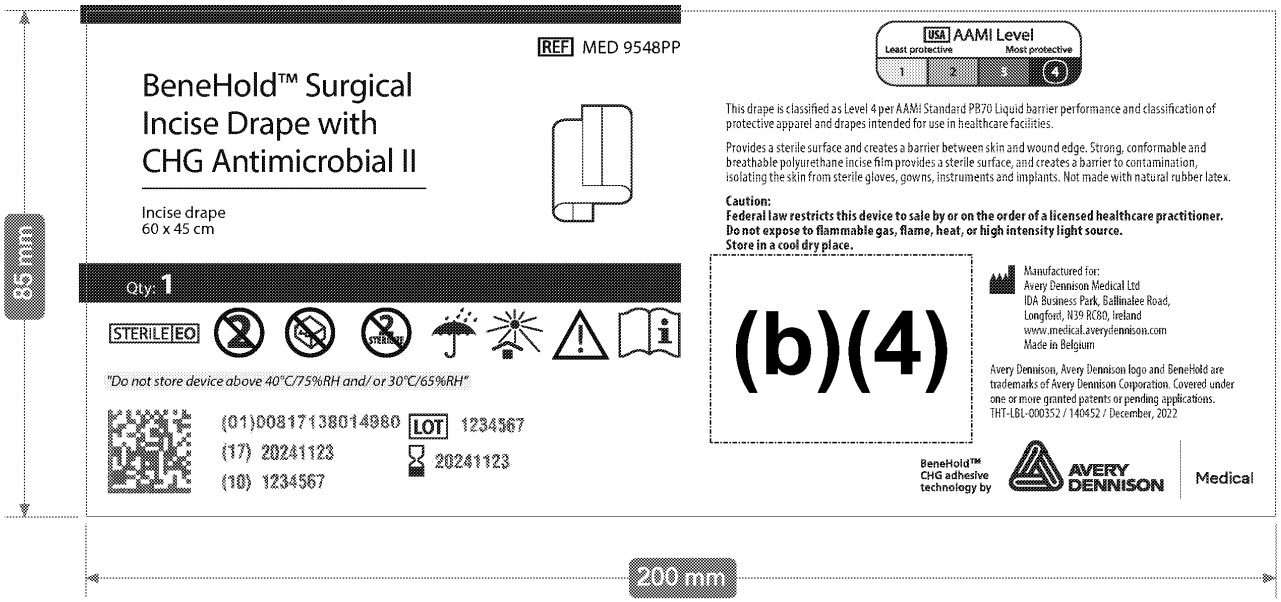


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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

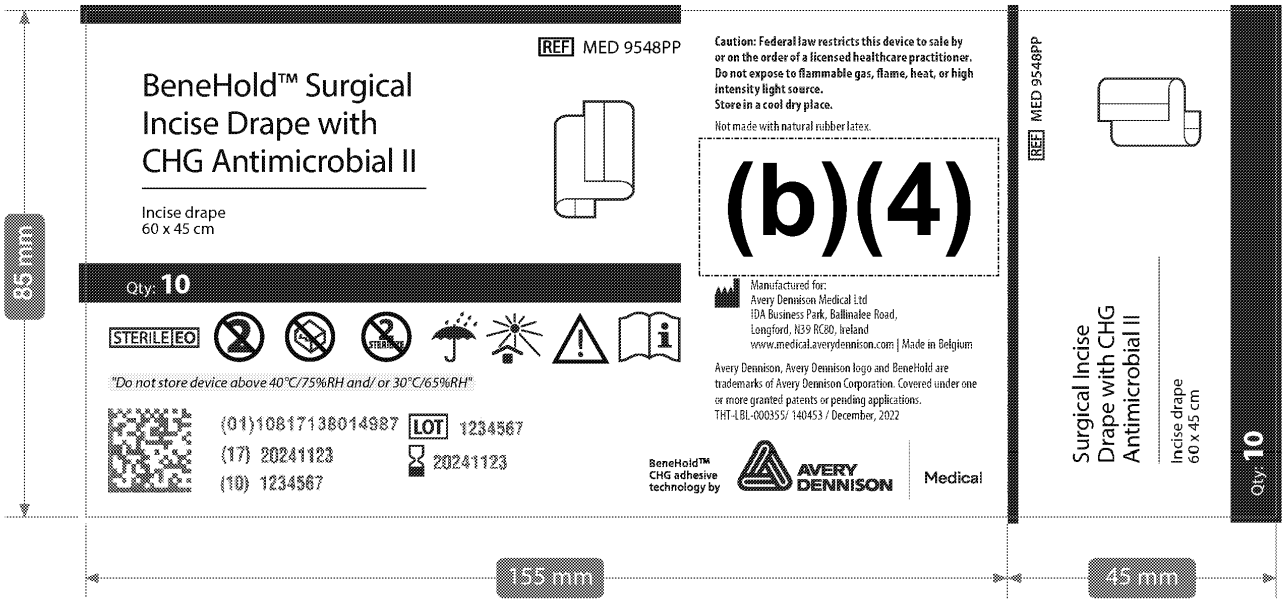


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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

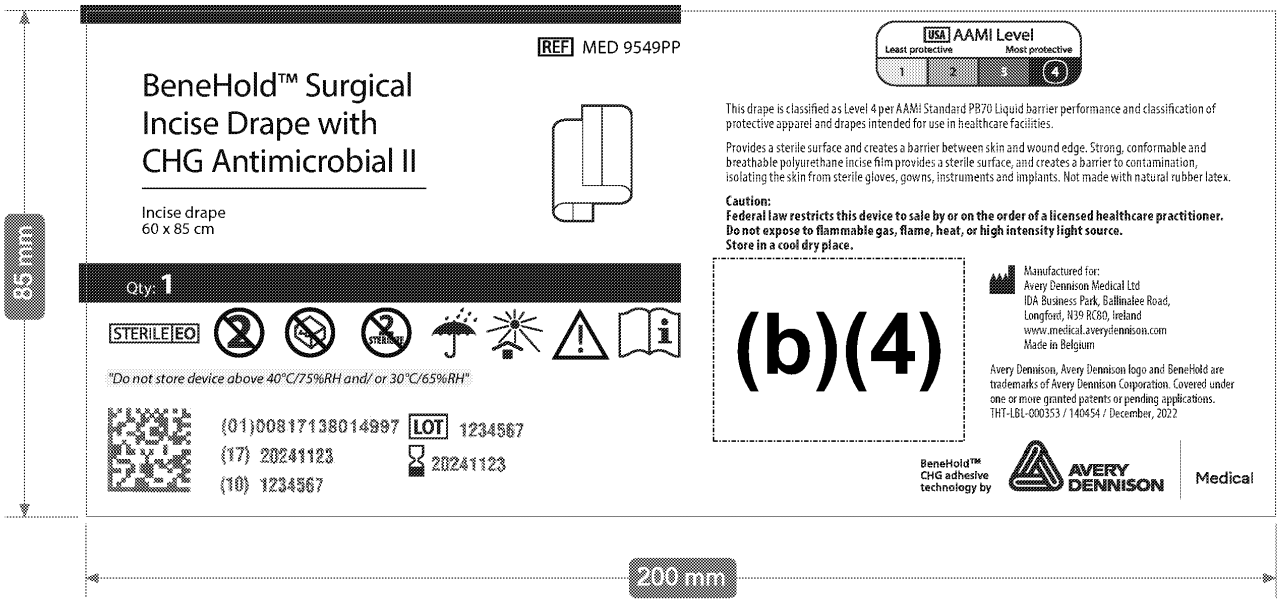


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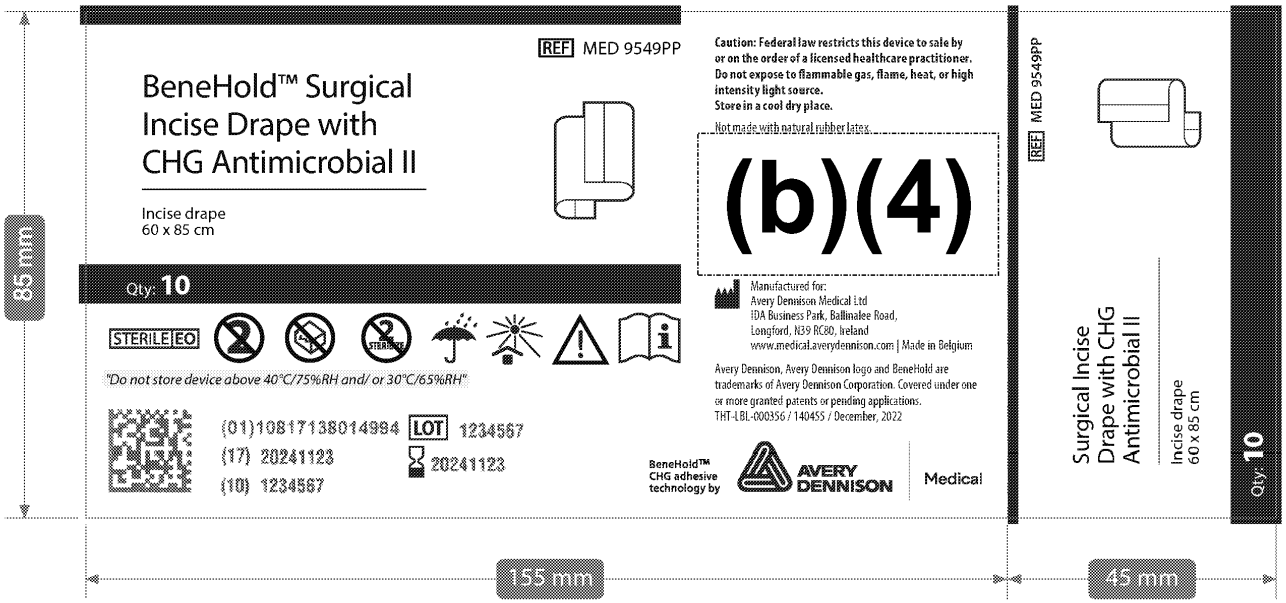


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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Section 16 – Software

This section is not applicable since the Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II does not contain any software.

Questions? Contact FDA/CDRH/OC/DBC at CDRH-GUIDANCE@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Section 8- Financial Certification or Disclosure Statement

The certification of Financial Interests and arrangements of Clinical Investigators, FDA Form 3454, for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II and (b)(4) Financial Disclosure Letter may be found within Attachment 8.1 and 8.2 respectively. In addition, a Statement of Compliance for Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II may be found in attachment 8.3.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 8.1 Financial Disclosure Statement, FDA Form 3454

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: May 31, 2025

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Princeton Consumer Research	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

(b)(6)	
	DATE *(mm/dd/yyyy)* 02/14/2025

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Operations
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 8.2 PCR (b)(4) and (b)(4) Financial Disclosure Letter

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Financial Disclosure of Principal Investigator to Sponsor

The following information is obtained in accordance with 21 CFR part 54. (b)(6)
Principal Investigator of studies (b)(4), reports the following:

(b)(6)

I have not entered into any financial arrangement with the sponsor of the covered studies, whereby the value of the compensation to me for conducting the study could be influenced b the outcome of the study.

I have not received any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation, in the form of equipment, retainer for ongoing consultation, or honoraria.

I do not have any proprietary interest in the product(s) tested in the above listed studies.

I do not have any significant equity interest, as defined in the 21 CFR 544.2(b), in the sponsor of the covered study.

(b)(6)

Name

Principal Investigator

Title

(b)(4)

Firm/Organization

(b)(6)

Signature

11 / 28 / 2022

Date (MM/DD/YYYY)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Doc ID: (b)(4)

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4) (b)(4)

TITLE	Financial Disclosure Letter
FILE NAME	Financial Disclos... and (b)(4)
DOCUMENT ID	(b)(4)
AUDIT TRAIL DATE FORMAT	MM / DD / YYYY
STATUS	Signed

Document history

SENT	**11 / 28 / 2022** 13:34:24 UTC-5	Sent for signature to (b)(6) (b)(6)
VIEWED	**11 / 28 / 2022** 13:51:14 UTC-5	Viewed by (b)(6) (b)(6)
(b)(6) SIGNED	**11 / 28 / 2022** 13:51:57 UTC-5	Signed by (b)(6) (b)(6)
COMPLETED	**11 / 28 / 2022** 13:51:57 UTC-5	The document has been completed.

Powered by (b)(4)

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Attachment 8.3 Statement of Compliance

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Statement of Compliance

[21 CFR Part 50 and 56]

The investigation for the Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II was conducted in compliance with applicable requirements in the Protection of Human Subjects regulations in 21 CFR part 50 and the Institutional Review Boards regulations in 21 CFR part 56.

The subjects were informed of the nature, purpose and known risk of the study both orally and in writing. The subjects provided their written informed consent before participating in the study. The approval of the Institutional Review Board was obtained prior to initiation of the study.

(b)(6)

Sr. R&D Engineer
7070 Spinach Drive
Mentor, OH 44060

January 20, 2023

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RMONR
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-8521

Subject Matter Expert (SME) Review

Date: April 21, 2023

SME Reviewer: Maureen OBrien

Expertise: Animal Study

Applicable Review Guide (if used): [Choose Review Guide]

Submission # K230645

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Optional Classification Information:	
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories
Pro Code(s): Class: [Choose] Reg #:	Reg Name:
Rx/OTC: [Choose Option]	

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Section 11 Executive Summary

(b)(4)

Questions? Contact DAICDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

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Section 20 – Performance Testing – Clinical

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is indicated for use as an incise drape with continuous antimicrobial activity. It is intended for external use only. (b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 20.1 FDA Form 3674 Certification of Compliance

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Form Approved: OMB No. 0910-0616. Expiration Date: 4/30/2024. See PRA Statement below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance

Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. Name of Sponsor/Applicant/Submitter
Avery Dennison Medical Ltd

2. Date of the Application/Submission
02/14/2023

3. Address

Address 1 *(Street address, P.O. box, company name c/o)*
IDA Business Park, Ballinalee Road

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City	State/Province/Region	ZIP or Postal Code
Longford	Longford	N39 RC80

Country
Ireland

4. Telephone and Fax Numbers *(Include country code if applicable and area code)*

(Tel): +353 43 33 49586

(Fax): +353 43 3349566

PRODUCT INFORMATION

5. **For Drugs/Biologics:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).
For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)

Surgical Drape and Drape Accessories; (Product code: KKX); BencHold™ Surgical Incise Drape with CHG antimicrobial II, MED 9547PP, MED 9548PP, MED 9549PP

Continuation Page for #5

APPLICATION / SUBMISSION INFORMATION

6. Type of Application/Submission Which This Certification Accompanies

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. Include IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/Other Number *(If number previously assigned)*

If BLA was selected in item 6, provide Supplement Number

8. Serial Number Assigned to Application/Submission Which This Certification Accompanies

CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes *(See instructions for additional information and explanation)*

☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☒ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that the requirements of 42 U.S.C. 282(j), including any applicable provisions of 42 CFR part 11, have been met.

Certification Statement / Information section continued on page 2

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

CERTIFICATION STATEMENT / INFORMATION *(Continued)*

10. If you checked box C, in number 9, provide the National Clinical Trial (NCT) Number(s) for any "applicable clinical trial(s)," for which you (the sponsor/applicant/submitter) are the "responsible party" under 42 U.S.C. § 282(j)(1)(a)(i), section 402(j)(1)(a)(i) of the Public Health Service Act referenced in the application/ submission which this Certification accompanies. (Add continuation page as necessary.)

NCT Number(s):

Continuation Page for #10

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Name and Title of the Person who Signs Number 15

Name	Title
(b)(6)	Sr. R&D Engineer

12. Address

Address 1 *(Street address, P.O. box, company name c/o)*	
IDA Business Park, Ballinalee Road	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	
City	State/Province/Region
Longford	Longford
Country	ZIP or Postal Code
Ireland	N39 RC80

13. Telephone and Fax Numbers *(Include country code if applicable and area code)*

(Tel): +1 440-309-7245

(Fax): +353 43 3349566

14. Date of Certification

02/14/2023

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative *(Sign)*

Sign

(b)(6)

This section applies only to requirements of the Paperwork Reduction Act of 1995.

*****DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*****

The burden time for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/ submission) per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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INSTRUCTIONS FOR COMPLETION OF FORM FDA 3674 – CERTIFICATION OF COMPLIANCE

Under 42 U.S.C. § 282(j)(5)(B), with Requirements for ClinicalTrials.gov Data Bank

Form FDA 3674 must accompany an application/submission, including certain amendments, supplements, and resubmissions, submitted under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.

1. Name of Sponsor/Applicant/Submitter – This is the name of the sponsor/applicant/submitter of the drug/ biologic/device application/submission which the certification accompanies. The name must be identical to that listed on the application/submission.

2. Date – This is the date of the application/submission which the certification accompanies or should have accompanied, if submitted at a subsequent date.

3. & 4. Provide complete address, telephone number, and fax number of the sponsor/applicant/submitter.

5. Product Information – ***For Drugs/Biologics:*** Provide the established, proprietary name, and/or chemical/ biochemical/blood product/cellular/ gene therapy name(s) for the product covered by the application/ submission. Include all available names by which the product is known. ***For Devices:*** Provide the common or usual name, classification, trade or proprietary or model name(s), and/or model number(s). Include all available names/model numbers by which the product is known.

Use a continuation page only if you have filled in all available spaces.

6. Type of Application/Submission – Identify the type of application/submission which the certification accompanies by checking the appropriate box. If the name of the type of application/submission is not identified (i.e. a new IND clinical protocol), check the box labeled "Other."

7. IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/Other Number – If FDA has previously assigned a number associated with the application/ submission which this certification accompanies, list that number in this field. For example, if the application/submission accompanied by this certification is an IND protocol amendment and the IND number has already been issued by FDA, that number should be provided in this field.

8. Serial Number – In some instances a sequential serial number is assigned to the submission/application. If there is such a serial number, provide it in this field. If there is no such number, leave this field blank.

9. Certification – This section contains three different check-off boxes.

Box A should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply because no data from clinical trials are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies.

Box B should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply at the time of submission of the certification to any clinical trials for which data are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies.

Box C should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do apply, on the date the certification is signed, to some or all of the clinical trials for which data are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies and for which the sponsor/ applicant/submitter is the "responsible party" of the applicable clinical trial included in the application/ submission. This means that, as of the date the certification is signed, the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, and any provisions of 42 CFR part 11 that apply to one or more of the applicable clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies have been met by the sponsor/applicant/ submitter as the "responsible party."

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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10. National Clinical Trial (NCT) Numbers – If you have checked Box C in number 9 (Certification), provide the NCT Number obtained from *www.ClinicalTrials.gov* for each applicable clinical trial for which the sponsor/ applicant/submitter is the "responsible party" and for which data is included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. Type only the number, as the term "NCT" will be added automatically before number. Include any and all NCT numbers that, as of the date the certification is signed, have been assigned to the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies. Multiple NCT numbers may be required for a particular certification, depending on the number of "applicable clinical trials" for which data is included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies and for which the sponsor/applicant/submitter is the "responsible party." Leave this field blank if you have checked Box 9.C but, at the time the certification is completed, you have not yet received any NCT number(s) for the "applicable clinical trial(s)" for which data is included, relied upon, or otherwise referred to in the application/ submission. Use a continuation page only if you have filled in all available spaces.

11. Name and Title of Person Who Signed In number 11 – Include the name and title of the person who is signing the certification. If the person signing the certification is not the sponsor/applicant/submitter of the application/submission, he or she must be an authorized representative of the sponsor/applicant/submitter.

12 & 13. Provide the full address, telephone and fax numbers of the person who is identified in number 11 and signs the certification in number 15.

14. Provide the date the certification is signed. This date may be different from the date provided in number 2.

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative – The person signing the certification must sign in this field.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 20.2 Statement of Compliance

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Statement of Compliance

[21 CFR Part 50 and 56]

The investigation for the Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II was conducted in compliance with applicable requirements in the Protection of Human Subjects regulations in 21 CFR part 50 and the Institutional Review Boards regulations in 21 CFR part 56.

The subjects were informed of the nature, purpose and known risk of the study both orally and in writing. The subjects provided their written informed consent before participating in the study. The approval of the Institutional Review Board was obtained prior to initiation of the study.

(b)(6)

Sr. R&D Engineer
7070 Spinach Drive
Mentor, OH 44060

January 20, 2023

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 20.3 Validation of Adhesive Performance of BeneHold™ Surgical Incise Drape with CHG antimicrobial II on Dry Skin (Protocol)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 20.4 Validation of Adhesive Performance of BeneHold™ Surgical Incise Drape with CHG antimicrobial II on Fragile Skin (Protocol)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 20.5 Validation of Adhesive Performance of BeneHold™ Surgical Incise Drape with CHG antimicrobial II on Dry Skin (Report)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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AVERY DENNISON	Document Type:	Validation Report
	Document Title:	Dry Skin Design Validation Report for (b)(4) BeneHold Surgical Incise Drape with CHG
	Document Number, Revision:	(b)(4)

Dry Skin Design Validation Report for (b)(4) BeneHold Surgical Incise Drape with CHG

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Attachment 20.6 Validation of Adhesive Performance of BeneHold™ Surgical Incise Drape with CHG antimicrobial on II Fragile Skin (Report)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

AVERY DENNISON	Document Type:	Validation Report
	Document Title:	Fragile Skin Design Validation Report for (b)(4) BeneHold Surgical Incise Drape with CHG
	Document Number, Revision:	(b)(4)

Fragile Skin Design Validation Report for (b)(4) BeneHold Surgical Incise Drape with CHG

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Section 7- Class III Summary and Certification

This section is not applicable since the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is a Class II device per FDA product Code KKX.

Questions? Contact FDA/CDRH/OC/EDRO at CDRHGUIDANCE@fda.hhs.gov or 301-796-8118

Dear Elaine,

Thank you for getting back to me quickly. It seems GMT time is 4 hour ahead of EST. I am wondering whether you are available any time today between 12:30 – 3 pm GMT (which is my 8:30-11am EST) so we can have a quick 30-min call?

Best regards,
Yongqing

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Sent: Thursday, October 19, 2023 3:46 PM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: K230645@docs.fda.gov
Subject: Re: [EXTERNAL] K230645 Update

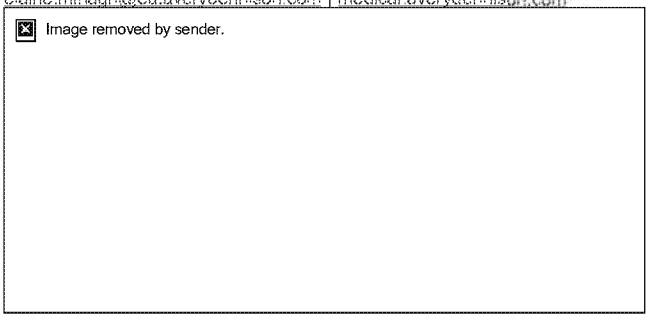
CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Yongqing

Thank you for getting back to me so quickly, we are of course disappointed to hear that there are additional issues.
We can make ourselves available for a call tomorrow, it's difficult to suggest a time when I don't know your time zone.
However, I have provisionally booked the required individuals for 12.00 GMT.
If this does not work for you, just suggest another time and I can arrange it on my end.

Best wishes

Elaine
Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)
elaine.minagh@eu.averydennison.com | medical.averydennison.com



https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Thu, 19 Oct 2023 at 16:38, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Ms. Minagh,
>
> Thank you for working with us hardly to address our concerns. (b)(4)
> (b)(4)
>
> Please let me know your thoughts. Thank you!
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** Elaine Minagh <elaine.minagh@eu.averydennison.com>
> **Sent:** Thursday, October 19, 2023 9:24 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** K230645@docs.fda.gov
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Dr Yongqing
>
> It is a pleasure to work with you on this submission.
> We have received your query and are working very hard to formulate a response that will satisfy you.
> However, I fear that we do not have enough time to coordinate this to a satisfactory level.
>
> Is it possible that we could receive an extension until Monday the 23rd of October?

Many thanks and best regards

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)
elaine.minagh@eu.averydennison.com | medical.averydennison.com

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https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Tue, 17 Oct 2023 at 19:30, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

Dear Ms. Elaine Minagh,

Thank you for working with us on this submission. We are reviewing the provided supplement S001 and have the following information for you to address. Please provide your response at your early convenience but not later than **the COB of this Thursday (October 19, 2023).**

(b)(4)

Please contact me if you have any questions.

Best regards,
Yongqing

From: Chen, Yongqing
Sent: Tuesday, October 10, 2023 8:11 AM
To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for letting me know this contact change. Good luck for your new move!

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for you.

Best regards,
Yongqing

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Tuesday, October 10, 2023 7:43 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen,

I hope you are well!

I am writing to inform you that I am leaving Avery Dennison at the end of this month and will therefore no longer be the point of contact for the current submission K230645.

My colleague Elaine Minagh, copied on this message, will become the point of contact for future correspondence regarding the Avery Dennison submission. I have provided Elaine's contact information below:

Elaine Minagh, Regulatory Affairs Manager
Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73, Ireland
Telephone (b)(6)
e-mail: elaine.minagh@eu.averydennison.com

Thank you for your support on this submission.

Please let me know if you have any questions.

Best Wishes,
Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: +(b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com> wrote:

> Thank you for the update Mr Chen!
>
> Have a great day,
>
> Lizzie
>
> **Lizzie Gallantine, Ph.D** | Project Manager Europe | Avery Dennison Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: +(b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
>
> Image removed by sender.
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>
> On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:
>
> > Dear Dr. Gallantine,
> > The supplement has been received on Monday and the team review has been starting on Monday (09/25/2023).
> >
> > Respectfully,
> > Yongqing

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

From: Chen, Yongqing
Sent: Tuesday, September 26, 2023 8:27 AM
To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,
Thank you for the update. It might take one or more days for DCC to notify the appropriate Center/Office. I will let you know when the supplement has been assigned to me.

Respectfully,
Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Tuesday, September 26, 2023 8:16 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good Morning Mr Chen,

The USB file has now arrived in Silver Creek. Could you let us know when you have received it, please?

Thank you,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Dr. Gallantine,
>
> Thank you for letting us know and look forward to working with you on this submission.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Sent:** Monday, September 25, 2023 5:31 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Dear Mr Chen,
>
> We have completed our response to the hold letter for K230645. The documents on a USB file were shipped on Friday 22 September and are currently in transit (b)(4)
>
> We have separated each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if you have any questions.
>
> Best Wishes,
>
> Lizzie
>
> **Lizzie Gallantine, Ph.D** | Project Manager Europe | Avery Dennison Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

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Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Good morning Ms. Bartakovics,
>
> Thank you for keeping us updated on your submission. I think your approach is reasonable for your purpose. We would appreciate, in your response document/letter, if you can guide us the location of your (b)(4) this will help us to quickly find them without missing any important information.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> **Sent:** Tuesday, August 29, 2023 10:16 AM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Good Morning Mr. Chen-
>
> I am winding down my time with Avery Dennison and therefore met with the team this morning to discuss our response to the hold letter for K230645. I just wanted to confirm that the response needs to be submitted as an e-copy that has been verified through the e-submitter tool. Since there are additional reports and documents to submit, we plan to add those documents into folders as attachments to our response. There are quite a few questions to address so it seemed as though a folder approach made the most sense for organizational purposes. If there is a better approach, please let me know so we may adopt that template.
>
> Much appreciated.
>
> Have a nice day.
>
> Regards,
>
> **Lisa Bartakovics**
> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
>
> m: (b)(6)
> 7100 Lindsay Dr. Mentor, OH 44060
>
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> averydennison.com medical.averydennison.com
>
> On Mon, Aug 21, 2023 at 9:02 AM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:
>
> > Hi Lizzie,
> >
> > Thank you very much for sending me your contact info. Look forward to working with you on this submission.
> >
> > Best regards,
> > Yongqing
> >
> > ---
> >
> > **From:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> > **Sent:** Monday, August 21, 2023 9:15 AM
> > **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> > **Cc:** Elaine Minagh <elaine.minagh@eu.averydennison.com>; Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> > **Subject:** Re: [EXTERNAL] K230645 Update
> >
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Hi Yongqing

I hope you're well! My contact information is:

Lizzie Gallantine, PhD., Project Manager Europe
Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland
Telephone: (b)(6)
e-mail: elizabeth.gallantine@eu.averydennison.com

Thank you!

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Ms. Gallantine,
>
> Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our system? Thank you!
>
> **Error! Filename not specified.**
> Please let me know if you have any questions.
>
> Best regards,
> Yongqing
>
> ---
>
> **From:** Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> **Sent:** Friday, August 18, 2023 4:24 PM
> **To:** Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> **Cc:** ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Elaine Minagh <elaine.minagh@eu.averydennison.com>
> **Subject:** Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
> Dear Mr. Chen-
>
> I hope you have had an enjoyable summer and this email finds you well.
>
> I am writing to inform you that I am leaving Avery Dennison at the end of the month and will therefore no longer be the point of contact for submission K230645.
>
> Elizabeth Gallantine, copied on this message, will serve as the point of contact for future correspondence regarding the Avery Dennison submission. She will provide updates regarding the response to the hold letter and coordinate all future correspondence.
>
> It has been a pleasure working with you and I hope to work with you again in the future.
>
> Please let me know if you have any questions.
>
> Regards,
> Lisa Bartakovics
>
> On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:
>
> > Dear Ms. Bartakovics,
> >
> > Thank you for keeping me updated and please let me know if you have any questions for us.
> >
> > Best regards,
> > Yongqing

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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From: Lisa Bartakovics <lisa.bartakovics@averydennison.com>
Sent: Thursday, June 1, 2023 12:20 PM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: regulatoryaffairs regulatoryaffairs <regulatoryaffairs@eu.averydennison.com>
Subject: [EXTERNAL] K230645 Update

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Dear Mr. Chen-

Thank you again for the teleconference, we greatly appreciate your time and that of the team.

(b)(4)

Therefore, Avery Dennison plans to respond to all of the points within the Hold Letter for K230645 in early September. I wanted to provide an update so that you are aware we are working on the items identified in the Hold Letter and will respond back to you as soon as (b)(4) is completed.

Please let me know if you have any further questions.

Thank you and have a nice day.

Regards,

Lisa Bartakovics
Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical

m: (b)(6)
7100 Lindsay Dr. Mentor, OH 44060

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averydennison.com medical.averydennison.com

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Lisa Bartakovics
Senior Director Global Regulatory Affairs and Quality
Avery Dennison Medical

m: (b)(6)
7100 Lindsay Dr. Mentor, OH 44060

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Ref. Major Deficiency - Question 1

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AVERY DENNISON | Medical

Premarket Notification 510(k) Statement

I certify that, in my capacity as Regulatory Affairs Manager of Avery Dennison Medical Ltd, I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61.

(b)(6)

Elaine Minagh, Regulatory Affairs Manager

24 October 2023

Premarket Notification **K230645**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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510(k) Summary

Avery Dennison Medical Ltd.

BeneHold™ Surgical Incise Drape with CHG antimicrobial II

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Section 11 Executive Summary

Background

Avery Dennison is a market leader in adhesive technology and the contract manufacturer of several adhesive surgical drapes. Furthermore, Avery Dennison c (b)(4)

(b)(4)

(b)(4) Therefore, in July 2021, Avery Dennison received clearance for its first antimicrobial drape, the BeneHold™ Surgical Incise Drape with CHG antimicrobial (K202208). Based upon the strong market interest in a drape containing CHG antimicrobial, Avery Dennison improved upon the formulation of its first antimicrobial drape to design an equivalent device with improved antimicrobial performance. Hence the BeneHold™ Surgical Incise Drape with CHG antimicrobial II was designed and developed by Avery Dennison. The BeneHold™ Surgical Incise Drape with CHG antimicrobial II contains (b)(4) of CHG and is indicated for professional use only.

Table 11.1
Predicate Device

	BeneHold™ Surgical Incise Drape with CHG antimicrobial
Common Name	Incise Drape
Trade Name	BeneHold™ Surgical Incise Drape with CHG antimicrobial
510(k) Submitted/Holder	Avery Dennison
510(k) Number	K202208
Product Code	KKX
Regulation	878.4370

The predicate device for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is the Avery Dennison Benehold Surgical Incise Drape with CHG antimicrobial. The Avery Dennison drape (K202208) contains the same antimicrobial agent and shares equivalent design, the same manufacturing process/ facility and performance characteristics with the new Benehold drape II.

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Table 11.2 Comparison of Proposed and Predicate Device			
Characteristics	**Proposed** Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II	**Predicate** BeneHold™ Surgical Incise Drape with CHG antimicrobial	Conclusion
Intended Use	The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is indicated for use as an incise drape with continuous antimicrobial activity (in vitro) from 30 minutes through 4 hours of use against the following organisms: *S. aureus, E. coli, P. aeruginosa, C. albicans, S. epidermidis, E. faecalis,* and *E. aerogenes. F. oxysporum*. The current testing on *E. Faecalis* and *F.oxysporum* did not reach a 4-log reduction at 4 hours. It is intended for external use only. Correlation between in vitro results and any clinical event has not been tested.	The BeneHold"' Surgical Incise Drape with CHG is indicated for use as an incise drape with continuous antibacterial activity (in vitro) from 2.5 to 4 hours against the following organisms; S. aureus, S. epiderrnidis, E. faecalis, E. coli, P. aeruginosa and E. aerogenes. It is intended for external use only. Correlation between in vitro results and any clinical event has not been tested.	Exceeds the performance of the BeneHold™ Surgical Incise Drape with CHG antimicrobial
Design Materials	Polyurethane film carrier	Polyurethane film carrier	Same
Design Materials	Device uses a Silicone Coated Release Liner	Device uses a Silicone Coated Release Liner	Same
Design Technology	CHG is an antimicrobial agent	CHG is an antimicrobial agent	Same
Design Technology	Drape sizes: 30 x 35 cm 60 x 45 cm 60 x 85 cm	Drape sizes: 30 x 35 cm 60 x 45 cm 60 x 85 cm	

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Table 11.2
Comparison of Proposed and Predicate Device

Design Technology	(b)(4)		
Design Technology			
Sterilization Method	Sterilized by Ethylene Oxide	Sterilized by Ethylene Oxide	Same
Sterility Assurance Level	SAL 10^{-6}	SAL 10^{-6}	Same
Operational Technology	(b)(4)		
Operational Technology			
Operational Technology			
Performance			

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Table 11.2
Comparison of Proposed and Predicate Device

(b)(4)

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the BeneHold™ Surgical Incise Drape with CHG antimicrobial utilize an antimicrobial agent in order to achieve their intended use. (b)(4)

(b)(4)

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the BeneHold™ Surgical Incise Drape with CHG antimicrobial have substantially equivalent performance. The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the BeneHold™ Surgical Incise Drape with CHG antimicrobial were comparatively evaluated for antimicrobial efficacy, moisture vapor transmission rate, tensile strength, fragile and dry skin study, flammability, barrier performance and conformability. The test results revealed the two devices to be substantially equivalent.

The Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the predicate BeneHold™ Surgical Incise Drape with CHG antimicrobial were subjected to an in vivo animal surgical wound porcine study. (b)(4)

(b)(4)

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(b)(4)

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(b)(4)

In summary, both of the Skin Studies successfully demonstrate that the BeneHold™ Surgical Incise Drape with CHG antimicrobial II performance is equivalent to the BeneHold™ Surgical Incise Drape with CHG antimicrobial in relation to the following criteria:

- does not cause skin damage upon removal after a procedure
- adheres to the patient's skin throughout the duration of use
- adheres at the edges of the incision
- is compatible with commonly used antiseptic skin preparations

The Moisture Vapor Transmission Rate (MVTR) testing was conducted to determine the breathability of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II per BS EN

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13726-1:2002. The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the predicate device were evaluated. The test method used to evaluate the MVTR of the test articles was the "fluid handling capacity (absorbency plus moisture vapor transmission rate, liquid in contact)" method as described in Section 3.3 of BS EN 13726-1:2002. The test report may be found in section 12 of this submission.

The acceptance criteria for the MVTR study was that the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is at least as breathable as the predicate device. See Section 22 for a copy of the literature article.

(b)(4)

Based on the aforementioned data, it can be concluded that the MVTR of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is substantially equivalent to the BeneHold™ Surgical Incise Drape with CHG antimicrobial. The testing methodology may be found within Section 18 of this 510(k) notification.

The Tensile Strength study was conducted for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II to demonstrate that the device does not tear or fragment during use per ASTM D882.

(b)(4)

(b)(4)

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(b)(4)

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(b)(4)

In summary, performance testing demonstrates that the key performance characteristics of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II are substantially equivalent to the BeneHold™ Surgical Incise Drape with CHG antimicrobial device. The acceptance criteria were met for all characteristics evaluated and comparison against the predicate demonstrated equivalent performance. The performance tests included:

- In-vitro CHG Release
- Antimicrobial efficacy

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- Moisture Vapor Transmission Rate
- Tensile strength
- Fragile skin study
- Dry skin study
- Flammability
- Barrier performance
- Conformability

A complete list of performance specifications and the corresponding test methodologies may be found within section 18 of this 510(k) submission.

Biocompatibility testing was performed according to ISO 10993 for cytotoxicity (direct contact), sensitization, irritation, acute systemic toxicity, material mediated pyrogenicity, endotoxin (Limulus Amebocyte Lysate) and hemolysis at (b)(4) CHG. The resulting testing, conducted by an outside laboratory, demonstrated the Benehold Incise Drape with CHG antimicrobial II achieved acceptable results per ISO 10993. Furthermore, the only patient contacting material within the drape is the CHG-containing adhesive as shown in the Table 11.4 below.

The results achieved were acceptable per the acceptance criteria set forth within ISO 10993. The testing of a drape containing (b)(4) CHG is evidence that the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is safe at the CHG (b)(4) and thereby justifies the product specification.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-EOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

The table below summarizes the biocompatibility test results for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II. Refer to biological risk assessment (b)(4) found in Section 15 for a detailed overview and acceptability of the safety testing for BeneHold™ Surgical Incise Drape with CHG antimicrobial II.

Table 11.5
Biocompatibility Results for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Test	Method	Results
Cytotoxicity	ISO Direct Contact Method according to ISO 10993-5: Biological Evaluation of Medical Devices – Part 5: Tests for In Vitro Cytotoxicity (Refer to (b)(4) in Section 15)	(b)(4)
Sensitization	Guinea Pig Maximization test according to ISO 10993-10: Biological Evaluation of Medical Devices – Part 10: Tests for Skin Sensitization (Refer to (b)(4) in Section 15)	
Irritation	Rabbit Animal Skin Irritation according to ISO 10993-23, Biological evaluation of medical devices - Part 23: Tests for irritation. (Refer to (b)(4) in Section 15)	

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Table 11.5 Biocompatibility Results for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II		
Test	Method	Results
Acute Systemic Toxicity	Mice: Acute Systemic toxicity in mice according to ISO 10993-11 Biological evaluation of medical devices – Part 11: Tests for systemic toxicity (Refer to (b)(4) in Section 15)	(b)(4)
Material Medicated Pyrogenicity	USP rabbit Pyrogen Study according to ISO 10993-11 Biological evaluation of medical devices – Part 11: Tests for systemic toxicity (Refer to (b)(4) in Section 15)	
Hemolysis	ASTM F756, Standard Practice for Assessment of Hemolytic Properties of Materials and ISO 10993-4, Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood. (Refer to (b)(4) in Section 15)	
Endotoxin	(b)(4)	

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Finally, the Intended Use of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is equivalent to the predicate device.

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is substantially equivalent to the BeneHold™ Surgical Incise Drape with CHG antimicrobial in design, function, performance and Intended Use. he conclusions drawn from the nonclinical and clinical tests presented within this regulatory submission demonstrate that the BeneHold™ Surgical Incise Drape with CHG antimicrobial II device is as safe, as effective, and performs as well as or better then the legally marketed predicate device BeneHold™ Surgical Incise Drape with CHG antimicrobial. In addition, the verification and validation data do not raise different questions of safety or effectiveness when compared to the predicate device, the BeneHold™ Surgical Incise Drape with CHG antimicrobial.

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Section 12 – Substantial Equivalence Discussion

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is substantially equivalent to the predicate BeneHold™ Surgical Incise Drape with CHG antimicrobial.

The predicate device for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is the BeneHold™ Surgical Incise Drape with CHG antimicrobial (first Avery Dennison design iteration of the antimicrobial drape). The BeneHold™ Surgical Incise Drape with CHG antimicrobial II contains the same antimicrobial agent as the cleared Avery Dennison drape (K202208) and shares equivalent design, manufacturing and performance characteristics. The antimicrobial performance of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II exceeds that of the BeneHold™ Surgical Incise Drape with CHG antimicrobial within K202208.

(b)(4)

The listing information for the predicate BeneHold™ Surgical Incise Drape with CHG antimicrobial is listed in Table 12.1 below:

Table 12.1 Predicate Device	
	Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial
Common Name	Incise Drape
Trade Name	Avery Dennison Benehold Surgical Incise Drape with CHG antimicrobial
510(k) Submitted/Holder	Avery Dennison
510(k) Number	K202208
Product Code	KKX
Regulation	878.4370

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A detailed comparison of the *proposed* BeneHold™ Surgical Incise Drape with CHG antimicrobial II, *and the predicate* BeneHold™ Surgical Incise Drape with CHG antimicrobial is provided in Table 12.2 below.

Table 12.2
Comparison of Proposed and Predicate Device

Characteristic	**Proposed** BeneHold™ Surgical Incise Drape with CHG antimicrobial II	**Predicate** BeneHold™ Surgical Incise Drape with CHG antimicrobial	Conclusion
Intended Use	The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is indicated for use as an incise drape with continuous antimicrobial activity (in vitro) from 30 minutes through 4 hours of use against the following organisms: *S. aureus, E. coli, P. aeruginosa, C. albicans, S. epidermidis, E. faecalis,* and *E. aerogenes. F. oxysporum*. The current testing on *E. Faecalis* and *F.oxysporum* did not reach a 4-log reduction at 4 hours. It is intended for external use only. Correlation between in vitro results and any clinical event has not been tested.	The BeneHold™ Surgical Incise Drape with CHG is indicated for use as an incise drape with continuous antibacterial activity (in vitro) from 2.5 to 4 hours against the following organisms; S. aureus, S. epiderrnidis, E. faecalis, E. coli, P. aeruginosa and E. aerogenes. It is intended for external use only. Correlation between in vitro results and any clinical event has not been tested.	Equivalent to BeneHold™ Surgical Incise Drape with CHG antimicrobial.
Design Materials	(b)(4)		
Design Materials			

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Table 12.2 Comparison of Proposed and Predicate Device			
Characteristic	**Proposed** BeneHold™ Surgical Incise Drape with CHG antimicrobial II	**Predicate** BeneHold™ Surgical Incise Drape with CHG antimicrobial	Conclusion
Design Technology	CHG is an antimicrobial agent	CHG is an antimicrobial agent	Same
Design Technology	Drape sizes: 30 x 35 cm 60 x 45 cm 60 x 85 cm	Drape sizes: 30 x 35 cm 60 x 45 cm 60 x 85 cm	Equivalent
Design Technology	(b)(4)		
Design Technology			
Sterilization Method	Sterilized by Ethylene Oxide	Sterilized by Ethylene Oxide	Same
Sterility Assurance Level	SAL 10^{-6}	SAL 10^{-6}	Same
Operational Technology	(b)(4)		
Operational Technology			
Operational Technology			

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Table 12.2 Comparison of Proposed and Predicate Device			
Characteristic	**Proposed** BeneHold™ Surgical Incise Drape with CHG antimicrobial II	**Predicate** BeneHold™ Surgical Incise Drape with CHG antimicrobial	Conclusion
Performance	(b)(4)		
Antimicrobial Efficacy (in-vitro)			

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For purposes of this submission, the following nomenclature for device name(s) appear within the test reports as listed within Table 12.2a.

(b)(4)

Design Discussion

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the BeneHold™ Surgical Incise Drape with CHG antimicrobial utilize antimicrobial agents in order to achieve their intended use. Furthermore, the devices employ a polyurethane film as the breathable adhesive carrier and an adhesive made of common industry materials. The results of design verification and validation demonstrate the substantial equivalence of the proposed and predicate device.

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the BeneHold™ Surgical Incise Drape with CHG antimicrobial utilize the same exact design technology to achieve their intended use. The two drapes have similar device construction and the same size configurations. The BeneHold™ Surgical Incise Drape with CHG antimicrobial was the design platform for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II (essentially the next generation of the existing drape).

Operational Discussion

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the BeneHold™ Surgical Incise Drape with CHG antimicrobial have equivalent operational technology. The devices are applied to skin via adhesion and elute the antimicrobial agent through the

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moisture secreted by the skin. In addition, the drapes are used to provide a viral and bacterial barrier for the surgical site during a medical procedure.

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II and the BeneHold™ Surgical Incise Drape with CHG antimicrobial employ the exact same manufacturing process to achieve the inclusion of CHG into the adhesive. The two drapes have similar device construction and utilize the exact same coating equipment within the Avery facility.

Performance Discussion

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II has equivalent performance when compared to the BeneHold™ Surgical Incise Drape with CHG antimicrobial. The drapes were evaluated for antimicrobial efficacy, moisture vapor transmission rate, tensile strength, performance through a fragile and dry skin evaluation, flammability, barrier performance and conformability. A summary of comparison may be found within Table 12.2.

Antimicrobial Performance

In-vivo antimicrobial efficacy

(b)(4)

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(b)(4)

Therefore, it can be concluded that the conformability (extensibility and permanent set) of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is equivalent to the BeneHold™ Surgical Incise Drape with CHG antimicrobial. The complete test methodology along with the report may be found within section 18 of this submission.

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The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is equivalent to the BeneHold™ Surgical Incise Drape with CHG antimicrobial in design, function, performance and Intended Use. The data contained within this regulatory submission demonstrates the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is as safe and effective as the predicate BeneHold™ Surgical Incise Drape with CHG antimicrobial.

In addition, the verification and validation data do not raise different questions of safety or effectiveness when compared to the predicate device.

Biocompatibility

The table below summarizes the biocompatibility test results for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II versus the predicate device. Refer to biological risk assessment (b)(4) in Section 15 for a detailed overview and acceptability of the safety testing for BeneHold™ Surgical Incise Drape with CHG antimicrobial II.

Table 12.15
Biocompatibility Results

Test	BeneHold™ Surgical Incise Drape with CHG antimicrobial II	BeneHold™ Surgical Incise Drape with CHG antimicrobial
Cytotoxicity per ISO 10993-5: Biological Evaluation of Medical Devices – Part 5: Tests for In Vitro Cytotoxicity	(b)(4)	
Sensitization per ISO 10993-10: Biological Evaluation of Medical Devices – Part 10: Tests for Skin Sensitization		
Irritation per ISO 10993-		

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Table 12.15 Biocompatibility Results		
Test	BeneHold™ Surgical Incise Drape with CHG antimicrobial II	BeneHold™ Surgical Incise Drape with CHG antimicrobial
23, Biological evaluation of medical devices - Part 23: Tests for irritation	(b)(4)	
Acute Systemic Toxicity per ISO 10993-11 Biological evaluation of medical devices – Part 11: Tests for systemic toxicity		
Material Mediated Pyrogenicity per ISO 10993-11 Biological evaluation of medical devices – Part 11: Tests for systemic toxicity		
Hemolysis per ASTM F756, Standard Practice for Assessment of Hemolytic Properties of Materials and ISO 10993-4, Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood.		
USP <85>, Bacterial Endotoxins Test and USP <161>, Medical Devices-Bacterial Endotoxin and Pyrogen Tests.		

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(b)(4)

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Section 13 – Proposed Labeling

The Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II is substantially equivalent to the (b)(4) and the BeneHold™ Surgical Incise Drape with CHG antimicrobial (K202208). The Intended Use of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is the exact same as that of the (b)(4) The product labeling for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II was drafted per the requirements found within 21 CFR Part 801 Labeling. Any symbols used within the device labeling were per ISO 15223-1:2021 which is an FDA recognized standard [Recognition number 5-134].

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II will be sold in a sterile and non-sterile state (Ethylene Oxide method). The non-sterile configuration of the drape will be labeled as such and sold to kit manufacturers for inclusion within convenience kits. The sterilization of the entire convenience kit is the responsibility of the kit packing entity. The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is a prescription device which may be sold only to medical professionals which is displayed on the packaging per FDA requirements.

Packaging configuration

The device consists of one individual BeneHold™ Surgical Incise Drape with CHG antimicrobial II within a sterile barrier pouch. The pouch material is made of Ethylene Oxide (EO) permeable Tyvek and bleached silicone coated greaseproof paper. The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is packaged into an individual pouch and then sterilized and assembled into a carton which contains ten (10) drapes each. Each individual drape complies with FDA labeling requirements.

The shelf-life (expiration date) of the device is printed in-line on all levels of packaging (pouch, carton, and shipper). Additionally, the Unique Device Identification (UDI) labeling

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is printed on all levels of packaging per 21 CFR Part 801 (Subpart B). The device labeling is summarized in the table below and the corresponding labels are included for review.

Table 13.1
Labeling for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Size	Part Number	Label	Reference
Small Drape 30 x 35 cm	MED 9547PP	Pouch	Attachment 13.1
		Primary Carton	Attachment 13.2
Medium Drape 60 x 45 cm	MED 9548PP	Pouch	Attachment 13.3
		Primary Carton	Attachment 13.4
Large Drape 60 x 85 cm	MED 9549PP	Pouch	Attachment 13.5
		Primary Carton	Attachment 13.6
Small, Medium and Large Drape	One IFU for all three sizes (MED 9547PP, 9548PP, 9549PP)	Instructions for Use	Attachment 13.7

Additionally, the attachments contain the Instructions for Use for the (b)(4) predicate devices, (b)(4) and the BeneHold™ Surgical Incise Drape with CHG antimicrobial may be found in attachments 13.8 and 13.9 respectively.

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Attachment 13.1 Small Pouch

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Attachment 13.2 Small Carton

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Attachment 13.3 Medium Pouch

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(b)(4)

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Attachment 13.4 Medium Carton

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(b)(4)

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Attachment 13.5 Large Pouch

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(b)(4)

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Attachment 13.6 Large Carton

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Attachment 13.7 Instructions for Use, BeneHold™ Surgical Incise Drape with CHG antimicrobial II

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(b)(4)

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Attachment 13.8 Instructions for Use,

(b)(4)

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(b)(4)

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Attachment 13.9 Instructions for Use, Predicate BeneHold™ Surgical Incise Drape with CHG antimicrobial

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496 mm

124 mm | 124 mm | 124 mm | 124 mm

90 mm | 90 mm | 90 mm | 45 mm | 90 mm | 270 mm

BeneHold® CHG adhesive technology by AVERY DENNISON Medical

BeneHold™ Surgical Incise Drape with CHG antimicrobial



REF MED 9542P - Single Small
MED 9543P - Single Medium
MED 9544P - Single Large

STERILE EO (MfgPro #) xxxxxx GBL-PKG-000148-A

en

Indications for Use:

BeneHold ™ Surgical Incise Drape with CHG antimicrobial is indicated for use as an incise drape with continuous antimicrobial activity. It is intended for external use only.

Product Description:

BeneHold ™ Surgical Incise Drape with CHG antimicrobial is a sterile adhesive film that is applied pre-operatively to the skin. The film adheres and conforms to body contours providing a sterile surface on top of the skin prior to surgery. The incise drape consists of a transparent, orange tinted polyurethane film coated with a transparent, CHG acrylic adhesive. CHG, a broad spectrum antimicrobial/fungal agent, known to inhibit bacterial growth, has been formulated into the acrylic adhesive. The surgeon incises through the adhesive film and skin ensuring a sterile film border all the way to the edge of the incision. The drape has adhesive properties strong enough to hold down barrier drapes and prevent lift at the margins of the incision.
The transparent film is breathable, allowing oxygen and moisture vapor exchange, yet is impermeable to external contaminants, including fluids (waterproof), bacteria, viruses* and yeast. The CHG contained in the adhesive provides antimicrobial activity against microorganisms commonly associated with surgical site infections.

In vitro testing (kill time and log reduction) demonstrates that the BeneHold ™ Surgical Incise Drape with CHG antimicrobial has an antimicrobial effect against a variety of gram-positive bacteria, gram-negative bacteria and yeast. The drape has been shown to have antimicrobial effectiveness for up to 4 hours. Clinical studies to evaluate reduction in infection have not been performed.

*In vitro testing shows that the transparent film of the BeneHold ™ Surgical Incise Drape with CHG antimicrobial is an effective barrier to viruses larger than 27 nm in size if the drape remains intact. These results have not been studied with regard to prevention of viral infection. No clinical study has been conducted regarding the ability of the drape to prevent viral infections.

Note: The BeneHold ™ Surgical Incise Drape with CHG antimicrobial is not expected to be effective against mold, such as Aspergillus.

Precautions:
Do not stretch the drape before applying it to the skin. Drapes applied under tension can cause trauma to the skin.

To ensure good adhesion and to help prevent skin irritation, remove detergent residues and allow all skin preparations and prep solutions to dry completely before applying the drape to the skin.

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare practitioner.

For proper use, directions should be trained in the use of this device.

Warning:

- DO NOT USE THE BENEHOLD ™ SURGICAL INCISE DRAPE WITH CHG ANTIMICROBIAL ON PREMATURE INFANTS OR INFANTS YOUNGER THAN 2 MONTHS OF AGE. USE OF THIS PRODUCT ON PREMATURE INFANTS MAY RESULT IN HYPERSENSITIVITY REACTIONS OR NECROSIS OF THE SKIN.
- FOR EXTERNAL USE ONLY. DO NOT ALLOW CONTACT OF THIS DEVICE WITH EARS, EYES, MOUTH OR MUCOUS MEMBRANES.
- DO NOT USE THIS DEVICE ON PATIENTS WITH A KNOWN HYPERSENSITIVITY TO CHLORHEXIDINE GLUCONATE. ADVERSE REACTIONS SUCH AS IRRITATIONS, SENSITIZATION AND GENERALIZED ALLERGIC REACTIONS HAVE BEEN REPORTED WITH THE USE OF CHLORHEXIDINE GLUCONATE
- STOP USING THE BENEHOLD ™ SURGICAL INCISE DRAPE WITH CHG ANTIMICROBIAL IF THE PATIENT EXPERIENCES SYMPTOMS SUCH AS: WHEEZING OR DIFFICULTY BREATHING, SWELLING FACE, HIVES THAT CAN QUICKLY PROGRESS TO MORE SERIOUS SYMPTOMS, SEVERE RASH OR SHOCK (WHICH IS A LIFE-THREATENING CONDITION THAT OCCURS WHEN THE BODY IS NOT GETTING ENOUGH BLOOD FLOW). THESE SYMPTOMS ARE ASSOCIATED WITH AN ALLERGIC REACTION TO CHG
- IF ALLERGIC REACTIONS OCCUR, DISCONTINUE USE IMMEDIATELY AND, IF SEVERE, CONTACT A PHYSICIAN.
- DO NOT DEFIBRILLATE THROUGH PLASTIC AS ARCING, INEFFECTIVE DEFIBRILLATION OR PATIENT INJURY MAY OCCUR.
- INTENDED FOR SINGLE PATIENT USE ONLY.
- DO NOT USE ON IMMUNE COMPROMISED PATIENTS OR PATIENTS WITH UNDERLYING SKIN PATHOLOGY WHICH COMPROMISES THE EPIDERMAL BARRIER. USE OF THIS PRODUCT MAY RESULT IN EROSIVE CONTACT DERMATITIS.
- INTENDED FOR SINGLE PATIENT USE ONLY.
- DO NOT REUSE. AS WITH ALL ADHESIVE-BASED PRODUCTS, ADHESIVE EFFECTIVENESS AND FUNCTIONALITY CAN DECLINE AFTER THE FIRST USE AND THE PRODUCT WILL NOT PERFORM AS SPECIFIED. REUSE MAY LEAD TO INFECTION OR OTHER ILLNESS/INJURY.
- KEEP AWAY FROM DIRECT SUNLIGHT. STORE IN A COOL, DRY PLACE. DO NOT USE IF PACKAGING IS DAMAGED. DO NOT RESTERILIZE.

Instructions for Use:

Failure to follow the manufacturer's instructions may result in complications including skin irritation and/or infection. If any damage to the packaging is observed, the sterility of the drape may be compromised. Do not use the drape and contact the Avery Dennison Medical Customer Support team at 1-440-534-3111.

Site Preparation:

1. Prepare and disinfect the operative site in accordance with facility protocols.
2. Ensure the skin is clean, dry and free of detergent, lotion and soap residues.
3. Disinfect the test site with Chlorascrip or Duraprep in advance.
4. Allow prepped skin to dry completely before applying the drape. This will promote optimal adhesion to the skin and help minimize skin irritation.

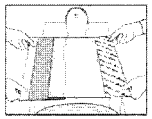
BeneHold ™ Surgical Incise Drape with CHG antimicrobial

REF MED 9542P, MED 9543P, MED 9544P

Drape Application:

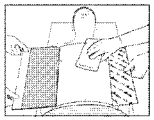
1. Remove the drape from the sterile package using aseptic technique. Open the pouch from the discon end.
2. Hold the drape with the printed side of the handlebar facing up. Separate the printed handlebar from the white handlebar. The incise drape will need to be unfolded fully prior to application in order for the drape to adhere properly to the patient's body.
   a. A two person application is recommended for best practice. Standing at opposite sides of the patient, person #1 holds the handlebar at each edge with the printed side facing up.
   b. Person #2 grasps the white liner handlebar located underneath the printed handlebar at each edge and slowly pulls the sterile liner away from the CHG adhesive coated drape exposing the adhesive side of the drape over the patient's skin.
   c. Position the drape on the patient to cover the prepped operative site and begin removing the liner.

Application steps 2a, 2b and 2c



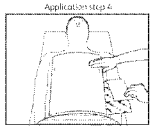
d. Using a sterile towel or surgical glove, press down firmly on the film. First where the drape will be contacting the skin along the intended incision line to ensure good adhesion to the skin. Working away from the incision site continue to smooth the drape by pressing firmly without pressure to achieve a wrinkle free incision site.

Application step 2d



3. Remove the rest of the liner and discard.
4. If desired, remove the printed handlebar. Place fingers on the drape next to the handle and begin tearing the handle with the other hand.

Application step 4



Drape Removal.

1. Gently peel back drape at 180-degree angle from the skin folding the film back onto itself. Maintain a 180-degree angle while pulling the film away from the skin.

Removal step 1. (Correct)



Removal step 1. (Incorrect)



Additional Information:

BeneHold™ Surgical Incise Drape with CHG antimicrobial	
Product REF	MED 9542PP
Drape Size	417 mm x 350 mm
Quantity per Box	10

Product REF	MED 9543PP
Drape Size	727 mm x 450 mm
Quantity per Box	10

Product REF	MED 9544PP
Drape Size	727 mm x 450 mm
Quantity per Box	10

Manufactured for:
Avery Dennison Belgie BVBA
Tiblokkenlaan 1,
2300 Turnhout, Belgium
www.medical.averydennison.com

Made in the Belgium

Avery Dennison, the triangle logo and BeneHold are registered trademarks of Avery Dennison Corporation

Covered under one or more granted patents or pending applications.

May 2020
xxxxx
GBL-PKG-000148-A

Explanation of Symbols Used on Labeling:

- Do not reuse
- Caution, Consult instructions for use
- Do not use if package is damaged
- STERILE EO — Sterile, Method of sterilization: Ethylene Oxide
- Do not resterilize
- Store in cool dry place
- Keep away from direct sunlight
- Use by (YYYY-MM-DD)
- LOT — Batch code

AVERY DENNISON | Medical

THE INFORMATION LISTED BELOW MUST APPEAR ON ALL VENDOR PROOFS (COLORKEYS, MATCHPRINTS/CHROMALINS) OR THEY WILL BE REJECTED							
AW	DESCRIPTION	SPEC. NO.	PAGE	PMS COLORS	PROCESS MATCH COLORS	SPECIAL INSTRUCTIONS	APPROVAL SIGNATURE / DATE
XXXXXX GBL-PKG-000148-A	BeneHold™ Surgical Incise Drape with CHG Antimicrobial		1 of 1	■ PANTONE Black C	NONE	Red die lines do not print. Dimensions do not print.	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

OFFICE OF SURGICAL AND INFECTION CONTROL DEVICES
DIVISION OF INFECTION CONTROL AND PLASTIC SURGERY DEVICES
OFFICE OF PRODUCT EVALUATION AND QUALITY

MEDICAL OFFICER MEMORANDUM

Date: 4/20/2023

From: Michael Matsuura, MD
Medical Officer
CDRH/OHT4/DHT4A

TO: Yongqing Chen, PhD
Lead Reviewer
CDRH/OHT4/DHT4B

CC: Bifeng Quan, PhD
Assistant Director
CDRH/OHT4/DHT4B

Submission Number: K230645

Consult Number: CON237399

Applicant/Sponsor: Avery Dennison Medical

Device Trade or Propriety Name: BeneHold Surgical Incise Drape with CHG II

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

This concludes my clinical review of: K230645

Thank you for the privilege of consulting on this submission.

Respectfully,

Michael J. Matsuura -S

Digitally signed by Michael J. Matsuura -S
Date: 2023.04.20 10:48:08 -04'00'

Michael Matsuura, MD
Medical Officer
Office of Surgical and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
CDRH\OHT4\DHT4A\RASD Team
U.S. Food and Drug Administration

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

For record.

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Sent: Tuesday, October 31, 2023 7:54 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Subject: [EXTERNAL] Re: K230645/S001 Review Complete

CAUTION. This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Yongqing

Thank you for your email and for sharing this news.
We have made the requested changes to our (b)(4) and I have a copy available today to share with you.

Thanks again for all your assistance with this submission.

Best regards to you.

Elaine
Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.,
IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)
elaine.minagh@eu.averydennison.com | medical.averydennison.com

Image removed by sender.

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Wed, 25 Oct 2023 at 20:28, Yongqing Chen [CHENYO] <yongqing.chen@fda.hhs.gov> wrote:

> October 25, 2023
>
> We have completed our review. Please refer to the attached letter for details.
>
> If you have any questions, please contact the lead reviewer assigned to your submission, Yongqing Chen.
>
> *** This is a system-generated email notification ***

The information transmitted is intended only for the person or entity to which it is addressed and may contain confidential and/or privileged material. Any review, retransmission, dissemination or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is prohibited. If you received this in error, please contact the sender and delete the material from any device.

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---

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Dear Ms. Minagh,

Thank you for your prompt response and help! I will let you know if we have any further questions for you.

Best regards,

Yongqing

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Sent: Wednesday, October 25, 2023 6:45 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <kelsey.kaht@averydennison.com>; Annelies Luyts <annelies.luyts@eu.averydennison.com>; Shan Perkin <shan.perkin@eu.averydennison.com>; Sarah Suy <sarah.suy@eu.averydennison.com>; K230645@docs.fda.gov

Subject: Re: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr Chen

(b)(4)

I want to thank you for your guidance throughout this entire process.

I look forward to hearing from you soon.

Best Regards

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)

elaine.minagh@eu.averydennison.com<mailto:firstname.lastname@eu.averydennison.com> | medical.averydennison.com<https://medical.averydennison.com/en/home.html>

[Image removed by sender.]

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Tue, 24 Oct 2023 at 21:28, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Callantine,

Thank you again for working with us on this submission. (b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Please let me know if you have other questions.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Tuesday, October 24, 2023 11:26 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>; Angel Boateng
<angel.boateng@eu.averydennison.com<mailto:angel.boateng@eu.averydennison.com>>; Kelsey Kaht <kelsey.kaht@averydennison.com<mailto:kelsey.kaht@averydennison.com>>; Annelies Luyts
<annelies.luyts@eu.averydennison.com<mailto:annelies.luyts@eu.averydennison.com>>; Shan Perkin <shan.perkin@eu.averydennison.com<mailto:shan.perkin@eu.averydennison.com>>; Sarah Suy <sarah.suy@eu.averydennison.com<mailto:sarah.suy@eu.averydennison.com>>

Subject: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

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Dear Mr. Chen

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Please find in attachment our responses to your comments with the supporting documentation.

Thank you once again for your support with this submission. Please let us know if you have any further questions.

Kind Regards,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: + (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RMONR
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-4779

Subject Matter Expert (SME) Review

Date: October 11, 2023

SME Reviewer: Lianji Jin

Expertise: Chemical Characterization

Submission # K230645/S001

Applicable Review Guide (if used): [Choose Review Guide]

Is this review for a Pre-Submission, Submission Issue Request, or Expedited Program (Breakthrough/STeP) Interaction? No

Applicant: Avery Dennison Medical Ltd.

Device Trade Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Optional Classification Information:

Pro Code(s): KKX **Class:** II **Reg #:** 878.4370

Reg Name: Surgical Drape And Drape Accessories

Rx/OTC: Rx

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Avery Dennison Medical Ltd.
Elaine Minagh
Regulatory Affairs Manager
IDA Business Park, Ballinalee Road
Longford, Longford N39 DX73
Ireland

Re: K230645
Trade/Device Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Regulation Number: 21 CFR 878.4370
Regulation Name: Surgical Drape And Drape Accessories
Regulatory Class: Class II
Product Code: KKX
Dated: September 22, 2023
Received: September 25, 2023

Dear Elaine Minagh:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Bifeng Qian, M.D., Ph.D.
Assistant Director
DHT4B: Division of Infection Control
and Plastic and Reconstructive Surgery Devices
OHT4: Office of Surgical
and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Dear Mr Chen

(b)(4)

I want to thank you for your guidance throughout this entire process.

I look forward to hearing from you soon.

Best Regards

Elaine

*Elaine Minagh *| Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. |

Tel: (b)(6)

(Mobile)

elaine.minagh@eu.averydennison.com <firstname.lastname@eu.averydennison.com>

| medical.averydennison.com

<https://medical.averydennison.com/en/home.html>

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Tue, 24 Oct 2023 at 21:28, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

wrote:

> Dear Ms. Callantine,

>

>

>

> Thank you again for working with us on this submission. (b)(4)

(b)(4)

>

>

>

>

>

>

>

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Please let me know if you have other questions.

Best regards,

Yongqing

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Tuesday, October 24, 2023 11:26 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>; Angel Boateng <
> angel.boateng@eu.averydennison.com>; Kelsey Kaht <
> kelsey.kaht@averydennison.com>; Annelies Luyts <
> annelies.luyts@eu.averydennison.com>; Shan Perkin <
> shan.perkin@eu.averydennison.com>; Sarah Suy <
> sarah.suy@eu.averydennison.com>
> *Subject:* [EXTERNAL] AD Confidential: Response to hold questions 23
> October (K230645)
>
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> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
> Dear Mr. Chen
>
> Please find in attachment our responses to your comments with the
> supporting documentation.
>
> Thank you once again for your support with this submission. Please let us
> know if you have any further questions.
>
> Kind Regards,
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

>

>

> Lizzie

>

> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison

> Medical Ltd

> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:

> +353 43 33 49586 | Direct Line: + 353 43 331 1341

> Mobile: + (b)(6)

> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

>

> [image: Image removed by sender.]

> <https://medical.averydennison.com/en/home.html>

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> <https://medical.averydennison.com/en/home/insights.html> | Product

> Selector

> <https://secure-web.cisco.com/14wkNq_kT901mhLZcceG7Cv10-YEPvOc0hdRlb1-Wjn_Yu48868xGjIFN86-CMusDvrd43NKEwPIdWwnayLVJH3VON7CMpQrIOEOPL2x9jo1bBD6KFSTb5PqLV5-_d3IEPKhRZRVDssO3FBZyqvLoabQxcexsta-nIbh9N3RJU_I3wPI5XPOp-pgFSE5q9ZBmOddz0FqJcgO7DOXsfKpbfw/https%3A%2F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

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496 mm

124 mm | 124 mm | 124 mm | 124 mm

90 mm | 90 mm | 90 mm | 90 mm

45 mm | 90 mm | 270 mm

BeneHold™ Surgical Incise Drape with CHG Antimicrobial II

REF MED 9547PP
MED 9548PP
MED 9549PP

STERILIZED

BeneHold™ CHG adhesive technology by AVERY DENNISON Medical

Indications for Use:

The BeneHold™ Surgical Incise Drape with CHG Antimicrobial II is indicated for use as an incise drape with continuous antimicrobial activity (*in vitro*) from 30 minutes through 4 hours of use against the following organisms: *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, *E. aerogenes*, and *C. albicans*. In vitro testing on the subject drape has also shown continuous antimicrobial activity from 30 minutes through 2.5 hours against *E. faecalis* and *F. oxysporum*. It is intended for external use only. Correlation between *in vitro* results and any clinical event has not been tested.

Product Description:

The BeneHold™ Surgical Incise Drape with CHG Antimicrobial II is a sterile adhesive film that is applied to the skin immediately after draping the patient. The film adheres and conforms to body contours providing a sterile surface on top of the skin prior to surgery. The incise drape consists of a transparent orange tinted polyurethane film coated with a transparent CHG acrylic adhesive. CHG, a broad spectrum antibacterial/antifungal agent known to inhibit bacterial growth, has been formulated into the acrylic adhesive. The surgeon incises through the adhesive film and skin ensuring a sterile film barrier all the way to the edge of the incision. The drape has adhesive properties strong enough to hold down barrier drapes and prevent lift at the margins of the incision.

The transparent film is breathable, allowing moisture vapor exchange, yet is impermeable to external contaminants, including fluids (waterproof) and bacteria. The CHG contained in the adhesive provides antimicrobial activity against microorganisms commonly associated with surgical site infections, viruses larger than 27 nm in diameter.

In vitro testing (kill time and log reduction) demonstrates that the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II has an antimicrobial effect against gram-positive bacteria, gram-negative bacteria and yeast and mold. Correlation between in vitro results and any clinical event has not been tested.

BeneHold™ Surgical Incise Drape with CHG Antimicrobial II meets the ASTM F1671 Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System standard. The BeneHold™ Surgical Incise Drape with CHG Antimicrobial II is a Level 4 barrier per ANSI/AAMI PB70.

Precautions:

Do not stretch the drape before applying it to the skin. Drapes applied under tension can cause trauma to the skin.

To ensure good adhesion and to help prevent skin irritation, remove detergent residues and allow all skin preparations and protectants to dry completely before applying the drape to the skin.

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare practitioner.

For proper use, clinicians should be trained in the use of this device.

Warning:

- DO NOT USE THE BENEHOLD™ SURGICAL INCISE DRAPE WITH CHG ANTIMICROBIAL II ON PREMATURE INFANTS OR INFANTS YOUNGER THAN 2 MONTHS OF AGE. USE OF THIS PRODUCT ON PREMATURE INFANTS MAY RESULT IN HYPERSENSITIVITY REACTIONS OR NECROSIS OF THE SKIN.
- FOR EXTERNAL USE ONLY. DO NOT ALLOW CONTACT OF THIS DEVICE WITH EARS, EYES, MOUTH OR MUCOUS MEMBRANES.
- THE SAFETY AND EFFECTIVENESS OF BENEHOLD™ SURGICAL INCISE DRAPE WITH CHG ANTIMICROBIAL II HAS NOT BEEN ESTABLISHED IN CHILDREN UNDER 18 YEARS OF AGE.
- DO NOT USE THIS DEVICE ON PATIENTS WITH A KNOWN HYPERSENSITIVITY TO CHLORHEXIDINE GLUCONATE. ADVERSE REACTIONS SUCH AS IRRITATIONS, SENSITIZATION AND GENERALIZED ALLERGIC REACTIONS HAVE BEEN REPORTED WITH THE USE OF CHLORHEXIDINE GLUCONATE.
- STOP USING THE BENEHOLD™ SURGICAL INCISE DRAPE WITH CHG ANTIMICROBIAL II IF THE PATIENT EXPERIENCES SYMPTOMS SUCH AS: WHEEZING OR DIFFICULTY BREATHING, SWELLING FACE, HIVES THAT CAN QUICKLY PROGRESS TO MORE SERIOUS SYMPTOMS, SEVERE RASH OR SHOCK (WHICH IS A LIFE THREATENING CONDITION THAT OCCURS WHEN THE BODY IS NOT GETTING ENOUGH BLOOD FLOW). THESE SYMPTOMS ARE ASSOCIATED WITH AN ALLERGIC REACTION TO CHG.
- IF ALLERGIC REACTIONS OCCUR, DISCONTINUE USE IMMEDIATELY AND, IF SEVERE, CONTACT A PHYSICIAN.
- DO NOT DEFIBRILLATE THROUGH PLASTICS AS ARCING, INEFFECTIVE DEFIBRILLATION OR PATIENT INJURY MAY OCCUR.
- DO NOT USE ON IMMUNE COMPROMISED PATIENTS OR PATIENTS WITH UNDERLYING SKIN PATHOLOGY WHICH COMPROMISES THE EPIDERMAL BARRIER. USE OF THIS PRODUCT MAY RESULT IN EROSIVE CONTACT DERMATITIS.
- INTENDED FOR SINGLE PATIENT USE ONLY.
- DO NOT REUSE. AS WITH ALL ADHESIVE-BASED PRODUCTS, ADHESIVE EFFECTIVENESS AND FUNCTIONALITY CAN DECLINE AFTER THE FIRST USE AND THE PRODUCT WILL NOT PERFORM AS SPECIFIED. REUSE MAY LEAD TO INFECTION OR OTHER ILLNESS/INJURY.
- KEEP AWAY FROM DIRECT SUNLIGHT. DO NOT USE IF PACKAGING IS DAMAGED. DO NOT RESTERILIZE.
- DO NOT STORE THE PRODUCT UNDER EQUAL OR WORSE CONDITIONS OF 40°C/75%RH AND 30°C/65%RH

Instructions for Use:

Failure to follow the manufacturer's instructions may result in complications including skin irritation and/or maceration. If any damage to the packaging is observed, the sterility of the drape may be compromised. Do not use the drape and contact the Cardinal Health™ Customer Support team at (800) 326-6457.

Site Preparation:

1. Prepare and disinfect the operative site in accordance with facility protocols.
2. Ensure the skin is clean, dry and free of detergent, lotion and soap residues.
3. Allow prepped skin to dry completely before applying the drape. This will promote optimal adhesion to the skin and help minimize skin irritation.

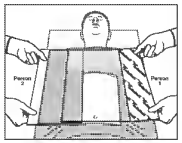
Benehold™ Surgical Incise Drape with CHG Antimicrobial II

REF MED 9547PP, MED 9548PP, MED 9549PP

Drape Application:

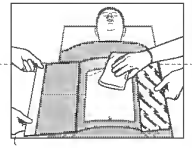
1. Open the pouch from the chevron end. Remove the drape from the sterile package using aseptic technique.
2. Remove the parchment paper overwrap from the drape while maintaining the sterile integrity of the drape.
3. Hold the drape with the printed side of the handlebar facing up. Separate the printed handlebar from the white handlebar.
   a. A two person application is recommended for best practice. Standing at opposite sides of the patient, person #1 holds the handlebar at each edge with the printed side facing up above the patient's body. (See application step #3a,b,c illustration)
   b. Person #2 grasps the white liner handlebar at each edge, located underneath the printed handlebar, and slowly pulls the white liner evenly away from the CHG adhesive coated drape, exposing the adhesive side of the drape over the patient's skin. When unfolding the drape both persons should place their hands at the outer corners of the edges, keeping a slight tension on the drape to keep it as wrinkle free as possible. *(See application step #3a,b,c illustration)*
   c. Stop pulling when you see a clear edge when the drape is fully extended and while the bottom liner is still attached. Position the drape on the patient to cover the prepped operative site and where the incise drape will be firmly attached to the surgical drape. Begin removing the liner. *(See application step #3a,b,c illustration)*

Application steps 3a, 3b and 3c



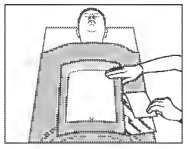
   d. Using a sterile towel or surgical glove, press down firmly on the film where the drape will be contacting the skin along the intended incision line to ensure good adherence to the skin. Working away from the incision site continue to smooth the drape by pressing firmly without stretching, without pulling to achieve a wrinkle free incision site. *(See application step #3d illustration)*

Application step 3d



4. Remove the rest of the liner and discard.
5. If desired, remove the printed handlebar. Peel the handlebar back to the perforation point and then place thumb on the drape next to the handle. With the other hand, begin tearing the handle to remove the handlebar. (See application step #4 illustration)

Application step 5

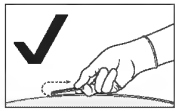


Drape Removal:

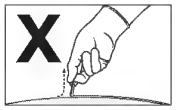
After closing the incision, remove the drape from the patient by gently peeling back onto itself. Maintain a 180-degree angle while pulling the film away from the skin.

Note: Skin of elderly patients is typically fragile and requires greater care when applying and removing adhesive products.

Note: Correct removal technique



Note: Incorrect removal technique



Additional Information:

Product REF	MED 9547PP
Product Name	BeneHold™ Surgical Incise Drape with CHG II
Usable Drape Size	30 cm x 35 cm
Quantity per Carton	10

Product REF	MED 9548PP
Product Name	BeneHold™ Surgical Incise Drape with CHG II
Usable Drape Size	60 cm x 45 cm
Quantity per Carton	10

Product REF	MED 9549PP
Product Name	BeneHold™ Surgical Incise Drape with CHG II
Usable Drape Size	60 cm x 85 cm
Quantity per Carton	10

(b)(4)

Manufactured for:
Avery Dennison Medical LTD
IDA Business Park, Ballinalee Road,
Longford, N39 RC80, Ireland
www.medical.averydennison.com

(b)(4)

Explanation of Symbols Used on Labeling:

	Do not re-use
	Caution
	Consult instructions for use
	Do not use if package is damaged
STERILIZED	Sterile. Method of sterilization: Ethylene Oxide.
	Do not resterilize
	Keep Dry
	Keep Away from Sunlight
	Use by (YYYY-MM-DD)
LOT	Batch code

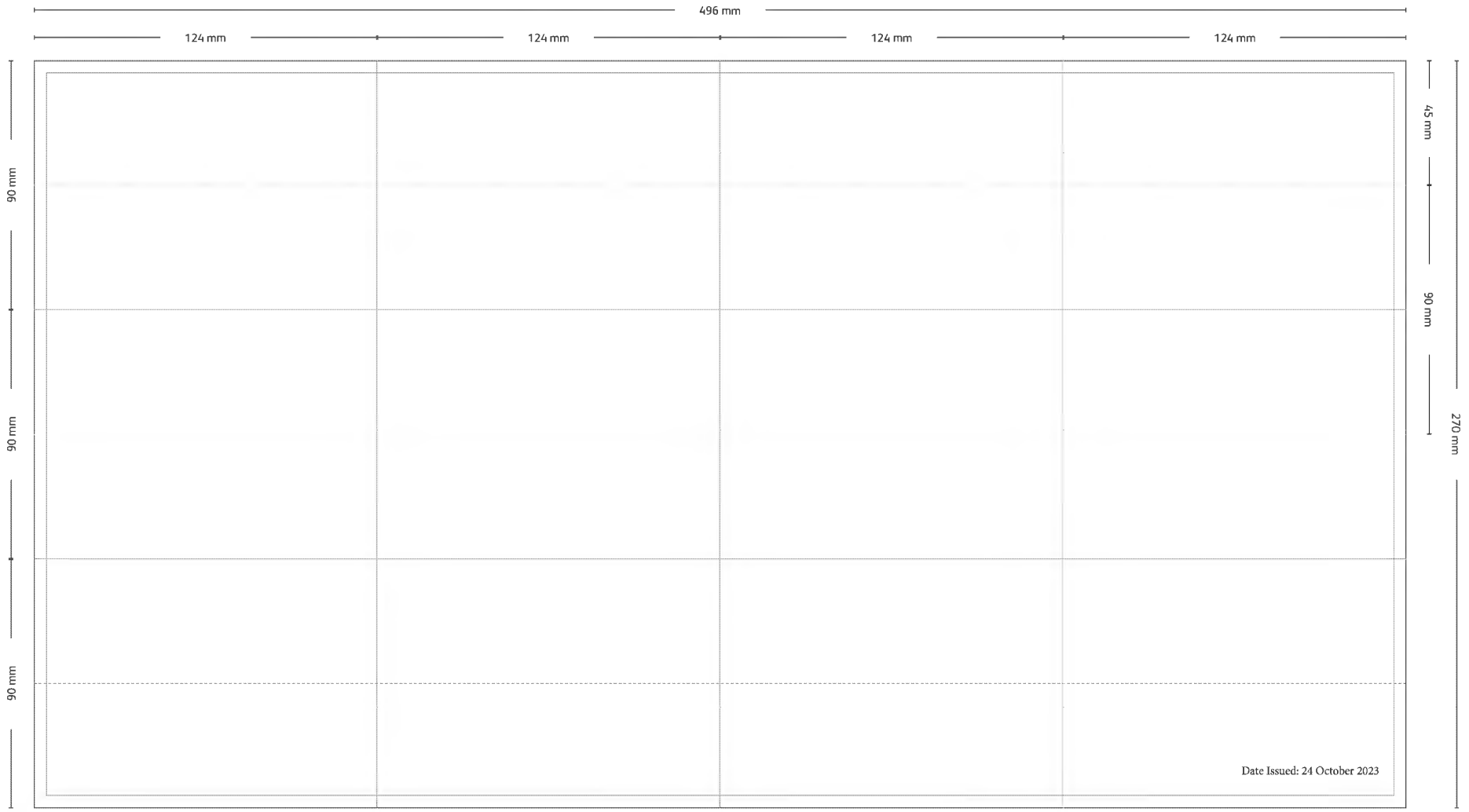
Date Issued: 24 October 2023

AVERY DENNISON | Medical

THE INFORMATION LISTED BELOW MUST APPEAR ON ALL VENDOR PROOFS (COLORKEYS, MATCHPRINTS/CHROMALINS) OR THEY WILL BE REJECTED							
AW	DESCRIPTION	SPEC. NO.	PAGE	PMS COLORS	PROCESS MATCH COLORS	SPECIAL INSTRUCTIONS	APPROVAL SIGNATURE / DATE
(b)(4)	BeneHold™ Surgical Incise Drape with CHG Antimicrobial II IFU U.S. Region		1 of 2	■ PANTONE Black C	NONE	Red die lines do not print. Dimensions do not print.	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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AW	DESCRIPTION	SPEC. NO.	PAGE	PMS COLORS	PROCESS MATCH COLORS	SPECIAL INSTRUCTIONS	APPROVAL SIGNATURE / DATE
(b)(4)	BeneHold™ Surgical Incise Drape with CHG Antimicrobial II IFU U.S. Region		2 of 2	■ PANTONE Black C	NONE	Red die lines do not print. Dimensions do not print.	

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Dear Ms. Elaine Minagh,

Thank you for working with us on this submission. We are reviewing the provided supplement S001 and have the following information for you to address. Please provide your response at your early convenience but not later than the COB of this Thursday (October 19, 2023).

(b)(4)

Please contact me if you have any questions.

Best regards,

Yongqing

From: Chen, Yongqing

Sent: Tuesday, October 10, 2023 8:11 AM

To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for letting me know this contact change. Good luck for your new move!

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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information for this submission and we will let you know if we have any questions for you.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Tuesday, October 10, 2023 7:43 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen,

I hope you are well!

I am writing to inform you that I am leaving Avery Dennison at the end of this month and will therefore no longer be the point of contact for the current submission K230645.

My colleague Elaine Minagh, copied on this message, will become the point of contact for future correspondence regarding the Avery Dennison submission. I have provided Elaine's contact information below:

Elaine Minagh, Regulatory Affairs Manager

Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73, Ireland

Telephone: (b)(6)

e-mail: elaine.minagh@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>

Thank you for your support on this submission.

Please let me know if you have any questions.

Best Wishes,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: + (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>> wrote:

Thank you for the update Mr Chen!

Have a great day,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: +(b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Dr. Gallantine,

The supplement has been received on Monday and the team review has been starting on Monday (09/25/2023).

Respectfully,

Yongqing

From: Chen, Yongqing

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Sent: Tuesday, September 26, 2023 8:27 AM

To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for the update. It might take one or more days for DCC to notify the appropriate Center/Office. I will let you know when the supplement has been assigned to me.

Respectfully,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Tuesday, September 26, 2023 8:16 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good Morning Mr Chen,

The USB file has now arrived in Silver Creek. Could you let us know when you have received it, please?

Thank you,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: +(b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing
<Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Dr. Gallantine,

Thank you for letting us know and look forward to working with you on this submission.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Monday, September 25, 2023 5:31 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr Chen,

We have completed our response to the hold letter for K230645. The documents on a USB file were shipped on Friday 22 September and are currently in transit (b)(4)
(b)(4)

We have separated each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if you have any questions.

Best Wishes,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: + (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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spI55uupICUMOIuUIw8Rwd-DL-
JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing
<Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Good morning Ms. Bartakovics,

Thank you for keeping us updated on your submission. I think your approach is reasonable for your purpose. We would appreciate, in your response document/letter, if you can guide us the location of your (b)(6) this will help us to quickly find them without missing any important information.

Best regards,

Yongqing

From: Lisa Bartakovics
<lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Tuesday, August 29, 2023 10:16 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison
.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Good Morning Mr. Chen-

I am winding down my time with Avery Dennison and therefore met with the team this morning to discuss our response to the hold letter for K230645. I just wanted to confirm that the response needs to be submitted as an e-copy that has been verified through the e-submitter tool. Since there are additional reports and documents to submit, we plan to add those documents into folders as attachments to our response. There are quite a few questions to address so it seemed as though a folder approach made the most sense for organizational purposes. If there is a better approach, please let me know so we may adopt that template.

Much appreciated.

Have a nice day.

Regards,

Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: (b)(6)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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On Mon, Aug 21, 2023 at 9:02â€¯AM Chen, Yongqing
<Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Hi Lizzie,

Thank you very much for sending me your contact info. Look forward to working with you on this submission.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Monday, August 21, 2023 9:15 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>; Lisa Bartakovics
<lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Hi Yongqing

I hope you're well! My contact information is:

Lizzie Gallantine, PhD., Project Manager Europe

Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland

Telephone: (b)(6)

e-mail:
elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>

Thank you!

Lizzie

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Gallantine,

Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our system? Thank you!

Error! Filename not specified.

Please let me know if you have any questions.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Friday, August 18, 2023 4:24 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>; Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Dear Mr. Chen-

I hope you have had an enjoyable summer and this email finds you well.

I am writing to inform you that I am leaving Avery Dennison at the end of the month and

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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will therefore no longer be the point of contact for submission K230645.

Elizabeth Gallantine, copied on this message, will serve as the point of contact for future correspondence regarding the Avery Dennison submission. She will provide updates regarding the response to the hold letter and coordinate all future correspondence.

It has been a pleasure working with you and I hope to work with you again in the future.

Please let me know if you have any questions.

Regards,

Lisa Bartakovics

On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Bartakovics,

Thank you for keeping me updated and please let me know if you have any questions for us.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Thursday, June 1, 2023 12:20 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: regulatoryaffairs regulatoryaffairs <regulatoryaffairs@eu.averydennison.com<mailto:regulatoryaffairs@eu.averydennison.com>>

Subject: [EXTERNAL] K230645 Update

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Dear Mr. Chen-

Thank you again for the teleconference, we greatly appreciate your time and that of the team.

(b)(4)

Therefore, Avery Dennison plans to respond to all of the points within the Hold Letter for K230645 in early September. I wanted to provide an update so that you are aware we are working on the items identified in the Hold Letter and will respond back to you as soon as (b)(4) is completed.

Please let me know if you have any further questions.

Thank you and have a nice day.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Regards,

Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: (b)(6)

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44060<https://www.google.com/maps/search/7100+Lindsay+Dr.+Mentor,+OH+44060?entry=gmail&source=g>

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--

Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: (b)(6)

7100 Lindsay Dr. Mentor, OH 44060

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Dr Yongqing

It is a pleasure to work with you on this submission.
We have received your query and are working very hard to formulate a response that will satisfy you.
However, I fear that we do not have enough time to coordinate this to a satisfactory level.

Is it possible that we could receive an extension until Monday the 23rd of October?

Many thanks and best regards

Elaine

*Elaine Minagh *| Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. |
Tel: + (b)(6)
(Mobile)

elaine.minagh@eu.averydennison.com <firstname.lastname@eu.averydennison.com>
| medical.averydennison.com
<https://medical.averydennison.com/en/home.html>

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Tue, 17 Oct 2023 at 19:30, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov> wrote:

> Dear Ms. Elaine Minagh,
>
>
>
> Thank you for working with us on this submission. We are reviewing the
> provided supplement S001 and have the following information for you to
> address. Please provide your response at your early convenience but not
> later than *the COB of this Thursday (October 19, 2023).*
>
>
>
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> (b)(4)
>
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>

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

> Please contact me if you have any questions.
>
>
>
> Best regards,
>
> Yongqing
>
>
>
>
>
> *From:* Chen, Yongqing
> *Sent:* Tuesday, October 10, 2023 8:11 AM
> *To:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* RE: [EXTERNAL] K230645 Update
>
>
>
> Dear Dr. Gallantine,
>
>
>
> Thank you for letting me know this contact change. Good luck for your new
> move!
>
>
>
> Ms. Elaine Minagh, thank you for going to work with us. I will update the
> contact information for this submission and we will let you know if we have
> any questions for you.
>
>
>
> Best regards,
>
> Yongqing

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> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Tuesday, October 10, 2023 7:43 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not
> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
> Dear Mr. Chen,
>
> I hope you are well!
>
> I am writing to inform you that I am leaving Avery Dennison at the end of
> this month and will therefore no longer be the point of contact for the
> current submission K230645.
>
> My colleague Elaine Minagh, copied on this message, will become the point
> of contact for future correspondence regarding the Avery Dennison
> submission. I have provided Elaine's contact information below:
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

> Elaine Minagh, Regulatory Affairs Manager
>
> Avery Dennison Medical Ltd.
>
> IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73,
> Ireland
>
> Telephone: (b)(6)
>
> e-mail: elaine.minagh@eu.averydennison.com
> <elizabeth.gallantine@eu.averydennison.com>
>
>
>
> Thank you for your support on this submission.
>
>
>
> Please let me know if you have any questions.
>
>
>
> Best Wishes,
>
> Lizzie
>
> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison
> Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:
> +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
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> On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE <

> elizabeth.gallantine@eu.averydennison.com> wrote:

>

> Thank you for the update Mr Chen!

>

>

>

> Have a great day,

>

>

>

> Lizzie

>

> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison

> Medical Ltd

> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:

> +353 43 33 49586 | Direct Line: + 353 43 331 1341

> Mobile: (b)(6)

> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

>

> [image: Image removed by sender.]

> <https://medical.averydennison.com/en/home.html>

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> On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

> wrote:

>

> Dear Dr. Gallantine,

>

> The supplement has been received on Monday and the team review has been

> starting on Monday (09/25/2023).

>

>

>

> Respectfully,

>

> Yongqing

>

>

>

> *From:* Chen, Yongqing

> *Sent:* Tuesday, September 26, 2023 8:27 AM

> *To:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>

> *Subject:* RE: [EXTERNAL] K230645 Update

>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> Dear Dr. Gallantine,
>
> Thank you for the update. It might take one or more days for DCC to notify the appropriate Center/Office. I will let you know when the supplement has been assigned to me.
>
>
> Respectfully,
>
> Yongqing
>
>
> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Tuesday, September 26, 2023 8:16 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
> CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.
>
>
> Good Morning Mr Chen,
>
>
> The USB file has now arrived in Silver Creek. Could you let us know when you have received it, please?
>
>
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

> Thank you,
>
>
>
> Lizzie
>
> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison
> Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:
> +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
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>
> On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Dear Dr. Gallantine,
>
>

> Thank you for letting us know and look forward to working with you on this
> submission.
>
>
>
> Best regards,
>
> Yongqing
>
>
>
> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Monday, September 25, 2023 5:31 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
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> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Dear Mr Chen,
>
>
>
> We have completed our response to the hold letter for K230645.
> The documents on a USB file were shipped on Friday 22 September and are
> currently in transit (b)(4)
>
>
>
> We have separated each question and response into a separate file complete
> with the relevant attachments to allow you to more easily navigate our
> response. Please let us know if you have any questions.

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>

>

>

> Best Wishes,

>

>

>

> Lizzie

>

>

>

> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison

> Medical Ltd

> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:

> +353 43 33 49586 | Direct Line: + 353 43 331 1341

> Mobile: (b)(6)

> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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spI55uupICUMOIuUIw8Rwd-DL-
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F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

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> On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> wrote:
>
> Good morning Ms. Bartakovics,
>
>
>
> Thank you for keeping us updated on your submission. I think your approach
> is reasonable for your purpose. We would appreciate, in your response
> document/letter, if you can guide us the location of your (b)(4)
> (b)(4) this will help us to quickly find them without
> missing any important information.
>
>
>
> Best regards,
>
> Yongqing
>
>
>
> *From:* Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> *Sent:* Tuesday, August 29, 2023 10:16 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
> CAUTION: This email originated from outside of the organization. Do not
> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Good Morning Mr. Chen-
>
>
>
> I am winding down my time with Avery Dennison and therefore met with the

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> team this morning to discuss our response to the hold letter for K230645. I
> just wanted to confirm that the response needs to be submitted as an e-copy
> that has been verified through the e-submitter tool. Since there are
> additional reports and documents to submit, we plan to add those documents
> into folders as attachments to our response. There are quite a few
> questions to address so it seemed as though a folder approach made the most
> sense for organizational purposes. If there is a better approach, please
> let me know so we may adopt that template.
>
>
>
> Much appreciated.
>
>
>
> Have a nice day.
>
>
>
> Regards,
>
>
> *Lisa Bartakovics*
>
> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
>
>
>
> m: (b)(6)
>
> 7100 Lindsay Dr. Mentor, OH 44060
>
>
>
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>

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> medical.averydennison.com <https://medical.averydennison.com/en/home.html>
>
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>
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>
> On Mon, Aug 21, 2023 at 9:02â€¯AM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Hi Lizzie,
>
>
>
> Thank you very much for sending me your contact info. Look forward to
> working with you on this submission.
>
>
>
> Best regards,
>
> Yongqing
>
>
>
> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Monday, August 21, 2023 9:15 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>; Lisa
> Bartakovics <lisa.bartakovics@averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
>

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> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Hi Yongqing
>
>
>
> I hope you're well! My contact information is:
>
>
>
> Lizzie Gallantine, PhD., Project Manager Europe
>
> Avery Dennison Medical Ltd.
>
> IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80,
> Ireland
>
> Telephone: (b)(6)
>
> e-mail: elizabeth.gallantine@eu.averydennison.com
>
>
>
> Thank you!
>
>
>
> Lizzie
>
>
>
> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison
> Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:
> +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)

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> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

>

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> <https://medical.averydennison.com/en/home.html>

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> Selector

> <https://secure-web.cisco.com/171Rs-7v4aDq7dEhkA8m-xeEroyziv0B9-2ORcBfvLsuvmZOn2dWHkRKeP7p7o3Yv9mIvflpWjh15YlsvCtg5aiAMWGB3MtKV6aietR8j4kIOQ77xCR7u8z8-ddPIQjqUyaHxnRQFK6_b6JLfpRKnNnPczsUAmE6awMgovHe3UD56sOtHpvlEHIsZ69MbkJGvgJyg6nY-rniQIjnIE-s-wiLZSCf7zuctgeWyXwcXM90/https%3A%2F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

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> On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

> wrote:

>

> Dear Ms. Gallantine,

>

>

>

> Thank you in advance for working with us. If you do not mind, would you

> please send me your contact information as the format showing below so I

> can update the submission in our system? Thank you!

>

>

>

> *Error! Filename not specified.*

>

> Please let me know if you have any questions.

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> Best regards,
>
> Yongqing
>
>
>
> *From:* Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> *Sent:* Friday, August 18, 2023 4:24 PM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>;
> Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
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> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Dear Mr. Chen-
>
>
>
> I hope you have had an enjoyable summer and this email finds you well.
>
>
>
> I am writing to inform you that I am leaving Avery Dennison at the end of
> the month and will therefore no longer be the point of contact for
> submission K230645.
>
>
>
> Elizabeth Gallantine, copied on this message, will serve as the point of

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> contact for future correspondence regarding the Avery Dennison submission.
> She will provide updates regarding the response to the hold letter and
> coordinate all future correspondence.
>
>
>
> It has been a pleasure working with you and I hope to work with you again
> in the future.
>
>
>
> Please let me know if you have any questions.
>
>
>
> Regards,
>
> Lisa Bartakovics
>
>
>
>
>
> On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Dear Ms. Bartakovics,
>
>
>
> Thank you for keeping me updated and please let me know if you have any
> questions for us.
>
>
>
> Best regards,
>
> Yongqing
>

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> *From:* Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> *Sent:* Thursday, June 1, 2023 12:20 PM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* regulatoryaffairs regulatoryaffairs <
> regulatoryaffairs@eu.averydennison.com>
> *Subject:* [EXTERNAL] K230645 Update
>
> CAUTION: This email originated from outside of the organization. Do not
> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
> Dear Mr. Chen-
>
> Thank you again for the teleconference, we greatly appreciate your time
> and that of the team.
>
> (b)(4)
>
> Therefore, Avery Dennison plans to respond to all of the points within
> the Hold Letter for K230645 in early September. I wanted to provide an
> update so that you are aware we are working on the items identified in the
> Hold Letter and will respond back to you as soon as (b)(4) is completed.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

> Please let me know if you have any further questions.
>
> Thank you and have a nice day.
>
> Regards,
>
> *Lisa Bartakovics*
>
> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
>
> m: (b)(6)
>
> 7100 Lindsay Dr. Mentor, OH 44060
> <https://www.google.com/maps/search/7100+Lindsay+Dr.+Mentor,+OH+44060?entry=gmail&source=g>
>
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> *Lisa Bartakovics*
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> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
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> m: (b)(6)
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> 7100 Lindsay Dr. Mentor, OH 44060
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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RM4620
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-9433

Premarket Notification 510(k) Review

Date: October 25, 2023

Reviewer: Yongqing Chen

510(k)# K230645/S001 Subject: Traditional

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Contact Name: Elaine Minagh	**Contact Title:** Regulatory Affairs Manager
Correspondent Firm: Avery Dennison Medical Ltd.	**Phone:** (b)(6) **Email:** elaine.minagh@eu.averydennison.com
Received Date: September 25, 2023	**Due Date:** October 25, 2023
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories

Predicate Devices:

Submission #	Pro Code	Device Trade Name	Applicant
K202208	KKX	BeneHold Surgical Incise Drape with CHG antimicrobial	Avery Dennison Belgie BVBA

Recommendation

I recommend that the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is/are Substantially Equivalent (SESE)

(b)(5)

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Digital Signature Concurrence Table (Doc ID: 04500.15.05)	
This document represents a high-level summary of the Agency's determination on whether the applicant's device is substantially equivalent to a legally marketed predicate device. In determining whether the subject device is substantially equivalent to a predicate device, we carefully considered the relevant regulatory and statutory criteria for Agency decision-making under 21 CFR part 807 and section 513(i) of the Federal Food, Drug and Cosmetic Act (FD&C Act). We considered the burden that may be incurred by the applicant's attempt to follow the premarket notification process. The deficiencies provided in this review, if any, represent the required minimum information necessary to support a substantial equivalence determination. Therefore, we believe that we have considered the least burdensome requirements, under section 513(i)(1)(D) of the FD&C Act, for a 510(k) determination of substantial equivalence.	
For each of the specific issues identified in the recommended requests to the applicant above, I and/or if applicable contributing consulting reviewer(s) (and or supervisors), have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s). I also confirm, if applicable, that contributing consulting reviewers (and or supervisors) have provided the above attestation.	
Reviewer Sign-Off	Yongqing Chen -S 2023.10.25 15:45:21 -04'00'

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Traditional 510(k) Premarket Notification
Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II

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Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RM4536
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
301-796-0270

Subject Matter Expert (SME) Review

Date: April 3, 2023

SME Reviewer: Sreekanth Gutala

Expertise: Chemistry related consult

Submission # K230645

Applicable Review Guide (if used): Not Applicable

Is this review for a Pre-Submission, Submission Issue Request, or Expedited Program (Breakthrough/STeP) Interaction? No

Applicant: Avery Dennison Medical Ltd.

Device Trade Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Optional Classification Information:

Pro Code(s): KKX **Class:** II **Reg #:** 878.4370

Reg Name: Surgical Drape And Drape Accessories

Rx/OTC: Rx

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(b)(5)

Digital Signature Concurrence Table (Doc ID: 04504.04.00)	
For each of the specific issues identified in the recommended requests to the applicant above, I have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability for requests: mentioned in section II above that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s).	
Reviewer Sign-Off	Sreekanth Gutala -S Digitally signed by Sreekanth Gutala -S Date: 2023.05.01 14:17:41 -04'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 15.10

(b)(4)

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(b)(4)

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Attachment 15.12

BeneHold Surgical Incise Drape with CHG II Placebo Cytotoxicity Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

ASTM Hemolysis Study - Extract and Direct Contact Method

TEST ARTICLE NAME

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OC/DIDSI CDRH-FOISTAFF-US@fda.hhs.gov or 301-796-8118

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GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

ASTM Hemolysis Study - Extract and Direct Contact Method

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 15.13

BeneHold Surgical Incise Drape with CHG Cytotoxicity Report

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GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

CONFIDENTIAL

STUDY TITLE

Cytotoxicity Study Using the ISO Direct Contact Method

TEST ARTICLE NAME

(b)(4) BeneHold Surgical Incise Drape with CHG

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OSE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

STUDY TITLE

Cytotoxicity Study Using the ISO Direct Contact Method

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOIASTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.14

BeneHold Surgical Incise Drape with CHG Irritation Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

CONFIDENTIAL

STUDY TITLE

ISO Skin Irritation Study in Rabbits

TEST ARTICLE NAME

(b)(4) BeneHold Surgical Incise Drape with CHG

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

STUDY TITLE

ISO Skin Irritation Study in Rabbits

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.15

BeneHold Surgical Incise Drape with CHG Sensitization Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

CONFIDENTIAL

STUDY TITLE

ISO Guinea Pig Maximization Sensitization Test

TEST ARTICLE NAME

(b)(4) BeneHold Surgical Incise Drape with CHG

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCD/DID at CDRH-FOISTAFF-US@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

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(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

STUDY TITLE

ISO Guinea Pig Maximization Sensitization Test

(b)(4)

Questions? Contact FDA/CDRH/OSE/DID at CDRH-FOIST@FDA.HHS.GOV or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.16

BeneHold Surgical Incise Drape with CHG Acute Systemic Toxicity Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

CONFIDENTIAL

STUDY TITLE

ISO Acute Systemic Toxicity Study in Mice

TEST ARTICLE NAME

(b)(4) BeneHold Surgical Incise Drape with CHG

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OSE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

7070 Spinach Drive Building 19
Mentor, OH 44060

STUDY TITLE

ISO Acute Systemic Toxicity Study in Mice

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTAFF-US@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.17

BeneHold Surgical Incise Drape with CHG Endotoxin Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060

CONFIDENTIAL

STUDY TITLE

USP Limulus Amebocyte Lysate (LAL) Test - Kinetic-Turbidimetric Method

TEST ARTICLE NAME

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OC/ODID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060

CONFIDENTIAL

STUDY TITLE

USP Limulus Amebocyte Lysate (LAL) Test - Kinetic-Turbidimetric Method

TEST ARTICLE NAME

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OSE/DI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060

CONFIDENTIAL

STUDY TITLE

USP Limulus Amebocyte Lysate (LAL) Test - Kinetic-Turbidimetric Method

TEST ARTICLE NAME

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCD/DID at CDRH-FOISTAFF-US@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

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PROTOCOL

TEST FACILITY

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Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060

STUDY TITLE

USP Limulus Amebocyte Lysate (LAL) Test - Kinetic-Turbidimetric Method

TEST ARTICLE NAME

(b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTAFFUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Dear Yongqing

Thank you for getting back to me so quickly, we are of course disappointed to hear that there are additional issues.
We can make ourselves available for a call tomorrow, it's difficult to suggest a time when I don't know your time zone.
However, I have provisionally booked the required individuals for 12.00 GMT.
If this does not work for you, just suggest another time and I can arrange it on my end.

Best wishes

Elaine

*Elaine Minagh *| Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. |
Tel: (b)(6)
(Mobile)

elaine.minagh@eu.averydennison.com <firstname.lastname@eu.averydennison.com>
| medical.averydennison.com
<https://medical.averydennison.com/en/home.html>

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Thu, 19 Oct 2023 at 16:38, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
wrote:

> Dear Ms. Minagh,
>
>
>
> Thank you for working with us hardly to address our concerns. (b)(4)
>
> (b)(4)
>
> wondering whether we can have a short phone call today or tomorrow.
>
>
>
> Please let me know your thoughts. Thank you!
>
>
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

> Best regards,
>
> Yongqing
>
>
>
>
>
> *From:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Sent:* Thursday, October 19, 2023 9:24 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* K230645@docs.fda.gov
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
> CAUTION: This email originated from outside of the organization. Do not
> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Dr Yongqing
>
>
>
> It is a pleasure to work with you on this submission.
>
> We have received your query and are working very hard to formulate a
> response that will satisfy you.
>
> However, I fear that we do not have enough time to coordinate this to a
> satisfactory level.
>
>
>
> Is it possible that we could receive an extension until Monday the 23rd of
> October?
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

>
>
> Many thanks and best regards
>
>
>
> Elaine
>
>
> *Elaine Minagh *| Regulatory Affairs Manager | Avery Dennison Medical
> Ltd.
>
> IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel:
*(b)(6)
> (*Mobile)
>
> elaine.minagh@eu.averydennison.com
> <firstname.lastname@eu.averydennison.com> | medical.averydennison.com
> <https://medical.averydennison.com/en/home.html>
>
> [image: Image removed by sender.]
>
> https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html
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>
>
>
> On Tue, 17 Oct 2023 at 19:30, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Dear Ms. Elaine Minagh,
>
>
>
> Thank you for working with us on this submission. We are reviewing the
> provided supplement S001 and have the following information for you to
> address. Please provide your response at your early convenience but not
> later than *the COB of this Thursday (October 19, 2023).*
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Please contact me if you have any questions.

Best regards,

Yongqing

From: Chen, Yongqing
Sent: Tuesday, October 10, 2023 8:11 AM
To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>
Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for letting me know this contact change. Good luck for your new move!

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for you.

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

> Best regards,
>
> Yongqing
>
>
>
>
>
>
>
> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Tuesday, October 10, 2023 7:43 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
> CAUTION: This email originated from outside of the organization. Do not
> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Dear Mr. Chen,
>
>
>
> I hope you are well!
>
>
>
> I am writing to inform you that I am leaving Avery Dennison at the end of
> this month and will therefore no longer be the point of contact for the
> current submission K230645.
>
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> My colleague Elaine Minagh, copied on this message, will become the point
> of contact for future correspondence regarding the Avery Dennison
> submission. I have provided Elaine's contact information below:
>
>
>
> Elaine Minagh, Regulatory Affairs Manager
>
> Avery Dennison Medical Ltd.
>
> IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73,
> Ireland
>
> Telephone: (b)(6)
>
> e-mail: elaine.minagh@eu.averydennison.com
> <elizabeth.gallantine@eu.averydennison.com>
>
>
>
> Thank you for your support on this submission.
>
>
>
> Please let me know if you have any questions.
>
>
>
> Best Wishes,
>
> Lizzie
>
> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison
> Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:
> +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: + (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> <https://secure-web.cisco.com/13p-IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tCspI55uupICUMOIuUIw8Rwd-DL-JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

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>

> On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE <

> elizabeth.gallantine@eu.averydennison.com> wrote:

>

> Thank you for the update Mr Chen!

>

>

>

> Have a great day,

>

>

>

> Lizzie

>

> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison

> Medical Ltd

> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:

> +353 43 33 49586 | Direct Line: + 353 43 331 1341

> Mobile: + (b)(6)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

>

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>

> On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

> wrote:

>

> Dear Dr. Gallantine,

>

> The supplement has been received on Monday and the team review has been

> starting on Monday (09/25/2023).

>

>

>

> Respectfully,

>

> Yongqing

>

>

>

> *From:* Chen, Yongqing

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> *Sent:* Tuesday, September 26, 2023 8:27 AM
> *To:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* RE: [EXTERNAL] K230645 Update
>
>
>
> Dear Dr. Gallantine,
>
> Thank you for the update. It might take one or more days for DCC to notify
> the appropriate Center/Office. I will let you know when the supplement has
> been assigned to me.
>
>
>
> Respectfully,
>
> Yongqing
>
>
>
> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Tuesday, September 26, 2023 8:16 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
> CAUTION: This email originated from outside of the organization. Do not
> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Good Morning Mr Chen,
>
>
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> The USB file has now arrived in Silver Creek. Could you let us know when
> you have received it, please?
>
>
>
> Thank you,
>
>
>
> Lizzie
>
> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison
> Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:
> +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
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JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>
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>
> On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

> wrote:
>
> Dear Dr. Gallantine,
>
>
>
> Thank you for letting us know and look forward to working with you on this
> submission.
>
>
>
> Best regards,
>
> Yongqing
>
>
>
> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Monday, September 25, 2023 5:31 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
> CAUTION: This email originated from outside of the organization. Do not
> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Dear Mr Chen,
>
>
>
> We have completed our response to the hold letter for K230645.
> The documents on a USB file were shipped on Friday 22 September and are
> currently in transit (b)(4)
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

>
>
> We have separated each question and response into a separate file complete
> with the relevant attachments to allow you to more easily navigate our
> response. Please let us know if you have any questions.
>
>
>
> Best Wishes,
>
>
>
> Lizzie
>
>
>
> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison
> Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:
> +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
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>
>
>
>
> On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Good morning Ms. Bartakovics,
>
>
>
> Thank you for keeping us updated on your submission. I think your approach
> is reasonable for your purpose. We would appreciate, in your response
> document/letter, if you can guide us the location of your (b)(4)
> (b)(4) this will help us to quickly find them without
> missing any important information.
>
>
>
> Best regards,
>
> Yongqing
>
>
>
> *From:* Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> *Sent:* Tuesday, August 29, 2023 10:16 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
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> click links or open attachments unless you recognize the sender and know
> the content is safe.
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> Good Morning Mr. Chen-
>
>
>
> I am winding down my time with Avery Dennison and therefore met with the
> team this morning to discuss our response to the hold letter for K230645. I
> just wanted to confirm that the response needs to be submitted as an e-copy
> that has been verified through the e-submitter tool. Since there are
> additional reports and documents to submit, we plan to add those documents
> into folders as attachments to our response. There are quite a few
> questions to address so it seemed as though a folder approach made the most
> sense for organizational purposes. If there is a better approach, please
> let me know so we may adopt that template.
>
>
>
> Much appreciated.
>
>
>
> Have a nice day.
>
>
>
> Regards,
>
>
> *Lisa Bartakovics*
>
> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
>
>
>
> m: (b)(6)
>
> 7100 Lindsay Dr. Mentor, OH 44060
>
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> averydennison.com <https://www.averydennison.com/>
> medical.averydennison.com <https://medical.averydennison.com/en/home.html>
>
>
>
>
>
> On Mon, Aug 21, 2023 at 9:02â€¯AM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Hi Lizzie,
>
>
>
> Thank you very much for sending me your contact info. Look forward to
> working with you on this submission.
>
>
>
> Best regards,
>
> Yongqing
>
>
>
> *From:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
> *Sent:* Monday, August 21, 2023 9:15 AM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* Elaine Minagh <elaine.minagh@eu.averydennison.com>; Lisa

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> Bartakovics <lisa.bartakovics@averydennison.com>
>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
>
>
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> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Hi Yongqing
>
>
>
> I hope you're well! My contact information is:
>
>
>
> Lizzie Gallantine, PhD., Project Manager Europe
>
> Avery Dennison Medical Ltd.
>
> IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80,
> Ireland
>
> Telephone: (b)(6)
>
> e-mail: elizabeth.gallantine@eu.averydennison.com
>
>
>
> Thank you!
>
>
>
> Lizzie
>
>

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> *Lizzie Gallantine, Ph.D* | Project Manager Europe | Avery Dennison
> Medical Ltd
> IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel:
> +353 43 33 49586 | Direct Line: + 353 43 331 1341
> Mobile: (b)(6)
> elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com
>
> *Error! Filename not specified.*
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> <https://www.linkedin.com/showcase/avery-dennison-medical/> | YouTube
> <https://www.youtube.com/user/AveryDennisonVideo> | News
> <https://medical.averydennison.com/en/home/insights.html> | Product
> Selector
> <https://secure-web.cisco.com/171Rs-7v4aDq7dEhkA8m-xeEroyziv0B9-2ORcBfvLsuvmZOn2dWHkRKeP7p7o3Yv9mIvflpWjh15YlsvCtg5aiAMWGB3MtKV6aietR8j4kIOQ77xCR7u8z8-ddPIQjqUyaHxnRQFK6_b6JLfpRKnNnPczsUAmE6awMgovHe3UD56sOtHpvlEHIsZ69MbkJGvgJyg6nY-rniQIjnIE-s-wiLZSCf7zuctgeWyXwcXM90/https%3A%2F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>
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>
> On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Dear Ms. Gallantine,
>
>
>
> Thank you in advance for working with us. If you do not mind, would you
> please send me your contact information as the format showing below so I
> can update the submission in our system? Thank you!
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

> *Error! Filename not specified.*
>
> Please let me know if you have any questions.
>
> Best regards,
>
> Yongqing
>
> *From:* Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> *Sent:* Friday, August 18, 2023 4:24 PM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Elaine Minagh <elaine.minagh@eu.averydennison.com>
> *Subject:* Re: [EXTERNAL] K230645 Update
>
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>
> Dear Mr. Chen-
>
> I hope you have had an enjoyable summer and this email finds you well.
>
> I am writing to inform you that I am leaving Avery Dennison at the end of the month and will therefore no longer be the point of contact for

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> submission K230645.
>
>
>
> Elizabeth Gallantine, copied on this message, will serve as the point of
> contact for future correspondence regarding the Avery Dennison submission.
> She will provide updates regarding the response to the hold letter and
> coordinate all future correspondence.
>
>
>
> It has been a pleasure working with you and I hope to work with you again
> in the future.
>
>
>
> Please let me know if you have any questions.
>
>
>
> Regards,
>
> Lisa Bartakovics
>
>
>
>
>
> On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> wrote:
>
> Dear Ms. Bartakovics,
>
>
>
> Thank you for keeping me updated and please let me know if you have any
> questions for us.
>
>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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> Best regards,
>
> Yongqing
>
>
>
>
>
> *From:* Lisa Bartakovics <lisa.bartakovics@averydennison.com>
> *Sent:* Thursday, June 1, 2023 12:20 PM
> *To:* Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
> *Cc:* regulatoryaffairs regulatoryaffairs <
> regulatoryaffairs@eu.averydennison.com>
> *Subject:* [EXTERNAL] K230645 Update
>
>
>
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> click links or open attachments unless you recognize the sender and know
> the content is safe.
>
>
>
> Dear Mr. Chen-
>
>
>
> Thank you again for the teleconference, we greatly appreciate your time
> and that of the team.
>
>
>
> (b)(4)
>

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> Therefore, Avery Dennison plans to respond to all of the points within
> the Hold Letter for K230645 in early September. I wanted to provide an
> update so that you are aware we are working on the items identified in the
> Hold Letter and will respond back to you as soon as (b)(4) is completed.
>
>
>
> Please let me know if you have any further questions.
>
>
>
> Thank you and have a nice day.
>
>
>
>
>
> Regards,
>
>
> *Lisa Bartakovics*
>
> Senior Director Global Regulatory Affairs and Quality
> Avery Dennison Medical
>
>
>
> m: (b)(6)
>
> 7100 Lindsay Dr. Mentor, OH 44060
>
<https://www.google.com/maps/search/7100+Lindsay+Dr.+Mentor,+OH+44060?entry=gmail&source=g>
>
> Facebook <https://www.facebook.com/AveryDennisonCorporation> Twitter
> <https://twitter.com/AveryDennison> LinkedIn
> <https://www.linkedin.com/company/avery-dennison/>
>
>

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> averydennison.com <https://www.averydennison.com/>

> medical.averydennison.com <https://medical.averydennison.com/en/home.html>

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> *Lisa Bartakovics*

>

> Senior Director Global Regulatory Affairs and Quality

> Avery Dennison Medical

>

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> m: (b)(6)
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> 7100 Lindsay Dr. Mentor, OH 44060
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Section 15 – Biocompatibility

Avery Dennison's BeneHold™ Surgical Incise Drape with CHG antimicrobial II is a sterile adhesive coated film that is applied preoperatively to the skin. The CHG contained within the adhesive provides antimicrobial activity against the microorganisms commonly associated with surgical site infections.

(b)(4)

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II has been evaluated for biocompatibility according to ISO 10993-1:2018 to determine if there are any biological risks that may arise from the use of the device as intended. In addition, The BeneHold™ Surgical Incise Drape with CHG antimicrobial II was also subjected to Chemical Characterization with a toxicological risk assessment and finally Endotoxin, and Direct and

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In-direct Hemolysis testing based upon FDA direction obtained during the review of K202208 (previous Avery Dennison submission). A summary of the biocompatibility results for the proposed device is detailed below in addition to the subsequent test methodology employed.

Test Methodology

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 15.1

BeneHold Surgical Incise Drape with CHG II Cytotoxicity Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

Cytotoxicity Study Using the ISO Direct Contact Method

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

Cytotoxicity Study Using the ISO Direct Contact Method

(b)(4)

Questions? Contact FDA/CDRH/OCE/DI at CDRH-FOIASTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.2

BeneHold Surgical Incise Drape with CHG II Sensitization Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

ISO Guinea Pig Maximization Sensitization Test

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DI... at CDRH-FOIA-STATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

ISO Guinea Pig Maximization Sensitization Test

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOIASTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.3

BeneHold Surgical Incise Drape with CHG II Irritation Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

ISO Intracutaneous Irritation Study – Extract

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

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(b)(4)

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(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

ISO Intracutaneous Irritation Study - Extract

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.4

BeneHold Surgical Incise Drape with CHG II Acute Systemic Toxicity Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

ISO Acute Systemic Toxicity Study in Mice

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

ISO Acute Systemic Toxicity Study in Mice

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 15.5

BeneHold Surgical Incise Drape with CHG II Material Mediated Pyrogenicity Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

USP Rabbit Pyrogen Study, Material Mediated

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OSE/DIDT at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

USP Rabbit Pyrogen Study, Material Mediated

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Attachment 15.6

BeneHold Surgical Incise Drape with CHG II Hemolysis Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

GLP REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

ASTM Hemolysis Study - Extract and Direct Contact Method

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OSE/DIDSI at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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GLP PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)

Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

ASTM Hemolysis Study - Extract and Direct Contact Method

(b)(4)

Questions? Contact FDA/CDRH/OCE/DCA at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 15.7

BeneHold Surgical Incise Drape with CHG II Endotoxin Report

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

AVERY DENNISON	Document Type:	Verification Report
	Document Title:	(b)(4) Incise Drape with CHG Endotoxin (LAL) Testing Report
	Document Number, Revision:	(b)(4)

(b)(4) Incise Drape with CHG Endotoxin (LAL) Testing Report

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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(b)(4)

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(b)(4)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 15.8

BeneHold Surgical Incise Drape with CHG II Extraction Testing

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

REPORT

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

CONFIDENTIAL

STUDY TITLE

ISO 10993-18 - Chemical Characterization

TEST ARTICLE NAME

Surgical Incise Drape with CHG (b)(4)

TEST ARTICLE IDENTIFICATION

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DI... at CDRH-FOI...TATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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STUDY PROTOCOL

TEST FACILITY

(b)(4)

SPONSOR

(b)(4)
Avery Dennison Medical
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

STUDY TITLE

ISO 10993-18 - Chemical Characterization Program

TEST ARTICLE

Surgical Incise Drape with CHG (b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 15.9

BeneHold Surgical Incise Drape with CHG II Biological Risk Assessment

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-4745; Released by CDRH on 08-26-2024

(b)(4)

(b)(4)

Project Number: (b)(4)
Version: (b)(4)

CONFIDENTIAL

Biological Risk Assessment

Device Name: BeneHold CHG Surgical Incise Drape (b)(4)

Prepared for:

Avery Dennison Medical
(b)(4)
7070 Spinach Drive, Building 19
Mentor, Ohio 44060
United States

Prepared by:

(b)(4)

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

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U.S. FOOD & DRUG ADMINISTRATION

October 25, 2023

Avery Dennison Medical Ltd.
Elaine Minagh
Regulatory Affairs Manager
IDA Business Park, Ballinalee Road
Longford, Longford N39 DX73
Ireland

Re: K230645
Trade/Device Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Regulation Number: 21 CFR 878.4370
Regulation Name: Surgical Drape And Drape Accessories
Regulatory Class: Class II
Product Code: KKX
Dated: September 22, 2023
Received: September 25, 2023

Dear Elaine Minagh:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device"

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).
Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

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Sincerely,

Bifeng Qian -S

Bifeng Qian, M.D., Ph.D.
Assistant Director
DHT4B: Division of Infection Control
and Plastic and Reconstructive Surgery Devices
OHT4: Office of Surgical
and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

From: Abraham, Sojan
To: Chen, Yongqing
Cc: Dugard, Christopher; Essuman, Edward
Subject: Consult CON2324335
Date: Monday, October 16, 2023 3:38:42 PM

Hi Yongqing,

(b)(5)

Thanks
Sojan

From: CDRH Center Tracking System <cdrhcts@cdrh.fda.gov>
Sent: Monday, October 16, 2023 4:01 AM
To: Abraham, Sojan <Sojan.Abraham@fda.hhs.gov>
Subject: [CTS ALERT] Consult CON2324335 is coming due **(b)(5)**

October 16, 2023

This consult is coming due **(b)(5)** in the Center Tracking System (CTS) :

Consult Number	CON2324335
Consult Type	Biocompatibility
Parent Document #	K230645/S001
Requestor	Yongqing Chen
Requestor Home	CDRH\OHT4\DHT4B\THT4B2
Consult Home	CDRH\OHT4\DHT4B\THT4B1
Consultant	Sojan Abraham
Due Date	**(b)(5)**

You may visit the Center Tracking System (CTS) at: https://cts.fda.gov/division-tracking for more information.

Please contact Yongqing Chen [CHENYO] at yongqing.chen@fda.hhs.gov if you have any questions or comments.

This is an automated e-mail. Please do not reply to this message.

*** This is a system-generated email notification ***

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RM4620
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-9433

Premarket Notification 510(k) Review

Post-Review Reminders

- ☐ Final Check: Ensure your documentation accurately reflects the final recommendation prior to signature (e.g., Review Summary, data in the Device Description section, the Labeling section, etc)
- ☐ Complete CTS: Procode, Clinical Trials, Combo Product, MR compatibility
- ☐ Ensure the content of the 510(k) Summary is accurate (N/A if a 510(k) Statement was provided instead).
- ☐ For SE Decisions: Upload SE Letter, and PDFs of IFU form and 510(k) Summary (if included) in DocMan.

To add reminders, type the reminder in the text field to the left then press the Tab key.

Date: May 5, 2023

Reviewer: Yongqing Chen

510(k)# K230645 Subject: Traditional

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Contact Name: Lisa Bartakovics	**Contact Title:** Senior Director Global Regulatory Affairs and Quality
Correspondent Firm: Avery Dennison Medical Ltd.	**Phone:** (b)(6) **Email:** regulatoryaffairs@eu.averydennison.com
Received Date: March 8, 2023	**Due Date:** June 6, 2023
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories

Predicate Devices:

Submission #	Pro Code	Device Trade Name	Applicant
(b)(5)			
K202208	KKX	BeneHold Surgical Incise Drape with CHG antimicrobial	Avery Dennison Belgie BVBA

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Digital Signature Concurrence Table (Doc ID: 04500.15.05)	
This document represents a high-level summary of the Agency's determination on whether the applicant's device is substantially equivalent to a legally marketed predicate device. In determining whether the subject device is substantially equivalent to a predicate device, we carefully considered the relevant regulatory and statutory criteria for Agency decision-making under 21 CFR part 807 and section 513(i) of the Federal Food, Drug and Cosmetic Act (FD&C Act). We considered the burden that may be incurred by the applicant's attempt to follow the premarket notification process. The deficiencies provided in this review, if any, represent the required minimum information necessary to support a substantial equivalence determination. Therefore, we believe that we have considered the least burdensome requirements, under section 513(i)(1)(D) of the FD&C Act, for a 510(k) determination of substantial equivalence.	
For each of the specific issues identified in the recommended requests to the applicant above, I and/or if applicable contributing consulting reviewer(s) (and or supervisors), have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s). I also confirm, if applicable, that contributing consulting reviewers (and or supervisors) have provided the above attestation.	
Reviewer Sign-Off	Yongqing Chen -S 2023.05.05 12:57:45 -04'00'

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Minor Deficiency - Question 5

(b)(4)

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Major Deficiency - Question 10

(b)(4)

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Section 10 – Device Description

Background

Avery Dennison is a market leader in adhesive technology and the contract manufacturer of several adhesive surgical drapes. Furthermore, Avery Dennison developed the technology for the (b)(4) which contains CHG formulated into the adhesive of an IV dressing. Based upon these core competencies, Avery Dennison decided to expand its CHG adhesive technology to include the application of a surgical drape containing the CHG antimicrobial agent.

In July 2021, Avery Dennison received clearance for its first antimicrobial drape, the BeneHold™ Surgical Incise Drape with CHG antimicrobial (K202208). Based upon the strong market interest in a drape containing CHG antimicrobial, Avery Dennison improved upon the formulation of its first antimicrobial drape to design an equivalent device with improved antimicrobial performance. Hence the BeneHold™ Surgical Incise Drape with CHG antimicrobial II was designed and developed by Avery Dennison. The BeneHold™ Surgical Incise Drape with CHG antimicrobial II contains (b)(4) of CHG and is indicated for professional use only (just as its predecessor cleared within K202208).

The selection of predicate devices for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II was straight-forward. (b)(4)

(b)(4)

(b)(4). The second predicate for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is the Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial Drape which was cleared in July 2021 by FDA and contains the same antimicrobial agent (K202208). The Avery Dennison BeneHold™ Surgical Incise Drape with CHG antimicrobial II utilizes the same exact design, manufacturing and performance characteristics as its predecessor within submission K202208, however it has improved antimicrobial efficacy as demonstrated in the log reduction data. Therefore, there are two predicate devices for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II.

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Table 10.1 Predicate Devices		
	(b)(4)	BeneHold™ Surgical Incise Drape with CHG antimicrobial (b)(4)
Common Name		Incise Drape
Trade Name		BeneHold™ Surgical Incise Drape with CHG antimicrobial
510(k) Submitted/Holder		Avery Dennison
510(k) Number		K202208
Product Code		KKX
Regulation		878.4370

(b)(4)

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II maintains a sterile field by acting as a barrier to external contamination while providing antimicrobial protection through the inclusion of CHG within the skin contacting layer. The antimicrobial properties of the device reduce the growth and migration of skin flora during surgical procedures. The drape consists of a transparent film with an acrylic adhesive which is applied preoperatively to the skin and contains Chlorhexidine Gluconate (CHG), a well-known antiseptic agent with broad-spectrum antimicrobial and antifungal activity. The surgeon will be able to incise through the adhesive film and skin, ensuring a sterile film barrier all the way to the edge of the incision. The incise drape is a barrier to liquid (waterproof), bacteria, viruses and protects the surgical site from outside contamination. In vitro testing (barrier and log reduction) demonstrates that the BeneHold Surgical Incise Drape

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with CHG antimicrobial II has an antimicrobial effect against, and is a barrier to, the passage of a variety of gram-positive and gram-negative bacteria yeast and mold. The BeneHold Surgical Incise Drape with CHG antimicrobial II is indicated for use as an incise drape with continuous antimicrobial activity. It is intended for external use only.

Per 21 CFR 3.2 (e), the BeneHold™ Surgical Incise Drape with CHG antimicrobial II is identified as a combination product. Avery Dennison will comply with the applicable US FDA Regulations for a combination product.

Device Configurations

The resulting device, a high-tack CHG adhesive drape with fast acting antimicrobial efficacy, was designed to meet the needs of surgical clinicians. The device will initially be offered in three sizes, both sterile and non-sterile, using the exact same device construction. The sterile configurations will be individually pouched with a SAL of 10^{-6} achieved through EO sterilization by a third-party entity. The non-sterile configurations will be bulk packaged into large bags, labeled as requiring further processing (non-sterile), and shipped to kit packing entities for inclusion within convenience kits. The kit packing entity will subsequently sterilize the Benehold Drape with CHG antimicrobial II as part of the convenience kit sterilization process.

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Table 10.2 Device Configurations		
Configuration	Device Description	Size
Pouched (sterile) and packaged in carton	MED 9547PP Small Incise Drape	30 x 35 cm
Pouched (sterile) and packaged in carton	MED 9548PP Medium Incise Drape	60 x 45 cm
Pouched (sterile) and packaged in carton	MED 9549PP Large Incise Drape	60 x 85 cm
Non-Sterile (bulk packaged) for inclusion within Convenience Kit	MED 9547PB Small Incise Drape	30 x 35 cm
Non-Sterile (bulk packaged) for inclusion within Convenience Kit	MED 9548PB Medium Incise Drape	60 x 45 cm
Non-Sterile (bulk packaged) for inclusion within Convenience Kit	MED 9549PB Large Incise Drape	60 x 85 cm

Device Design, Performance and Diagrams

There are several critical design characteristics for an antimicrobial surgical drape including antimicrobial efficacy, moisture vapor transmission rate, tensile strength, flammability, barrier properties and conformability.

The antimicrobial efficacy of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II was one the most critical attributes of the device. The ability to demonstrate antimicrobial activity against microorganisms commonly associated with surgical site infections (SSIs) was deemed significant and was therefore specifically evaluated versus the predicate devices. (b)(4)

(b)(4)

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(b)(4)

Device Biocompatibility and Diagrams

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II was subjected to biocompatibility testing per the guidelines issued within ISO 10993-1 for a surface contacting device with limited contact with breached or compromised surfaces:

- Cytotoxicity
- Irritation
- Sensitization
- Systemic Toxicity
- Material Mediated Pyrogenicity

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II was also subjected to the following tests based upon FDA direction obtained during the review of K202208 (previous Avery Dennison Drape 510(k) submission):

- Endotoxin
- Direct and In-direct Hemolysis

The resulting testing, conducted by an outside laboratory, demonstrated that the BeneHold™ Surgical Incise Drape with CHG antimicrobial II achieved acceptable results per ISO 10993 and was equivalent to (b)(4) Furthermore, the only patient contacting material within the drape is the CHG-containing adhesive as shown in the Table 10.11 below.

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Table 10.12
Components of the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

(b)(4)

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For record.

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Sent: Tuesday, October 24, 2023 11:26 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <kelsey.kaht@averydennison.com>; Annelies Luyts <annelies.luyts@eu.averydennison.com>; Shan Perkin <shan.perkin@eu.averydennison.com>; Sarah Suy <sarah.suy@eu.averydennison.com>

Subject: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen

Please find in attachment our responses to your comments with the supporting documentation.

Thank you once again for your support with this submission. Please let us know if you have any further questions.

Kind Regards,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: +(b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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Avery Dennison Medical Ltd.
IDA Business Park, Ballinalee Road
Longford, N39 RC80, Ireland
Phone: +353 43 33 49586
Fax: +353 43 3349566

Traditional 510(k) Notification

15 February 2023

U.S. Food and Drug Administration
Centre for Devices and Radiological Health
10903 New Hampshire Avenue
Document Control Center WO66-G609
Silver Spring, MD 20993-0002

Subject: 510(k) Notification for the BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Dear Madam or Sir:

Pursuant to Section 745(b) of the FD&C Act per section 1136 of FDASIA, Avery Dennison Medical Ltd. is submitting an e-copy of this Traditional 510(k) for your review. Additionally, the e-copy is accompanied with the original signed cover letter. Thank you.

Regards,

(b)(6)

Lisa Bartakovics
Sr. Global Director, Regulatory Affairs and Quality Assurance
Avery Dennison
Phone: (b)(6)
E-mail: regulatoryaffairs@eu.averydennison.com

Classification: Avery Dennison - Secret

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Dear Ms. Callantine,

Thank you again for working with us on this submission. (b)(4)

(b)(4)

Please let me know if you have other questions.

Best regards,
Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>
Sent: Tuesday, October 24, 2023 11:26 AM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <kelsey.kaht@averydennison.com>; Annelies Luyts <annelies.luyts@eu.averydennison.com>; Shan Perkin <shan.perkin@eu.averydennison.com>; Sarah Suy <sarah.suy@eu.averydennison.com>
Subject: [EXTERNAL] AD Confidential: Response to hold questions 23 October (K230645)

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen

Please find in attachment our responses to your comments with the supporting documentation.

Thank you once again for your support with this submission. Please let us know if you have any further questions.

Kind Regards,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd
IDA Business Park, Bellinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341
Mobile: (b)(6)
elizabeth.gallantine@eu.averydennison.com | medical.averydennison.com

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Section 18 – Performance Testing, Bench

An important aspect of the substantial equivalence determination of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II is the performance of the device in relation to critical key indicators. The key attributes of a BeneHold™ Surgical Incise Drape with CHG Antimicrobial II include the following;

- Static Shear
- Liner Release
- Peel Adhesion
- Moisture Vapor Transmission Rate
- Packaging Seal Strength
- Blue Dye Penetration
- Chlorhexidine (CHG) Content
- Para-Chloroaniline (PCA) Content
- Antimicrobial Efficacy
- Barrier Performance
- Flammability
- Minimum Effective Concentration
- CHG In Vitro Release
- Conformability
- Tensile Strength

The BeneHold™ Surgical Incise Drape with CHG Antimicrobial II product portfolio consists of three different sizes; Small, Medium and Large, see Table 18.1. (b)(4) (b)(4). All three sizes share this same device construction and CHG formulation. Therefore, the testing performed on one size is applicable to all the others. The sections below provide detailed testing methodologies.

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Table 18.1 BeneHold™ Surgical Incise Drape with CHG Antimicrobial II			
Device	MED9547P (small)	MED9548P (medium)	MED9549P (large)
Drape Size	30 x 35cm	60 x 45 cm	60 x 85 cm
Adhesive	CHG-containing adhesive - (b)(4)		
Carrier	(b)(4)		
Liner			
Handlebar			

Testing of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II was performed to ensure that the drape satisfied the specified design requirements. Table 18.2 summarizes the testing that was performed to confirm acceptability.

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing							
Test Performed	Objective	Device Description and Sample Size*	Applicable Standard	Avery Dennison Test Method	Acceptance Criteria	Results	Un-expected Results
Static shear	(b)(4)						
Liner release							
Peel adhesion							
MVTR							
Packaging seal strength (end seal)							

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing	
Test Performed	
Packaging seal strength (side and chevron seals)	
Blue dye penetration	
CHG content	
PCA content	

(b)(4)

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing	
Test Performed	
Antimicrobial efficacy	(b)(4)
Barrier performance	

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing	
Test Performed	(b)(4)

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing	
Test Performed	
Flammability	(b)(4)
Minimum effective concentration	

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing	
Test Performed	
CHG *in vitro* release	(b)(4)
Conformability	

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing	
Test Performed	
	(b)(4)
Tensile Strength	

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Table 18.2 Summary of the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II Performance Testing	
Test Performed	(b)(4)
(b)(4)	

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Performance testing for the BeneHold™ Surgical Incise Drape with CHG Antimicrobial II:

Description of Test Methodology:

(b)(4)

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Attachment 18.1 Drape Shelf-life Stability Report (includes (b)(4) Drape Performance Testing)

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Stability Report
BeneHold Surgical Incise Drape with CHG Antimicrobial II (b)(4)

(b)(4)

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.1.1 Static Shear Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.1.2 Liner Release Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.1.3 Peel Adhesion Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.1.4 MVTR Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.1.5 CHG and PCA Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.1.6 CHG In Vitro Release Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.2 Pouch Shelf-life Stability Report (includes (b)(4) Pouch Performance Testing)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.2.1 Packaging Seal Strength Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.2.2 Blue Dye Penetration Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.3 Synthetic blood Penetration Report and Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.4 Wet bacterial Penetration Report and Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Attachment 18.5 Viral penetration Report and Test Method

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Attachment 18.6 Flammability Report and Test Method

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Attachment 18.7 Antimicrobial Efficacy Reports and Test Methods

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Attachment 18.8 Minimum Effective Concentration Report

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Attachment 18.9 Conformability Reports

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Attachment 18.10 Tensile Strength Report

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Major Deficiency - Question 4

(b)(4)

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Stability Report
BeneHold Surgical Incise Drape with CHG Antimicrobial II (b)(4)

(b)(4)

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(b)(4)

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Dear Elaine,

Thank you for getting back to me quickly. It seems GMT time is 4 hour ahead of EST. I am wondering whether you are available any time today between 12:30 â€" 3 pm GMT (which is my 8:30-11am EST) so we can have a quick 30-min call?

Best regards,

Yongqing

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Sent: Thursday, October 19, 2023 3:46 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: K230645@docs.fda.gov

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Yongqing

Thank you for getting back to me so quickly, we are of course disappointed to hear that there are additional issues.

We can make ourselves available for a call tomorrow, it's difficult to suggest a time when I don't know your time zone.

However, I have provisionally booked the required individuals for 12.00 GMT.

If this does not work for you, just suggest another time and I can arrange it on my end.

Best wishes

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)

elaine.minagh@eu.averydennison.com<mailto:firstname.lastname@eu.averydennison.com> | medical.averydennison.com<https://medical.averydennison.com/en/home.html>

[Image removed by sender.]

https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Thu, 19 Oct 2023 at 16:38, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Minagh,

Thank you for working with us hardly to address our concerns. (b)(4) (b)(4) (b)(4) I am wondering whether we can have a short phone call today or tomorrow.

Please let me know your thoughts. Thank you!

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Best regards,

Yongqing

From: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Sent: Thursday, October 19, 2023 9:24 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: K230645@docs.fda.gov<mailto:K230645@docs.fda.gov>

Subject: Re: [EXTERNAL] K230645 Update

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Dr Yongqing

It is a pleasure to work with you on this submission.

We have received your query and are working very hard to formulate a response that will satisfy you.

However, I fear that we do not have enough time to coordinate this to a satisfactory level.

Is it possible that we could receive an extension until Monday the 23rd of October?

Many thanks and best regards

Elaine

Elaine Minagh | Regulatory Affairs Manager | Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel: (b)(6) (Mobile)

elaine.minagh@eu.averydennison.com<mailto:firstname.lastname@eu.averydennison.com> | medical.averydennison.com<https://medical.averydennison.com/en/home.html>

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https://medical.averydennison.com/en/home/medica-duesseldorf-2023.html

On Tue, 17 Oct 2023 at 19:30, Chen, Yongqing
<Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Elaine Minagh,

Thank you for working with us on this submission. We are reviewing the provided supplement S001 and have the following information for you to address. Please provide your response at your early convenience but not later than the COB of this Thursday (October 19, 2023).

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(4)

Please contact me if you have any questions.

Best regards,

Yongqing

From: Chen, Yongqing

Sent: Tuesday, October 10, 2023 8:11 AM

To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for letting me know this contact change. Good luck for your new move!

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for you.

Best regards,

Yongqing

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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From: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Tuesday, October 10, 2023 7:43 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr. Chen,

I hope you are well!

I am writing to inform you that I am leaving Avery Dennison at the end of this month and will therefore no longer be the point of contact for the current submission K230645.

My colleague Elaine Minagh, copied on this message, will become the point of contact for future correspondence regarding the Avery Dennison submission. I have provided Elaine's contact information below:

Elaine Minagh, Regulatory Affairs Manager

Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 DX73, Ireland

Telephone: (b)(6)

e-mail:
elaine.minagh@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>

Thank you for your support on this submission.

Please let me know if you have any questions.

Best Wishes,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison
.com>> wrote:

Thank you for the update Mr Chen!

Have a great day,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586
| Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.
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IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tC
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JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing
<Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Dr. Gallantine,

The supplement has been received on Monday and the team review has been starting on
Monday (09/25/2023).

Respectfully,

Yongqing

From: Chen, Yongqing

Sent: Tuesday, September 26, 2023 8:27 AM

To: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison
.com>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Subject: RE: [EXTERNAL] K230645 Update

Dear Dr. Gallantine,

Thank you for the update. It might take one or more days for DCC to notify the appropriate Center/Office. I will let you know when the supplement has been assigned to me.

Respectfully,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Tuesday, September 26, 2023 8:16 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good Morning Mr Chen,

The USB file has now arrived in Silver Creek. Could you let us know when you have received it, please?

Thank you,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Dear Dr. Gallantine,

Thank you for letting us know and look forward to working with you on this submission.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE
<elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Monday, September 25, 2023 5:31 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh
<elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Mr Chen,

We have completed our response to the hold letter for K230645. The documents on a USB file were shipped on Friday 22 September and are currently in transit (b)(4) (b)(4)

We have separated each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if you have any questions.

Best Wishes,

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com> | medical.averydennison.com<http://medical.averydennison.com>

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Selector<https://secure-web.cisco.com/13p-IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tCspI55uupICUMOIuUIw8Rwd-DL-JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Good morning Ms. Bartakovics,

Thank you for keeping us updated on your submission. I think your approach is reasonable for your purpose. We would appreciate, in your response document/letter, if you can guide us the location of your (b)(4) this will help us to quickly find them without missing any important information.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Tuesday, August 29, 2023 10:16 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Good Morning Mr. Chen-

I am winding down my time with Avery Dennison and therefore met with the team this morning to discuss our response to the hold letter for K230645. I just wanted to confirm that the response needs to be submitted as an e-copy that has been verified through the e-submitter tool. Since there are additional reports and documents to submit, we plan to add those documents into folders as attachments to our response. There are quite a few questions to address so it seemed as though a folder approach made the most sense for organizational purposes. If there is a better approach, please let me know so we may adopt that template.

Much appreciated.

Have a nice day.

Regards,

Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: (b)(6)

7100 Lindsay Dr. Mentor, OH 44060

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medical.averydennison.com<https://medical.averydennison.com/en/home.html>

On Mon, Aug 21, 2023 at 9:02â€¯AM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Hi Lizzie,

Thank you very much for sending me your contact info. Look forward to working with you on this submission.

Best regards,

Yongqing

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>

Sent: Monday, August 21, 2023 9:15 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>; Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Hi Yongqing

I hope you're well! My contact information is:

Lizzie Gallantine, PhD., Project Manager Europe

Avery Dennison Medical Ltd.

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland

Telephone: (b)(6)

e-mail: elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>

Thank you!

Lizzie

Lizzie Gallantine, Ph.D | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland| Tel: +353 43 33 49586 | Direct Line: + 353 43 331 1341

Mobile: (b)(6)

elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Gallantine,

Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our system? Thank you!

Error! Filename not specified.

Please let me know if you have any questions.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Friday, August 18, 2023 4:24 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com<mailto:elizabeth.gallantine@eu.averydennison.com>>; Elaine Minagh <elaine.minagh@eu.averydennison.com<mailto:elaine.minagh@eu.averydennison.com>>

Subject: Re: [EXTERNAL] K230645 Update

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Dear Mr. Chen-

I hope you have had an enjoyable summer and this email finds you well.

I am writing to inform you that I am leaving Avery Dennison at the end of the month and will therefore no longer be the point of contact for submission K230645.

Elizabeth Gallantine, copied on this message, will serve as the point of contact for future correspondence regarding the Avery Dennison submission. She will provide updates regarding the response to the hold letter and coordinate all future correspondence.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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It has been a pleasure working with you and I hope to work with you again in the future.

Please let me know if you have any questions.

Regards,

Lisa Bartakovics

On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>> wrote:

Dear Ms. Bartakovics,

Thank you for keeping me updated and please let me know if you have any questions for us.

Best regards,

Yongqing

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com<mailto:lisa.bartakovics@averydennison.com>>

Sent: Thursday, June 1, 2023 12:20 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov<mailto:Yongqing.Chen@fda.hhs.gov>>

Cc: regulatoryaffairs regulatoryaffairs <regulatoryaffairs@eu.averydennison.com<mailto:regulatoryaffairs@eu.averydennison.com>>

Subject: [EXTERNAL] K230645 Update

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Dear Mr. Chen-

Thank you again for the teleconference, we greatly appreciate your time and that of the team.

(b)(4)

Therefore, Avery Dennison plans to respond to all of the points within the Hold Letter for K230645 in early September. I wanted to provide an update so that you are aware we are working on the items identified in the Hold Letter and will respond back to you as soon as (b)(4) is completed.

Please let me know if you have any further questions.

Thank you and have a nice day.

Regards,

Lisa Bartakovics

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: (b)(6)

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Lisa Bartakovics

Senior Director Global Regulatory Affairs and Quality

Avery Dennison Medical

m: (b)(6)

7100 Lindsay Dr. Mentor, OH 44060

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Dear Yongqing
 Thank you for getting back to me so quickly,Â we are of course disappointed to hear that there are additional issues. We can make ourselves available for a call tomorrow, it's difficult to suggest a time when I don't know your time zone. However, I have provisionally booked the required individuals for 12.00 GMT. If this does notÂ work for you, just suggest another time and I can arrange it on my end.

 BestÂ wishes
 ElaineÂ Elaine MinaghÂ | Regulatory Affairs Manager | Avery Dennison Medical Ltd.Â
 IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel:Â (b)(6)Mobile) elaine.minagh@eu.averydennison.comÂ |Â medical.averydennison.comÂ <img src="https://lh3.googleusercontent.com/3I1CtTXFmdVl5ycrHK4fW0nuEEYdbNKQwXUgW8uS3JmjwYhSief3MyakQ4bpieNDx4nx_dSKctTZ7LWcttOlQqa9NrX7TaVEqBHmzqMTu59-lT62PvvGLWIuotbTET7zOF4CMJw-QUI-SwS1t4Sgv00" width="446" height="212" style="background-color:transparent;color:rgb(0,0,0);font-family:"Nunito Sans",sans-serif;font-size:11pt;margin-left:0px;margin-top:0px">

Dear Ms. Minagh,<u></u><u></u>

<u></u>Â <u></u>

Thank you for working with us hardly to address our concerns.

(b)(4)

we can have a short phone call today or tomorrow. <u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

<u></u>Â <u></u>

Please let me know your thoughts. Thank you!<u></u><u></u>

<u></u>Â <u></u>

Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

<u></u>Â <u></u>

<u></u>Â <u></u>

From: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Sent: Thursday, October 19, 2023 9:24 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: K230645@docs.fda.gov

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

<u></u>Â <u></u>

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<u></u>Â <u></u>

DrÂ Yongqing<u></u><u></u>

<u></u>Â <u></u>

It is a pleasure to work with you on this submission.<u></u><u></u>

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<div>

<p class="MsoNormal">We have receivedÂ your query and are working very hard to
formulate a response that will satisfy you.<u></u><u></u></p>

</div>

<div>

<p class="MsoNormal">However, I fearÂ that we do not have enough time to coordinate
this to a satisfactory level.<u></u><u></u></p>

</div>

<div>

<p class="MsoNormal">Â <u></u><u></u></p>

</div>

<div>

<p class="MsoNormal">Is it possible that we could receiveÂ an extension until Monday
the 23rd of October?<u></u><u></u></p>

</div>

<div>

<p class="MsoNormal"><u></u>Â <u></u></p>

</div>

<div>

<p class="MsoNormal">Many thanks and best regardsÂ <u></u><u></u></p>

</div>

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<p class="MsoNormal"><u></u>Â <u></u></p>

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<div>

<p class="MsoNormal">ElaineÂ Â <u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p style="margin:0in"><b><span style="font-size:10pt;font-family:Arial,sans-
serif;color:rgb(80,0,80)">Elaine MinaghÂ </span></b><span style="font-size:10pt;font-
family:Arial,sans-serif">| Regulatory Affairs Manager | Avery Dennison Medical Ltd.Â
</span><u></u><u></u></p>

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<p style="margin:0in;background-image:initial;background-position:initial;background-
repeat:initial">

<span style="font-size:7.5pt;font-family:Arial,sans-serif">IDA Business Park,
Ballinalee Road, Longford, N39 DX73. Ireland. | Tel:Â </span><b><span style="font-
size:10pt;font-family:Roboto;letter-spacing:0.15pt">[ (b)(6) ] (</span></b><span
style="font-size:10pt;font-family:Arial,sans-serif">Mobile)</span><u></u><u></u></p>

<p style="margin:0in;background-image:initial;background-position:initial;background-
repeat:initial">

<span style="font-size:10pt;font-family:Arial,sans-serif"><a
href="mailto:firstname.lastname@eu.averydennison.com" target="_blank"><span
style="color:rgb(17,85,204)">elaine.minagh@eu.averydennison.com</span></a>Â |Â
</span><a href="https://medical.averydennison.com/en/home.html" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">medical.averydennison.com</span></a><span style="font-
size:10pt;font-family:Arial,sans-serif;color:black">Â </span><u></u><u></u></p>

<p style="margin:0in;background-image:initial;background-position:initial;background-
repeat:initial">

<span style="border:1pt solid windowtext;padding:0in"><img border="0" width="446"
height="212" style="width: 4.6458in; height: 2.2083in;" id="m_-
8389467685260170717Picture_x0020_1" src="cid:18b49705d982df834601" alt="Image removed
by sender."></span><u></u><u></u></p>

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<p class="MsoNormal"><a href="https://medical.averydennison.com/en/home/medica-
duesseldorf-2023.html"
target="_blank">https://medical.averydennison.com/en/home/medica-duesseldorf-
2023.html</a><u></u><u></u></p>

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<p class="MsoNormal">On Tue, 17 Oct 2023 at 19:30, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

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<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin-left:4.8pt;margin-right:0in">

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<p class="MsoNormal">Dear Ms. Elaine Minagh,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you for working with us on this submission. We are reviewing
the provided supplement S001 and have the following information for you to address.
Please provide your response

at your early convenience but not later than <b>the COB of this Thursday (October 19,
2023).</b><u></u><u></u></p>

<p class="MsoNormal"><span style="color:rgb(0,112,192)">Â </span><u></u><u></u></p>

<p class="MsoNormal" style="margin-left:0.5in">

<span style="color:rgb(0,112,192)">
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(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745, Released by CDRH on 08-26-2024

(b)(4)

Â <u></u><u></u>

Please contact me if you have any questions.<u></u><u></u>

Â <u></u><u></u>

Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

Â <u></u><u></u>

Â <u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

From: Chen, Yongqing

Sent: Tuesday, October 10, 2023 8:11 AM

To: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Subject: RE: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

Dear Dr. Gallantine,<u></u><u></u>

Â <u></u><u></u>

Thank you for letting me know this contact change. Good luck for your new move!<u></u><u></u>

Â <u></u><u></u>

Ms. Elaine Minagh, thank you for going to work with us. I will update the contact information for this submission and we will let you know if we have any questions for you.<u></u><u></u>

Â <u></u><u></u>

Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

Â <u></u><u></u>

Â <u></u><u></u>

Â <u></u><u></u>

From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Sent: Tuesday, October 10, 2023 7:43 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Â <u></u><u></u>

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.<u></u><u></u>

Â <u></u><u></u>

Dear Mr. Chen,Â

<u></u><u></u>

Â <u></u><u></u>

I hope you are well!<u></u><u></u>

Â <u></u><u></u>

IÂ am writing to inform you that I am leaving Avery Dennison at the end of this month and will therefore no longer be the point of contact for the current submission K230645.<u></u><u></u>

Â <u></u><u></u>

My colleague Elaine Minagh, copied on this message, will become the point of contact for future correspondence regarding the Avery Dennison submission. I have provided Elaine's

contact information below:<u></u><u></u>

Â <u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p class="MsoNormal">Elaine Minagh, Regulatory Affairs Manager<u></u><u></u></p>

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<div>

<p class="MsoNormal">Avery Dennison Medical Ltd.<u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-serif;color:rgb(41,41,41)">IDA
Business Park, Ballinalee Road, Longford, County Longford, N39 DX73,
Ireland</span><u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-
serif;color:rgb(41,41,41)">Telephone: 00Â </span><span style="font-family:Arial,sans-
serif;letter-spacing:0.15pt">(b)(6)</span><u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-serif;color:rgb(41,41,41)">e-
mail:Â <a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com</a></span><u></u><u></u></p>

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<p class="MsoNormal">Thank you for your support on this submission.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Please let me know if you have any questions.<u></u><u></u></p>

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<p class="MsoNormal">Best Wishes,<u></u><u></u></p>

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<p class="MsoNormal">Lizzie<u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+(b)(6)
(b)(6) br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><u></u><u></u></p>

<p style="margin:0in"><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-serif;border:1pt
none windowtext;padding:0in;text-decoration:none"><img border="0" width="245"
height="82" style="width: 2.5555in; height: 0.8541in;" id="m_-838946768526017071 7m_-
3733366803405760289m_-1891516952761364032m_8099847791546314356Picture_x0020_1"
src="cid:18b49705d982df834601" alt="Image removed by
sender."></span></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |

</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/13p-
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spI55uupICUMOIuUIw8Rwd-DL-
JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html" target="_blank">
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Product Selector</a></span><u></u><u></u></p>

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<p class="MsoNormal">On Thu, 28 Sept 2023 at 14:57, ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;
wrote:<u></u><u></u></p>

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<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

<div>

<p class="MsoNormal">Thank you for the update Mr Chen!

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<p class="MsoNormal">Have a great day,Â <u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Lizzie<br clear="all">
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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+ (b)(6)
(b)(6) <br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><u></u><u></u></p>

<p style="margin:0in"><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-serif;border:1pt
none windowtext;padding:0in;text-decoration:none"><img border="0" width="245"
height="82" style="width: 2.5555in; height: 0.8541in;" id="m_-838946768526017071 7m_-
3733366803405760289m_-1891516952761364032m_8099847791546314356Picture_x0020_2"
src="cid:18b49705d982df834601" alt="Image removed by
sender."></span></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |

</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/13p-
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spI55uupICUMOIuUIw8Rwd-DL-
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JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p class="MsoNormal">On Thu, 28 Sept 2023 at 14:56, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

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<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Dear Dr. Gallantine,<u></u><u></u></p>

<p class="MsoNormal">The supplement has been received on Monday and the team review has
been starting on Monday (09/25/2023).<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Respectfully,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> Chen, Yongqing
```


Sent: Tuesday, September 26, 2023 8:27 AM

To: ELIZABETH GALLANTINE <<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com>

Cc: Elaine Minagh <<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com>

Subject: RE: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

Dear Dr. Gallantine,<u></u><u></u>

Thank you for the update. It might take one or more days for DCC
to notify the appropriate Center/Office. I will let you know when the supplement has
been assigned to me.<u></u><u></u>

Â <u></u><u></u>

Respectfully,<u></u><u></u>

Yongqing<u></u><u></u>

Â <u></u><u></u>

<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

From: ELIZABETH GALLANTINE <<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com>

Sent: Tuesday, September 26, 2023 8:16 AM

To: Chen, Yongqing <<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov>

Cc: Elaine Minagh <<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com>

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

CAUTION:<span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
click links or open attachments unless you recognize the sender and know the content is
safe.<u></u><u></u>

Â <u></u><u></u>

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p class="MsoNormal">Good Morning Mr Chen,Â

<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">The USB file has now arrived in Silver Creek. Could you let us
know when you have received it, please?<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Thank you,Â <u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Lizzie<br clear="all">

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Lizzie Gallantine, Ph.DÂ | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â Tel: +353 43 33 49586Â |Â Direct Line: + 353 43 331 1341Â

Mobile:Â + (b)(6) (b)(6)

elizabeth.gallantine@eu.averydennison.comÂ |Â medical.averydennison.com<u></u><u></u>

<a href="https://medical.averydennison.com/en/home.html" target="_blank">Error! Filename not

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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specified.</span></b></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
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family:Arial,sans-serif;color:black"> |</span><a
href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |

</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/13p-
IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tC
spI55uupICUMOIuUIw8Rwd-DL-
JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

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<p style="margin-right:1.25in;margin-bottom:0in;margin-left:0in">

<span style="font-size:9.5pt">Â </span><u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p class="MsoNormal">On Mon, 25 Sept 2023 at 13:35, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

</div>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Dear Dr. Gallantine,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you for letting us know and look forward to working with you
on this submission.<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Best regards,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;

<br>

<b>Sent:</b> Monday, September 25, 2023 5:31 AM<br>

<b>To:</b> Chen, Yongqing &lt;<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt;<br>

<b>Cc:</b> Elaine Minagh &lt;<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com</a>&gt;<br>

<b>Subject:</b> Re: [EXTERNAL] K230645 Update<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

<div style="border:1pt solid rgb(156,101,0);padding:2pt">

<p class="MsoNormal" style="line-height:12pt;background:rgb(255,235,156)">

<span style="font-size:10pt;color:rgb(156,101,0)">CAUTION:</span><span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
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safe.</span><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Dear Mr Chen,Â
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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Â <u></u><u></u>

We have completed our response to the hold letter for K230645. TheÂ documents on a USB file were shippedÂ on Friday 22 September and are currentlyÂ in transit (b)(4).<u></u><u></u>

Â <u></u><u></u>

We have separatedÂ each question and response into a separate file complete with the relevant attachments to allow you to more easily navigate our response. Please let us know if

you have any questions.<u></u><u></u>

Â <u></u><u></u>

Best Wishes,Â <u></u><u></u>

Â <u></u><u></u>

Lizzie<u></u><u></u>

Â <u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+ (b)(6)
(b)(6) <br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><u></u><u></u></p>

<p style="margin:0in"><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;border:1pt
none windowtext;padding:0in;text-decoration:none">Error! Filename not
specified.</span></b></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |

</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/13p-
IKygdxH0O3mJPKZfEf2yYEtQvy3QE50FEzMCMAiSxcFIxCXtuQZPCZubLZifUpL4aLc5CVYMXPKutKRfcOuV9tC
spI55uupICUMOIuUIw8Rwd-DL-
JTjyfSkVBiRzWJc93kn6TeSNTsSXYwltCrmy80CmrR_YDD9u8cWHISufq_V7Zp0EoA3Pew6PzV2o/https%3A%2
F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

<p style="margin:0in">Â <u></u><u></u></p>

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<p style="margin-right:1.25in;margin-bottom:0in;margin-left:0in">

<span style="font-size:9.5pt">Â </span><u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p class="MsoNormal">On Tue, 29 Aug 2023 at 15:59, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

</div>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Good morning Ms. Bartakovics,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you for keeping us updated on your submission. I think your
approach is reasonable for your purpose. We would appreciate, in your response
document/letter, if you can guide

us the location of your [redacted], this will help us to
quickly find them without missing any important information.<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Best regards,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> Lisa Bartakovics &lt;<a
href="mailto:lisa.bartakovics@averydennison.com"
target="_blank">lisa.bartakovics@averydennison.com</a>&gt;

<br>

<b>Sent:</b> Tuesday, August 29, 2023 10:16 AM<br>

<b>To:</b> Chen, Yongqing &lt;<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt;<br>

<b>Cc:</b> ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
```

[redacted]: (b)(4)

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;<br>

<b>Subject:</b> Re: [EXTERNAL] K230645 Update<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

<div style="border:1pt solid rgb(156,101,0);padding:2pt">

<p class="MsoNormal" style="line-height:12pt;background:rgb(255,235,156)">

<span style="font-size:10pt;color:rgb(156,101,0)">CAUTION:</span><span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
click links or open attachments unless you recognize the sender and know the content is
safe.</span><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Good Morning Mr. Chen-<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">I am winding down my time with Avery Dennison and therefore met
with the team this morning to discuss our response to the hold letter for K230645. I
just wanted to confirm that

the response needs to be submitted as an e-copy that has been verified through the e-
submitter tool. Since there are additional reports and documents to submit, we plan to
add those documents into folders as attachments to our response. There are quite a few

questions to address so it seemed as though a folder approach made the most sense for
organizational purposes. If there is a better approach, please let me know so we may
adopt that template.<u></u><u></u></p>

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<p class="MsoNormal">Much appreciated.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Have a nice day.<u></u><u></u></p>
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Regards,<u></u><u></u></p>

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<p style="margin:0in"><b><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Lisa Bartakovics</span></b><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Senior Director Global Regulatory Affairs and Quality<br>

Avery Dennison Medical</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">m: (b)(6) </span><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">7100 Lindsay Dr. Mentor, OH 44060</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin:0in"><span style="font-size:9pt;font-family:Arial,sans-
serif;color:black;border:1pt none windowtext;padding:0in">Error! Filename not
specified.</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin-bottom:0in"><a
href="https://www.facebook.com/AveryDennisonCorporation" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Facebook</span></a><span style="font-size:10pt;font-
family:Arial,sans-serif;color:rgb(67,67,67)">

Â  </span><a href="https://twitter.com/AveryDennison" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-serif;color:black">Twitter</span></a><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(67,67,67)"> Â

</span><a href="https://www.linkedin.com/company/avery-dennison/" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-
serif;color:black">LinkedIn</span></a><u></u><u></u></p>

<p class="MsoNormal"><br>

<a href="https://www.averydennison.com/" target="_blank"><span style="font-
size:10pt;font-family:Arial,sans-
serif;color:black">averydennison.com</span></a><b><span style="font-size:10pt;font-
family:Arial,sans-serif;color:black"> Â

</span></b><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">medical.averydennison.com</span></a><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">On Mon, Aug 21, 2023 at 9:02â€¯AM Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

</div>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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<p class="MsoNormal">Hi Lizzie,<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Thank you very much for sending me your contact info. Look forward
to working with you on this submission.<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p class="MsoNormal">Best regards,<u></u><u></u></p>

<p class="MsoNormal">Yongqing<u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

<p class="MsoNormal"><b>From:</b> ELIZABETH GALLANTINE &lt;<a
href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a>&gt;

<br>

<b>Sent:</b> Monday, August 21, 2023 9:15 AM<br>

<b>To:</b> Chen, Yongqing &lt;<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt;<br>

<b>Cc:</b> Elaine Minagh &lt;<a href="mailto:elaine.minagh@eu.averydennison.com"
target="_blank">elaine.minagh@eu.averydennison.com</a>&gt;; Lisa Bartakovics &lt;<a
href="mailto:lisa.bartakovics@averydennison.com"
target="_blank">lisa.bartakovics@averydennison.com</a>&gt;<br>

<b>Subject:</b> Re: [EXTERNAL] K230645 Update<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

<div style="border:1pt solid rgb(156,101,0);padding:2pt">
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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.<u></u><u></u>

Â <u></u><u></u>

Hi Yongqing

<u></u><u></u>

Â <u></u><u></u>

I hope you're well! My contact information is:<u></u><u></u>

Â <u></u><u></u>

Lizzie Gallantine, PhD., Project Manager Europe<u></u><u></u>

Avery Dennison Medical Ltd.<u></u><u></u>

IDA Business Park, Ballinalee Road, Longford, County Longford, N39 RC80, Ireland<u></u><u></u>

Telephone: (b)(6)<u></u><u></u>

e-mail:

elizabeth.gallantine@eu.averydennison.com<u></u><u></u>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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<p class="MsoNormal"><span style="font-family:Arial,sans-
serif;color:rgb(41,41,41)">Thank you!</span><u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-
serif;color:rgb(41,41,41)">Lizzie</span><u></u><u></u></p>

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<p class="MsoNormal"><br clear="all">

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Lizzie Gallantine, Ph.DÂ | Project Manager Europe | Avery Dennison Medical Ltd

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â Tel: +353 43 33 49586Â |Â Direct Line: + 353 43 331 1341Â

Mobile:Â + (b)(6) (b)(6)

elizabeth.gallantine@eu.averydennison.comÂ |Â medical.averydennison.com<u></u><u></u>

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Connect with Us:

Twitter<span style="font-size:7.5pt;font-

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

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family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.youtube.com/user/AveryDennisonVideo" target="_blank"><span
style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">

</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |

</span><a href="https://medical.averydennison.com/en/home/insights.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
web.cisco.com/171Rs-7v4aDq7dEhkA8m-xeEroyziv0B9-
2ORcBfvLsuvmZOn2dWHkRKeP7p7o3Yv9mIvflpWjh15YlsvCtg5aiAMWGB3MtKV6aietR8j4kIOQ77xCR7u8z8-
ddPIQjqUyaHxnRQFK6_b6JLfpRKnNnPczsUAmE6awMgovHe3UD56sOtHpvlEHIsZ69MbkJGvgJyg6nY-
rniQIjnIE-s-
wiLZSCf7zuctgeWyXwcXM90/https%3A%2F%2Fmedical.averydennsion.com%2Fen%2Fhome%2Fproduct-
selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

<p style="margin:0in">Â <u></u><u></u></p>

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<p style="margin-right:1.25in;margin-bottom:0in;margin-left:0in">

<span style="font-size:9.5pt">Â </span><u></u><u></u></p>

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<p class="MsoNormal">On Fri, 18 Aug 2023 at 22:07, Chen, Yongqing &lt;<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov</a>&gt; wrote:<u></u><u></u></p>

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<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

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Dear Ms. Gallantine,<u></u><u></u>

Â <u></u><u></u>

Thank you in advance for working with us. If you do not mind, would you please send me your contact information as the format showing below so I can update the submission in our

system? Thank you!<u></u><u></u>

Â <u></u><u></u>

Error! Filename not specified.<u></u><u></u>

Please let me know if you have any questions.<u></u><u></u>

Â <u></u><u></u>

Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

Â <u></u><u></u>

From: Lisa Bartakovics <lisa.bartakovics@averydennison.com>

Sent: Friday, August 18, 2023 4:24 PM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>; Elaine Minagh <elaine.minagh@eu.averydennison.com>

Subject: Re: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.<u></u><u></u>

Â <u></u><u></u>

Dear Mr. Chen-<u></u><u></u>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">I hope you have had an enjoyable summer and this email finds you
well.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">I am writing to inform you that I am leaving Avery Dennison at the
end of the month and will therefore no longer be the point of contact for submission
K230645.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Elizabeth Gallantine, copied on this message, will serve as the
point of contact for future correspondence regarding the Avery Dennison submission. She
will provide updates regarding

the response to the hold letter and coordinate all future
correspondence.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">It has been a pleasure working with you and I hope to work with
you again in the future.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Please let me know if you have any questions.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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Regards,<u></u><u></u>

Lisa Bartakovics<u></u><u></u>

Â <u></u><u></u>

Â <u></u><u></u>

On Thu, Jun 1, 2023 at 12:05 PM Chen, Yongqing <<a
href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov> wrote:<u></u><u></u>

<blockquote style="border-top:none;border-right:none;border-bottom:none;border-left:1pt
solid rgb(204,204,204);padding:0in 0in 0in 6pt;margin:5pt 0in 5pt 4.8pt">

Dear Ms. Bartakovics,<u></u><u></u>

Â <u></u><u></u>

Thank you for keeping me updated and please let me know if you
have any questions for us.<u></u><u></u>

Â <u></u><u></u>

Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

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<div style="border-right:none;border-bottom:none;border-left:none;border-top:1pt solid
rgb(225,225,225);padding:3pt 0in 0in">

From: Lisa Bartakovics <<a
href="mailto:lisa.bartakovics@averydennison.com"
target="_blank">lisa.bartakovics@averydennison.com>

Sent: Thursday, June 1, 2023 12:20 PM

To: Chen, Yongqing <<a href="mailto:Yongqing.Chen@fda.hhs.gov"
target="_blank">Yongqing.Chen@fda.hhs.gov>

Cc: regulatoryaffairs regulatoryaffairs <<a
href="mailto:regulatoryaffairs@eu.averydennison.com"
target="_blank">regulatoryaffairs@eu.averydennison.com>

Subject: [EXTERNAL] K230645 Update<u></u><u></u>

Â <u></u><u></u>

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.<u></u><u></u>

Â <u></u><u></u>

Dear Mr. Chen-<u></u><u></u>

Â <u></u><u></u>

Thank you again for the teleconference, we greatly appreciate your time and that of the team.<u></u><u></u>

Â <u></u><u></u>

(b)(4)

(b)(4)

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Therefore, Avery Dennison plans to respond to all of the points within theÂ Hold Letter for K230645 in early September. I wanted to provide an update so that you are aware we are

working on the items identified in the Hold Letter and will respond back to you as soon as (b)(4) is completed.<u></u><u></u>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Please let me know if you have any furtherÂ questions.Â
<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Thank you and have a nice day.<u></u><u></u></p>

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<p class="MsoNormal">Â <u></u><u></u></p>

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<p class="MsoNormal">Regards,<u></u><u></u></p>

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<p class="MsoNormal"><br clear="all">

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<p style="margin:0in"><b><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Lisa Bartakovics</span></b><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Senior Director Global Regulatory Affairs and Quality<br>

Avery Dennison Medical</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">m: (b)(6) /span><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black"><a
href="https://www.google.com/maps/search/7100+Lindsay+Dr.+Mentor,+OH+44060?entry=gmail&
amp;source=g" target="_blank">7100 Lindsay Dr. Mentor, OH
44060</a></span><u></u><u></u></p>

<p style="margin-bottom:0in"><a
href="https://www.facebook.com/AveryDennisonCorporation" target="_blank"><span
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style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Facebook</span></a><span style="font-size:10pt;font-
family:Arial,sans-serif;color:rgb(67,67,67)">

Â  </span><a href="https://twitter.com/AveryDennison" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-serif;color:black">Twitter</span></a><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(67,67,67)"> Â

</span><a href="https://www.linkedin.com/company/avery-dennison/" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-
serif;color:black">LinkedIn</span></a><u></u><u></u></p>

<p class="MsoNormal"><br>

<a href="https://www.averydennison.com/" target="_blank"><span style="font-
size:10pt;font-family:Arial,sans-
serif;color:black">averydennison.com</span></a><b><span style="font-size:10pt;font-
family:Arial,sans-serif;color:black"> Â

</span></b><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">medical.averydennison.com</span></a><u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-serif">The information
transmitted is intended only for the person or entity to which it is addressed and may
contain confidential and/or privileged

material. Any review, retransmission, dissemination or other use of, or taking of any
action in reliance upon, this information by persons or entities other than the
intended recipient is prohibited. If you received this in error, please contact the
sender

and delete the material from any device.</span><u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-serif">For details about the
personal information we process and why, please see ourÂ <a
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href="https://www.averydennison.com/en/home/legal-and-privacy-notices.html"
target="_blank">Privacy

Notice</a></span><u></u><u></u></p>

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<p style="margin:0in"><b><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Lisa Bartakovics</span></b><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Senior Director Global Regulatory Affairs and Quality<br>

Avery Dennison Medical</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">m: (b)(6) </span><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">7100 Lindsay Dr. Mentor, OH 44060</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin:0in"><span style="font-size:9pt;font-family:Arial,sans-
serif;color:black;border:1pt none windowtext;padding:0in">Error! Filename not
specified.</span><u></u><u></u></p>

<p class="MsoNormal">Â <u></u><u></u></p>

<p style="margin-bottom:0in"><a
href="https://www.facebook.com/AveryDennisonCorporation" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-
serif;color:black">Facebook</span></a><span style="font-size:10pt;font-
family:Arial,sans-serif;color:rgb(67,67,67)">

Â  </span><a href="https://twitter.com/AveryDennison" target="_blank"><span
style="font-size:10pt;font-family:Arial,sans-serif;color:black">Twitter</span></a><span
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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(67,67,67)"> Â

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style="font-size:10pt;font-family:Arial,sans-
serif;color:black">LinkedIn</span></a><u></u><u></u></p>

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<a href="https://www.averydennison.com/" target="_blank"><span style="font-
size:10pt;font-family:Arial,sans-
serif;color:black">averydennison.com</span></a><b><span style="font-size:10pt;font-
family:Arial,sans-serif;color:black"> Â

</span></b><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:10pt;font-family:Arial,sans-
serif;color:black">medical.averydennison.com</span></a><u></u><u></u></p>

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<p class="MsoNormal"><span style="font-family:Arial,sans-serif">For details about the
personal information we process and why, please see ourÂ <a
href="https://www.averydennison.com/en/home/legal-and-privacy-notices.html"
target="_blank">Privacy

Notice</a></span><u></u><u></u></p>

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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href="https://www.averydennison.com/en/home/legal-and-privacy-notices.html"
target="_blank">Privacy

Notice</a></span><u></u><u></u></p>

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Major Deficiency - Question 1

(b)(4)

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510(k) Summary

Avery Dennison Medical Ltd.

BeneHold™ Surgical Incise Drape with CHG antimicrobial II

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Section 11 Executive Summary

(b)(4)

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Section 12 – Substantial Equivalence Discussion

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Dear Mr ChenÂ
 Following our review of your comments,Â (b)(4)

(b)(4)

process. I look forward to hearing from you soon.
 Best RegardsÂ
 ElaineÂ Â Â <br clear="all"> Elaine MinaghÂ | Regulatory Affairs Manager | Avery Dennison Medical Ltd.Â
 IDA Business Park, Ballinalee Road, Longford, N39 DX73. Ireland. | Tel:Â +(b)(6) (Mobile) elaine.minagh@eu.averydennison.comÂ |Â medical.averydennison.comÂ <img src="https://lh3.googleusercontent.com/3I1CtTXFmdVl5ycrHK4fW0nuEEYdbNKQwXUgW8uS3JmjwYhSief3MyakQ4bpieNDx4nx_dSKctTZ7LWcttOlQqa9NrX7TaVEqBHmzqMTu59-lT62PvvGLWIuotbTET7zOF4CMJw-QUI-SwS1t4Sgv00" width="446" height="212" style="background-color:transparent;color:rgb(0,0,0);font-family:"Nunito Sans",sans-serif;font-size:11pt;margin-left:0px;margin-top:0px">

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(b)(4)

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Please let me know if you have other questions.<u></u><u></u>

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Best regards,<u></u><u></u>

Yongqing<u></u><u></u>

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From: ELIZABETH GALLANTINE <elizabeth.gallantine@eu.averydennison.com>

Sent: Tuesday, October 24, 2023 11:26 AM

To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>

Cc: Elaine Minagh <elaine.minagh@eu.averydennison.com>; Angel Boateng <angel.boateng@eu.averydennison.com>; Kelsey Kaht <<a

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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target="_blank">kelsey.kaht@averydennison.com</a>&gt;; Annelies Luyts &lt;<a
href="mailto:annelies.luyts@eu.averydennison.com"
target="_blank">annelies.luyts@eu.averydennison.com</a>&gt;; Shan Perkin &lt;<a
href="mailto:shan.perkin@eu.averydennison.com"
target="_blank">shan.perkin@eu.averydennison.com</a>&gt;;

Sarah Suy &lt;<a href="mailto:sarah.suy@eu.averydennison.com"
target="_blank">sarah.suy@eu.averydennison.com</a>&gt;<br>

<b>Subject:</b> [EXTERNAL] AD Confidential: Response to hold questions 23 October
(K230645)<u></u><u></u></p>

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style="font-size:10pt;color:rgb(156,101,0)">CAUTION:</span><span style="font-
size:10pt;color:black"> This email originated from outside of the organization. Do not
click links or open attachments

unless you recognize the sender and know the content is safe.<u></u><u></u></span></p>

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<p class="MsoNormal">Dear Mr. Chen <u></u><u></u></p>

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<p class="MsoNormal">Please find in attachment our responses to your comments with the
supporting documentation.<u></u><u></u></p>

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<p class="MsoNormal">Thank you once again for your support with this submission. Please
let us know if you haveÂ any further questions.<u></u><u></u></p>

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<p class="MsoNormal">Kind Regards,Â <u></u><u></u></p>

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<p class="MsoNormal">Lizzie<br clear="all">

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<p><b><span style="font-size:7.5pt;font-family:Arial,sans-serif;color:black">Lizzie
Gallantine, Ph.D</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(41,41,41)">Â | Project Manager Europe | Avery Dennison Medical Ltd<br>

IDA Business Park, Ballinalee Road, Longford, N39 RC80, Ireland|Â </span><span
style="font-size:10pt;font-family:Arial,sans-serif;color:rgb(34,34,34)">Tel: +353 43 33
49586Â |Â Direct Line: + 353 43 331 1341Â <br>

</span><span style="font-size:10pt;font-family:Arial,sans-serif">Mobile:<b>Â
</b></span><span style="font-size:7.5pt;font-family:Arial,sans-serif">+ (b)(6)
(b)(6) <br>

<span style="color:blue"><a href="mailto:elizabeth.gallantine@eu.averydennison.com"
target="_blank">elizabeth.gallantine@eu.averydennison.com</a></span>Â |Â <span
style="color:blue"><a href="http://medical.averydennison.com"
target="_blank">medical.averydennison.com</a></span></span><span style="font-
family:Arial,sans-serif"><u></u><u></u></span></p>

<p style="margin:0in"><a href="https://medical.averydennison.com/en/home.html"
target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-serif;border:1pt
none windowtext;padding:0in;text-decoration:none"><img border="0" width="245"
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7077073969337393549Picture_x0020_1" src="cid:18b6667ca47f8ba20431" alt="Image removed
by sender."></span></a><u></u><u></u></p>

<p style="margin:0in"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">Connect with Us:</span><a href="https://twitter.com/ADMedical"
target="_blank"><b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:black">

</span></b><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">Twitter</span></a><span style="font-size:7.5pt;font-
family:Arial,sans-serif;color:black"> |</span><a
href="https://www.linkedin.com/showcase/avery-dennison-medical/" target="_blank"><span
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serif;color:rgb(17,85,204)">LinkedIn</span></a><span style="font-size:7.5pt;font-
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</span><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">YouTube</span></a><span style="font-size:7.5pt;font-
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target="_blank"><span style="font-size:7.5pt;font-family:Arial,sans-
serif;color:rgb(17,85,204)">News</span></a><span style="font-size:7.5pt;font-
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family:Arial,sans-serif;color:rgb(17,85,204)"><a href="https://secure-
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Fproduct-selector.html" target="_blank">

Product Selector</a></span><u></u><u></u></p>

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Please Note: FDA's comments for the AINN Hold Letter for K230645 are provided below in bold, italic, type followed by the response of Avery Dennison.

MAJOR DEFICIENCY LIST

(b)(4)

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AVERY DENNISON | Medical

25 October 2023

U.S. Food and Drug Administration
Centre for Devices and Radiological Health
10903 New Hampshire Avenue
Document Control Center WO66-G609
Silver Spring, MD 20993-0002

Subject: Withdrawal of the 510(k) Summary and replace with the 510(k) Statement.

Premarket Notification K230645,
BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Dear Madam or Sir:

Please find our request to replace the use of the 510k Summary for K230645 with the 510K Statement.

Regards

(b)(6)

25 October 2023

Elaine Minagh,
Regulatory Affairs Manager
Avery Dennison Medical
Phone: (b)(6)
E-mail: elaine.minagh@eu.averydennison.com

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RM4620
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-9433

Premarket Notification 510(k) Review

Post-Review Reminders

- ☐ Final Check: Ensure your documentation accurately reflects the final recommendation prior to signature (e.g., Review Summary, data in the Device Description section, the Labeling section, etc)
- ☐ Complete CTS: Procode, Clinical Trials, Combo Product, MR compatibility
- ☐ Ensure the content of the 510(k) Summary is accurate (N/A if a 510(k) Statement was provided instead).
- ☐ For SE Decisions: Upload SE Letter, and PDFs of IFU form and 510(k) Summary (if included) in DocMan.

To add reminders, type the reminder in the text field to the left then press the Tab key.

Date: May 5, 2023

Reviewer: Yongqing Chen

510(k)# K230645 Subject: Traditional

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Contact Name: Lisa Bartakovics	**Contact Title:** Senior Director Global Regulatory Affairs and Quality
Correspondent Firm: Avery Dennison Medical Ltd.	**Phone:** (b)(6) **Email:** regulatoryaffairs@eu.averydennison.com
Received Date: March 8, 2023	**Due Date:** June 6, 2023
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories

Predicate Devices:

Submission #	Pro Code	Device Trade Name	Applicant
(b)(5)			
K202208	KKX	BeneHold Surgical Incise Drape with CHG antimicrobial	Avery Dennison Belgie BVBA

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Ref. Major Deficiency - Question 3

(b)(4)

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

U.S. FOOD & DRUG ADMINISTRATION

October 25, 2023

Avery Dennison Medical Ltd.
Elaine Minagh
Regulatory Affairs Manager
IDA Business Park, Ballinalee Road
Longford, Longford N39 DX73
Ireland

Re: K230645
Trade/Device Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Regulation Number: 21 CFR 878.4370
Regulation Name: Surgical Drape And Drape Accessories
Regulatory Class: Class II
Product Code: KKX
Dated: September 22, 2023
Received: September 25, 2023

Dear Elaine Minagh:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device"

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).
Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

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Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

Sincerely,

Bifeng Qian -S

Bifeng Qian, M.D., Ph.D.
Assistant Director
DHT4B: Division of Infection Control
and Plastic and Reconstructive Surgery Devices
OHT4: Office of Surgical
and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*

K230645

Device Name

BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Indications for Use *(Describe)*

The BeneHold™ Surgical Incise Drape with CHG antimicrobial II is indicated for use as an incise drape with continuous antimicrobial activity (in vitro) from 30 minutes through 4 hours of use against the following organisms: S. aureus, S. epidermidis, E. coli, P. aeruginosa, E. aerogenes, and C. albicans. In vitro testing on the subject drape has also shown continuous antimicrobial activity from 30 minutes through 2.5 hours against E. faecalis and F. oxysporum. It is intended for external use only. Correlation between in vitro results and any clinical event has not been tested.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

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U.S. FOOD & DRUG ADMINISTRATION

eConsult Cover Sheet

Consult Number:	CON2324334
Document Number:	K230645/S001
Applicant:	Avery Dennison Medical Ltd.
Trade Name:	BeneHold Surgical Incise Drape with CHG antimicrobial II
Consult Type:	Toxicology and Chemical Risk Assessment
Requestor:	Yongqing Chen [CHENYO] yongqing.chen@fda.hhs.gov
Requestor Home:	CDRH\ OHT4\ DHT4B\ THT4B2
Requested Consultant:	Angela Burke -S (Affiliate) Digitally signed by Angela Burke -S (Affiliate) Date: 2023.10.24 08:28:01 -05'00'
Gatekeeper / Consultant:	Angela Burke [ANGELA.BURKE] angela.burke@fda.hhs.gov ; 479-579-8521
Consultant Home:	CDRH\ OPEQ
Date Requested:	(b)(5)
Due Date:	

(b)(5)

Since no specific outstanding issues/requests were identified/recommended to the applicant above following the AINN Hold Letter sent to the Sponsor on October 17, 2023, no statements of bases for the responses were provided or no applicable and/or relevant final rule, statue, final guidance, or FDA-recognized consensus standards were cited.

Reviewer Sign-Off: Angela Burke -S (Affiliate)
Digitally signed by Angela Burke -S (Affiliate)
Date: 2023.10.24 08:28:16 -05'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RMONR
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-4779

Subject Matter Expert (SME) Review

Date: October 11, 2023

SME Reviewer: Lianji Jin

Expertise: Chemical Characterization

Submission # K230645/S001

Applicable Review Guide (if used): [Choose Review Guide]

Is this review for a Pre-Submission, Submission Issue Request, or Expedited Program (Breakthrough/STeP) Interaction? No

Applicant: Avery Dennison Medical Ltd.

Device Trade Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Optional Classification Information:

Pro Code(s): KKX **Class:** II **Reg #:** 878.4370

Reg Name: Surgical Drape And Drape Accessories

Rx/OTC: Rx

(b)(5)

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Digital Signature Concurrence Table (Doc ID: 04504.04.00)	
For each of the specific issues identified in the recommended requests to the applicant above, I have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability for requests: add all relevant numbers here, else delete that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s).	
Reviewer Sign-Off	Lianji Jin -S Digitally signed by Lianji Jin -S Date: 2023.10.11 18:49:15 -04'00'

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RMONR
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
240-402-8521

Subject Matter Expert (SME) Review

Date: October 12, 2023

SME Reviewer: Maureen OBrien

Expertise: Animal Study

Applicable Review Guide (if used): [Choose Review Guide]

Submission # K230645

Applicant: Avery Dennison Medical Ltd.	**Device Trade Name:** BeneHold™ Surgical Incise Drape with CHG antimicrobial II
Optional Classification Information:	
Pro Code(s): KKX **Class:** II **Reg #:** 878.4370	**Reg Name:** Surgical Drape And Drape Accessories
Pro Code(s): Class: [Choose] Reg #:	Reg Name:
Rx/OTC: [Choose Option]	

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
CDRH/OPEQ/OHTIV/DHTIVB
WO66 RM4536
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
301-796-0270

Subject Matter Expert (SME) Review

Date: April 3, 2023

SME Reviewer: Sreekanth Gutala

Expertise: Chemistry related consult

Submission # K230645

Applicable Review Guide (if used): Not Applicable

Is this review for a Pre-Submission, Submission Issue Request, or Expedited Program (Breakthrough/STeP) Interaction? No

Applicant: Avery Dennison Medical Ltd.

Device Trade Name: BeneHold™ Surgical Incise Drape with CHG antimicrobial II

Optional Classification Information:

Pro Code(s): KKX **Class:** II **Reg #:** 878.4370

Reg Name: Surgical Drape And Drape Accessories

Rx/OTC: Rx

(b)(5)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Contains Nonbinding Recommendations

Print Form

510(k) Acceptance Checklist

Not for use with Third Party 510(k)s

Choose Submission Type: ☒ **Traditional** ☐ **Abbreviated** ☐ **Special**

(Should be completed within 15 days of DCC receipt)
The following information is not intended to serve as a comprehensive review.
FDA recommends that the submitter include this completed checklist as part of the submission.

510(k) #: K230645 Date Received by DCC: Mar 8, 2023

Lead Reviewer: Yongqing Chen

Center: CDRH Office: OHT 4 Division: DHT4B

Decision:

◉ Accept. If Accept, notify submitter.

○ Refuse to Accept. If Refuse to Accept, notify submitter electronically and include a copy of this checklist.

Is an Addendum attached?: ○ Yes ◉ No Click paperclip icon on the left panel if Addendum is attached.

Note: If an element is left blank on the checklist, it does not mean the checklist is incomplete; it means the reviewer did not assess the element during the RTA review and that the element will be assessed during substantive review.

IMPORTANT - Many checklist elements include additional details regarding information to address the element that can be seen by hovering over the element (Example - Element 4 in Section A of the checklist).

Preliminary Questions **Answers in the shaded blocks indicate consultation with a Center advisor is needed. (Boxes checked in this section represent FDA's preliminary assessment of these questions at the time of administrative review.)**	**Yes**	**No**	**N/A**
1 Is the product a device (per section 201(h) of the FD&C Act) or a combination product (per 21 CFR 3.2(e)) with a device constituent part subject to review in a 510(k)? If it appears not to be a device (per section 201(h) of the FD&C Act) or such a combination product (per 21 CFR 3.2(e)), or you are unsure, consult with the CDRH Product Jurisdiction Officer or the CBER Product Jurisdiction Officer to determine the appropriate action, and inform management. *Provide a summary of the Product Jurisdiction Officer's determination/recommendation/action in the comment section below.* If the product does not appear to be a device or such a combination product, mark "No."	☒	☐	
Comments:			
2 Is the submission with the appropriate Center? If the product is a device or a combination product with a device constituent part, is it subject to review by the Center in which the submission was received? If you believe the submission is not with the appropriate Center or you are unsure, consult with the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer to determine the appropriate action and inform your management. *Provide a summary of the Product Jurisdiction Officer's determination/recommendation/action in the comment section below.* If submission should not be reviewed by your Center mark "No."	☒	☐	
Comments:			

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3 If a Request for Designation (RFD) was submitted for the device or combination product with a device constituent part and assigned to your center, identify the RFD # and confirm the following: **a) Is the device or combination product the same (e.g., design, formulation) as that presented in the RFD submission?** **b) Are the indications for use for the device or combination product identified in the 510(k) the same as those identified in the RFD submission?** If you believe the product or the indications presented in the 510(k) have changed from the RFD, or you are unsure, consult with the CDRH Product Jurisdiction Officer or the CBER Product Jurisdiction Officer to determine the appropriate action and inform your management. *Provide a summary of Product Jurisdiction Officer's determination/recommendation/action in the comment section below.* If the answer to either question above is no, mark "No." If there was no RFD, mark "N/A."	☐	☐	☒
Comments:			
4 Is the submission for a combination product that contains as a constituent part a drug that has the same active moiety as an approved drug with exclusivity as described in section 503(g)(5)(C)(ii)-(v) of the FD&C Act? If "Yes," then contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer to determine the appropriate action and inform your management. *Provide the summary of the Product Jurisdiction Officer's determination/recommendation/action in the comment section below.*	☒	☐	☐
Comments:			
5 Is this device type eligible for a 510(k) submission? If a 510(k) does not appear to be appropriate (e.g., class III type and PMA required, or class I or II type and 510(k)-exempt), consult with the appropriate CDRH or CBER staff during the acceptance review, provide a summary of the discussion with them, and indicate their recommendation/action in the comment section below. If 510(k) is not the appropriate regulatory submission, mark "No."	☒	☐	
Comments:			
6 Is there a pending PMA for the same device with the same indications for use? If "Yes," consult your management and CDRH Office of Product Evaluation and Quality/Office of Regulatory Programs/Division of Regulatory Programs 1 (Submission Support) (OPEQ/ORP/DRP1) or appropriate CBER staff to determine the appropriate action.	☐	☒	
Comments:			
7 If clinical studies have been submitted, is the submitter the subject of an Application Integrity Policy (AIP)? If "Yes," consult with the CDRH Office of Product Evaluation and Quality/ Office of Clinical Evidence and Analysis/Division of Clinical Science and Quality (OPEQ/OCEA/DCEA1) or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action, provide a summary of the discussion with them, and indicate their recommendation/action. If no clinical studies have been submitted, mark "N/A." Check on the AIP list at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/application-integrity-policy/application-integrity-policy-list.	☐	☐	☒
Comments:			

- If the answer to 1 or 2 appears to be "No," then stop review of the 510(k) and contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer.
- If the answer to 3a or 3b appears to be "No," then stop the review and contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer.
- If the answer to 4 is "Yes," then contact the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer, provide a summary of the discussion with them, and indicate their recommendation/action.
- If the answer to 5 is "No," the lead reviewer should consult management and other Center resources to determine the appropriate action. Note that, for a device which is clearly ineligible for a 510(k) submission (such as a device type which is class III requiring PMA or class I/II and 510(k) exempt), this may be considered a basis for a refusal to accept the submission. A 510(k) submitted for a class I/II, 510(k)-exempt device that trips the limitations of the exemption would not be refused on this basis.
- If the answer to 6 is "Yes," then stop review of the 510(k), contact the CDRH/OPEQ/ORP/DRP1, or appropriate CBER staff.
- If the answer to 7 is "Yes," then contact CDRH/OPEQ/OCEA/DCEA1 or CBER/OCBQ/DIS/BMB, provide a summary of the discussion with DCEA1 or BMB Staff, and indicate their recommendation/action.

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Organizational Elements

Failure to include these items should not result in an RTA designation.

*Submitters including the checklist with their submission should identify the page numbers where requested information located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	*Page #
1) Submission contains a Table of Contents	☒	☐	
2) Each section is labeled (e.g., headings or tabs designating Device Description section, Labeling section, etc.)	☒	☐	
3) All pages of the submission are numbered. *All pages should be numbered in such a manner that information can be referenced by page number. This may be done either by consecutively numbering the entire submission, or numbering the pages within a section (e.g., 12-1, 12-2…).*	☒	☐	
4) Type of 510(k) is identified (i.e., Traditional, Abbreviated, or Special). *If type of 510(k) is not designated, review as a Traditional 510(k).*	☒	☐	
Comments:			

Elements of a Complete Submission (RTA Items)

(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed.

- Any "No" answer will result in a "Refuse to Accept" decision; however, FDA staff has discretion to determine whether missing items are needed to ensure that the submission is administratively complete to allow the submission to be accepted or to request missing checklist items interactively from submitters during RTA review.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

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Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
A. Administrative					
1) All content used to support the submission is written in English (including translations of test reports, literature articles, etc.)	☒	☐		☐	
2) Submission identifies the following (FDA recommends use of the CDRH Premarket Review Submission Cover Sheet form (Form 3514, available at https://www.fda.gov/media/72421/download)):				☐	
a) Device trade/proprietary name	☒	☐			
b) Device class and panel OR Classification regulation OR Statement that device has not been classified with rationale for that conclusion	☒	☐			
3) Submission contains an Indication for Use Statement with Rx and/or OTC designated (see also 21 CFR 801.109, and FDA's final rule, "Use of Symbols in Labeling" (81 FR 38911), available at https://www.federalregister.gov/documents/2016/06/15/2016-13989/use-of-symbols-in-labeling). *See recommended format (https://www.fda.gov/media/86323/download).*	☒	☐		☐	
4) Submission contains a 510(k) Summary or 510(k) Statement.	☒	☐		☐	
5) Submission contains a Truthful and Accuracy Statement per 21 CFR 807.87(l) *See recommended format (https://www.fda.gov/medical-devices/premarket-notification-510k/premarket-notification-truthful-and-accurate-statement).*	☒	☐		☐	
6) Submission is a class III 510(k) device.	☐		☒	☐	
7) Submission contains clinical data	☒		☐	☐	
a) Submission includes completed Financial Certification (FDA Form 3454, available at https://www.fda.gov/media/70465/download) or Disclosure (FDA Form 3455, available at https://www.fda.gov/media/69872/download) information for each covered clinical study included in the submission. *Select "N/A" if the submitted clinical data is not a "covered clinical study" as defined in the guidance entitled "Financial Disclosures by Clinical Investigators", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/financial-disclosure-clinical-investigators.*	☒	☐	☐		
b) Submission includes completed Certification of Compliance with requirements of ClinicalTrials.gov Data Bank (see FDA Form 3674 which can be obtained at https://www.fda.gov/about-fda/reports-manuals-forms/forms) (42 U.S.C. 282(j)(5)(B)) for each applicable device clinical trial included in the submission. *Select "N/A" if the submitted clinical data is not an "applicable device clinical trial" as defined in Title VIII of FDAAA, Sec. 801(j)*	☒	☐	☐		

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c) Statements of Compliance for Clinical Investigations *Select "N/A" if the submission does not contain any clinical data from investigations (as defined in 21 CFR 812.3(h)) to demonstrate substantial equivalence.* *For multicenter clinical investigations involving both United States (US) and outside United States (OUS) sites, part (i) should be addressed for the US sites and part (ii) should be addressed for the OUS sites. 21 CFR 812.28 applies to all OUS clinical investigations that enroll the first subject on or after February 21, 2019.* *Please refer to the guidance document entitled "Acceptance of Clinical Data to Support Medical Device Applications and Submissions - Frequently Asked Questions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked for more information.*	☐		☐		
i) For each clinical investigation conducted in the US, the submission includes a statement that the investigation was conducted in compliance with 21 CFR parts 50, 56, and 812 (or, with respect to part 56, that is was not subject to the regulations under 21 CFR 56.104 or 56.105). **OR** The submission includes a brief statement of the reason for noncompliance with 21 CFR parts 50, 56, and/or 812.	☒	☐	☐		
ii) For each clinical investigation conducted OUS, the submission includes a statement that the clinical investigations were conducted in accordance with good clinical practice (GCP) as described in 21 CFR 812.28(a)(1). **OR** The submission includes a waiver request in accordance with 21 CFR 812.28(c). **OR** The submission includes a brief statement of the reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of subjects have been adequately protected.	☒	☐	☐		
8) The submission identifies prior submissions for the same device included in the current submission (e.g., submission numbers for a prior not substantially equivalent [NSE] determination, prior deleted or withdrawn 510(k), Q-Submission, IDE, PMA, etc.). **OR** States that there were no prior submissions for the subject device.	☒	☐		☐	
a) If there were prior submissions, the submitter has identified where in the current submission any issues related to a determination of substantial equivalence from prior submissions for this device are addressed.	☐	☐	☒		
9) The submission utilizes voluntary consensus standard(s) (See section 514(c) of the FD&C Act). *This includes both FDA-recognized and non-recognized consensus standards.*	☒		☐	☐	
a) The submission cites FDA-recognized voluntary consensus standard(s).	☒		☐		

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Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
i) The submission includes a Declaration of Conformity (DOC) as outlined in FDA's guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices. **OR** If citing general use of a standard as noted in FDA's guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices," the basis of such use is included along with the underlying information or data that supports how the standard was used.	☒	☐			
b) The submission cites non-FDA-recognized voluntary consensus standard(s).	☒		☐		
i) The basis of use is included along with the underlying information or data that supports how the standard was used.	☒	☐			
Combination Product Provisions - Per 503(g) of the FD&C Act. Select "N/A" if the product is not a combination product. 21 CFR 3.2(e). The remaining criteria in this section will be omitted from the checklist if "N/A" is selected. If you are unsure if the product is a combination product, consult with the CDRH Product Jurisdiction Officer or CBER Product Jurisdiction Officer.			☐		
10) Submission identifies the product as a combination product.	☒	☐		☐	
11) The combination product contains as a constituent part an approved drug as defined in section 503(g)(5)(B) of the FD&C Act. *Select "N/A" if the combination product does not contain as a constituent part an approved drug. Please also select "N/A" if a right of reference or use for the drug constituent part(s) is included with the submission. If "N/A" is selected, part a below is omitted from the checklist.*	☒		☐	☐	
a) The submission includes appropriate patent statement or certification and a statement that the submitter will give notice, as applicable. See section 503(g)(5)(A)&(C) of the FD&C Act.	☒	☐			
B. Device Description					
12) The device has a device-specific guidance document, special controls, and/or requirements in a device-specific classification regulation regarding the device description that is applicable to the subject device.	☐		☒	☐	
13) Descriptive information is present and consistent within the submission (e.g., the device description section is consistent with the device description in the labeling).	☒	☐		☐	
14) The submission includes descriptive information for the device, including the following:				☐	
a) A description of the principle of operation or mechanism of action for achieving the intended effect.	☒	☐			
b) A description of proposed conditions of use, such as surgical technique for implants; anatomical location of use; user interface; how the device interacts with other devices; and/or how the device interacts with the patient.	☒	☐	☐		
c) A list and description of each device for which clearance is requested.	☒	☐	☐		

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d) Submission contains representative engineering drawing(s), schematics, illustrations, photos and/or figures of the device. **OR** Submission includes a statement that engineering drawings, schematics, etc. are not applicable to the device (e.g., device is a reagent and figures are not pertinent to describe the device).	☒	☐			
15) Device is intended to be marketed with accessories and/or as part of a system.	☐		☒	☐	
C. Substantial Equivalence Discussion					
16) Submitter has identified a predicate device(s), including the following information:				☐	
a) Predicate device identifier provided (e.g., 510(k) number, De Novo number, reclassified PMA number, classification regulation reference, if exempt (e.g., 21 CFR 872.3710), or statement that the predicate is a preamendment device). For predicates that are preamendments devices, information is provided to document preamendments status. *Information regarding documenting preamendment status is available online (https://www.fda.gov/medical-devices/quality-and-compliance-medical-devices/preamendment-status).*	☒	☐			
b) The identified predicate(s) is consistent throughout the submission (e.g., the predicate(s) identified in the Substantial Equivalence section is the same as that listed in the 510(k) Summary (if applicable) and that used in comparative performance testing).	☒	☐			
17) Submission includes a comparison of the following for the predicate(s) and subject device and a discussion why any differences between the subject and predicate(s) do not impact safety and effectiveness [see section 513(i)(1)(A) of the FD&C Act and 21 CFR 807.87(f)] *See the FDA guidance document "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k for more information on comparing intended use and technological characteristics.*				☐	
a) Indications for Use	☒	☐			
b) Technology, including technical specifications, features, materials, and principles of operation	☒	☐			
D. Proposed Labeling (see also 21 CFR part 801 and 809 as applicable)					
18) Submission includes proposed package labels and labeling (e.g., instructions for use, package insert, operator's manual).	☒	☐		☐	
a) Indications for use are stated in labeling and are identical to Indications for Use form and 510(k) Summary (if 510(k) Summary provided).	☒	☐			
b) Labeling includes: - Statements of conditions, purposes or uses for which the device is intended (e.g., hazards, warnings, precautions, contraindications) (21 CFR 801.5) **AND** - Includes adequate directions for use (see 21 CFR 801.5) **OR** - Submission states that device qualifies for exemption per 21 CFR 801 Subpart D	☒	☐			

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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19) Labeling includes name and place of business of the manufacturer, packer, or distributor (21 CFR 801.1).	☒	☐		☐	
20) Labeling includes the prescription statement [see 21 CFR 801.109(b)(1)] or Rx Only symbol (see also Section 502(a) of the FD&C Act and FDA's final rule, "Use of Symbols in Labeling" (81 FR 38911), available at https://www.federalregister.gov/documents/2016/06/15/2016-13989/use-of-symbols-in-labeling).	☒	☐	☐	☐	
21) The device has a device-specific guidance document, special controls, and/or requirements in a device-specific classification regulation regarding labeling that is applicable to the subject device.	☐		☒		
22) If the device is an in vitro diagnostic device, provided labeling includes all applicable information required per 21 CFR 809.10.	☐	☐	☒	☐	
E. Sterilization					
If an *in vitro* diagnostic (IVD) device and sterilization is not applicable, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected.			☐		
☒ Provided sterile, intended to be single-use					
☐ Requires processing during its use-life					
☐ Non-sterile when used (and no processing required)					
☐ Information regarding the sterility status of the device is not provided. (If this box is checked, please also check one of the two boxes below.)					
☐ Sterility status not needed for this device (e.g., software-only device)					
☐ Sterility status needed or need unclear					
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination. *Please refer to the FDA guidance document "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling, for additional information.*					
23) Assessment of the need for cleaning and subsequent disinfection or sterilization information				☐	
a) Identification of device and/or accessories, if applicable, that are provided sterile.	☒	☐	☐		
b) Identification of device and/or accessories, if applicable, that are end user sterilized or disinfected.	☐	☐	☒		
c) Identification of device, and/or accessories, if applicable, that are reusable.	☐	☐	☒		
24) If the device and/or accessories, if applicable, are provided sterile:			☐	☐	
a) Sterilization method is stated for each device (including dose for radiation sterilization).	☒	☐			
b) A description of method to validate the sterilization parameters is provided for each proposed sterilization method (e.g., half-cycle method and full citation of FDA-recognized standard, including date).	☒	☐			

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Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
c) For devices sterilized using chemical sterilants such as ethylene oxide (EO) and hydrogen peroxide, submission states maximum levels of sterilant residuals remaining on the device and sterilant residual limits.	☒	☐	☐		
d) Sterility Assurance Level (SAL) is stated.	☒	☐			
e) Submission includes description of packaging.	☒	☐			
f) For products labeled "non-pyrogenic," a description of the method used to make the determination stated (e.g., limulus amebocyte lysate [LAL]).	☐	☐	☒		
25) If the device and/or accessory, if applicable, is reusable or end user sterilized or disinfected:			☒	☐	
a) Cleaning method is provided in labeling for each device and/or accessory, if applicable.	☐	☐	☐		
b) Disinfection method is provided in labeling for each device and/or accessory, if applicable.	☐	☐	☐		
c) Sterilization method is provided in labeling for each device and/or accessory, if applicable.	☐	☐	☐		
d) Device types in this submission are listed in the Federal Register (FR) Notice entitled "Validated Instructions for Use and Validation Data Requirements for Certain Reusable Medical Devices in Premarket Notifications" (Reprocessing FR Notice, available at https://www.federalregister.gov/documents/2017/06/09/2017-12007/medical-devices-validated-instructions-for-use-and-validation-data-requirements-for-certain-reusable).	☐		☐		
i) If device types in this submission are included in the Reprocessing FR Notice, the submission includes protocols and test reports for validating the reprocessing instructions.	☐	☐	☐		
26) The device has a device-specific guidance document, special controls, and/or requirement in a device-specific regulation regarding sterility and/or reprocessing that is applicable to the subject device.	☐		☒	☐	
F. Shelf Life					
27) Proposed shelf life/expiration date stated **OR** Statement that shelf-life is not applicable because of low likelihood of time-dependent product degradation	☒	☐	☐	☐	
28) For a sterile device, submission includes summary of methods used to establish that device packaging will maintain a sterile barrier for the entirety of the proposed shelf life.	☒	☐	☐	☐	
29) Submission includes summary of methods used to establish that device performance is maintained for the entirety of the proposed shelf-life (e.g., mechanical properties, coating integrity, pH, osmolality, etc.). **OR** Statement why performance data is not needed to establish maintenance of device performance characteristics over the shelf-life period.	☒	☐		☐	
G. Biocompatibility					
If an vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected.			☐		

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Submission states that there: (one of the below must be checked)		☐		☐	
☒ Are direct or indirect tissue-contacting components.					
☐ Are no direct or indirect tissue-contacting components.					
☐ Information regarding tissue contact status of the device is not provided (if this box checked, please also check one of the two boxes below).					
☐ Tissue contact information not needed for this device (e.g., software-only device)					
☐ Tissue contact information needed or need unclear					
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
30) Submission includes a list identifying each of tissue-contacting device component (e.g., implant, delivery catheter) and associated materials of construction for each component, including identification of color additives, if present.	☒	☐		☐	
31) Submission identifies contact classification (e.g., surface-contacting, less then 24 hour duration) for each tissue-contacting device component (e.g., implant, delivery catheter)	☒	☐		☐	
32) For a biocompatibility assessment of tissue-contacting components, submission includes: – Each relevant endpoint for the device (as identified in device-specific guidance, or Attachment A of the FDA guidance document entitled "Use of International Standard ISO 10993-1, `Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and), has been addressed. - For any testing performed, test protocol (including identification and description of test article including whether the test article is the device in its final finished form using the recommended approach in Attachment F of "Use of International Standard ISO 10993-1, `Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" methods, and pass/fail criteria), and analysis of results (including tables with data points and statistical analyses, where appropriate), as described in Attachment E of the guidance document entitled "Use of International Standard ISO 10993-1, `Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" provided for each completed test. **OR** A statement that biocompatibility testing is not needed with a rationale that considers all relevant endpoints (e.g., materials and manufacturing/processing are identical to the predicate).	☒	☐		☐	
H. Software					
Submission states that the device: (one of the below must be checked)		☐		☐	
☐ Does contain software/firmware					
☒ Does not contain software/firmware					
☐ Information on whether device contains software/firmware is not provided. (If this box is checked, please also check one of the two boxes below.)					
☐ Software/firmware information not needed for this device (e.g., surgical suture, condom)					

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Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
☐ Software/firmware information is needed or need unclear					
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
I. Cybersecurity					
Submission states that the device: *(one of the below must be checked)*		☐		☐	
☐ Does contain any external wired and/or wireless communication interfaces (Wired: USB, ethernet, SD, CD, RGA, etc. or Wireless: Wi-Fi, Bluetooth, RF, inductive, Cloud, etc.)					
☒ Does not contain external interfaces as described above					
☐ Information on whether device has external interfaces is not provided. (If this box is checked, please also check one of the two boxes below.)					
☐ Cybersecurity information not needed for this device (e.g., surgical suture, condom)					
☐ Cybersecurity information is needed or need unclear					
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
J. Electrical Safety and EMC					
Electrical Safety Submission states that the device: *(one of the below must be checked)*		☐		☐	
☐ Does require electrical safety evaluation					
☒ Does not require electrical safety evaluation					
☐ Information on whether device requires electrical safety evaluation is not provided. (If this box is checked, please also check one of the two boxes below.)					
☐ Electrical safety information not needed for this device (e.g., surgical suture, condom)					
☐ Electrical safety information is needed or need unclear					
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
EMC Submission states that the device: (one of the below must be checked)		☐		☐	
☐ Does require EMC evaluation					
☒ Does not require EMC evaluation					
☐ Information on whether device requires EMC evaluation is not provided. (If this box is checked, please also check one of the two boxes below.)					
☐ EMC information not needed for this device (e.g., surgical suture, condom)					
☐ EMC information is needed or need unclear					
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
K. Performance Data - General					

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Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
If an in vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from checklist if "N/A" is selected. Performance data criteria relating to IVD devices is addressed in Section K.			☐		
38) Summaries of the non-clinical laboratory studies and full test reports* are provided. *Summary and full test report content recommendations can be found in FDA's guidance "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket. If a submitter chooses to declare conformity to a voluntary consensus standard that FDA has recognized, submission of a full test report may not be necessary. Refer to 9a. See FDA's guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.	☒	☐	☐	☐	
a) Submission includes an explanation of how the data generated from each test supports a finding of substantial equivalence (e.g., comparison to predicate device testing, dimensional analysis, etc.).	☒	☐			
39) The device has a device-specific guidance document, special controls, and/or requirements in a device-specific classification regulation regarding performance data that is applicable to the subject device.	☐		☒	☐	
40) If literature is referenced in the submission, submission includes:			☐		
a) Legible reprints or a summary of each article.	☒	☐			
b) Discussion of how each article is applicable to support the substantial equivalence of the subject device to the predicate.	☒	☐			
41) For each completed animal study, the submission provides the following:			☐	☐	
a) Submission includes a study protocol which includes all elements as outlined in 21 CFR 58.120.	☒	☐			
b) Submission includes final study report which includes all elements outlined in 21 CFR 58.185.	☒	☐			
c) Submission contains a statement that the study was conducted in compliance with applicable requirements in the GLP regulation (21 CFR Part 58), or, if the study was not conducted in compliance with the GLP regulation, the submission explains why the noncompliance would not impact the validity of the study data provided to support a substantial equivalence determination.	☒	☐			
L. Performance Characteristics - In Vitro Diagnostic Devices Only **(Also see 21 CFR 809.10(b)(12))**					
Submission states that the device: (one of the below must be checked)				☐	
☐ is an in vitro diagnostic device.					
☒ is not an in vitro diagnostic device.					
If "is not" is selected, the performance data-related criteria below are omitted from the checklist.					

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Digital Signature Concurrence Table

Reviewer Sign-Off (digital signature required)	Yongqing Chen -S 2023.03.22 16:37:29 -04'00'
Management Sign-Off (digital signature required)	

Management review of checklist and concurrence with the decision is required.

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U.S. FOOD & DRUG ADMINISTRATION

eConsult Cover Sheet

Consult Number:	CON239422
Document Number:	K230645
Applicant:	Avery Dennison Medical Ltd.
Trade Name:	BeneHold Surgical Incise Drape with CHG antimicrobial II
Consult Type:	Toxicology and Chemical Risk Assessment
Requestor:	Yongqing Chen [CHENYO] yongqing.chen@fda.hhs.gov
Requestor Home:	CDRH\ OHT4\ DHT4B\ THT4B2
Requested Consultant:	
Gatekeeper / Consultant:	Angela Burke [ANGELA.BURKE] angela.burke@fda.hhs.gov ; 479-579-8521
Consultant Home:	CDRH\ OPEQ
Date Requested:	April 14, 2023
Due Date:	May 1, 2023
Instructions:	Thank you so much for willing to help us. Please review the TRA within the attachment 15.9. Please let me know if you have any questions/comments. Best, --Yongqing

For each of the specific issues identified in the recommended requests to the applicant above, I provided a statement of bases for the request(s); and cite as part of it an available, applicable, and relevant final rule, statue, final guidance, or FDA-recognized consensus standard for each.

Reviewer Sign-Off:

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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From: OBrien, Maureen [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=EA250E177C604E66A0CE9562FE1AE366-MAUREEN.OBR]
Sent: 10/12/2023 9:20:31 PM
To: Chen, Yongqing [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=54023f5be2c1404e8e42c417dfd62b9e-ChenYo]
CC: Abraham, Sojan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7942eceb45c447ecba5a310d497c097c-Sojan.Abrah]
Subject: RE: CTS Assignment Notification: K230645/S001 has been assigned to you
Attachments: K230645_AS Consult_S001_MTO.docm

Hi Yongqing and Sojan,

(b)(5)

Best regards,
Mo

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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(b)(5)

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(b)(5)

From: OBrien, Maureen
Sent: Thursday, 5 October 2023 09:56
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Cc: Abraham, Sojan <Sojan.Abraham@fda.hhs.gov>
Subject: RE: CTS Assignment Notification: K230645/S001 has been assigned to you

Hi Yongqing,

(b)(5)

Thank you,
Mo

From: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Sent: Thursday, 5 October 2023 09:53
To: OBrien, Maureen <Maureen.OBrien@fda.hhs.gov>
Cc: Abraham, Sojan <Sojan.Abraham@fda.hhs.gov>
Subject: RE: CTS Assignment Notification: K230645/S001 has been assigned to you

Good morning MO,

Welcome back!

I had a quick talk with Sojan this morning. (b)(5)

(b)(5)

Best,
Yongqing

From: Chen, Yongqing
Sent: Thursday, September 28, 2023 11:30 AM
To: Gutala, Sreekanth <Sreekanth.Gutala@fda.hhs.gov>; Matsuura, Michael <Michael.Matsuura@fda.hhs.gov>; Abraham, Sojan <Sojan.Abraham@fda.hhs.gov>; OBrien, Maureen <Maureen.OBrien@fda.hhs.gov>; Burke, Angela * <Angela.Burke@fda.hhs.gov>; Jin, Lianji <Lianji.Jin@fda.hhs.gov>
Subject: RE: CTS Assignment Notification: K230645/S001 has been assigned to you

Dear all,

Thank you so much again for helping us on this (b)(5)

Records processed under FOIA Request 2024-1745; Released by CDRH on 08-26-2024

This Monday (09/25/2023), the sponsor provided their responses to our AINN letter. I would like to request your further help to review responses and related additional information in this supplement. (b)(5)

(b)(5)

Below is a table show AINN deficiency number and their originally raised reviewers.

(b)(5)

Please let me know if you have any suggestions or comments.

Again, thank you so much for helping us on this submission!

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Best,
Yongqing

From: CDRH Center Tracking System <cdrhcts@cdrh.fda.gov>
Sent: Monday, September 25, 2023 1:48 PM
To: Chen, Yongqing <Yongqing.Chen@fda.hhs.gov>
Subject: CTS Assignment Notification: K230645/S001 has been assigned to you

September 25, 2023

This document has been assigned to you in the Center Tracking System (CTS).

Document # :	K230645/S001
Document Type :	510(k)
Workflow State :	Requires Recommendation
Assignor :	Bifeng Qian [BIFENG.QIAN]

You may visit the Center Tracking System (CTS) at: https://cts.fda.gov/division-tracking for more information.

Please contact Bifeng Qian [BIFENG.QIAN] at bifeng.qian@fda.hhs.gov or at 301-210-8782 if you have any questions or comments.

If you would like NOT to receive these messages in the future, please uncheck 'Receive Assignment Email Notification' checkbox
in the User Preferences section of your CTS user profile, accessible through the toolbar in CTS.

*** This is a system-generated email notification ***