Table of Contents

K021792

Bilayer Matrix Wound Dressing
510(K) SUMMARY

AUG 1 4 2002

Submitter's name and address:

Integra LifeSciences Corporation
311 Enterprise Drive
Plainsboro, NJ 08536 USA

Contact person and telephone number:

Diana M. Bordon
Manager, Regulatory Affairs,
(609) 275-0500

Date: May 23, 2002

Name of the device:

Proprietary Name:	Bilayer Matrix Wound Dressing
Common Name:	Wound Dressing
Classification Name:	Dressing, Product Code 79FRO

Substantial Equivalence:

Bilayer Matrix Wound Dressing is substantially equivalent in function and intended use to the following products which have been cleared to market under Premarket Notifications 510(k): Oasis™ SIS Wound Dressing II (K993948), Fortaderm™ Wound Dressing (K014129), VitaChoice™ Wound Dressing (K896455) and Biobrane® II Temporary Wound Dressing (K896110).

Intended Use:

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

Device Description:

Bilayer Matrix Wound Dressing is an advanced woundcare device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. The semi-permeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth.

Tests and Test Results

Biocompatibility studies have demonstrated Bilayer Matrix Wound Dressing to be non-cytotoxic, non-pyrogenic, non-irritating, non-sensitizing, non-hemolytic and non-toxic.

Conclusion

Valid scientific evidence through biocompatibility and physical property testing provide reasonable assurance that Bilayer Matrix Wound Dressing is safe and effective under the proposed conditions of use, and is, with respect to intended use and technological characteristics, substantially equivalent to the predicate devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 1 4 2002

Integra LifeSciences Corporation
Diana M. Bordon
Manager, Regulatory Affairs
311 Enterprise Drive
Plainsboro, New Jersey 08536

Re: K021792
Trade/Device Name: Bilayer Matrix Wound Dressing
Regulation Name: Wound Dressing
Regulatory Class: Unclassified
Product Code: FRO
Dated: May 30, 2002
Received: May 31, 2002

Dear Ms. Bordon:

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 (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. 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.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such 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.

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); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 21 CFR Part 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4659. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html

Sincerely yours,

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number: K021792

Device Name: Bilayer Matrix Wound Dressing

Indications for Use:

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

(PLEASE DO NOT WRITE BELOW THIS LINE–CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of General, Restorative and Neurological Devices

510(k) Number K021792

Prescription Use X
(Per 21 CFR 801.109)

OR

Over-the-Counter Use ____
(Optional Format 1-2-96)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 1 4 2002

Integra LifeSciences Corporation
Diana M. Bordon
Manager, Regulatory Affairs
311 Enterprise Drive
Plainsboro, New Jersey 08536

Re: K021792
Trade/Device Name: Bilayer Matrix Wound Dressing
Regulation Name: Wound Dressing
Regulatory Class: Unclassified
Product Code: FRO
Dated: May 30, 2002
Received: May 31, 2002

Dear Ms. Bordon:

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 (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. 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.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such 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.

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); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 21 CFR Part 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4659. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html

Sincerely yours,

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number: K021792

Device Name: Bilayer Matrix Wound Dressing

Indications for Use:

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

(PLEASE DO NOT WRITE BELOW THIS LINE–CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of General, Restorative and Neurological Devices

Prescription Use X
(Per 21 CFR 801.109)

OR

Over-the-Counter Use ____
(Optional Format 1-2-96)

510(k) Number K021792

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

May 31, 2002

INTEGRA LIFESCIENCES CORP.
311C ENTERPRISE DRIVE
PLAINSBORO, NJ 08536
ATTN: DIANA M. BORDON

510(k) Number: K021792
Received: 31-MAY-2002
Product: BILAYER MATRIX WOUND DRESSING

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

As a reminder, we would like to mention that FDA requires all 510(k) submitters to provide an indications for use statement on a separate page. If you have not included this indications for use statement in addition to your 510(k) summary (807.92), or a 510(k) statement (807.93), and your Truthful and Accurate statement, please do so as soon as possible. If the above mentioned requirements have been submitted, please do not submit them again. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC)(HFZ-401) at the above letterhead address. Correspondence sent to any address other than the DMC will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh.ode/A02-01.html.

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMICA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMICA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Staff
Office of Device Evaluation
Center for Devices and Radiological Health

K021792

INTEGRA

311C Enterprise Drive • Plainsboro, NJ 08536 • (609) 275-0500 • Fax: (609) 275-3684 • http://www.Integra-LS.com

Via Federal Express

May 30, 2002

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

RE: **Premarket Notification 510(k)**
Bilayer Matrix Wound Dressing

This notification is submitted pursuant to Section 510(k) of the Federal Food, Drug and Cosmetic Act and Code of Federal Regulations, Title 21, Part 807. Integra LifeSciences Corporation is submitting this information as a notification of intent to commercially distribute Bilayer Matrix Wound Dressing.

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use. Dressings have been classified as Class I, Product Code 79FRO.

Integra LifeSciences Corporation considers its intent to market this device as confidential commercial information and requests that the Food and Drug Administration hold as confidential all such information in this submission. Integra LifeSciences has taken precautions to protect the confidentiality of the intent to market this device.

(b)(4) [redacted]

If you have further questions or if you need additional information, please do not hesitate to contact me at (609) 936-2240, e-mail at dbordon@integra-ls.com, or by facsimile at (609)-275-3684.

Sincerely,

Diana M. Bordon

Ms. Diana M. Bordon
Manager of Special Projects
Regulatory Affairs

SM
I
SKILL 40

INTEGRA

311C Enterprise Drive • Plainsboro, NJ 08536 • (609) 275-0500 • Fax: (609) 275-3684 • http://www.Integra-LS.com

Via Federal Express

May 30, 2002

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

RE: **Premarket Notification 510(k)**
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(b)(4) [redacted]

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Sincerely,

Diana M. Bordon

Ms. Diana M. Bordon
Manager of Special Projects
Regulatory Affairs

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
Premarket Submission Cover Sheet

Date of Submission:	FDA Document Number:

Section A — Type of Submission

☒510(k)	☐IDE	☐PMA	☐PMA Supplement - Regular
☐510(k) Add'l information	☐IDE Amendment	☐PMA Amendment	☐PMA Supplement - Special
☐Special 510(k)	☐IDE Supplement	☐PMA Report	☐PMA Supplement - 30 day
	☐IDE Report		☐PMA Supplement - Panel Track

Section B1 — Reason for Submission - 510(k)s Only

☒New device ☐Additional or expanded indications ☐Change in technology, design, materials, or manufacturing process

☐Other reason (specify): *Comment section*

Section B2 — Reason for Submission -PMAs Only

☐New device
☐Withdrawal
☐Additional or expanded indications
☐Licensing agreement

☐Change in design, component, or specifications:
- ☐Software
- ☐Color additive
- ☐Other (specify below)

☐Location change:
- ☐Manufacturer
- ☐Sterilizer
- ☐Packager
- ☐Distributor

☐Labeling change:
- ☐Indications
- ☐Instructions
- ☐Performance Characteristics
- ☐Shelf life
- ☐Trade name
- ☐Other (specify below)

☐Process change:
- ☐Manufacturer
- ☐Sterilizer
- ☐Packager

☐Report submission:
- ☐Annual or periodic
- ☐Post-approval study
- ☐Adverse reaction
- ☐Device defect
- ☐Amendment

☐Response to FDA correspondence (specify below)
- ☐Request for applicant hold
- ☐Request for removal of applicant hold
- ☐Request for extension
- ☐Request to remove or add manufacturing site

☐Change in ownership
☐Change in correspondent

☐Other reason (specify):

Section B3 — Reason for Submission -IDEs Only

☐New device
☐Addition of institution
☐Expansion/extension of study
☐IRB certification
☐Request hearing
☐Request waiver
☐Termination of study
☐Unanticipated adverse effect

☐Change in:
- ☐Correspondent
- ☐Design
- ☐Informed consent
- ☐Manufacturer
- ☐Manufacturing
- ☐Protocol - feasibility
- ☐Sponsor

☐Response to FDA letter concerning:
- ☐Conditional approval
- ☐Deemed approved
- ☐Deficient final report
- ☐Deficient progress report
- ☐Deficient investigator report
- ☐Request of extension of time to respond to FDA
- ☐Request meeting

☐Emergency use:
- ☐Notification of emergency use
- ☐Additional information

☐Report submission:
- ☐Current investigator
- ☐Annual progress
- ☐Site waiver limit reached
- ☐Final

☐IOL submissions only:
- ☐Change in IOL style
- ☐Request for protocol waiver

☐Other reason (specify):

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	FDA Document Number:

Section C **Product Classification**

Product code: 79FRO	C.F.R. Section: 878.4060	Device class: ☒Class I ☐Class II
Classification Panel: General and Plastic Surgery		☐Class III ☐Unclassified

Section D **Information on 510(k) Submissions**

Product codes of devices to which equivalence is claimed:				Summary of, or statement concerning, safety and effectiveness data:
1 79KMF	2 79KMF	3 79KGX	4 79FRO	☒510(k) summary attached
5	6	7	8	☐510(k) statement

Information on devices to which substantial equivalence is claimed:

510(k) Number	Trade or proprietary or model name	Manufacturer
1 K993948	1 OASIS™ SIS Wound Dressing II	1 Cook Biotech, Inc.
2 K011026	2 FortaDerm™ Wound Dressing	2 Organogenesis, Inc.
3 K896455	3 VitaChoice™ Wound Dressing	3 Integra LifeSciences Corp.
4 K896110	4 Biobrane® II Temporary Wound Dressing	4 Bertek Pharmaceuticals, Inc.
5	5	5
6	6	6

Section E **Product Information - Applicable to All Applications**

Common or usual name or classification name: Wound Dressing

Common: Wound Dressing Classification Name: Dressing

Trade or proprietary or model name	Model number
1 Bilayer Matrix Wound Dressing	1
2	2
3	3
4	4
5	5
6	6

FDA document numbers of all prior related submissions (regardless of outcome):

1	2	3	4	5	6
7	8	9	10	11	12

Data included in submission: ☒Laboratory testing ☐Animal trials ☐Human trials

Indications (from labeling):

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

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		FDA Document Number:	
Section F	**Manufacturing/Packaging/Sterilization Sites**		
☒Original ☐Add ☐Delete	FDA establishment registration number: 1121308	☒Manufacturer ☐Contract manufacturer	☐Contract sterilizer ☐Repackager / relabeler
Company / Institution name: Integra LifeSciences Corporation			
Division name (if applicable):		Phone number (include area code): 609-275-0500	
Street address: 311 Enterprise Drive		Fax number (include area code): 609-275-3684	
City: Plainsboro	State / Province: NJ	Country: USA	ZIP / Postal Code: 08536
Contact name: Diana M. Bordon			
Contact title: Manager, Regulatory Affairs			
☒Original ☐Add ☐Delete	FDA establishment registration number: (b)(4)	☐Manufacturer ☐Contract manufacturer	☒Contract sterilizer ☐Repackager / relabeler
Company / Institution name: (b)(4)			
Division name (if applicable):		Phone number (include area code): (b)(4)	
Street address: (b)(4)		Fax number (include area code): (b)(4)	
City: (b)(4)	State / Province: (b)	Country: (b)	ZIP / Postal Code: (b)
Contact name: (b)(4)			
Contact title: (b)(4)			
☐Original ☐Add ☐Delete	FDA establishment registration number:	☐Manufacturer ☐Contract manufacturer	☐Contract sterilizer ☐Repackager / relabeler
Company / Institution name:			
Division name (if applicable):		Phone number (include area code):	
Street address:		Fax number (include area code):	
City:	State / Province:	Country:	ZIP / Postal Code:
Contact name:			
Contact title:			

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		FDA Document Number:	
Section G		**Applicant or sponsor**	
Company / Institution name: Integra LifeSciences Corporation		FDA establishment registration number: 1121308	
Division name (if applicable):		Phone number (include area code): 609-275-0500	
Street address: 311 Enterprise Drive		Fax number (include area code): 609-275-3684	
City: Plainsboro	State / Province: NJ	Country: USA	ZIP / Postal Code: 08536
Signature: Diana M Bordon			
Name: Diana M. Bordon			
Title Manager, Regulatory Affairs			
Section H		**Submission correspondent (if different from above)**	
Company / Institution name:		FDA establishment registration number:	
Division name (if applicable):		Phone number (include area code):	
Street address:		Fax number (include area code):	
City:	State / Province:	Country:	ZIP / Postal Code:
Signature:			
Name:			
Title			

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APPENDICES

510(k) PREMARKET NOTIFICATION

for

BILAYER

Matrix Wound Dressing

May 30, 2002

I. INTRODUCTORY INFORMATION

A. Device Name

Proprietary Name: Bilayer Matrix Wound Dressing (a definitive tradename has not been identified)
Common Name: Wound Dressing

B. Establishment Registration Number, Company Name, Address, and Manufacturing Facility

1. Firm Headquarters and Manufacturing Site

Integra LifeSciences Corporation
311 Enterprise Drive
Plainsboro, New Jersey 08536 USA
Telephone: 609-275-0500
Facsimile: 609-275-3684
Establishment Registration Number: 1121308

(b)(4) [redacted]

C. Classification of Device

The United States Food and Drug Administration has classified dressings as Class I.

Classification Name: Dressing, Product Code 79FRO, Class I
Classification panel: General and Plastic Surgery

D. Contact person and telephone number:

Diana M. Bordon
Manager of Special Projects, Regulatory Affairs
Telephone: 609-936-2240
Fax: 609-275-3684
e-mail: dbordon@integra-ls.com

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(b)(4)


F. FD&C ACT, Section 514 Compliance

No performance standards for wound dressings are in effect under Section 514 of the Act. Integra LifeSciences Corporation intends to be fully compliant with performance standards when they are issued.

II. 510(K) SUMMARY

As required by the Safe Medical Device Act of 1990, Section 513(i)(3)(A), a Premarket Notification 510(k) Summary for Bilayer Matrix Wound Dressing is included in **Appendix A**.

III. INTENDED USE

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

The "Indications for Use" of Bilayer Matrix Wound Dressing is provided on a separate page, in CDRH format, in **Appendix B.**

IV. TRUTHFUL AND ACCURATE STATEMENT

A Truthful and Accurate Statement is provided in **Appendix C.**

V. DESCRIPTION OF DEVICE

Bilayer Matrix Wound Dressing is an advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. The device serves as a wound dressing providing coverage of the wound with the collagen matrix contacting the wound. The semipermeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth follows. The scaffold is eventually remodeled as the patient's cells rebuild the damaged site. The silicone covering of the Bilayer

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Matrix Wound Dressing can be removed when the tissue underneath has healed, typically in 14 to 28 days.

After rinsing in sodium phosphate buffer, Bilayer Matrix Wound Dressing is placed between two polyethylene (PE) sheets with a die-cut insert between the silicone layer and the PE sheet for easy removal of the device from the PE sheet. The assembly is packaged flat in a Chevron sealable foil pouch (moisture and sterility barrier) and heat sealed. The Chevron peel foil pouch is placed into a Tyvek®/Mylar Chevron peel pouch, which provides the second sterile barrier. The pouch assemblies are packaged four high in boxes for e-beam irradiation prior to packaging in individual boxes or in a box holding five (5) pouches.

Introductory product sizes will be available as follows:

10.0 cm x 12.5 cm (4 in x 5 in)

10.0 cm x 25.0 cm (4 in x 10 in)

20.0 cm x 25.0 cm (8 in x 10 in)

Additional sizes will be offered as determined by physician requirements.

A. Photographs

Photographs of Bilayer Matrix Wound Dressing are provided in **Appendix D**.

VI. SUBSTANTIAL EQUIVALENCE

A. Predicate Devices

Bilayer Matrix Wound Dressing is substantially equivalent in function and intended use to the following products which have been cleared to market under Premarket Notifications 510(k): Oasis™ SIS Wound Dressing II, FortaDerm™ Wound Dressing, VitaChoice™ Wound Dressing and Biobrane® II Temporary Wound Dressing.

1. Oasis™ SIS Wound Dressing II
Cook Biotech, Incorporated; 510(k) K993948

SIS Wound Dressing II (tradename Oasis™) is composed of Porcine Small Intestinal Submucosa (SIS), an extracellular matrix comprised of natural growth factors and collagen[1]. It has the same mode of action and indication for use as Bilayer Matrix Wound Dressing. The indication for use is for the management of wounds and is intended for one-time use. Once placed on the wound bed, cells rapidly invade the SIS scaffold and capillary growth follows. The scaffold is eventually remodeled as the patient's cells rebuild the damaged site. The new tissue becomes completely "self."[2] Information on Oasis™ SIS Wound Dressing II, including the Package Insert and marketing brochure, is presented in **Appendix E-1.**

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[1] Oasis Brochure, Cook Biotech, Inc.; 2000.

[2] Oasis Brochure, Cook Biotech, Inc., 2000.

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2. **FortaDerm™ Wound Dressing**
   Organogenesis, Inc.; 510(k) K011026

FortaDerm™ Wound Dressing is a single layer fenestrated sheet composed of Porcine Small Intestinal Submucosa (SIS). It is indicated for the management of wounds and is intended for one-time use. Information on FortaDerm™ Wound Dressing is presented in **Appendix E-2.**

3. **VitaChoice™ Wound Dressing**
   Integra LifeSciences Corporation (Formerly Vitaphore Corp.); 510(k) K896455

VitaChoice™ Wound Dressing is comprised of two layers of different materials. The outer layer is made from a polyurethane-based wound dressing that is impermeable to water and bacteria, but permeable to moisture vapor and oxygen. The inner layer, contacting the skin, consists of a soft, white, pliable absorptive collagen sponge. VitaChoice™ Wound Dressing is indicated in the management of dermal ulcers and chronic wounds. Information on VitaChoice™ Wound Dressing is presented in **Appendix E-3.**

4. **Biobrane® II Temporary Wound Dressing**
   Bertek Pharmaceuticals, Inc. (Formerly Sterling Drug, Inc.); 510(k) K896110

Biobrane is a biocomposite dressing made from an ultra-thin, semipermeable silicone membrane mechanically bonded to a flexible knitted trifilament nylon fabric. A mixture of peptides derived from porcine dermal collagen is bonded to the nylon/silicone membrane. Biobrane is intended for the management of donor sites, clean debrided or excised superficial and partial thickness wounds, and as a protective covering over autografts. Information on Biobrane® II Temporary Wound Dressing, including the Package Insert, is presented in **Appendix E-4**.

B. Comparison Table

Table 1 is a feature comparison chart between the subject of this Premarket Notification, Bilayer Matrix Wound Dressing, and the currently marketed products:

Table 1: Substantial Equivalence Comparison Chart

Feature	Bilayer Matrix Wound Dressing	Oasis™ SIS Wound Dressing II	FortaDerm™ Wound Dressing	VitaChoice™ Wound Dressing	Biobrane® II Temporary Wound Dressing
Manufacturer	Integra LifeSciences Corporation	Cook Biotech, Incorporated	Organogenesis, Inc.	Integra LifeSciences Corporation (Formerly Vitaphore Corp.)	Bertek Pharmaceuticals, Inc. (Formerly Sterling Drug, Inc.)
510(k) No.	New Device. Not assigned	K993948	K011026	K896455	K896110
Classification	Dressing	Liquid Bandage	Liquid Bandage	Adhesive Tape and Bandage	Dressing
Product Code	79FRO	79KMF	79KMF	79KGX	79FRO
Indications for Use	Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds. The device is intended for one-time use.	Oasis™ Wound Dressing is intended for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns and skin tears) and draining wounds. The device is intended for one-time use.	Fortaderm™ Wound Dressing is intended for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns and skin tears) and draining wounds. The device is intended for one-time use.	VitaChoice™ Wound Dressing is indicated in the management of dermal ulcers and chronic wounds.	Biobrane is intended for the management of donor sites, clean debrided or excised superficial and partial thickness wounds, and as a protective covering over autografts.
Device Description	Bilayer Matrix Wound Dressing is an advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer.	Oasis Wound Dressing is primarily composed of porcine collagen that is supplied in sheet form in a variety of sizes.	FortaDerm Wound Dressing consists of a single-layer fenestrated sheet of porcine intestinal collagen. FortaDerm Wound Dressing is supplied dry in sheet form in a variety of sizes.	VitaChoice Wound Dressing is comprised of two layers of different materials. The outer layer is made from a polyurethane-based wound dressing that is impermeable to water and bacteria, but permeable to moisture vapor and oxygen. The inner layer, contacting the skin, consists of a soft, white, pliable absorptive collagen sponge.	Biobrane is a biocomposite dressing made from an unltra-thin, semipermeable silicone membrane mechanically bonded to a flexible knitted trifilament nylon fabric. A mixture of peptides derived from porcine dermal collagen is bonded to the nylon/silicone membrane.
Materials	Type I Collagen from bovine tendon and glycosaminoglycan; Medical-grade silicone membrane	Porcine Small Intestinal Submucosa (SIS), an extracellular matrix comprised of natural growth factors and collagen[3].	Porcine intestinal collagen.	Polyurethane-based wound dressing and Type I collagen sponge derived from bovine tendon.	Porcine dermal collagen peptides Silicone/nylon membrane

[3] Oasis Brochure, Cook Biotech, Inc.; 2000.

Feature	Bilayer Matrix Wound Dressing	Oasis™ SIS Wound Dressing II	FortaDerm™ Wound Dressing	VitaChoice™ Wound Dressing	Biobrane® II Temporary Wound Dressing
Mode of Operation	The semipermeable silicone membrane controls water vapor loss and provides a flexible adherent covering for the wound surface. The collagen–glycosaminoglycan matrix provides a scaffold for cellular invasion and capillary growth follows. The scaffold is eventually remodeled as the patient's cells rebuild the damaged site. The new tissue becomes completely "self."	SIS has a chemical composition comprised of natural growth factors that attract the patient's cells. The adjacent tissues begin delivering nutrients to the injured site. The cells rapidly invade the material and capillary growth follows. The SIS scaffold is eventually remodeled as the patient's cells rebuild the damaged site. The new tissue becomes completely "self."[4]	Information not available – equivalent to Oasis SIS Wound Dressing II (K993948).	Polyurethane-based film that is impermeable to water and bacteria, but permeable to moisture vapor and oxygen. The user has the additional choice of polyurethane foam to absorb excess exudate. The inner layer, contacting the skin, consists of a soft, pliable, absorptive collagen sponge.	Semipermeable membrane controls water vapor loss and provides a flexible adherent covering for the wound surface. It conforms to surface irregularities allowing joint movement and early ambulation and minimizes the proliferation of bacterial on the wound surface by minimizing dead space.
Contraindications	This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials. The device is not indicated for use in third degree burns.	This device is derived form a porcine source and should not be used in patients with known sensitivity to porcine material. The device is not indicated for use in third degree burns.	Information Not Available	VitaChoice Wound Dressing is not indicated for use on: Third-Degree Burns; Full Thickness Skin Wounds; Venous Stasis Ulcers; Patients with known sensitivities to collagen.	No contraindications provided in Package Insert.
Form	Sheet	Sheet	Sheet	Sheet	Sheet
Sizes	4 inch x 5 inch 4 inch x 10 inch 8 inch x 10 inch	Range from: 2cm x 4cm to 20cm x 40cm	Range from: 5cm x 5cm to 12cm x 36cm	5cm x 5cm to 12 x 36 cm	5 inches x 5 inches 5 inches x 15 inches 10 inches x 15 inches 15 inches x 20 inches
Biocompatibility	Passes panel of ISO 10993 tests: Dermal Irritation Dermal Sensitization Cytotoxicity Acute Systemic Toxicity Hemolysis Pyrogenicity	Passes biocompatibility panel of tests.	Passes biocompatibility panel of tests.	Passes panel of tests: Primary Skin Irritation Intracutaneous Toxicity Sensitization/Maximization Cytotoxicity Acute Systemic Toxicity Subcutaneous Implantation	Passes panel of tests: Skin Irritation Intracutaneous Irritation Sensitization Cytotoxicity Acute Systemic Toxicity Hemolysis Pyrogenicity
Sterile	Yes – [redacted] (b)(4)	Yes – Ethylene oxide gas	Yes – Gamma radiation 10^{-6} SAL	Yes – Ethylene oxide gas	Yes – Steam

[4] Oasis Brochure, Cook Biotech, Inc.; 2000.

VII. MATERIAL COMPOSITION

Bilayer Matrix Wound Dressing is manufactured by Integra LifeSciences Corporation and is composed of a semi-permeable polysiloxane (silicone) layer and a porous matrix of Type I collagen (ILS Collagen) and a glycosaminoglycan, (b)(4) ILS Collagen is highly purified, alkali treated Type I Collagen derived from bovine deep flexor tendon. All bovine tendon is obtained from United States Department of Agriculture (USDA) inspected facilities in the United States of America (USA). (b)(4)
(b)(4)

Bilayer Matrix Wound Dressing is manufactured from the same ILS Collagen as other collagen products manufactured by Integra LifeSciences Corporation. Bilayer Matrix Wound Dressing will be subjected to manufacturing processes, testing, inspection, and finished goods release specifications similar to the other collagen products manufactured by Integra LifeSciences Corporation.

The implantable, absorbable collagen medical devices manufactured by Integra LifeSciences Corporation have an extensive 20-year history of safety and effectiveness. Bilayer Matrix Wound Dressing is composed of the same ILS Collagen as the following products:

- BioMend Extend Absorbable Collagen Membrane 510(k) K992216
- Helideerm Collagen Wound Dressing 510(k) K990086
- DuraGen™ Dural Graft Matrix 510(k) K982180
- BioMend® Absorbable Collagen Membrane 510(k) K924408
- INTEGRA® Dermal Regeneration Template PMA 900033
- Neurocol™: Collagen Neurosponge 510(k) K891993
- VitaChoice® Collagen Wound Dressing 510(k) K896455
- VitaCuff® Percutaneous Infection Control Device 510(k) K861563
- HELISTAT® Absorbable Collagen Hemostatic Sponge PMA P850010
- CollaCote®, CollaPlug®, CollaTape® Absorbable Collagen Wound Dressings for Dental Surgery PMA P840062
- Collastat® Absorbable Collagen Hemostatic Sponge PMA P810006

A. COLLAGEN SAFETY

1. TSE Safety

The United States of America has one of the most stringent Bovine Spongiform Encephalopathy (BSE) Programs in the world. In response to the BSE problem, the Animal and Plant Health Inspection Service (APHIS) has prohibited the importation of live ruminants from countries where BSE is known to exist since 1989. This includes products derived from ruminants such as: bone meal, blood meal, offal, fat, meat meal, or glands. These ruminants may only be imported under special conditions for scientific or research purposes (United States Code of Federal Regulations 9 CFR Section 95). In April of 1998, the United States Food and Drug

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Administration (FDA) banned the use of materials containing protein derived from mammalian tissues in ruminant feed (21 CFR 589.2000). As of December 7, 2000, USDA prohibited all imports of rendered animal protein products, regardless of species, from the United Kingdom, other countries that have reported BSE and the remaining countries of Europe. The United States satisfies the criteria set by the Office of International Epizooties to be recognized as a BSE free country.

In accordance with European Standard EN 12442-2:2000, *Animal tissues and their Derivatives Utilized in the Manufacture of Medical Devices*, approved and controlled standard operating procedures for sourcing, collecting, handling, storage, and transport of materials of animal origin are used in the manufacture of Integra LifeSciences collagen products. These procedures are established, documented, implemented, and maintained by Integra LifeSciences Corporation as part of the Quality System. Integra LifeSciences Corporation has instituted a Standard Operating Procedure whereby every lot of tendon received is required to have certification to be of a bovine source of United States origin in order to be accepted for use in the manufacture of Integra LifeSciences collagen products. A system proposed by European Health Authorities and the World Health Organization (WHO) to classify risks of certain tissues, classifies the bovine tendon as Category IV, no risk factors for infectivity for BSE and scrapie.

Per German Federal Institute for Drugs and Medical Products (BfArM) guidelines entitled: *Notification on the marketing Authorisation and registration of drugs; Measures to avert risks associated with drugs, stage II*, 2000, Section A2.3, an inactivation capacity of 10^6 can be assumed using a one hour treatment of 1N sodium hydroxide at 20°C without any validation based on animal experiments. (b)(4) (b)(4) [redacted]

Integra LifeSciences Collagen products meet or exceed all US-FDA, European and Canadian guidelines for safety regarding TSE/BSE risks for human medical device products.

Information and Risk Analysis on the safety of Integra LifeSciences collagen products regarding BSE/TSE is in **Appendix F**.

2. Viral Safety

To assure the safety of the collagen used to manufacture Integra LifeSciences collagen products, a viral inactivation study was conducted by an independent certified laboratory. This study provides verification that agents, including viral contaminants, that may be present in the starting material are not present in the final purified product. In this study, the most robust processing step, sodium hydroxide treatment, was evaluated for its ability to inactivate the viral strains shown below. European Standards have recommended treatment with 1 N sodium hydroxide for one hour at 25°C as an effective method of viral inactivation. (b)(4) (b)(4) [redacted]

The sodium hydroxide treatment reduced the viral titer to non-detectable levels (b)(4) [redacted] for the following viruses: Human Immunodeficiency Virus Type I (HIV-1), Bovine Viral Diarrhea (BVDV), Infectious

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Bovine Rhinotracheitis (IBR), Parainfluenza virus Type 3 (P13), and Vesicular Stomatitis (VSV). The process effectively provides a (b)(4) safety margin during the purification of Integra LifeSciences Corporation collagen products.

(b)(4) [redacted]

C. SILICONE

The outer layer of Bilayer Matrix Wound Dressing consists of a silicone elastomer (b)(4) (b)(4) [redacted] The silicone elastomer is imbedded with (b)(4) [redacted] in order to distinguish it from the collagen-glycosaminoglycan layer. Integra LifeSciences receives a certification from the vendor that the Adhesive Silicone, Type A demonstrates a negative cytopathic effect.

(b)(4) [redacted]

VIII. MANUFACTURING PROCESS

A. Manufacturing

Bilayer Matrix Wound Dressing is manufactured by Integra LifeSciences Corporation at its facility in Plainsboro, NJ. The facility is registered as a United States Food and Drug Administration Medical Device manufacturing facility (Establishment Registration Number 1121308). The Integra LifeSciences facility is also ISO 9001/EN 46001/ISO 13485/Medical Device Directive certified. All manufacturing steps are carried out in controlled environment areas.

The Bilayer Matrix Wound Dressing manufacturing process complies with FDA Guidance Document *Medical Devices Containing Materials Derived from Animal Sources (except for in vitro Diagnostic Devices)* issued 11/6/98, and European Standards for animal tissue sourcing and viral inactivation. The manufacturing flow chart is provided in **Appendix H.**

B. Sterilization

Bilayer Matrix Wound Dressing is sterilized using (b)(4) [redacted] radiation. The sterilization process utilizes a dosimetric release program based on sub-lethal

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dose testing procedures that verify the efficacy of treatment at the theoretical Minimum Required Dose as determined by the product's Colony Forming Units per device. The sterilization process will be fully validated to a sterility assurance level of 10^{-6} utilizing AAMI Methods, per ANSI/AAMI/ISO 11137-1995 and EN 552:1994 + A1:1999 concerning sterilization of medical devices by irradiation.

(b)(4)

(b)(4) Biologic testing for sterilization validation and quarterly dose audits will be performed by an approved contract testing laboratory. Sterilization documentation is reviewed by Quality Assurance prior to the release of any product.

IX. PACKAGING

Bilayer Matrix Wound Dressing is rinsed with (b)(4) and then packaged between two sheets of polyethylene (PE) to decrease sticking of the collagen/GAG surface to the inner pouch surface and to increase rigidity. A polyethylene terephthalate glycol (PETG) tab is inserted between the silicone membrane and the polyethylene sheet to allow easy removal of the device. The device is then packaged in a heat-sealed Chevron foil pouch. The Chevron peel foil pouch is placed into a Tyvek®/Mylar Chevron peel pouch, which provides the second sterile barrier. All sealing parameters are validated according to protocol. Packaging is carried out in a controlled environment. The trays will be packaged in dispenser boxes containing a convenient number of individually packaged devices. Photographs of the product and primary package are provided in **Appendix D**.

X. PRODUCT CHARACTERIZATION

A. Biocompatibility

In accordance with the *Draft Guidance for the Preparation of a Premarket Notification for a Non-interactive Wound and Burn Dressing,* March 31, 1995, the following biological tests were conducted on the Collagen Silicone Bilayer Membrane (CSBM) of Bilayer Matrix Wound Dressing:

1. Cytotoxicity
2. Dermal Sensitization
3. Irritation
4. Acute Systemic Toxicity
5. Hemolysis
6. Pyrogenicity

All tests were conducted in accordance with International Standard ISO 10993-1:1992, *Biological evaluation of medical devices - Part 1: Guidance on selection of tests* and Good Laboratory Practices. All test results were acceptable.

These tests, supporting the safe use of Bilayer Matrix Wound Dressing for the management of wounds, are summarized below.

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1. Cytotoxicity

Test: Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract)

Conducted by: (b)(4) [redacted]

An *in vitro* biocompatibility study, based on the International Organization for Standardization 10993: *Biological Evaluation of Medical Devices, Part 5: Tests for Cytotoxicity: in vitro methods*, was conducted on the test article, Collagen-Silicone Bilayer Membrane, (b)(4) [redacted] to determine the potential for cytotoxicity. A single extract of the test article was prepared using single strength Minimum Essential Medium supplemented with 5% serum and 2% antibiotics (1X MEM). This test extract was placed onto three separate confluent monolayers of L-929 mouse fibroblast cells propagated in 5% CO_2. Three separate monolayers were prepared for the reagent control, negative control and for the positive control. All monolayers were incubated at 37°C in the presence of 5% CO_2 for 48 hours. The monolayer in the test, reagent control, negative control and positive control wells was examined microscopically at 48 hours to determine any change in cell morphology.

Under the conditions of this study, the 1X MEM test extract showed no evidence of causing cell lysis or toxicity. The 1X MEM test extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity). The reagent control, negative control and the positive control performed as anticipated.

This study was conducted in accordance with Good Laboratory Practices (GLP). A copy of this study is included in **Appendix I-1**.

2. Dermal Sensitization

Test: ISO Sensitization Study in the Guinea Pig

Conducted by: (b)(4) [redacted]

A guinea pig maximization test of Collagen-Silicone Bilayer Membrane, Identification No. (b)(4) [redacted] was conducted to evaluate the potential for delayed dermal contact sensitization. This study was conducted based on the requirements of the International Organization for Standardization 10993: *Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization.*

The test article was extracted in 0.9% sodium chloride USP (SC) and cottonseed oil, NF (CSO). Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract) in an attempt to induce sensitization. The vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the reagent control. All sites were scored at 24, 48 and 72 hours after patch removal.

Under the conditions of this study, the SC and CSO test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

This study was conducted in accordance with Good Laboratory Practices (GLP). A copy of the study is included in **Appendix I-2.**

3. Irritation

Test: ISO Skin Irritation Study in the Rabbit (Single Exposure)

Conducted by: (b)(4)

The test article, Collagen-Silicone Bilayer Membrane, Identification No. (b)(4) was evaluated for primary skin irritation in accordance with the guidelines of the International Organization for Standardization 10993: *Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization*. Two approximate 25 mm x 25 mm sections of the test article and control article were topically applied to the skin of three rabbits and left in place for 24 hours. The sites were graded for erythema and edema at 1, 24, 48, and 72 hours after removal of the single sample application.

Under the conditions of this study, no irritation was observed on the skin of the rabbits. The Primary Irritation Index for the test article was calculated to be 0.0. The response of the test article was categorized as negligible.

This study was conducted in accordance with Good Laboratory Practices (GLP). A copy of the study is included in **Appendix I-3.**

4. Acute Systemic Toxicity

Test: ISO Acute Systemic Toxicity Study in the Mouse (Extracts)

Conducted by: (b)(4)

The test article, Collagen-Silicone Bilayer Membrane, Identification No. (b)(4) was extracted in 0.9% sodium chloride USP solution and cottonseed oil, NF. These extracts were evaluated for systemic toxicity in accordance with the guidelines of the International Organization for Standardization 10993: *Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity*.

A single dose of the appropriate test article extract was injected into each of five mice per extract by either the intravenous or interpersonal route. Similarly, five mice were dosed with each corresponding reagent control. The animals were observed immediately and at 24, 48, and 72 hours after systemic injection.

Under the conditions of this study, there was no mortality or evidence of systemic toxicity from the extracts. Each test article met the test requirements.

This study was conducted in accordance with Good Laboratory Practices (GLP). A copy of this study is included in **Appendix I-4**.

5. Hemolysis

Test: *In Vitro* Hemolysis Study (Modified ASTM – Extraction Method)

Conducted by: (b)(4)

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The test article, Collagen-Silicone Bilayer Membrane, Identification No. (b)(4) was prepared in duplicate and then extracted in saline. The resulting extracts were evaluated to determine whether the presence of any leachable chemicals from the test article would cause *in vitro* red blood cell hemolysis. This study was based on the requirements of the International Organization for Standardization 10993: *Biological Evaluation of Medical Devices, Part 4: Selection of tests for interactions with blood.*

Blood was obtained from three rabbits, pooled, diluted and added to duplicate tubes of the test article extract. The negative control and positive control were similarly prepared. Each tube was gently inverted to uniformly mix the contents with the blood. The tubes were then maintained in a stationary position for 4 hour at 37°C. The percent transmission of the extract was spectrophotometrically measured at a wavelength of 540 nm.

Under the conditions of this study, the mean hemolytic index for the test article extract was 0%. The test article extract was non-hemolytic. The negative and positive controls performed as anticipated.

This study was conducted in accordance with Good Laboratory Practices (GLP). A copy of the study is included in **Appendix I-5.**

6. Pyrogenicity

Conducted by: Integra LifeSciences Corporation
Plainsboro, NJ

As finished goods release criteria, each lot of Bilayer Matrix Wound Dressing is tested for pyrogenicity using the current USP methods for Bacterial Endotoxins Test, in accordance with ISO 10993-11. This procedure entails direct determination of endotoxin content in the final product using a standardized Limulus Amebocyte Lysate (LAL) assay with a sensitivity of less than 0.03 EU/mL. Material is only released for distribution once it has been certified as being non-pyrogenic with the requirement of less than 0.5 EU/ml.

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B. PHYSICAL CHARACTERIZATION

The performance characteristics of Bilayer Matrix Wound Dressing are determined by the physical and chemical tests used to ensure acceptable performance (in particular, chemical composition, adequate porosity, collagen integrity and control of wound moisture loss). These tests include determination of pore size, extent of collagen denaturation, degree of cross-linking, GAG (b)(4) content and water vapor permeability. Bilayer Matrix Wound Dressing is intended to be used as a wound dressing and must provide immediate wound coverage and physical protection during wound healing. The drapeability of Bilayer Matrix Wound Dressing must be sufficiently pliable to conform to the wound bed.

1. Pore Size

The pore size specification for Bilayer Matrix Wound Dressing is in the range of (b)(4) (b)(4) Integra LifeSciences Corporation has validated an automated method of determining pore size utilizing (b)(4) This validation gives a range of (b)(4) and demonstrates a correspondence to the original functional specification range of (b)(4) Testing to determine pore size is conducted on lyophilized sponge samples of all batches of Bilayer Matrix Wound Dressing manufactured at Integra LifeSciences Corporation and all batches must meet the specification for pore size before release.

2. Collagen Nativity

To ensure that the native helical configuration of collagen is not significantly altered in the manufacturing process, the helical content of Bilayer Matrix Wound Dressing is determined using Fourier Transform Infrared (FTIR) Spectrophotometry. The ratio of the absorbance at (b)(4) (helical marker bands sensitive to gelatin content) to that at (b)(4) (total protein) is calculated for every batch of Bilayer Matrix Wound Dressing manufactured at Integra LifeSciences Corporation. For release of final product, the value of this ratio must be greater than (b)

3. Degree of Cross-linking

The degree of cross-linking of Bilayer Matrix Wound Dressing is a determinant of collagen-GAG membrane integrity. The degree of cross-linking is determined using a colorimetric assay for the amino acids released when samples of the product are subjected to enzymatic hydrolysis. A release specification of (b)(4) units by this assay has been established.

4. Glycosaminoglycan (b)(4) Content

In the assay used to determine GAG content, the collagen-GAG matrix of the Bilayer Matrix Wound Dressing is hydrolyzed with (b)(4) and (b)(4) liberated from the (b)(4) is reacted with (b)(4) and quantified using visible spectroscopy. A release specification of (b)(4) for (b)(4) in the lyophilized sponge of Bilayer Matrix Wound Dressing has been established.

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5. Control of Wound Moisture Loss

Bilayer Matrix Wound Dressing is a bilayer membrane system consisting of a collagen-GAG membrane and a semipermeable polysiloxane (silicone) layer. Bilayer Matrix Wound Dressing is applied such that the collagen-GAG membrane is in contact with the wound bed, and the thin silicone layer is placed out and away from the wound. The silicone layer acts to control moisture loss from the wound as well as providing the product with improved mechanical properties.

6. Drapeability

The Bilayer Matrix Wound Dressing must be sufficiently pliable to conform to the contour of the wound bed. Thus, testing was performed to determine the ability of the Bilayer Matrix Wound Dressing to conform to a curved surface. The product should be able to conform to both concave and convex curved surfaces. Below is a brief summary of the drapeability testing performed on the Bilayer Matrix Wound Dressing. The detailed test report is provided in **Appendix J.**

The results of the testing demonstrate that samples of Bilayer Matrix Wound Dressing were sufficiently pliable to conform to the surface of rods (b)(4) centimeters in diameter, regardless of whether the samples were tested with silicone against or away from the rod. For all samples tested, the width (W) between the free ends was always less than or equal to the diameter of the rod (D), indicating that the sample had conformed to rod contour.

C. Final Product Specifications

Finished Goods Release Testing is performed by Quality Control personnel on each lot of Bilayer Matrix Wound Dressing prior to disposition. The parameters tested have been selected on the basis of design control criteria and are outlined in **Table 2** (In Process testing) and **Table 3** (Final Product testing) below, along with acceptance criteria.

Table 2: BILAYER MATRIX WOUND DRESSING - Lyophilized Sponge

Test Name	Requirements
Pore Area by Scanning Electron Microscopy and Image Analysis	(b)(4) in diameter for surface and cross-section
FTIR Test for Denaturing Collagen	Ratio of absorbance of helical protein (b)(4) to total protein (b)(4) Not Less Than (b)
(b)(4) Assay	(b)(4) by weight

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Table 3: BILAYER MATRIX WOUND DRESSING - Final Product Testing

Test Name	Requirements		
Appearance (color, uniformity, integrity, delamination)	Pass		
Dimensions	4 in x 5 in	4 in x 10 in	8 in x 10 in
Length:	4.8 to 5.2 in	9.8 to 10.2 in	9.8 to 10.2 in
Width:	3.8 to 4.2 in	3.8 to 4.2 in	7.8 to 8.2 in
Pyrogens	Must be <0.50 EU/ml		
Enzyme Degradation (AH-52)	(b)(4)		
Water permeability (AH-53)	(b) mg/hr/cm^2		
Cytotoxicity	Non-cytotoxic		

D. Stability of Product

Stability studies on three lots of Bilayer Matrix Wound Dressing in the final packaging are currently being conducted according to an approved protocol and Integra LifeSciences Standard Operating Procedures. These studies include short-term storage at elevated temperature and long-term, real-time stability studies. The results of these studies determine the shelf-life of the product.

1. Accelerated Stability Study

Three lots of each 4 inch x 5 inch size and 8 inch x 10 inch size Bilayer Matrix Wound Dressing, are subjected to an on-going accelerated temperature stability program. Product is tested after sterilization for all product release tests including functional testing and cytotoxicity to establish baseline results. Sufficient product is stored under controlled conditions at (b) and final product specification testing will be conducted at (b)(4) months from the date of manufacture. Test results are compared to baseline results to establish there is no change in performance of the product to finished goods release specifications, including cytotoxicity. Refer to **Appendix K** for information on the methodology for accelerated aging.

2. Real-Time Stability Study

Bilayer Matrix Wound Dressing is being subjected at two sizes, 4 inch x 5 inch and 8 inch x 10 inch, to a (b)(4) each real-time stability program for product stored at the recommended storage condition of (b)(4) Each lot is tested at (b)(4) (b)(4) months from the date of manufacture.

Test results for each interval are compared to the final product specifications, which include functional testing and cytotoxicity. All test results for all intervals will meet the final product release specifications and will be comparable in performance to the baseline results. These data will verify the performance of the device and package integrity during the intended shelf life of the product.

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XI. PROPOSED LABELING

The draft product labeling is provided in **Appendix L-1** and the draft Information for Use (Package Insert) for Bilayer Matrix Wound Dressing is provided in **Appendix L-2**.

Promotional literature has not been prepared to date.

XII. CONCLUSION

Bilayer Matrix Wound Dressing is indicated for use in the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

Bilayer Matrix Wound Dressing is a member of a family of collagen products manufactured by Integra LifeSciences Corporation with an extensive and established twenty-year history of safety and effectiveness. Biocompatibility studies have demonstrated Bilayer Matrix Wound Dressing to be non-cytotoxic, non-sensitizing, non-irritating, non-toxic and non-hemolytic.

Valid scientific evidence through biocompatibility and physical property testing provide reasonable assurance that Bilayer Matrix Wound Dressing is safe and effective under the proposed conditions of use, and substantially equivalent to its predicate devices Oasis™ SIS Wound Dressing II, FortaDerm™ Wound Dressing, VitaChoice™ Wound Dressing and Biobrane® II Temporary Wound Dressing, delineated in this submission and meets the requirements for a Premarket Notification 510(k) as defined in CFR 21, Part 807.

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K0217

Bilayer Matrix Wound Dressing
510(K) SUMMARY

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Date: May 23, 2002

Name of the device:

Proprietary Name:	Bilayer Matrix Wound Dressing
Common Name:	Wound Dressing
Classification Name:	Dressing, Product Code 79FRO

Substantial Equivalence:

Bilayer Matrix Wound Dressing is substantially equivalent in function and intended use to the following products which have been cleared to market under Premarket Notifications 510(k): Oasis™ SIS Wound Dressing II (K993948), Fortaderm™ Wound Dressing (K014129), VitaChoice™ Wound Dressing (K896455) and Biobrane® II Temporary Wound Dressing (K896110).

Intended Use:

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

Device Description:

Bilayer Matrix Wound Dressing is an advanced woundcare device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. The semi-permeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth.

Tests and Test Results

Biocompatibility studies have demonstrated Bilayer Matrix Wound Dressing to be non-cytotoxic, non-pyrogenic, non-irritating, non-sensitizing, non-hemolytic and non-toxic.

Conclusion

Valid scientific evidence through biocompatibility and physical property testing provide reasonable assurance that Bilayer Matrix Wound Dressing is safe and effective under the proposed conditions of use, and is, with respect to intended use and technological characteristics, substantially equivalent to the predicate devices.

INDICATIONS FOR USE

510(k) Number: K021792

Device Name: Bilayer Matrix Wound Dressing

Indications for Use:

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

(PLEASE DO NOT WRITE BELOW THIS LINE–CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use X
(Per 21 CFR 801.109)

Or

Over-the-Counter Use ____
(Optional Format 1-2-96)

PREMARKET NOTIFICATION

TRUTHFUL AND ACCURATE STATEMENT

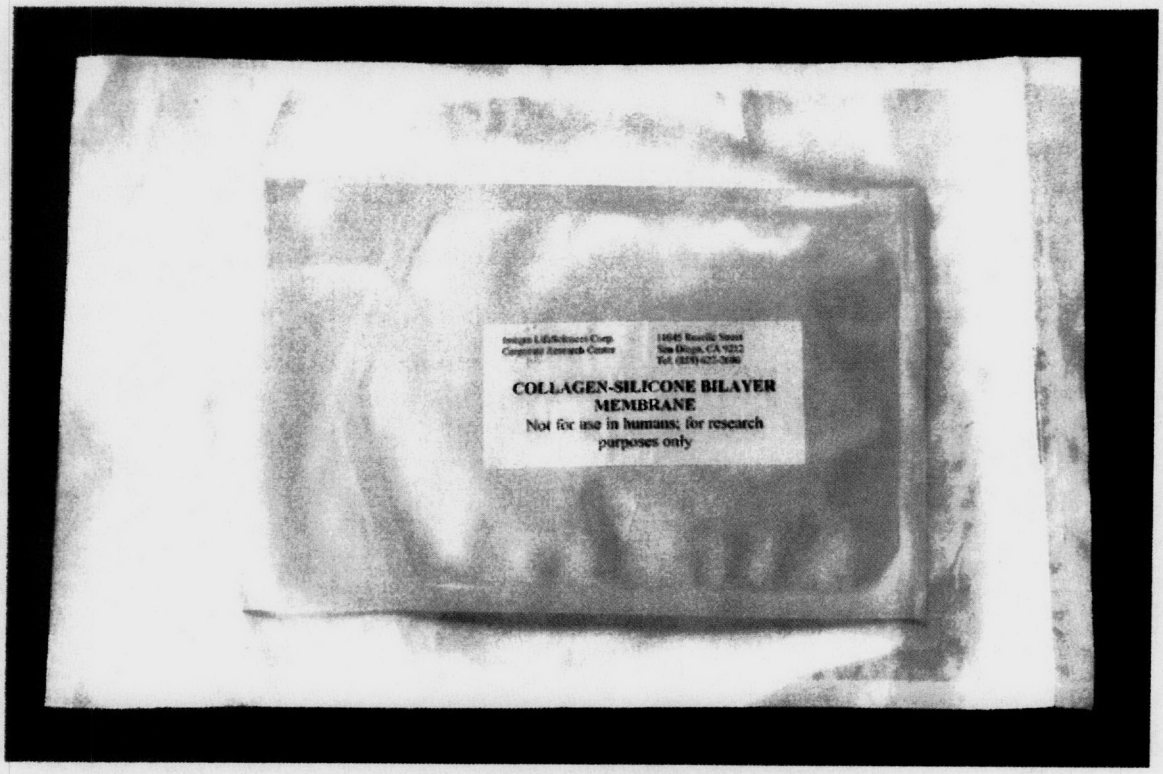
I, Diana M. Bordon, certify that, in my capacity as Regulatory Affairs Manager of Special Projects, I believe to the best of my knowledge, that all data and information submitted in the premarket notification for Bilayer Matrix Wound Dressing are truthful and accurate and that no material fact has been omitted.

Signature Diana M Bordon Date 30 May 2002

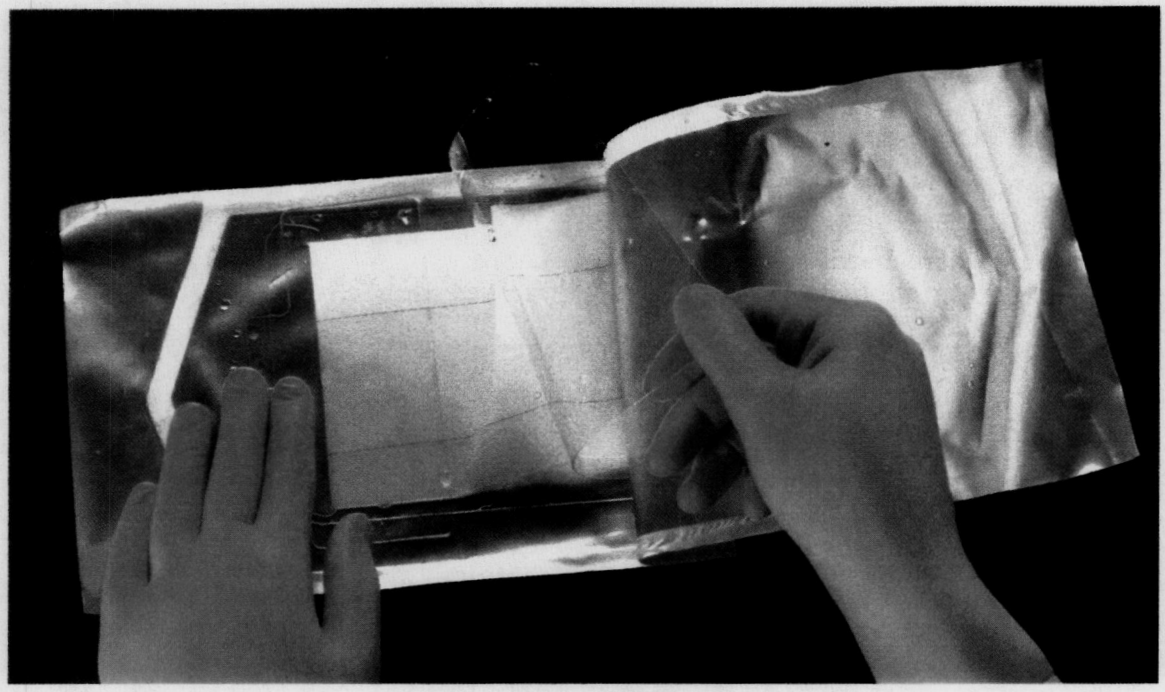
Diana M. Bordon
Manager of Special Projects
Regulatory Affairs
Integra LifeSciences Corporation

_____
Premarket Notification 510(k) Number

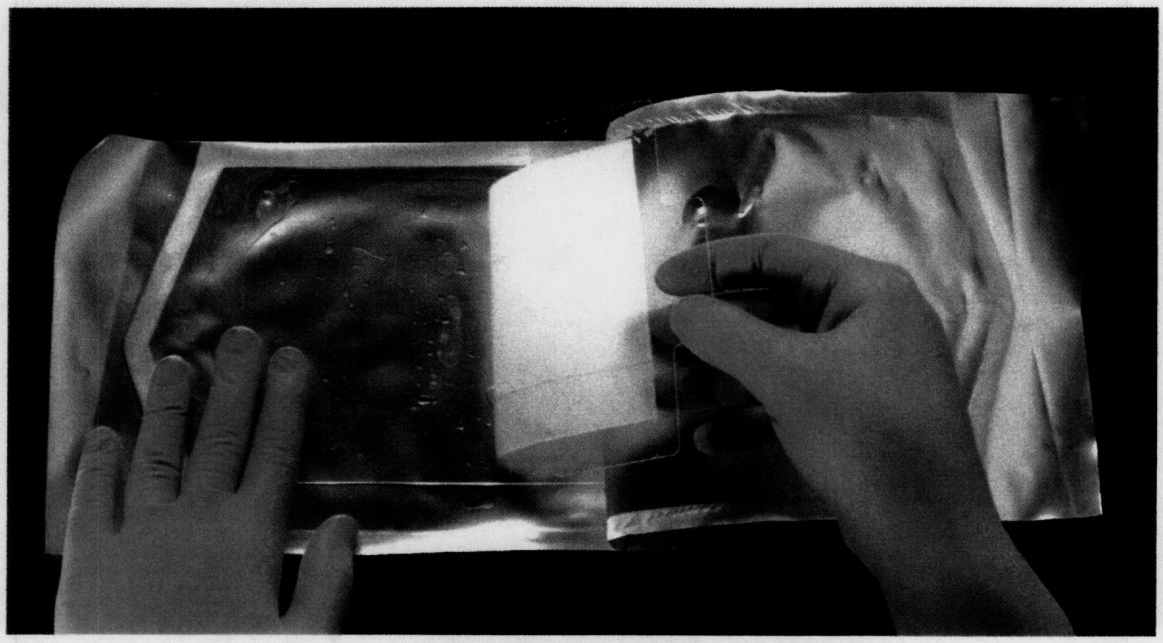
6C



Bilayer Wound Dressing
4 inch x 5 inch in peeled foil pouch
Outer Tyvek®/Mylar pouch and inner foil pouch



Bilayer Wound Dressing
4 inch x 5 inch in peeled foil pouch
The top sheet of polyethylene is being removed



Bilayer Wound Dressing
4 inch x 5 inch in peeled foil pouch
Lifted out by polyethylene terephthalate glycol (PETG) tab
Bottom polyethylene sheet remains in the package

Bilayer Wound Dressing
4 inch x 5 inch
Silicone side up

Bilayer Wound Dressing
4 inch x 5 inch
Collagen-Glycosaminoglycan side up

Device Classification Name	BANDAGE, LIQUID
Regulation Number	880.5090
510(k) Number	K993948
Device Name	SIS WOUND DRESSING II
Applicant	COOK BIOTECH, INC. 3055 KENT AVE. WEST LAFAYETTE, IN 47906 1076
Contact	NEAL E FEARNOT
Product Code	KMF
Date Received	11/22/1999
Decision Date	01/06/2000
Decision	SUBSTANTIALLY EQUIVALENT (SE)
Classification Advisory Committee	General & Plastic Surgery
Review Advisory Committee	General & Plastic Surgery
Statement/Summary/Purged Status	Summary only
SUMMARY/Approval Letter	SUMMARY
Type	Traditional
Reviewed by Third Party	No

K993948
JAN - 6 2000

9. 510(K) SUMMARY

Submitted By:

Neal E. Fearnot, Ph.D.
President
Cook Biotech, Incorporated
3055 Kent Avenue
West Lafayette, IN 47906
(765) 497-3355

November 18, 1999

Device:

Trade Name:	SIS Wound Dressing II
Common/Usual Name:	Topical Wound Dressing
Proposed Classification Name:	Unclassified (79KMF)

Intended Use:

The SIS Wound Dressing II is intended for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. The device is intended for one-time use.

Predicate Devices:

The SIS Wound Dressing II is similar to predicate collagen-based wound dressings that are currently marketed for the management of wounds including the SIS Wound Dressing (D.C. #K973170) manufactured by Cook Biotech, Incorporated, the FIBRACOL * Plus Collagen Wound Dressing with Alginate (D.C. #K982597) manufactured by Johnson and Johnson Medical, and the SkinTemp® Kollagen Wound Management Material (D.C. #K913023) and Medifil® Kollagen Particles (D.C. #K910944) manufactured by Biocore Medical Technologies.

Device Description:

The SIS Wound Dressing II is primarily composed of porcine collagen that is supplied in sheet form in sizes ranging from 2 x 4 cm to 20 x 40 cm.

Substantial Equivalence:

The SIS Wound Dressing II is similar with respect to indications for use, materials and physical construction to predicate devices in terms of section 510(k) substantial equivalency.

Discussion of Tests and Test Results:

The SIS Wound Dressing II was subjected to a panel of tests to assess biocompatibility. The SIS Wound Dressing II passed the requirements of all tests.

Conclusions Drawn from Tests:

This device is, with respect to intended use and technological characteristics, substantially equivalent to the predicate devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JAN - 6 2000

Neal E. Fearnot, Ph.D.
President
Cook Biotech Inc.
3055 Kent Avenue
West Lafayette, Indiana 47906

Re: K993948
Trade Name: SIS Wound Dressing II
Regulatory Class: II
Product Code: KMF
Dated: November 18, 1999
Received: November 22, 1999

Dear Dr. Fearnot:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to 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 (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. 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.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the current Good Manufacturing Practice requirement, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic (QS) inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

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This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4595. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html".

Sincerely yours,

James E. Dillard III
Acting Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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510(k) Number (if known): K993948

Device Name: **SIS Wound Dressing II**

Indications For Use:

The SIS Wound Dressing II is intended for the management of wounds including:

- **Partial and full-thickness wounds**
- **Pressure ulcers**
- **Venous ulcers**
- **Diabetic ulcers**
- **Chronic vascular ulcers**
- **Tunneled/undermined wounds**
- **Surgical wounds (donor sites/grafts, post-moh's surgery, post-laser surgery, podiatric, wound dehiscence)**
- **Trauma wounds (abrasions, lacerations, second-degree burns, and skin tears)**
- **Draining wounds.**

The device is intended for one-time use.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of General Restorative Devices
510(k) Number K993948

Prescription Use X OR Over-The-Counter Use ____
(Per 21 CFR 801.109)

SIS™ Technology

Welcome to SIS Technology

technology products & applications contact us

OASIS™
OASIS™ WOUND DRESSING

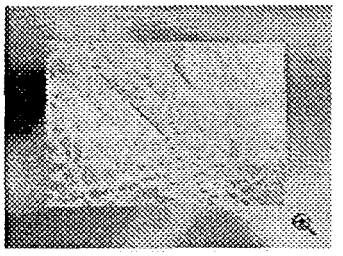
Applications

Oasis™ Wound Dressing is indicated for the management of wounds including:

- Partial and full-thickness wounds
- Venous ulcers
- Diabetic ulcers
- Drainage wounds
- Pressure ulcers
- Chronic vascular ulcers
- Trauma wounds (abrasions, lacerations, second-degree burns, skin tears)
- Surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence)

Product Information

OASIS™ WOUND DRESSING
DRY SHEET



Used for management of partial and full-thickness skin loss injury such as pressure and chronic vascular ulcers, diabetic ulcers, second degree burns, abrasions and autograft donor sites. Supplied sterile in peel-open packages. Intended for one-time use.

Go Directly to Oasis™ Ordering Information

Instructions for Use

These recommendations are designed to serve only as a general guideline. They are not intended to supersede institutional protocols or professional clinical judgement concerning patient care.

OASIS™ WOUND DRESSING
DRY SHEET
Oasis™ is supplied sterile in peel-open packages. Intended for one-time use. Oasis™ is indicated for the management of wounds including:

- Partial and full-thickness wounds
- Venous ulcers
- Diabetic ulcers
- Drainage wounds
- Pressure ulcers
- Chronic vascular ulcers
- Trauma wounds (abrasions, lacerations, second-degree burns, skin tears)
- Surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence)

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

CONTRAINDICATIONS

- This device is derived from a porcine source and should not be used in patients with known sensitivity to porcine material.

- The device is not indicated for use in third degree burns.

PRECAUTIONS

- **Do not resterilize.** Discard all open and unused portions of Oasis™.
- Device is sterile if the package is dry, unopened and undamaged. Do not use if the package seal is broken.
- The device must be used prior to the expiration date.
- Discard device if mishandling has caused possible damage or contamination.
- Oasis™ should not be applied until excessive exudate, bleeding, acute swelling and infection are controlled.

POTENTIAL COMPLICATIONS

The following complications are possible with the use of wound dressings. If any of these conditions occur, the device should be removed.

- Infection
- Chronic inflammation (Initial application of wound dressings may be associated with transient, mild, localized inflammation.)
- Allergic reaction
- Excessive redness, pain, swelling or blistering

SUGGESTED INSTRUCTIONS FOR USING OASIS™ WOUND DRESSING

NOTE: Always handle Oasis™ using aseptic technique.

1. Prepare wound area using standard methods to ensure wound is free of debris and necrotic tissue. If necessary, surgically debride the wound to ensure the wound edges contain viable tissue.

2. To apply, cut the dry sheet into a piece slightly larger than the outline of the wound area. If the wound is larger than a single sheet, then multiple sheets may be used. Overlap adjoining sheets to provide coverage of the entire wound. For ease of handling, apply Oasis™ by placing in a dry state over the wound and rehydrating the sheet using sterile saline or other isotonic solution. Alternatively, rehydrate the sheet by placing it in a bowl of sterile saline or other isotonic solution for at least one minute prior to use. Place the edge of the sheet in contact with the intact tissue. Smooth Oasis™ into place to ensure the sheet is in contact with the underlying wound bed.

NOTE: If excess exudate collects under the sheet, small

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openings can be cut in the sheet to allow the exudate to drain.

IMPORTANT: After application, use an appropriate, non-adherent, secondary dressing to maintain a moist wound environment. The optimum secondary dressing is determined by wound location, size, depth and user preference. Change the secondary dressing as needed to maintain a moist, clean wound area. Frequency of secondary dressing change will be dependent upon volume of exudate produced and type of dressing used. As healing occurs, sections of Oasis™ may gradually peel and may be removed during dressing changes. Do not forcibly remove sections of Oasis™ that may adhere to the wound. Alternatively, the Oasis™ may form into a caramel-colored gel, which can be rinsed away with gentle irrigation. On inspection, if Oasis™ is no longer covering the wound, place an additional piece of Oasis™ over the wound.

STORAGE
This device should be stored in a clean, dry location at room temperature.

STERILIZATION
This device has been sterilized with ethylene oxide.

For your convenience, we've provided the Oasis™ Wound Dressing Instructions for Use in 10 languages. Please choose your language to view an Adobe Acrobat PDF File:

Get Acrobat Reader

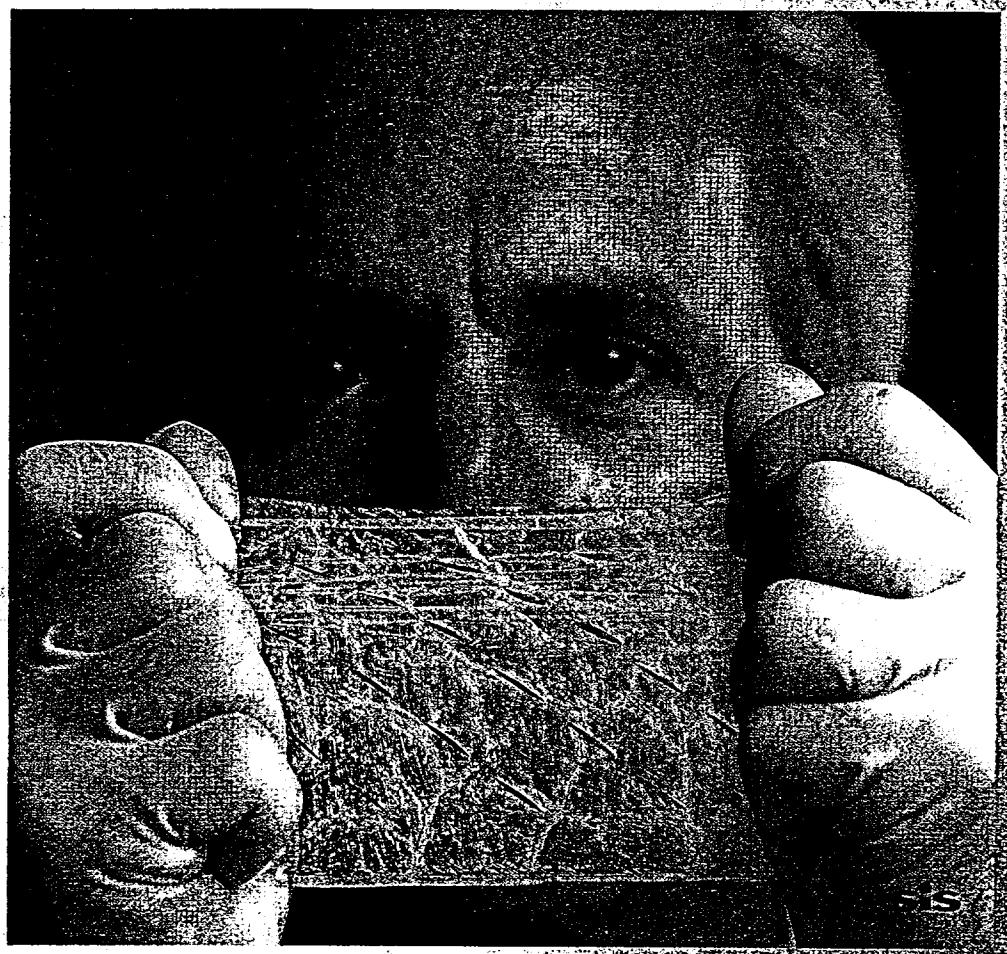
Danish Dutch English French
German Greek Italian Portugese
Spanish Swedish

Ordering Information

Please select your medical specialty from the list below for specific ordering information in Adobe Acrobat PDF Format:

- Dermatologist
- Emergency Medicine
- General Practitioner (GP)
- Obstetrics & Gynecology
- Otolaryngologist
- Podiatrist
- Plastic Surgeon
- Surgeon (General)
- Vascular Surgeon
- Wound Care Specialist
- Other Specialty

It took twelve years to develop a wound care solution this simple.



OASIS™ *A Revolutionary New Therapy for Healing*

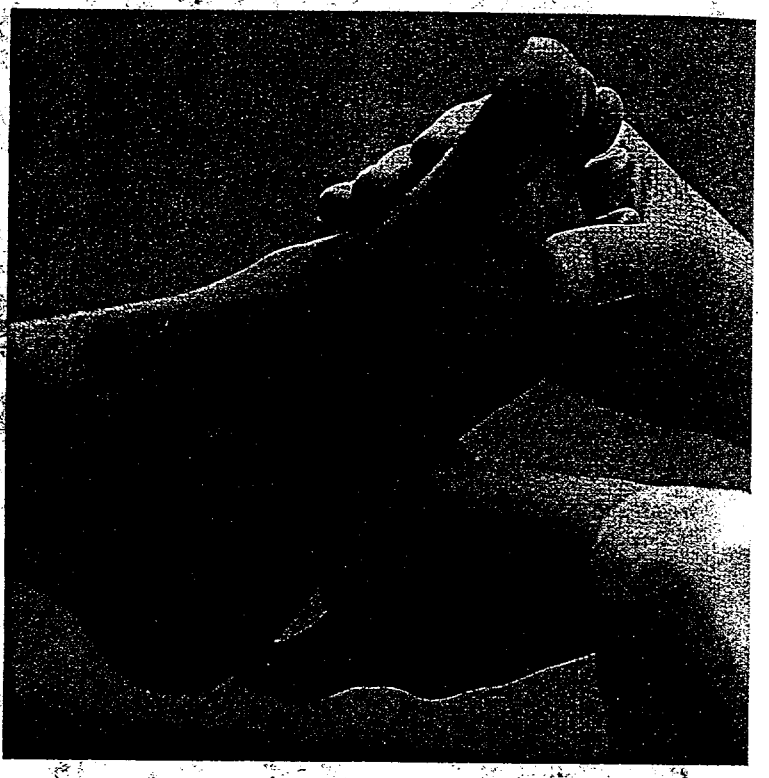
COOK®

E0010

OASIS™

Provides a foundation for natural healing.

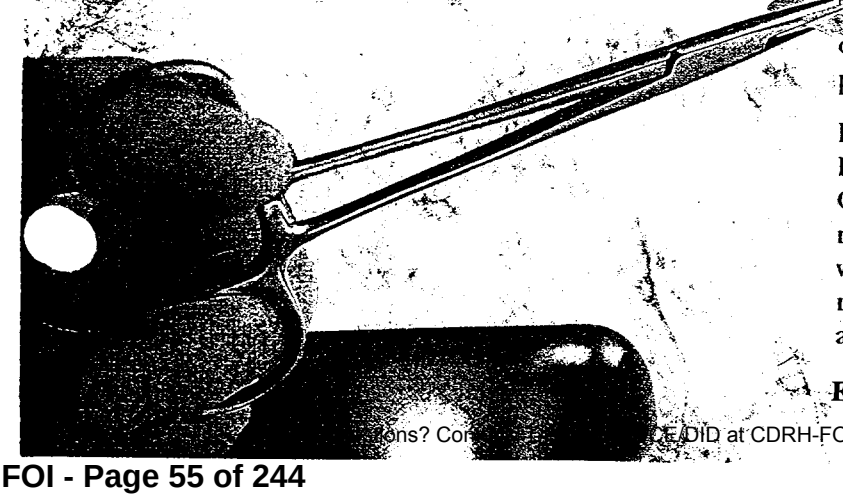
OASIS™ Wound Dressing can mean the end to months and even years of frustration caused by the search for an effective treatment for hard-to-heal wounds. OASIS works with your patient's own natural healing process to repair and regrow damaged tissue. As the patient's cells are attracted to the OASIS dressing, the wound area is gradually replaced with healthy restored tissue. Eventually, the OASIS is totally replaced. Cleared by the FDA, OASIS supports the healing of partial- and full-thickness skin injuries and non-healing wounds such as diabetic, venous and pressure ulcers, burns, abrasions, lacerations and surgical wounds.



OASIS is affordable advanced wound care therapy.

Unlike products derived from human tissue, OASIS is readily available, requires no special handling, and can be easily stored at room temperature for up to 18 months. It is also priced much lower than other tissue regeneration products. As a result, you can offer your patients advanced wound therapy for the cost of standard care.

OASIS is easy to apply and causes no adverse immune response. The dressing also is terminally sterilized to reduce the risk of pathogen contamination.

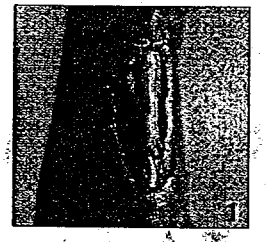


OASIS has proven results.

In one clinical study of eight adult patients treated with OASIS, two healed within four weeks, four patients healed within five to eight weeks and the remaining healed in just over eight weeks. The research results showed that OASIS caused no inflammation, infection or pain related to the product being applied to the patients' wounds. The study resulted in no sub-dressing seroma formation and all the wounds treated with OASIS progressed and healed. The research also showed that OASIS could be used in long-term care, outpatient and home care settings.[1]

In his OASIS research, Matthew A. Parmenter, DPM, concluded that OASIS, "Demonstrated that treatment of stagnant, non-healing skin wounds with OASIS resulted in rapid, complete healing with no adverse reactions."[1,2]

The OASIS Healing Process



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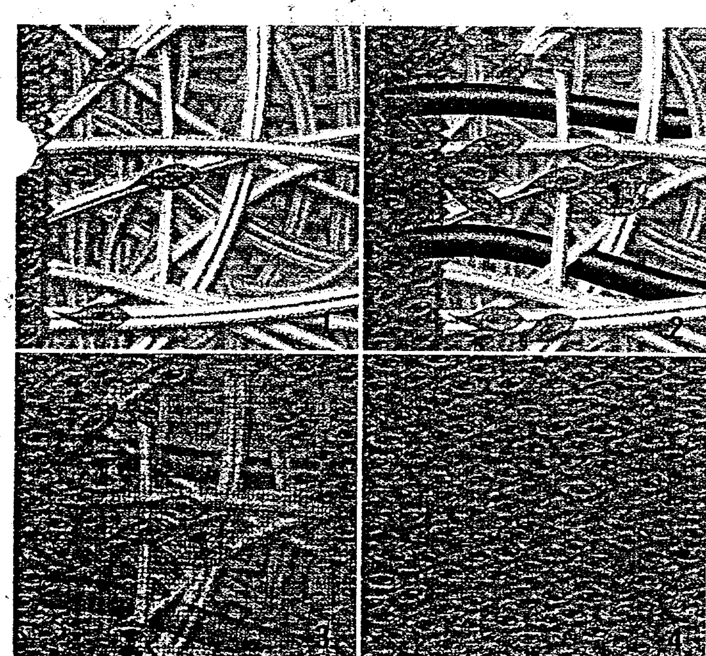
OASIS incorporates SIS technology.

OASIS is made from Small Intestinal Submucosa (SIS), a naturally-occuring, extracellular matrix comprised of natural growth factors and collagen—a protein that supports healing and provides strength to connective tissue. Under a microscope, SIS appears as a three-dimensional fibrous scaffold that helps guide the natural growth of new tissue. SIS mimics and helps restore the specific tissue it is replacing. The process is termed "smart remodeling."[3]

The SIS has a chemical composition comprised of natural growth factors that attract the patient's cells. The adjacent tissues begin delivering nutrients to the injured site and blood vessels start growing to support the new cells. The SIS scaffold is eventually remodeled as the patient's cells rebuild the damaged site.



1 After OASIS is applied, adjacent tissues begin delivering cells and nutrients.

2 The cells rapidly invade the OASIS material. Capillary growth follows, and even more nutrients are provided to the tissue.

3 OASIS is gradually replaced as the host system reinforces and rebuilds the damaged site with host tissue.

4 The new tissue becomes completely "self."

OASIS helps heal difficult wounds.

"One patient in my research was an active 35-year old male with recurring venous stasis ulcers. His ulcer was healed in eight weeks using OASIS and compression therapy. The patient realized it healed considerably faster than the three-four months it took for a similar ulcer to heal using moist wound dressing and compression."

— Marie Brown-Etris, RN CWOCN

"OASIS supported patient comfort, had a low frequency of dressing change, and was a cost-effective adjunct therapy for successful wound management."

— Matthew Parmenter, DPM

"Our patient presented with a very difficult, non-healing wound. We utilized multiple wound care regimes without success—the wound just wasn't healing. That's when we tried OASIS. Now the wound is healed. I'm pleased and we have a happy patient."

— [illegible], MD

E0012

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Delivered with COOK's outstanding customer service.

OASIS is one of the family of SIS technology products from COOK, a name synonymous with medical innovation, outstanding customer service and support. Founded in 1963 with international headquarters in Bloomington, Indiana, COOK is the largest privately held medical device manufacturer in the world. In addition to tissue regrowth, COOK is a leading global developer, manufacturer and distributor of diagnostic and interventional devices for radiology, cardiology, radiation oncology, neurology, general surgery, gastroenterology, vascular access, wound care, urology, obstetrics and gynecology, critical care and endovascular procedures.

To receive an OASIS application video or CD or to be contacted by a COOK Representative, call the COOK OASIS Professional Center toll free 1-800-829-8838, or visit us on the Web at www.cooksis.com.

OASIS *A Revolutionary New Therapy for Healing*

Brown-Etris M, Piantchello M, Shields D, Burns H. (1999) A Pilot Study to Evaluate Porcine Small Intestinal Submucosa as a Dressing for Partial Thickness Wounds. The 12th Annual Symposium on Advanced Wound Repair, April 24-27.

Lantis II, M. Use of OASIS Wound Dressing to Treat Partial Thickness Wounds: Four Case Studies.

Hodde JP, Record RD, Tullius RS, Badylak SF. "Fetal Small Intestinal Submucosa: A Biomaterial Conducive to Smart Tissue Remodeling," *Tissue Engineering: Current Perspectives*, Bell E (ed). Birkhauser Publishers, Cambridge, MA (April) 1993; 179-189.

COOK®

A world leader in tissue regrowth technology

Return to Search

Device Classification Name	BANDAGE, LIQUID
Regulation Number	880.5090
510(k) Number	K011026
Device Name	FORTADERM WOUND DRESSING
Applicant	ORGANOGENESIS, INC. 150 DAN RD. CANTON, MA 02021
Contact	PATRICK R BILBO
Product Code	KMF
Date Received	04/04/2001
Decision Date	06/13/2001
Decision	SUBSTANTIALLY EQUIVALENT (SE)
Classification Advisory Committee	General & Plastic Surgery
Review Advisory Committee	General & Plastic Surgery
Statement/Summary/Purged Status	Summary only
SUMMARY/Approval Letter	SUMMARY
Type	Traditional
Reviewed by Third Party	No

K011026

JUN 13 2001

510(K) SUMMARY

Submitted by:
Organogenesis Inc.
150 Dan Road
Canton, Massachusetts 02021

Contact
Patrick R. Bilbo
Telephone: (781) 401-1155
Facsimile: (781) 401-1109

Date: April 4, 2001

Device:

Trade Name:	FortaDerm™ Wound Dressing
Common/Usual Name:	Topical Wound Dressing, Wound Management Biomaterial
Classification Name:	Dressing, Wound (79KMF)
Classification:	Unclassified

Predicate Device:
The relevant predicate device is the SIS Wound Dressing II (K993948) manufactured by Cook Biotech, Incorporated.

Statement of Substantial Equivalence:
The FortaDerm Wound Dressing is similar with respect to intended use, technological characteristics, materials and physical construction to the predicate device in terms of section 510(k) equivalency.

Intended Use:
The FortaDerm Wound Dressing is intended for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

Device Description:
FortaDerm Wound Dressing consists of a single-layer fenestrated sheet of porcine intestinal collagen. FortaDerm Wound Dressing is supplied dry in sheet form in sizes ranging from 5 x 5 cm to 12 x 36 cm. The device is packaged in sterile, sealed single pouches.

Performance Data:
FortaDerm Wound Dressing was subjected to a number of tests to assess biocompatibility and performance. The device passed the requirements of all tests.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN 1 3 2001

Mr. Patrick Bilbo
Director, New Products
Organogenesis, Inc.
150 Dan Road
Canton, Massachusetts 02021

Re: K011026
Trade/Device Name: FortaDerm™ Wound Dressing
Regulatory Class: Unclassified
Product Code: KMF
Dated: April 4, 2001
Received: April 4, 2001

Dear Mr. Bilbo:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we 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 (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. 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.

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This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4659. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

for Mark N Melkerson

Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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INDICATIONS FOR USE STATEMENT

Applicant: Organogenesis, Inc.

510(k) Number (if known): K011026

Device Name: FortaDerm™ Wound Dressing

Indications For Use:

The FortaDerm™ Wound Dressing is intended for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds.

The device is intended for one-time use.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

for Mark N Melkerson

(Division Sign-Off)
Division of General, Restorative
and Neurological Devices

510(k) Number K011026

Prescription Use X OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)

Device Classification Name	TAPE AND BANDAGE, ADHESIVE
Regulation Number	880.5240
510(k) Number	K896455
Device Name	VITACHOICE WOUND DRESSING
Applicant	VITAPHORE CORP. 1505 O'BRIEN DRIVE MENLO PARK, CA 94025
Contact	JAN TOMSIC
Product Code	KGX
Date Received	11/09/1989
Decision Date	02/15/1990
Decision	SUBSTANTIALLY EQUIVALENT (SE)
Classification Advisory Committee	General Hospital
Review Advisory Committee	General & Plastic Surgery
Statement/Summary/Purged Status	Purged, no summary or statement
Type	Traditional
Reviewed by Third Party	No

Draft Package Insert

VitaChoice ™ Wound Dressing

Description

VitaChoice™ Wound Dressing is designed to aid in the management of dermal ulcers and chronic wounds. It is comprised of two layers of different materials. The outer layer is made from a polyurethane-based wound dressing (either OpSite® or Allevyn®) that is impermeable to water and bacteria, but permeable to moisture vapor and oxygen. The inner layer, contacting the skin, consists of a soft, white, pliable absorptive collagen sponge. The collagen is derived from bovine tissue.

For maximum ability to met a variety of wound care needs, VitaChoice™ dressings are supplied in four ways:

(1) in a kit with OpSite®;

(2) in a kit with Allevyn®;

(3) as a composite dressing with an OpSite® backing;

(4) as a composite dressing with an Allevyn® backing.

Where the wound management goal involves absorption of significant amounts of wound exudate, the dressing of choice might be VitaChoice™ collagen sponge with Allevyn®. Allevyn is comprised of highly absorbent polyurethane foam with a semi-permeable polyurethane film backing. When wound exudate is not a critical issue, the dressing of choice might be VitaChoice™ collagen sponge with Opsite®. OpSite is a semi-permeable polyurethane film.

Indications for Use

VitaChoice™ Wound Dressing is indicated in the management of dermal ulcers and chronic wounds.

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Contraindications

VitaChoice™ Wound Dressing is not indicated for use on:

Third-Degree Burns;
Full Thickness Skin Wounds;
Venous Stasis Ulcers;
Patients with known sensitivities to collagen.

Precautions:

The VitaChoice™ Wound Dressing is not to be used on infected wounds.

Suggested Technique for the Application and Removal of VitaChoice™ Wound Dressing:

1. Cleanse the wound site using your standard procedure. Make sure the skin around the wound site is clean and dry.

2. Select the proper dressing size; allow the VitaChoice collagen sponge to completely cover the wound.

3. If the wound is relatively dry, sterile water or saline solution may be used to moisten either the wound or the collagen sponge prior to application of the dressing.

4. For VitaChoice™ supplied as a kit with OpSite®:

   Place the collagen sponge over the wound so that the sponge completely covers the wound. Apply slight pressure. Remove a small portion of the OpSite backing paper from along one edge and anchor OpSite to the skin so that the collagen sponge is approximately centered beneath the OpSite membrane. Remove the rest of the backing, carefully drape the OpSite membrane over the sponge, and smooth it onto the skin around the wound. Do not stretch the OpSite.

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For VitaChoice™ supplied as a kit with Allevyn®:

Place the collagen sponge over the wound so that the sponge completely covers the wound. Apply slight pressure. Place the patterned face of the Allevyn over the sponge and skin so that the sponge is approximately centered beneath the Allevyn dressing. Secure the dressing to the skin with tape or bandage.

For VitaChoice™ supplied as a composite dressing with OpSite®:

Remove a small part of the backing paper and anchor the dressing to the skin so that the collagen sponge portion of the dressing will completely cover the wound. Remove the rest of the backing and smooth onto the skin around the wound. Apply slight pressure to the wound while applying the dressing, but do not stretch the dressing.

For VitaChoice™ supplied as a composite dressing with Allevyn®:

Place the dressing over the wound so that the collagen sponge portion of the dressing completely covers the wound. Apply slight pressure. Secure the dressing to the skin with tape or bandage.

5. The dressing may be left undisturbed for up to seven (7) days as long as it is comfortable, and there is no leakage or clinical signs of infection. If leakage of exudate occurs, the dressing should be changed.

   It is expected that large or highly exudative wounds will require more frequent dressing changes.

6. Remove the dressing carefully. The collagen sponge will separate readily from the wound area without disturbing the healing tissue.

   It is recommended that any remaining collagen be cleansed from the wound prior to applying a new dressing.

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Adverse Reactions:

VitaChoice™ Wound Dressing should not be used on patients with known sensitivities to collagen. Discontinue use if signs of sensitivity appear.

How Supplied

VitaChoice™ Wound Dressing, supplied in sterile packaging, is intended for **Single Use Only.** Re-sterilization is not recommended.

Catalog Information:

(Catalog numbers and sizes to be determined.)

Manufactured by:

VITAPHORE CORPORATION
1505 O'BRIEN DRIVE
MENLO PARK, CA 94025

Return to Search

Device Classification Name	DRESSING
510(k) Number	K896110
Device Name	BIOBRANE(R) II
Applicant	STERLING DRUG, INC. 90 PARK AVENUE NEW YORK, NY 10016
Contact	LINDA L NARDONE,PHD
Product Code	FRO
Date Received	10/23/1989
Decision Date	11/28/1989
Decision	SUBSTANTIALLY EQUIVALENT (SE)
Classification Advisory Committee	General & Plastic Surgery
Review Advisory Committee	General & Plastic Surgery
Statement/Summary/Purged Status	Purged, no summary or statement
Type	Traditional
Reviewed by Third Party	No

(Database Updated February 7, 2002)

BIOBRANE®

BIOBRANE®-L

temporary wound dressing

CE 0197

STERILE

INSTRUCTIONS

BIOBRANE is a biocomposite dressing made from an ultrathin, semipermeable silicone membrane mechanically bonded to a flexible knitted trifilament nylon fabric; BIOBRANE-L utilizes a monofilament nylon. A nontoxic mixture of highly purified peptides derived from porcine dermal collagen has been bonded to the nylon/silicone membrane to provide a highly flexible and conformable composite dressing with adherence properties and a hydrophilic, biocompatible surface.

The semipermeable silicone membrane controls water vapor loss at rates comparable to normal skin and provides a flexible adherent covering for the wound surface. It conforms to surface irregularities allowing joint movement and early ambulation and minimizes the proliferation of bacteria on the wound surface by minimizing dead space.

BIOBRANE/BIOBRANE-L is applied with **FABRIC (DULL) SIDE DOWN**, wrinkle-free against a wound surface from which all loose or necrotic skin has been debrided or excised. Initial adherence results from the fibrin on the clean wound surface preferentially bonding to the collagen surface of the dressing. Stronger secondary adherence results from physical entrapment of fibrin and tissue ingrowth into the nylon fabric.

The lower weight monofilament thread utilized in BIOBRANE-L results in less secondary adherence.

Wound Selection

The differences in adherence between BIOBRANE and BIOBRANE-L should be considered relative to the wound. Suggested uses are as follows:

BIOBRANE	Clean partial thickness burn wounds Donor sites
BIOBRANE-L	Meshed autografts

Warning: In rare instances, allergic reactions to BIOBRANE/BIOBRANE-L have been reported. If a patient shows evidence of an allergic reaction, BIOBRANE/BIOBRANE-L should be removed and its use discontinued.

Application

- Application should be to freshly debrided or excised wounds, or meshed autografts containing less than 10^5 bacteria/g tissue.
  Caution: The debridement or excision must be done thoroughly to remove all coagulum or eschar. BIOBRANE/BIOBRANE-L will not adhere to dead tissue and any remaining necrotic tissue may cause infection.
- Establish hemostasis prior to application of BIOBRANE/BIOBRANE-L.
- Apply **FABRIC (DULL) SIDE DOWN**, wrinkle-free against the wound surface with slight tension.
- Note: If less secondary adherence is desired (*e.g.* deeper donor sites or meshed autografts) BIOBRANE-L is recommended.
- Under slight tension immobilize BIOBRANE/BIOBRANE-L using staples, tape, sutures, or skin closure strips and wrap area with a dry gauze dressing or other stenting device to hold the dressing firmly in contact with the wound surface for 24 to 36 hours.

English
K094/1298

Nursing/Patient Instructions

24 Hours Postapplication

Do not remove the outer dressing. Do not get the dressing wet.
Do not move the covered area more than necessary.

24 to 36 Hours Postapplication

Remove the outer dressing down to the BIOBRANE/BIOBRANE-L and observe for the following:

- If the BIOBRANE/BIOBRANE-L is adherent and no fluid accumulation is present, rewrap with gauze for protection.
- If the BIOBRANE/BIOBRANE-L is loose, but the underlying tissue is still viable, aspirate or roll out any nonpurulent fluid collection, rewrap with a gauze dressing and observe in 24 hours for adherence.
- If the BIOBRANE/BIOBRANE-L is loose and there is purulent drainage underneath, remove the purulent nonadherent areas and use conventional topical antimicrobial therapy to reduce bacterial contamination to safe levels.

48 to 72 Hours Postapplication

- Remove the outer dressing down to the BIOBRANE/BIOBRANE-L and check for adherence. If adherent, the outer dressing need not be reapplied. If nonadherent, treat as referenced above.
- Observe the covered wound daily for bubbles and purulence and treat as referenced above. BIOBRANE/BIOBRANE-L should be removed from areas of the wound with signs of infection.
- Remove staples, tape, sutures, or skin closure strips 3 to 4 days postapplication or when adherence is achieved.
- Once the BIOBRANE/BIOBRANE-L is adherent, patients can be bathed according to standard burn unit protocols, and motion of the burned area can be initiated.

Removal

- Remove the BIOBRANE/BIOBRANE-L when the tissue underneath is healed, typically 7 to 14 days. The dressing should be dry and loose in spots, and the patient may report itching.
- If edges are loose, they can be trimmed away until the entire wound has healed.
- Remove by starting at one corner and pull gently. BIOBRANE/BIOBRANE-L will peel off healed tissue relatively easily. The application of a petroleum based ointment or soaking prior to removal facilitates the removal process.

Caution: If bleeding occurs, or if patient complains of excessive pain, stop and wait 1 to 2 additional days. Forced removal may result in wound reinjury. Also, if BIOBRANE/BIOBRANE-L becomes adherent to a partial thickness wound which has progressed to a full thickness wound, it should be removed in the operating room.

HOW SUPPLIED

Sterile, individually packaged pieces are available in the following sizes:

Size	Biobrane	Biobrane-L
5" x 5" (13 cm x 13 cm)	5 per box	5 per box
5" x 15" (13 cm x 38 cm)	5 per box	5 per box
10" x 15" (25 cm x 38 cm)	5 per box	5 per box
15" x 20" (38 cm x 50 cm)	1 per box	Not available

STORAGE

There are no special storage requirements. Results from shelf life studies performed on product that was stored for three years at room temperature indicated that the product remained sterile and pyrogen-free. Moreover, degradation of collagen peptides did not occur.

MANUFACTURED BY:

BERTEK PHARMACEUTICALS INC.
Morgantown, West Virginia, USA, 26505
Tel. 304-285-6420

EU Responsible Person:
(MDD 93/42/EEC)
MDSS GmbH
Burckhardtstr. 1
D-30163 Hannover
Germany
Tel. +49-511-6262-8630

English
K094/1298

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BIOBRANE® II
brand of temporary wound dressing

DESCRIPTION

BIOBRANE II is an adherent, flexible, temporary wound dressing intended for covering donor sites, clean, debrided or excised superficial and medium depth partial (2^{o}) thickness wounds, and as a protective covering over meshed autografts.

BIOBRANE II is a biocomposite of an ultrathin, semipermeable silicone membrane, mechanically bonded to a flexible knitted nylon fabric. A nontoxic, hypoallergenic mixture of highly purified peptides derived from porcine dermal collagen has been bonded to the above elastic membrane to provide the highly flexible and conformable composite dressing with excellent adherence properties and a hydrophilic, biocompatible surface.

The semipermeable silicone membrane controls water vapor loss at rates comparable to normal skin and provides a flexible adherent covering for the wound surface. It conforms to surface irregularities allowing joint movement and early ambulation and minimizes the proliferation of bacteria on the wound surface by minimizing dead space.

BIOBRANE II is applied with FABRIC (DULL) SIDE DOWN, wrinkle-free against a wound surface from which all loose necrotic skin has been debrided or excised. Initial adherence results from the fibrin in a clean wound surface preferentially bonding to the collagen surface of BIOBRANE II. Secondary stronger adherence results from physical entrapment by fibrin and tissue ingrowth into the nylon fabric.

BIOBRANE II is available with increased porosity and also with less secondary adherence.

BIOBRANE II (Regular Design)	SUGGESTED USES
POROUS (Green Label) Greater porosity helps minimize fluid accumulation Increased permeability to topical antimicrobials	To manage clean partial thickness wounds For wet wound management to minimize fluid accumulation For use in situations where maximum passage of transudate is desired
LARGE PORE (Red Label) (Same as green label, except more porous)	For relatively shallow donor sites To stabilize and protect meshed autografts

BIOBRANE II (Thin Design)*	To manage deeper donor sites
THIN LARGE PORE*	For widely meshed autografts
(Purple Label)	Large pores provide maximum fluid
Reduced secondary adherence	drainage
Maximum porosity (same as red label)	

*It is highly recommended that BIOBRANE be applied with slight tension and the use of staple or tape to immobilize it (with fabric side against the wound).

Protocols for BIOBRANE® II

Purpose: To apply over clean, debrided or excised superficial and medium depth partial (2^0) thickness wounds, donor sites, and expanded meshed autografts to protect tissue, control fluid loss, minimize infection, reduce pain, promote ambulation and wound healing, and minimize dressing changes.

Warning: In rare instances, allergic reactions to BIOBRANE II have been reported. If a patient shows evidence of an allergic reaction, BIOBRANE II should be removed and its use discontinued.

Application

- Application should be to freshly debrided or excised, or meshed autograft wounds containing less than 10^5 bacteria/g tissue.

Caution: The debridement or excision must be done thoroughly to remove all coagulum or eschar. BIOBRANE II will not adhere to dead tissue and any remaining necrotic tissue may cause infection.

- Establish hemostasis prior to application of BIOBRANE II.
- Apply FABRIC (DULL) SIDE DOWN, wrinkle-free against the wound surface with slight tension.

NOTE: If less secondary adherence is desired, ie, deeper donor sites or widely meshed autografts, the thin large pore (purple label) BIOBRANE II is recommended.

- Under slight tension immobilize the BIOBRANE II using staples, tape, sutures, or skin closure strips and wrap area with a dry gauze dressing or other stenting device to hold the BIOBRANE II firmly in contact with the wound surface for 24 to 36 hours.

BIOBRANE® II
brand of temporary wound dressing

Nursing/Patient Instructions
(The first 24 hours postapplication)
Do not remove the dressing.
Do not get the dressing wet.
Do not move the covered area more than necessary.

24 to 36 Hours Postapplication

Remove the outer dressing down to the BIOBRANE II and observe for the following:

- If BIOBRANE II is adherent and no fluid accumulation is present, rewrapping with gauze is now optional and is used simply for protection in active patients.
- If BIOBRANE II is loose, but the underlying tissue is still viable, aspirate or roll out any nonpurulent fluid collection, rewrap with a gauze dressing and observe in 24 hours for adherence.
- If BIOBRANE II is loose and there is purulent drainage underneath, remove purulent nonadherent areas and use conventional topical antimicrobial therapy to reduce bacterial contamination to safe levels.
- Observe the covered wound daily for bubbles and purulence and treat as referenced above. BIOBRANE II should be removed from areas of the wound with signs of infection.
- Remove staples, tape, sutures, or skin closure strips 3 to 4 days postapplication or when adherence is achieved.
- Once the BIOBRANE II is adherent, patients can be bathed according to standard burn unit protocols.
- Once BIOBRANE II is adherent, motion of the burned area can be initiated.

Removal

Donor sites, superficial and medium depth partial (2^{o}) thickness wounds:

- Remove the BIOBRANE II when the tissue underneath is healed. (Typically 7 to 14 days.) Appearance of the BIOBRANE II is dry, loose in spots and patients often report itching.
- If areas are loose, they can be trimmed away until the entire partial thickness wound has healed.
- Remove by starting at one corner and pull gently. The BIOBRANE II will peel off healed tissue relatively easily. (Soaking prior to removal facilitates the removal procedure and renders it more comfortable for the patient.)

Caution: If bleeding occurs, or if patient complains of excessive pain, stop and wait 1 to 2 additional days. Forced removal may result in wound reinjury.

If BIOBRANE II becomes adherent to a deep partial, or a deep partial which progresses to a full thickness wound, it should be removed in the operating room prior to autografting.

Meshed Autografts

Allow BICBRANE II to remain until the interstices of the meshed graft beneath BICBRANE II have filled by epithelial advance and BIOBRANE II can be removed without bleeding.

INTEGRA

311C Enterprise Drive • Plainsboro, NJ 08536 • (609) 275-0500 • Fax: (609) 275-3684 • http://www.Integra-LS.com

May 6, 2002

To Whom It May Concern:

Integra LifeSciences Corporation manufactures the Bilayer Matrix Wound Dressing from collagen obtained from bovine deep flexor tendon from the United States of America (USA) only. All bovine tendon is obtained from United States Department of Agriculture (USDA) inspected facilities in the United States of America (USA). Bovine Spongiform Encephalopathy (BSE) is not known to exist in the United States of America.

The United States of America has one of the most stringent BSE Programs in the world. In response to the BSE problem, the Animal and Plant Health Inspection Service (APHIS) has prohibited the importation of live ruminants from countries where BSE is known to exist since 1989. This includes products derived from ruminants such as: bone meal, blood meal, offal, fat, meat meal, or glands. These ruminants may only be imported under special conditions for scientific or research purposes (United States Code of Federal Regulations 9 CFR Section 95). In April of 1998, the United States Food and Drug Administration (FDA) banned the use of materials containing protein derived from mammalian tissues in ruminant feed (21 CFR 589.2000). As of December 7, 2000, USDA prohibited all imports of rendered animal protein products, regardless of species, from the United Kingdom, other countries that have reported BSE and the remaining countries of Europe. The United States satisfies the criteria set by the Office of International Epizooties to be recognized as a BSE free country.

In accordance with European Standard EN 12442-2:2000, *Animal tissues and their Derivatives Utilized in the Manufacture of Medical Devices*, approved and controlled standard operating procedures for sourcing, collecting, handling, storage, and transport of materials of animal origin are used in the manufacture of Bilayer Matrix Wound Dressing. These procedures are established, documented, implemented, and maintained by Integra LifeSciences Corporation as part of the Quality System. Integra LifeSciences Corporation has instituted a Standard Operating Procedure whereby every lot of tendon received is required to have certification to be of a bovine source of United States origin in order to be accepted for use in the manufacture of Bilayer Matrix Wound Dressing. In addition, bovine tendon is classified by European Health Authorities and the World Health Organization (WHO) as Category IV, having no infectivity risk for BSE and scrapie, which is the same classification as milk.

Per German Federal Institute for Drugs and Medical Products (BfArM) guidelines entitled: *Notification on the marketing Authorisation and registration of drugs; Measures to avert risks associated with drugs, stage II*, 1996, Section A2.3, an inactivation capacity of 10^6 can be assumed using a one hour treatment of 1N sodium hydroxide at 20°C without any validation based on animal experiments. (b)(4) [redacted] (b)(4) [redacted]

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A risk analysis according to the German Federal Institute for Drugs and Medical Products and taking into consideration the six risk-determining parameters delineated in EN 12442-1, *Animal Tissues and their Derivatives Utilized in the Manufacture of Medical Devices – Part 1: Analysis and Management of Risk* is as follows:

Parameter	Concretization in the Experiment	Class
Origin and keeping of cattle	Bovine tendon from USA only - Country where BSE is not known to exist. USA does not import animal meal (AM) and such body components from the UK or any country where BSE is known to exist	HRK – 7
Starting Materials	Tendon	MAT - 8
Inactivation of removal of infectious pathogens	(b)(4) [redacted]	ABR – 5*
Quantities of raw material required for one daily dose	< 1g and > 100 mg	APT - 3
Number of daily doses	1 – 9 DDs annually	ANZ – 2
Route of administration	Open wounds	APL -2
Exponent Sum Total – must be at least 20 before the product can be assumed to comply with the specifications for safety.		Exponent Sum Total: 27

*German Federal Institute for Drugs and Medical Products (BfArM) guidelines entitled: *Notification on the marketing Authorisation and registration of drugs; Measures to avert risks associated with drugs, stage II*, 28 March, 1996, Section A2.3, page 15.

Explanation of chart:

Parameter: Origin (HRK): Class 7 (Range of 1 to 8)

No case of BSE ever occurred in the herd.

No cattle have been included in the herd that lived in a country in which cases of BSE are known.

Import ban for animal (AM) and such body components of cattle from the UK, which are used to produce AM (that means practically everything except pure skeletal muscles).

The country in which either no cases of BSE have ever been reported, and in which since early 1992 BSE must be reported an effective veterinarian-medical surveillance exists which would most likely discover isolated cases of BSE, and also in which an import ban on cattle from the UK exists since at least July 1990.

Parameter: Raw Material (MAT): Class 8 (Range of 0 to 8) – Tendon

This classification is made according to the biological type of animal raw material used in the production. Tendon is in material class 8, considered to have low or no infectivity with BSE or scrapie.

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Parameter: Reduction and Inactivation of Infectious Agents (ABR): 5– Quotient ≥ 10^5 and < 10^6

An inactivation capacity of 6 powers of ten in a one hour treatment with a 1N solution of Sodium Hydroxide at 20°C and needs no animal experimental validation. Refer to German Federal Institute for Drugs and Medical Products (BfArM) guidelines entitled: *Notification on the marketing Authorization and registration of drugs; Measures to avert risks associated with drugs, stage II*, 28 March, 1996, Section A2.3, page 15.

(b)(4) [redacted]

Parameter: Raw Materials per daily dose (APT): Class 3 (Range of 0 to 3)

The Raw Materials per daily dose would be ≤ 1 gram and > 100 mg.

Parameter: Number of daily doses (ANZ): Class 2 (Range of 0 to 2) – Short-term 1 - 9 DD/yr.

Parameter: Application Route (APL): Class 2 (Range of 0 to 7) – Application would involve placing the material in open wounds.

The safety goal defined for drugs is assumed to be achieved if the exponent sum total is at least 20. The exponent sum total for Bilayer Matrix Wound Dressing as defined is 27, which in this rating system exceeds the minimal value for a product to be considered safe.

All cattle receive ante-mortem and post-mortem inspections by an USDA Veterinarian and are certified to be wholesome and to be deemed fit for human consumption. The method used to obtain the bovine tendon after slaughter is extremely low risk for any contamination by central nervous system tissue. The steers are immobilized, hung by one leg and exsanguinated. The tendon is removed from one leg of the steer prior to removal of the head, hide, or evisceration of the body. (b)(4) [redacted]
(b)(4) [redacted]

A viral inactivation study for the collagen manufacturing process was conducted by an independent certified laboratory. In this study, the sodium hydroxide treatment was evaluated for its ability to inactivate the following viral strains: Human Immunodeficiency Virus Type I (HIV), Bovine Viral Diarrhea (BVD), Infectious Bovine Rhinotracheitis (IBR), Parainfluenza Virus Type 3 (PI3), Vesicular Stomatitis (VSV). For these viruses, the sodium hydroxide treatment reduced the viral titer to non-detectable levels within the (b)(4) [redacted]
(b)(4) [redacted] Since all the viral inactivation takes place within the first hour, the process effectively provides a 40-fold excess safety margin during the purification of Integra LifeSciences Corporation bovine derived products.

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Integra LifeSciences Collagen products meet or exceed all US-FDA, European and Canadian guidelines for safety regarding TSE/BSE risks for human medical device products.

If you require additional information, please do not hesitate to contact me at (609) 936-2240 or by facsimile at (609) 275-3684.

Sincerely,

Diana M. Bordon
Manager
Regulatory Affairs

DMB/dm

Enclosure

Council of Europe
EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES

CERTIFICATION OF SUITABILITY OF MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

Certificate No. R0-CEP 2000-372-Rev 01

Name of the substance:
ABSORBABLE COLLAGEN SPONGE

Name of holder:
INTEGRA LIFESCIENCES CORPORATION
105 Morgan Lane
USA – NJ 08536 Plainsboro

Site of production:
INTEGRA LIFESCIENCES CORPORATION
105 Morgan Lane
USA – NJ 08536 Plainsboro

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2000-372-REV 00

After examination of the information provided on the origin of raw material and type of tissue used and on the manufacturing process for this substance on the site of production mentioned above, USA – NJ 08536 Plainsboro, we certify that the substance ABSORBABLE COLLAGEN SPONGE meets the criteria described in the monograph Products with risk of transmitting agents of animal spongiform encephalopathies (no. 1483, Ph. Eur. 4th Ed. and any subsequently revised version).

- country of origin of source materials: United States of America
- nature of animal tissues used in manufacture: Bovine tendons

The submitted dossier must be updated every five years or after any significant modification of the manufacturing method, the country of origin or the nature of the tissues used that may alter the risk of transmitting animal spongiform encephalopathy agents or require changing the specifications of the monograph.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as GMP and ISO 9001, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country of origin of the source material.

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.29 47 - Fax 03.88.41.27.71 - E-mail: certification@pheur.org

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This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (93) 5 as amended] for a period of five years starting from **9 July 2001**. Moreover, it is granted according to the provisions of Directive 75/318/EEC amended and Directive 81/852/EEC amended and the related guidelines.

This certificate has 33 lines only.

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 23 October 2001

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

INTEGRA LIFESCIENCES CORPORATION, as holder of the certificate of suitability

R0-CEP 2000-372-Rev 01 for ABSORBABLE COLLAGEN SPONGE

hereby authorises .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

Date and Signature *(of the CEP holder)*:

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.29 47 - Fax 03.88.41.27.71 - E-mail: certification@pheur.org

SPEAR PRODUCTS INC.

SUPPLIER OF BOVINE AND PORCINE RAW MATERIALS FOR USE IN
PHARMACEUTICAL, BIOLOGICAL RESEARCH, AND MANUFACTURING

Post Office Box 37
Quakertown, PA 18951
Tel: (215) 529-7545
Fax: (215) 529-7546

March 11, 2002

ADDITIONAL DECLARATION OF SLAUGHTER VERIFICATION

To Whom it May Concern:

On file with the USDA office is a notarized statement from SPEAR PRODUCTS stating that:

> All Bovine and Porcine Glands, Organs and Tissue collected by SPEAR PRODUCTS originate from certified USDA inspected plants.
>
> All slaughtered animals are given ante and post-mortem inspections and those that are found wholesome are passed for human consumption.

SPEAR PRODUCTS INC.

Jerry Spear
Operations Manager

JS:ms

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(b)(4) Testing 8 pages removed

FACTSHEET

Veterinary Services

APHIS

United States Department of Agriculture

Animal and Plant Health Inspection Service

March 2001

Foot-and-Mouth Disease

Foot-and-mouth disease (FMD) is a severe, highly communicable viral disease of cattle and swine. It also affects sheep, goats, deer, and other cloven-hooved ruminants. FMD is not recognized as a zoonotic disease.

This country has been free of FMD since 1929, when the last of nine U.S. outbreaks was eradicated.

The disease is characterized by fever and blister-like lesions followed by erosions on the tongue and lips, in the mouth, on the teats, and between the hooves. Many affected animals recover, but the disease leaves them debilitated. It causes severe losses in the production of meat and milk.

Because it spreads widely and rapidly and because it has grave economic as well as clinical consequences, FMD is one of the animal diseases that livestock owners dread most.

What Causes It

The disease is caused by a virus. The virus survives in lymph nodes and bone marrow at neutral pH, but destroyed in muscle when in pH<6.0 i.e. after rigor mortis. The virus can persist in contaminated fodder and the environment for up to one month, depending on the temperature and pH conditions.

There are at least seven separate types and many subtypes of the FMD virus. Immunity to one type does not protect an animal against other types.

How It Spreads

FMD viruses can be spread by animals, people, or materials that bring the virus into physical contact with susceptible animals. An outbreak can occur when:

- People wearing contaminated clothes or footwear or using contaminated equipment pass the virus to susceptible animals.
- Animals carrying the virus are introduced into susceptible herds.
- Contaminated facilities are used to hold susceptible animals.
- Contaminated vehicles are used to move susceptible animals.
- Raw or improperly cooked garbage containing infected meat or animal products is fed to susceptible animals.
- Susceptible animals are exposed to materials such as hay, feedstuffs, hides, or biologics contaminated with the virus.
- Susceptible animals drink common source contaminated water.
- A susceptible cow is inseminated by semen from an infected bull.

Signs

Vesicles (blisters) followed by erosions in the mouth or on the feet and the resulting slobbering or lameness are the best known signs of the disease. Often blisters may not be observed because they easily rupture, leading to erosions.

Some of these other signs may appear in affected animals during an FMD outbreak:

- Temperatures rise markedly, then usually fall in about 2 to 3 days.
- Ruptured vesicles discharge either clear or cloudy fluid and leave raw, eroded areas surrounded by ragged fragments of loose tissue.
- Sticky, foamy, stringy saliva is produced.
- Consumption of feed is reduced because of painful tongue and mouth lesions.
- Lameness with reluctance to move is often observed.
- Abortions often occur.
- Milk flow of infected cows drops abruptly.
- Conception rates may be low.
- FMD can lead to myocarditis (inflammation of the muscular walls of the heart) and death, especially in newborn animals.

Animals do not normally regain lost weight for many months. Recovered cows seldom produce milk at their former rates.

Confusion With Other Diseases

FMD can be confused with several similar, but less harmful, diseases, such as vesicular stomatitis, bluetongue, bovine viral diarrhea, and foot rot in

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cattle, vesicular exanthema of swine, and swine vesicular disease. Whenever mouth or feet blisters or other typical signs are observed and reported, laboratory tests must be completed to determine whether the disease causing them is FMD.

Where FMD Occurs

While the disease is widespread around the world, North America, Central America, Australia, New Zealand, Chile, and some countries in Europe are considered free of FMD. Various types of FMD virus have been identified in Africa, South America, Asia, and part of Europe.

Prevention and Control

FMD is one of the most difficult animal infections to control. Because the disease occurs in many parts of the world, there is always a chance of its accidental introduction into the United States.

Animals and animal byproducts from areas known to be infected are prohibited entry into this country.

Livestock animals in this country are highly susceptible to FMD viruses. If an outbreak occurred in the United States, this disease could spread rapidly to all sections of the country by routine livestock movements unless it was detected early and eradicated immediately.

If FMD were to spread unchecked, the economic impact could reach billions of dollars in the first year. Deer and wildlife populations could become infected rapidly and could be a source for reinfection of livestock.

What You Can Do

You can support U.S. efforts against FMD by:

- Watching for slobbering, lameness, and other signs of FMD in your herd; and
- Immediately reporting any unusual or suspicious signs of disease to your veterinarian, to State or Federal animal disease control officials, or to your county agricultural agent.

If FMD should appear in your animals, your report will set in motion an effective State and Federal eradication program.

Your participation is vital. Both the early recognition of disease signs and the prompt notification of veterinary officials are essential if eradication is to be carried out successfully. Your warning may prevent FMD from becoming established in the United States, or, if it does spread, reduce the time and money needed to wipe it out.

Additional Information

For more information about FMD, contact
USDA, APHIS, Veterinary Services
Emergency Programs
4700 River Road, Unit 41
Riverdale, MD 20737–1231
Telephone (301) 734–8073
Fax (301) 734–7817

The APHIS Emergency Operations Center
(800) 940–6524
e-mail: emoc@aphis.usda.gov

Current information on animal diseases and suspected outbreaks is also available on the Internet at http://www.aphis.usda.gov.

USDA
United States Department of Agriculture
Animal and Plant Health Inspection Service
Veterinary Services

March 8, 2001

Judith E. O'Grady
Sr. Vice President
Regulatory Affairs, Quality Assurance,Clinical Affairs
Integra LifeSciences Corporation
105 Morgan Lane
Plainsboro, New Jersey 08536

Dear Ms. O'Grady:

As per your request I have listed the information and pertinent regulations to prohibit the entry of BSE into the United States.

1. Bovine Spongiform Encephalopathy (BSE) has **NOT** been detected in the United States, and USDA has worked aggressively and proactively since 1989 to keep it that way. The measures APHIS has taken in this regard include prohibitions and/or restrictions on certain animal and product imports; ongoing surveillance for signs of the disease in the United States; preparation of an emergency response plan in the unlikely event an introduction were to occur; and ongoing educational efforts. APHIS actively shares information and coordinates closely with other Federal agencies, as well as the States, livestock and affiliated industries, veterinary and research communities, and consumer groups, in order to ensure that the US has a uniform approach to transmissible spongiform encephalopathies which is based on sound scientific information.

APHIS has had a comprehensive surveillance program in place in the United States (since 1990) to ensure timely detection and swift response in the unlikely event that an introduction of BSE were to occur. This surveillance program incorporates both the location of imports from the United Kingdom or other countries which have detected BSE, and targeted active and passive surveillance for either BSE or any other TSE in cattle.

Samples of BSE surveillance of adult cattle are obtained from:

1. Field cases of cattle exhibiting signs of neurological disease
2. Cattle condemned at slaughter for neurological reasons
3. Rabies-negative cattle submitted to public health laboratories
4. Neurological cases submitted to veterinary diagnostic laboratories and teaching hospitals
5. Random sampling of aged dairy cattle which are non-ambulatory at slaughter (ie. fallen stock).

Cattle showing evidence of neurologic disease when presented for slaughter are condemned upon antemortem inspection. Samples of brain tissue are submitted for diagnosis to the National Veterinary Services Laboratory.

As of January 31, 2001, 12,103 brains had been examined for BSE or another form of a transmissible spongiform encephalopathy in cattle. The use of immunohistochemistry for the detection of the abnormal form of the prion protein was introduced in 1994. As of 1997 our surveillance tests all samples submitted to the National Veterinary Services Laboratory (NVSL) by both histopathology and immunohistochemistry. No evidence of either condition has been found.

2. BSE is a legally reportable disease in the United States under Title 9 Code of Federal Regulations (CFR) Parts 161 and 71, effective November 1986.

3. Scrapie is a legally reportable disease in the United States under Title 9 CFR Parts 161, 71 and 79.

4. Tissues from BSE suspect cases must be submitted for a laboratory diagnosis in the United States under Title 9 CFR Parts 161 and 71, effective November 1986.

5. Tissues from scrapie suspect cases must be submitted for a laboratory diagnosis in the United States under Title 9 CFR Parts 161, 71, 79 and 54.

6. The importation of all live ruminants (bovines, progeny of affected cattle, sheep, goats, etc.) is prohibited from the United Kingdom, other countries which have reported BSE, and the remaining countries of Europe due to high risk factors associated with BSE. The regulations are in Title 9 Code of Federal Regulations, Part 92. The prohibition for countries known to have BSE was effective July 1989. The prohibition on the remaining countries of Europe was effective as of December 12, 1997.

In addition, Title 9 Code of Federal Regulations, Parts 94, 95 and 96 prohibit the entry of most ruminant products including meat and bone meal, blood meal, bone meal, offal, etc. from the countries as listed above. The prohibition for countries known to have BSE was effective 1989. The prohibition on the remaining countries of Europe was effective as of December 12, 1997.

7. The feeding of most mammalian protein to ruminants has been prohibited under the authority of the Food and Drug Administration. The regulation is in Title 21, Code of Federal Regulation, Part 589. This was effective as of August 4, 1997.

Given the above, the United States satisfies the criteria set by the Office of International Epizooties to recognized as a BSE free country.

If I can be of further assistance please do not hesitate to contact me.

Sincerely,

Linda A. Detwiler
Senior Staff Veterinarian
USDA, APHIS, Veterinary Services

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FDA BACKGROUNDER

CURRENT & USEFUL INFORMATION FROM THE FOOD & DRUG ADMINISTRATION

BSE: Background, Current Concerns and U.S. Response

The recent increase in cases of bovine spongiform encephalopathy (BSE) found in some European countries has revived public concern about the safety of eating beef and using other animal-derived products. The largest increase of this fatal neurological disorder in cattle (commonly called "mad cow disease") occurred in France, which reported 99 cases in 2000, compared to 31 cases in 1999. The incidence of BSE-infected cattle is also rising in Belgium and Ireland. Some countries that have not previously seen BSE in their native cattle, including Germany, Spain, Denmark, and Italy, reported their first cases in 2000.

First identified in the United Kingdom (UK) in 1986, BSE peaked in the UK in January 1993 at almost 1,000 new cases per week. The UK has reported more than 180,000 total cases of BSE, and about 1,800 cases have been found elsewhere in the European Union (EU).

Because of the UK's aggressive actions to eradicate BSE since it was first identified, the number of BSE cases is falling sharply in that country. The sudden rise in reported BSE cases in other European countries may, in part, reflect increased testing by some countries, particularly Switzerland and France. In addition, because of the long incubation period of BSE (two to eight years), cows being identified now with BSE may have become infected several years ago.

Rendered feed ingredients contaminated with an infectious agent are believed to be the source of BSE infection in cattle. Some of the feed given to cattle includes ingredients processed from remnants of slaughtered animals, such as meat-and-bone meal (MBM), which may harbor the agent that causes BSE. Although the material is cooked, the BSE agent can survive.

BSE may have originated from giving cows feed that contained MBM derived from sheep infected with scrapie (an infectious neurological disease in sheep and goats, similar to BSE in cows). There is strong evidence, and general agreement, that the original outbreak of BSE in Europe was amplified by feeding MBM prepared from BSE-infected cattle to young calves.

No cases of disease in humans or livestock caused by BSE have ever been detected in the United States. BSE has thus far been kept out of this country largely through the combined efforts of the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), the Centers for Disease Control and Prevention (CDC), other federal organizations, and state regulatory and health agencies. These organizations have taken aggressive actions to reduce the risk that BSE could be introduced and spread in this country. These actions build on a continuing program of prevention, education, surveillance, testing, and emergency preparation.

BSE in Cattle Linked to Disease in People

In 1996, British scientists traced a link between a new variant of Creutzfeldt-Jakob disease (CJD), a rare but fatal disease in humans, and BSE in cattle. Both the new variant CJD and the classic CJD are slow degenerative diseases of the central nervous system whose symptoms include dementia and loss of motor skills. There is no known treatment and the outcome is ultimately death. Only the new variant—not the classic—CJD is believed to be caused by exposure to the BSE agent, most likely through certain foods.

CJD and the new variant CJD (nvCJD) belong to a family of diseases known as transmissible spongiform encephalopathies (TSEs). These diseases, so named because of the spongy appearance of the infected brain tissue, are caused by a transmissible agent that is not yet fully understood. In addition to nvCJD and CJD, three other human TSEs are known, including kuru, which was first recorded in 1957 in the Fore natives of the New Guinea highlands.

Classic CJD occurs sporadically worldwide at a

rate of approximately one case per 1 million people per year, and the new variant CJD and other human TSEs are even more rare.

In addition to BSE, other TSEs have been detected in some species of animals (sheep, goats, mink, deer, elk, and domestic and exotic cats). Most TSEs—with the exception of nvCJD—are species-specific, with no evidence of natural transmission between animals and people.

On March 20, 1996, the UK reported 10 cases of nvCJD. As of Feb. 2, 2001, 98 cases of nvCJD have been suspected or confirmed in the EU. With the exception of three cases in France and one case in Ireland, all have occurred in the UK.

Patients who have acquired nvCJD have been younger and have had the disease longer than patients with classic CJD. (The average age for death from nvCJD has been 27.5 versus 68 in CJD, and the average time to death after the onset of clinical symptoms is 13 months for nvCJD versus less than six months for CJD.)

Britain's Spongiform Encephalopathy Advisory Committee (SEAC) has reported that the BSE agent is the likely cause of the nvCJD. This conclusion was based on studies conducted at the Institute for Animal Health in Edinburgh, Scotland, the Imperial College School of Medicine, London, and the University of California in San Francisco.

No cases of nvCJD have been detected in the United States through CDC's surveillance program. In fact, no illnesses in livestock or humans caused by BSE have ever been diagnosed in the United States, despite 10 years of active surveillance.

Transmission and Testing

Current research suggests the agent that causes BSE and other TSEs is a "prion," an abnormal protein with a novel mode of replication and transmission. Cattle may contract the disease from feed containing animal byproducts contaminated with this protein.

The BSE agent is highly resistant to most disinfectants that normally inactivate viruses or bacteria, such as heat, ultraviolet light, and ionizing radiation. BSE agents do not appear to stimulate an immune response, and so, as yet, cannot be detected with a blood test for antibodies or prevented with a vaccine.

No evidence exists to indicate that BSE spreads through routine contact between cattle or from routine contact between cattle and humans or other species. Some evidence suggests that transmission from mother to fetus may occur at a low level, but this conclusion has not been confirmed. Recent studies have shown that certain healthy animals can get BSE from injections of blood from a BSE-infected animal. F. Houston and Nora Hunter of the Institute For Animal Health, Compton, Newbury, UK, and Edinburgh, UK, reported successful BSE transmission to a healthy sheep that received 400 milliliters of blood from a donor sheep infected with BSE (*Lancet,* September 2000).

Currently, no test can readily detect BSE in a live animal or detect TSEs in healthy humans. The main laboratory method used to confirm a diagnosis is to examine brain tissue after death. Researchers are working to develop new test methods to detect TSEs in live animals and humans.

The U.S. Response

The United States has aggressive BSE surveillance and prevention programs in place. FDA's restrictions on certain animal feed ingredients and its import alerts on cattle products are a critical part of this program. In addition, USDA has an import ban on certain cattle and cattle products, and CDC has established surveillance and investigation programs for suspected human TSE cases.

USDA's Animal and Plant Health Inspection Service (APHIS) introduced import restrictions in 1989, when it banned the import of all live ruminants (cud-chewing animals, such as cows, sheep, and goats) from the UK.

On Dec. 12, 1997, APHIS expanded its prohibition on certain imports to include live ruminants and most ruminant products from all of Europe.

USDA's Food Safety and Inspection Service (FSIS) inspects cattle before they go to slaughter if they show signs of BSE or other central nervous system impairment. Any animals displaying these signs are condemned, and the meat is not allowed to be used in human food. The animal brains are submitted to USDA's National Veterinary Services Laboratories for analysis. Approximately 12,000 cattle brains from nearly every state and Puerto Rico have been examined, with no evidence of BSE or other TSE found to date.

FDA is responsible for ensuring that animal feeds are safe and produce no human health hazards when used in food-producing animals. On

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June 5, 1997, FDA published a final regulation that prohibits the use of most mammalian protein in the manufacture of animal feeds given to ruminants. The regulation, which became effective on Aug. 4, 1997, also requires manufacturers to use appropriate process and control systems to ensure that feed for ruminants does not contain the prohibited mammalian tissue.

To ensure that industry was complying with the animal feed regulation, FDA, with assistance from state feed control officials, has conducted nearly 10,000 inspections since January 1998. Inspected firms include feed mills, ruminant feeders, dairy farms, renderers, protein blenders, feed haulers, and distributors. More than three-fourths of all of the inspected facilities were found to be in compliance with the regulation, and nearly 85 percent of the 180 renderers handling prohibited materials were in compliance. The compliance of rendering plants is particularly important because they are the source of most domestic MBM. Sites initially found not to be in compliance have shown a high percentage of compliance upon re-inspection.

Using an innovative, education-oriented partnership program, FDA continues to enforce its 1997 feed regulation. FDA has sponsored workshops for state veterinarians and feed control officials from all 50 states, Puerto Rico, the U.S. Virgin Islands, and Canada. In addition, a joint satellite teleconference with the Association of American Feed Control Officials, the American Feed Industry Association, and the National Grain and Feed Association was broadcast in 1998 throughout the United States and Canada to describe the requirements of the regulations and answer questions from callers. FDA has also developed an interactive CD-ROM that provides information on the regulation and what is expected of those to whom the regulation applies. The CD-ROM is available to FDA, the states, and the regulated industry.

To continue its comprehensive efforts to try to head off a BSE problem in the United States, FDA is conducting additional inspections, and is re-inspecting facilities that were found non-compliant upon initial inspection. Based on the evaluation of the inspections conducted from 1998 through 2000, FDA will revise its compliance strategy to try to assure its goal of 100 percent compliance with the feed regulation.

FDA and USDA recently took further emergency action to prevent potentially cross-contaminated products from entering the United States. On Dec. 7, 2000, APHIS banned all imports of rendered animal proteins, regardless of species, from 31 countries listed as BSE-positive or as presenting an undue risk of introducing BSE into the United States. Prohibited products include MBM, meat meal, bone meal, blood meal, tankage (dried animal residues), and offal (organs, such as brain and liver, and trimmings, such as tails and hooves). FDA has also announced an import alert, allowing its inspectors to detain shipments from these 31 countries of animal feed (including pet food), animal feed ingredients, and other products of animal origin intended for human or animal use.

Protecting Medical Products

In addition to protecting the American cattle herd from BSE, FDA also has taken steps to protect medical products (such as drugs, blood, vaccines, and medical devices) for human use. In 1990, FDA intensified its review of new product applications for human medical products derived from or containing bovine (cattle) sources. FDA recommended to manufacturers of these new products that they not purchase as components animal tissues or products that originated in a country where native cattle have been diagnosed with BSE.

In 1993, and again in 1996, FDA issued letters to the manufacturers of drugs, biologics and medical devices advising them that in the manufacture of FDA-regulated products intended for human use, they should not use materials derived from cattle born, raised or slaughtered in countries where BSE is known to exist. Again in 2000, FDA reissued the same advice to vaccine and other biological manufacturers regarding bovine materials from countries listed by APHIS as having BSE or with an undue risk of introducing BSE into the United States.

FDA will continue its close collaboration with the scientific community and with public health officials, at home and abroad, to take the appropriate preventive actions in response to the growing and changing knowledge concerning TSEs in its ongoing effort to protect the health of Americans and of U.S. cattle herds.

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Rules and Regulations

Federal Register
Vol. 66, No. 50
Wednesday, March 14, 2001

DEPARTMENT OF AGRICULTURE

Animal and Plant Health Inspection Service

9 CFR Part 94

[Docket No. 01–018–1]

Change in Disease Status of Great Britain and Northern Ireland Because of Foot-and-Mouth Disease

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Interim rule and request for comments.

SUMMARY: We are amending the regulations governing the importation of certain animals, meat, and other animal products by removing Great Britain (England, Scotland, Wales, and the Isle of Man) and Northern Ireland from the list of regions considered to be free of rinderpest and foot-and-mouth disease. We are taking this action because the existence of foot-and-mouth disease has been confirmed there. The effect of this action is to prohibit or restrict the importation of any ruminant or swine into any fresh (chilled or frozen) meat and other products of ruminants or swine into the United States from Great Britain or Northern Ireland.

DATES: This interim rule was effective on January 15, 2001. We invite you to comment on this docket. We will consider all comments that we receive by May 14, 2001.

ADDRESSES: Please send four copies of your comment (an original and three copies) to: Docket No. 01–018–1, Regulatory Analysis and Development; PPD, APHIS, Suite 3C03, 4700 River Road, Unit 118, Riverdale, MD 20737–1238.

Please state that your comment refers to Docket No. 01–018–1.

You may read any comments that we receive on this docket in our reading room. The reading room is located in room 1141 of the USDA South Building, 14th Street and Independence Avenue SW., Washington, DC. Normal reading room hours are 8 a.m. to 4:30 p.m., Monday through Friday, except holidays. To be sure someone is there to help you, please call (202) 690–2817 before coming.

APHIS documents published in the **Federal Register**, and related information, including the names of organizations and individuals who have commented on APHIS dockets, are available on the Internet at http://www.aphis.usda.gov/ppd/rad/webrepor.html.

FOR FURTHER INFORMATION CONTACT: Dr. Gary Colgrove, Assistant Director, Sanitary Trade Issues, National Center for Import and Export, VS, APHIS, 4700 River Road Unit 38, Riverdale, MD 20737–1231; (301) 734–4356.

SUPPLEMENTARY INFORMATION:

Background

The regulations in 9 CFR part 94 (referred to below as the regulations) govern the importation of specified animals and animal products into the United States in order to prevent the introduction of various animal diseases including rinderpest, foot-and-mouth disease (FMD), African swine fever, hog cholera, and swine vesicular disease. These are dangerous and destructive communicable diseases of ruminants and swine. Section 94.1 of the regulations lists regions of the world that are declared free of rinderpest or free of both rinderpest and FMD. Rinderpest or FMD exists in all other regions of the world not listed. Section 94.11 of the regulations lists regions of the world that have been declared free of rinderpest and FMD, but that are subject to certain restrictions because of their proximity to or trading relationships with rinderpest- or FMD-affected regions.

Prior to the effective date of this interim rule, Great Britain (England, Scotland, Wales, and Isle of Man) and Northern Ireland were listed in §§ 94.1 and 94.11 as regions considered to be free of rinderpest and FMD. However, on February 19, 2001, a suspected outbreak of FMD was detected in Essex, England. On February 12, 2001, the Chief Veterinary Officer of United Kingdom's Ministry of Agriculture, Fisheries and Food (MAFF) notified us and the Office International des Epizooties (OIE) with clinical confirmation of the FMD diagnosis. Additional outbreaks of FMD have subsequently been confirmed elsewhere in Great Britain. On February 27, 2001, a suspected outbreak of FMD was detected in Meigh, County Armagh, Northern Ireland. Northern Ireland's Agriculture Minister reported clinical confirmation of the FMD diagnosis on March 1, 2001.

MAAF and Northern Ireland's Department of Agriculture and Rural Development (NIDARD) are still investigating the virus' mode of introduction into the affected areas and are conducting extensive surveillance outside the quarantined areas to ensure that the disease is confined to those locations within the quarantined areas where the outbreaks are known to have occurred. Until the results of the epidemiological investigation and the surveillance activities are known, we believe that it is necessary to impose restrictions on all of Great Britain (England, Scotland, Wales, and Isle of Man) and Northern Ireland to protect the livestock of the United States from FMD.

Therefore, we are amending the regulations in § 94.1 by removing Great Britain (England, Scotland, Wales, and Isle of Man) and Northern Ireland from the list of regions that have been declared to be free of rinderpest and FMD. We are also removing Great Britain (England, Scotland, Wales, and Isle of Man) and Northern Ireland from the list in § 94.11 of regions that are declared to be free of these diseases, but that are subject to certain restrictions because of their proximity to or trading relationships with rinderpest- or FMD-affected regions. As a result of this action, the importation into the United States of any ruminant or swine and any fresh (chilled or frozen) meat and other products of ruminants and swine from any part of Great Britain (England, Scotland, Wales, and Isle of Man) and Northern Ireland is prohibited or restricted. We are making these amendments effective retroactively to January 15, 2001, because the disease may have been present in the affected areas for some time before it was initially detected.

Although we are removing Great Britain (England, Scotland, Wales, and Isle of Man) and Northern Ireland from the list of regions considered to be free

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of rinderpest and FMD, we recognize the MAFF and NIDARD responded immediately to the detection of FMD by imposing restrictions on the movement of ruminants, swine, and ruminant and swine products from the affected areas and by initiating measures to eradicate the disease. We intend to reassess this situation at a future date in accordance with the standard of the OIE. As part of that reassessment process, we will consider all comments received on this interim rule. This future reassessment will enable us to determine whether it is necessary to continue to prohibit or restrict the importation of ruminants or swine and any fresh (chilled or frozen) meat and other products of ruminants or swine from Great Britain and Northern Ireland, or whether we can restore Great Britain and Northern Ireland to the list of regions in which FMD is not known to exist, or regionalize portions of Great Britain or Northern Ireland as FMD-free.

Emergency Action

This rulemaking is necessary on an emergency basis to prevent the introduction of FMD into the United States. Under these circumstances, the Administrator has determined that prior notice and opportunity for public comment are contrary to the public interest and that there is good cause under 5 U.S.C. 553 for making this rule effective less than 30 days after publication in the **Federal Register**.

We will consider comments that are received within 60 days of publication of this rule in the **Federal Register**. After the comment period closes, we will publish another document in the **Federal Register**. The document will include a discussion of any comments we receive and any amendments we are making to the rule as a result of the comments.

Executive Order 12866 and Regulatory Flexibility Act

This rule has been reviewed under Executive Order 12866. For this action, the Office of Management and Budget has waived its review process required by Executive Order 12866.

We are amending the regulations governing the importation of certain animals, meat, and other animal products by removing Great Britain (England, Scotland, Wales, and Isle of Man) and Northern Ireland from the list of regions considered to be free of rinderpest and FMD. We are taking this action because the existence of FMD has been confirmed there. The effect of this action is to prohibit or restrict the importation of any ruminant or swine and any fresh (chilled or frozen) meat and other products of ruminants or swine into the United States from Great Britain or Northern Ireland on or after January 15, 2001. This action is necessary to protect the livestock of the United States from FMD.

This emergency situation makes timely compliance with section 604 of the Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*). impracticable. We are currently assessing the potential economic effects of this action on small entities. Based on that assessment, we will either certify that the rule will not have a significant economic impact on a substantial number of small entities or publish a final regulatory flexibility analysis.

Executive Order 12988

This rule has been reviewed under Executive Order 12988, Civil Justice Reform. This rule: (1) Preempts all State and local laws and regulations that are inconsistent with this rule; (2) has retroactive effect to January 15, 2001; and (3) does not require administrative proceedings before parties may file suit in court challenging this rule.

Paperwork Reduction Act

This rule contains no new information collection or recordkeeping requirements under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

List of Subjects in 9 CFR Part 94

Animal diseases, Imports, Livestock, Meat and meat products, Milk, Poultry and poultry products, Reporting and recordkeeping requirements.

Accordingly, we are amending 9 CFR part 94 as follows:

PART 94—RINDERPEST, FOOT-AND-MOUTH DISEASE, FOWL PEST (FOWL PLAGUE), EXOTIC NEWCASTLE DISEASE, AFRICAN SWINE FEVER, HOG CHOLERA, AND BOVINE SPONGIFORM ENCEPHALOPATHY: PROHIBITED AND RESTRICTED IMPORTATIONS

1. The authority citation for part 94 continues to read as follows:

Authority: Title IV, Pub.L. 106–224, 114 Stat. 438, 7 U.S.C. 7701–7772; 7 U.S.C. 450; 19 U.S.C. 1306; 21 U.S.C. 111, 114a, 134a, 134b, 134c, 134f, 136, and 136a; 31 U.S.C. 9701; 42 U.S.C. 4331 and 4332; 7 CFR 2.22, 2.80, and 371.4.

§ 94.1 [Amended]

2. In § 94.1, paragraph (a)(2) is amended by removing the words "Great Britain (England, Scotland, Wales, and Isle of Man)" and "Northern Ireland,".

§ 94.11 [Amended]

3. In § 94.11, paragraph (a) is amended by removing the words "Great Britain (England, Scotland, Wales, and Isle of Man)" and "Northern Ireland,".

Done in Washington, DC, this 9th day of March 2001.

Bobby R. Acord,

Acting Administrator, Animal and Plant Health Inspection Service.

[FR Doc. 01–6403 Filed 3–13–01; 8:45 am]

BILLING CODE 3410–34–M

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

14 CFR Part 39

[Docket No. 2000–NE–48–AD; Amendment 39–12142; AD 2001–05–06]

RIN 2120–AA64

Airworthiness Directives; BMW Rolls-Royce GmbH Models BR700–710A1–10 and BR700–710A2–20 Turbofan Engines

AGENCY: Federal Aviation Administration, DOT.

ACTION: Final rule; request for comments.

SUMMARY: This amendment adopts a new airworthiness directive (AD) that is applicable to BMW Rolls-Royce (RR) GmbH models BR700–710A1–10 turbofan engines with fan disk part numbers (P/N's) BRR18803, BRR19248, or BRR20791 installed, and BR700–710A2–20 turbofan engines with fan disks P/N's BRR19248 or BRR20791 installed. This action requires initial and repetitive inspections of these fan disks for cracks, and if necessary replacement with serviceable parts. This amendment is prompted by reports of cracks in several fan disks in the dovetail area. The actions specified in this AD are intended to detect cracks in the fan disk, that could result in an uncontained engine failure and damage to the airplane.

DATES: Effective March 29, 2001. The incorporation by reference of certain publications listed in the regulations is approved by the Director of the Federal Register as of March 29, 2001.

Comments for inclusion in the Rules Docket must be received on or before May 14, 2001.

ADDRESSES: Submit comments to the Federal Aviation Administration (FAA), New England Region, Office of the Regional Counsel, Attention: Rules Docket No. 2000–NE–48–AD, 12 New England Executive Park, Burlington, MA

FACTSHEET

Veterinary Services

APHIS

United States Department of Agriculture

Animal and Plant Health Inspection Service

March 2001

Foot-and-mouth disease Q's and A's

Q: What is foot-and-mouth disease (FMD)?
A: FMD is a highly contagious and economically devastating disease of cattle and swine. It also affects sheep, goats, deer, and other cloven-hooved ruminants. Many affected animals recover, but the disease leaves them debilitated. FMD causes severe losses in the production of meat and milk. Because it spreads widely and rapidly and because it has grave economic as well as physical consequences, FMD is one of the animal diseases that livestock owners dread most. The disease does not affect food safety or humans.

Q: What are the potential economic ramifications of an FMD outbreak in the United States?
A: An FMD outbreak in the United States could potentially cost the U.S. livestock industry billions of dollars in losses in the first year.

Q: Can people get the disease from animals?
A: It is not believed to readily affect humans. There was one recorded case in Britain in 1966. The effects of the disease for that person were similar to flu with some blisters. The disease has no implications for the human food chain. People, however, can spread the virus to animals because it can remain in human nasal passages for as long as 28 hours.

Q: How do you get rid of foot-and-mouth disease?
A: The virus can be killed off by heat, low humidity, or some disinfectants. It is only rarely fatal, although it is more likely to kill very young animals. There is no cure for the disease, and it usually runs its course in 2 or 3 weeks with most animals recovering, although some animals take up to 6 months to fully recover.

Q: If most animals don't die, why go to such great lengths to eradicate it?
A: The disease is highly contagious with nearly 100 percent of exposed animals becoming infected. If the disease became widespread in any country there would be disastrous economic consequences. For example, the most serious effects of the disease in dairy cattle are loss of milk and yield.

Q: What is the U.S. Department of Agriculture (USDA) doing to protect the United States from foot-and-mouth disease?
A: In order to protect U.S. livestock from the introduction of FMD, USDA implemented an interim rule on February 21, prohibiting or restricting the importation into the United States of live swine and ruminants and any fresh swine or ruminant meat (chilled or frozen) or products from Great Britain or Northern Ireland. USDA's FMD policy has been to be proactive and preventative. As a result, the interim rule is effective retroactively. Products dated after January 14 are not permitted entry into the United States. This rule has not yet been published in the *Federal Register.*

Q: What is USDA doing to prevent travelers from bringing FMD into the United States?
A: There is no change in the regulation regarding U.S. surveillance measures of travelers for FMD. However, ports of entry have been notified to enhance surveillance of travelers coming from Europe, particularly the United Kingdom (UK) because that area is now considered to be at high risk for FMD.

Q: What should travelers do if they are planning to visit a farm or are in contact with livestock while abroad?
A: All international travelers must state on their Customs declaration form whether or not they have been on a farm or in contact with livestock and if they are bringing any meat or dairy products from their travels back with them. APHIS officials will inspect the baggage of all travelers who indicate they have been on a farm or in contact with livestock. Any soiled footwear must be disinfected with detergent

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and bleach. If travelers are around livestock in the UK and they have livestock at home in the United States, they should avoid contact with their animals for 5 days after returning. In addition, soiled clothing must be washed and disinfected prior to returning to the United States.

Q: Can travelers bring animal products back to the United States from Europe?
A: Any ruminant or swine products (cattle, sheep, goats, deer, and other cloven-hooved animals included), with the exception of hard cheeses and canned products with a shelf life, will be confiscated.

Q: How can farmers support USDA in its efforts to prevent FMD in the United States?
A: As always, farmers can support U.S. efforts against FMD by watching for excessive salivating, lameness, and other signs of FMD in their herd and immediately reporting any unusual or suspicious signs of disease to their veterinarian, State or Federal animal disease control officials, or their county agricultural agent. Garbage feeders are encouraged to fully cook their feed before giving it to livestock.

Additional Information

For more information about FMD, contact:

USDA, APHIS, Veterinary Services
Emergency Programs
4700 River Road, Unit 41
Riverdale, MD 20737-1231
Telephone (301) 734-8073
Fax (301) 734-7817

Current information on animal diseases and suspected outbreaks is also available on the Internet at http://www.aphis.usda.gov.

USDA United States Department of Agriculture
Animal and Plant Health Inspection Service
Veterinary Services

More Detailed Information on USDA Restrictions on Products from Countries with Foot-and-Mouth Disease

The basis for USDA-APHIS restrictions on products from countries affected with foot-and-mouth disease (FMD) is contained in Title 9, Code of Federal Regulations (CFR), Parts 94-98. These sections list certain specific products which are prohibited, but also exempt certain products which do not present a risk of transmission of FMD.

In addition, these sections allow USDA the latitude to write permits for products which have been adequately processed such that they do not present a risk of transmission of FMD. This approach allows flexibility in dealing with a wide range of products which otherwise would not be allowed.

The following is a summary of the restrictions on products from countries affected with FMD:

(1) Prohibited products (with the CFR citation listed):

- live ruminants (9 CFR Part 94.1)
- live swine (9 CFR Part 94.1)
- fresh (chilled or frozen) meat of ruminant or swine (9 CFR Part 94.1)
- fresh (chilled or frozen) products derived from ruminants or swine (other than meat and milk/milk products) (9 CFR 94.2)
- fresh (chilled or frozen) organs, glands, extracts or secretions derived from ruminants or swine (9 CFR 94.3) *NOTE: exceptions are allowed under permit, with additional processing for pharmaceutical or biological purposes
- ruminant or swine semen (9 CFR Part 98.34)
- ruminant or swine embryos (9 CFR Part 98.12)

(2) Meat and meat products:

-Cured or cooked meat and meat products may be allowed entry under certain conditions as specified in 9 CFR Part 94.4.
-Dried or cured meat is allowed entry if it meets the following conditions: all bones have been removed, the meat was held in an unfrozen, fresh condition for at least

3 days, and then was thoroughly cured and dried to a minimum moisture to protein ratio of 2.25:1.
-Canned meat is allowed entry if it is deboned meat that has been commercially heat processed in a hermetically sealed container such that it is shelf stable without refrigeration.
-Cooked meat is also allowed entry, but the cooking process and establishment must be approved in advance by APHIS.

(3) Milk products:

-Milk products are addressed in 9 CFR Part 94.16.
-The following products are specifically exempt from this part and are therefore allowed unrestricted entry from FMD-affected countries: cheese (except cheese with liquid or containing other restricted items such as meat), butter, and butteroil. Also, such things as yogurt, cream liqueurs and chocolate products are not restricted.

-Milk products which are in concentrated liquid form and have been heat processed in a hermetically sealed container such that they are shelf stable without refrigeration are allowed entry.
-Dry milk and dry milk products may be allowed entry with consignment to approved establishments for further processing or storage.
-Other milk products, such as condensed milk, sterilized milk, casein and caseinates, lactose, etc. may be allowed entry under permit if the processing conditions are such that they would inactivate the FMD virus or if they are intended for industrial use.
-Milk and milk products which do not fall into the above categories are prohibited.

(4) Restricted entry products:
The following products are not allowed unrestricted entry from countries affected with FMD, but they are not completely prohibited either. This means that they can be imported without a permit under certain restrictions, with the primary restriction being consignment upon arrival to an approved establishment for further processing.

- untanned hides and skins (9 CFR Part 95.5)
- raw, unwashed wool, hair and bristles (9 CFR Part 95.7)
- glue stock, defined as [3]fleshings, hide cuttings and parings, tendons, or other collagenous parts of animal carcasses[2] (9 CFR Part 95.9)
- untreated bones, horns and hoofs (9 CFR Part 95.11)

- blood meal, blood albumin, bone meal, intestines and other animal byproducts for industrial use (9 CFR Part 95.15)
- glands, organs, ox gall or bile, bone marrow, and like materials (9 CFR Part 95.17)

(5) Restricted entry products - import permit required:
Many other processed products derived from ruminant or swine by-products may be allowed entry under import permit conditions. There is no consolidated list of these products, as new products are continuously being developed. An importer will submit a permit application form, detailing the processing conditions of the product. If it is determined that the process will inactivate the FMD virus, then a permit will be issued and the product will be allowed entry under those conditions.

The specific CFR citations can be accessed through the Internet at the Government Printing Office website. The URL for this site is as follows: www.access.gpo.gov/nara/cfr/index.html

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USDA NEWS RELEASE

United States Department of Agriculture • Office of Communications • 1400 Independence Avenue, SW
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*** CLARIFICATION ***
720-4623

Kevin Herglotz (202)

Release No. 0044A.01
(301)734-6464

Kimberley Smith

USDA ANNOUNCES ADDITIONAL MEASURES TO GUARD AGAINST FOOT-AND-MOUTH DISEASE

WASHINGTON, March 13, 2001--**The U.S. Department of Agriculture today announced it is temporarily prohibiting the importation of swine and ruminant, and any fresh swine or ruminant meat (chilled or frozen) and other products of swine and ruminants from the European Union. This does not include cooked pork products.**

This temporary action is being taken following confirmation of foot-and-mouth disease in France. On February 21, USDA announced similar actions regarding the United Kingdom and Northern Ireland. These measures are part of a coordinated prevention program to ensure the disease does not spread into the United States.

In recent weeks, USDA has stepped up measures to guard against foot-and-mouth disease. These actions include:

• **Temporarily prohibiting the importation of swine and ruminant, and any fresh swine or ruminant meat (chilled or frozen) and other products of swine and ruminants from the European Union.** These restrictions augment those already in place on ruminants and ruminant products to prevent the introduction of BSE into the U.S.;

• Prohibiting travelers from carrying into the United States any agricultural products, particularly animal products, that could spread the disease. Passengers are required to identify any farm contact to Customs and USDA officials. All baggage is subject to inspection. Violations could result in penalties of up to $1,000;

• Sending a team of experts (40 federal, state and University officials) to the European Union to monitor, evaluate and assist in containment efforts;

• Heightened alert at ports of entry and airports to ensure passengers, luggage and cargo are checked as appropriate. This includes placing additional inspectors and dog teams at airports to check incoming flights and passengers;

• Heightened alert and coordination with state agriculture officials and other USDA officials stationed around the globe to monitor the situation; and

• Public education campaign that includes additional signage in airports, public service announcements, information hotline, website, and other tools to inform the public about this important issue and steps they can take to prevent it from entering the United States.

FMD is a highly contagious and economically devastating disease of ruminants and swine. The United States has been free of FMD since 1929. FMD is one of the animal diseases that livestock owners dread most because it spreads widely and rapidly and because it has grave economic consequences. Humans are not susceptible to the disease.

Current information on foot-and-mouth disease and traveler questions and answers are available on the Internet at http://www.usda.gov/

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CC all VS LB

USDA United States Department of Agriculture Animal and Plant Health Inspection Service

For Passengers Traveling To The United States From FMD Infected Regions of the World

In response to the increasing number of foot-and-mouth disease (FMD) outbreaks worldwide, travelers to the United States from infected regions need to take steps to help prevent the accidental introduction of the disease into this country.

FMD is not considered a human health risk but humans can carry the virus on their clothing, shoes, body (particularly the throat and nasal passages) and personal items. The disease is extremely contagious and spreads easily among cloven-hoofed animals such as cattle, sheep, pigs, goats and deer. Introduction of FMD into this country would be disastrous to the American livestock industry andwildlife community. For this reason all visits to farms or other livestock facilties in FMD infected areas and all food items and other materials of plant or animal origin in the traveler's possession **must** be reported on the U.S. Customs Declaration Form upon entering the country.

The following preventive measures should be taken by travelers to the United States from FMD infected countries:

1. Avoid farms, sale barns, stockyards, animal laboratories, packing houses, zoos, fairs or other animal facilities for 5 days prior to travel.

2. Before travel to the United States, launder or dry clean all clothing and outerwear. All dirt and soil should be removed from shoes by thorough cleaning prior to wiping with cloth dampened with a bleach solution. (5 tablespoons of household bleach in 1 gallon of water). Luggage and personal items (including watches, cameras, laptops, CD players and cell phones), if soiled, should be wiped with a cloth dampened with a bleach solution.

3. Avoid contact with livestock or wildlife for 5 days after arrival in the United States. **Extra** precautionary measures should be taken by people traveling from farms in infected locales to visit or work on farms in the United States. It is advisable that employers or sponsors provide arriving travelers with a clean set of clothing that can be worn after the visitor showers and shampoos thoroughly. Visitor's traveling clothes should be laundered or dry cleaned immediately. Off-farm activities should be scheduled for the visitor's first 5 days in-country and contact with livestock or wildlife should be strictly avoided

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USDA:APHIS
:Veterinary Services

Mercer Corporate Park
320 Corporate Blvd.
Robbinsville NJ 08691

Phone: 609-259-8387
FAX: 609-259-2477
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To: *New Jersey Animal Product Exporters Approved Establishments*
From: *Anna Carolina Welsch, Acting AVIC*
cc:
Date: *March 15, 2001*
Subject: Recent ban of imported products from the European Union

Due to the recent occurrence of Foot and Mouth disease in Great Britain, Northern Ireland, and France, USDA-APHIS-Veterinary Services has prohibited the importation of certain animals, meat, and other animal products from the European Union. The enclosed information is being provided to clarify this ban.

Enclosed please find:

- March 14, 2001 Federal Register Docket 01-018-1 which banned the importation of certain animals, meat, and other animal products from Great Britain and Northern Ireland
- More Detailed Information on USDA Restrictions on Products from Countries with FMD - this document lists banned products and products which may still be imported without restriction. Some types of products may be allowed entry under an import permit.
- Fact sheets on Foot and Mouth Disease
- News Release
- Info for Passengers

Import permits may be obtained by contacting USDA-APHIS-Veterinary Services National Center for Import and Export, Permits and Information Services Unit at 301-734-3277. Additional information on Foot and Mouth Disease and USDA's response is available on the Internet at **www.usda.aphis.gov** Foot and Mouth Disease information is accessed by clicking on "Foot and Mouth Disease" under the Hot Topics Heading at the bottom of the home page.

Please call our office 9609-259-8387) if you have further questions.

ACW

Anna Carolina Welsch
Acting Area Veterinarian in Charge

Enclosures

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Reportable Diseases and Conditions

Overview

As an accredited veterinarian, you are responsible for notifying the State or Federal veterinarian of any undiagnosed or unusual disease conditions that are reportable and/or foreign. The State or Federal veterinarian will determine how the case is to be handled and give you specific instructions at that time. If the Area Veterinarian-in-Charge of your State determines that an investigation is warranted, a Federal Foreign Animal Disease Diagnostician will be assigned to the case. Most States provide a list of reportable diseases that should be used to supplement the list of diseases in table 6. Call your State or Federal veterinarian for such a list.

Table 6—Reportable diseases and conditions[1]

Avian
Avian influenza
Ornithosis
Psittacosis (chlamydiosis and ornithosis)
Salmonellosis caused by *Salmonella enteritidis* (SE)
Velogenic viscerotropic Newcastle disease
Bovine
Akabane
Anthrax
Bluetongue
Bovine babesiosis (Texas fever, piroplasmosis)
Bovine spongiform encephalopathy (BSE)
Brucellosis
Contagious bovine pleuropneumonia
East coast fever (coastal fever, theileriosis)
Ephemeral fever (3-day sickness)
Foot-and-mouth disease
Gonderiosis (theileriosis)
Heartwater
Hemorrhagic septicemia (Asiatic type 1 "shipping fever")
Ibaraki
Infectious petechial fever
Louping ill
Lumpy skin disease (pseudourticaria)
Malignant catarrhal fever
Paratuberculosis
Pseudorabies
Rift valley fever
Rinderpest (cattle plague)
Scabies
Screwworm
Sweating sickness (tick-borne toxicosis)
Tuberculosis
Trypanosomiasis (nagana)
Vesicular stomatitis
Wesselborne disease

Table 6—Reportable diseases and conditions[1]

Caprine–Ovine
Bluetongue
Borna disease
Brucellosis caused by *Brucella meletensis* and *B. ovis*
Caseous lymphadenitis
Contagious agalactia of sheep and goats
Contagious caprine pleuropneumonia
Foot-and-mouth disease
Goat and sheep pox
Gonderiosis (theileriosis)
Heartwater
Nairobi sheep disease
Peste des petits ruminants (kata)
Screwworm
Tuberculosis
Rift valley fever
Scabies
Scrapie
Vesicular stomatitis
Visna–Maedi (chronic progressive pneumonia)

Equine
African horse sickness
Babesiosis (piroplasmosis)
Contagious equine metritis
Dourine (equine trypanosomiasis)
Eastern equine encephalomyelitis
Epizootic lymphangitis
Equine infectious anemia
Equine rhinopneumonitis
Equine viral arteritis
Glanders
Rift valley fever
Ulcerative lymphangitis
Venezuelan equine encephalomyelitis
Vesicular stomatitis
Western equine encephalomyelitis

Porcine
African swine fever
Brucellosis
Foot-and-mouth disease
Hog cholera
Porcine babesiosis
Pseudorabies
Swine vesicular disease
Teschen disease (porcine encephalomyelitis)
Vesicular exanthema
Vesicular stomatitis

All species
Rabies
Exotic myiasis

[1] This list will vary from State to State.

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§ 94.20 Importation of pork from Sonora, Mexico.

Notwithstanding any other provisions of this part, fresh (chilled or frozen) pork from the State of Sonora, Mexico, may be imported into the United States under the following conditions:

(a) The pork is meat from swine that have been born, raised and slaughtered in Sonora;

(b) The pork has not been in contact with pork from regions other than those listed in §94.9(a) as regions where hog cholera is not known to exist; and

(c) An authorized official of Mexico certifies on the foreign meat inspection certificate required by §327.4 of this title that the above conditions have been met.

[62 FR 25443, May 9, 1997, as amended at 62 FR 56023, Oct. 28, 1997]

§ 94.21 Restrictions on importation of beef from Argentina.

Notwithstanding any other provisions of this part, fresh (chilled or frozen) beef from Argentina may be exported to the United States under the following conditions:

(a) The meat is beef that originated in Argentina;

(b) The meat came from bovines that were moved directly from the premises of origin to the slaughterhouse without any contact with other animals;

(c) The meat has not been in contact with meat from regions other than those listed in §94.1(a)(2);

(d) The meat came from bovines that originated from premises where foot-and-mouth disease and rinderpest have not been present during the lifetime of any bovines slaughtered for export of meat;

(e) Foot-and-mouth disease has not been diagnosed in Argentina within the previous 12 months;

(f) The meat came from bovines that originated from premises on which ruminants or swine have not been vaccinated with modified or attenuated live viruses for foot-and-mouth disease at any time during the lifetime of the bovines slaughtered for export of meat;

(g) The meat came from bovines that have not been vaccinated for rinderpest at any time during the lifetime of any of the bovines slaughtered for export of meat;

(h) The meat came from bovine carcasses that have been allowed to maturate at 40 to 50°F (4 to 10°C) for a minimum of 36 hours after slaughter and have reached a pH of 5.8 or less in the loin muscle at the end of the maturation period. Any carcass in which the pH does not reach 5.8 or less may be allowed to maturate an additional 24 hours and be retested, and, if the carcass still does not reach a pH of 5.8 or less after 60 hours, the meat from the carcass may not be exported to the United States;

(i) All bone, blood clots, and lymphoid tissue have been removed from the meat; and

(j) An authorized official of Argentina certifies on the foreign meat inspection certificate that the above conditions have been met.

[62 FR 34394, June 26, 1997, as amended at 62 FR 56024, Oct. 28, 1997]

PART 95—SANITARY CONTROL OF ANIMAL BYPRODUCTS (EXCEPT CASINGS), AND HAY AND STRAW, OFFERED FOR ENTRY INTO THE UNITED STATES

Sec.

AUTHORITY: 21 U.S.C. 111, 136, and 136a; 31 U.S.C. 9701; 7 CFR 2.22, 2.80, and 371.2(d).

SOURCE: 28 FR 5981, June 13, 1963, unless otherwise noted.

§95.1 Definitions.

Whenever in the regulations in this part the following words, names, or terms are used they shall be construed, respectively, to mean:

Administrator means the Administrator, Animal and Plant Health Inspection Service, or any individual authorized to act for the Administrator.

Animal and Plant Health Inspection Service means the Animal and Plant Health Inspection Service of the United States Department of Agriculture.

Animal byproducts means hides, skins, hair, wool, glue stock, bones, hoofs, horns, bone meal, hoof meal, horn meal, blood meal, meat meal, tankage, glands, organs, or other parts or products of ruminants and swine unsuitable for human consumption.

Approved chlorinating equipment means equipment approved by Veterinary Services as efficient for the disinfection of effluents against the contagions of foot-and-mouth disease and rinderpest.

Approved establishment means an establishment approved by Veterinary Services for the receipt and handling of restricted import animal byproducts.

Approved sewerage system means a drainage system equipped and operated so as to carry and dispose of sewage without endangering livestock through the contamination of streams or fields and approved by the Veterinary Services.

Approved warehouse means a warehouse having facilities approved by Veterinary Services for the handling and storage, apart from other merchandise, of restricted import products.

Blood meal means dried blood of animals.

Bone meal means ground animal bones and hoof meal and horn meal.

Department means the United States Department of Agriculture.

Deputy Administrator of Veterinary Services means the Deputy Administrator of Veterinary Services.

Glue stock means fleshings, hide cuttings and parings, tendons, or other collagenous parts of animal carcasses.

Hay and straw means dried grasses, clovers, legumes, and similar materials or stalks or stems of various grains, such as barley, oats, rice, rye, and wheat.

Inspector means an inspector of Veterinary Services.

Meat meal or tankage means the rendered and dried carcasses or parts of the carcasses of animals.

Region. Any defined geographic land area identifiable by geological, political, or surveyed boundaries. A region may consist of any of the following:

(1) A national entity (country);

(2) Part of a national entity (zone, county, department, municipality, parish, Province, State, etc.)

(3) Parts of several national entities combined into an area; or

(4) A group of national entities (countries) combined into a single area.

United States means the several States, the District of Columbia, Guam, the Northern Mariana Islands,

Puerto Rico, the Virgin Islands of the United States, and all other territories and possessions of the United States.

Veterinary Services means the Veterinary Services unit of the Animal and Plant Health Inspection Service, United States Department of Agriculture.

[28 FR 5981, June 13, 1963, as amended at 56 FR 19796, Apr. 30, 1991; 56 FR 63869, Dec. 6, 1991; 62 FR 56024, Oct. 28, 1997]

§ 95.2 Region of origin.

No products or materials specified in the regulations in this part shall be imported unless there be shown upon the commercial invoice, or in some other manner satisfactory to the Deputy Administrator, Veterinary Services, the name of the region of origin of such product or material: *Provided,* That the region of origin shall be construed to mean (a) in the case of an animal byproduct, the region in which such product was taken from an animal or animals, and (b) in the case of other materials, the region in which such materials were produced.

[28 FR 5981, June 13, 1963, as amended at 62 FR 56024, Oct. 28, 1997]

§ 95.3 Byproducts from diseased animals prohibited.

The importation of any animal byproduct taken or removed from an animal affected with anthrax, foot-and-mouth disease, or rinderpest is prohibited.

§ 95.4 Bone meal, blood meal, meat meal, offal, fat, glands, and serum from ruminants that have been in regions in which bovine spongiform encephalopathy exists.

(a) Except as provided in paragraphs (c) and (d) of this section, the importation of bone meal, blood meal, meat meal or tankage, offal, fat, and glands from ruminants that have been in any region listed in § 94.18 of this chapter, is prohibited.

(b) Except as provided in paragraphs (c) and (d) of this section, the importation of serum from ruminants that have been in any region listed in § 94.18 of this chapter is prohibited, except that serum from ruminants may be imported for scientific, educational, or research purposes if the Administrator determines that the importation can be made under conditions that will prevent the introduction of bovine spongiform encephalopathy into the United States. Serum from ruminants imported in accordance with this paragraph must be accompanied by a permit issued by the Animal and Plant Health Inspection Service in accordance with § 104.4 of this chapter, and must be moved and handled as specified on the permit.

(c) *Articles for cosmetics.* The importation of collagen, collagen products, amniotic liquids or extracts, placental liquids or extracts, serum albumin, and serocolostrum, derived from ruminants that have been in any region listed in § 94.18 of this chapter is prohibited unless the following conditions have been met:

(1) The article must be imported for use as an ingredient in cosmetics.

(2) The person importing the article must obtain a United States Veterinary Permit for Importation and Transportation of Controlled Materials and Organisms and Vectors by filing a permit application on VS form 16-3[1]

(3) The permit application must state the intended use of the article and the name and address of the consignee in the United States.

(d) *Transit shipment of articles.* Articles that are prohibited importation into the United States in accordance with this section may transit the United States for immediate export if the following conditions are met:

(1) The person moving the articles must obtain a United States Veterinary Permit for Importation and Transportation of Controlled Materials and Organisms and Vectors by filing a permit application on VS form 16-3[2]

(2) The articles must be sealed in leakproof containers bearing serial numbers during transit. Each container must remain sealed during the

[1] VS form 16-3 may be obtained from the Animal and Plant Health Inspection Service, Veterinary Services, National Center for Import-Export, 4700 River Road Unit 38, Riverdale, Maryland 20737-1231.

[2] VS form 16-3 may be obtained from the Animal and Plant Health Inspection Service, Veterinary Services, National Center for Import-Export, 4700 River Road Unit 38, Riverdale, Maryland 20737-1231.

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entire time that it is in the United States.

(3) The person moving the articles shall notify, in writing, the Plant Protection and Quarantine Officer at both the place in the United States where the articles will arrive and the port of export prior to such transit. The notification must include the:

(i) United States Veterinary Permit for Importation and Transportation of Controlled Materials and Organisms and Vectors permit number;

(ii) Times and dates of arrival in the United States;

(iii) Times and dates of exportation from the United States;

(iv) Mode of transportation; and

(v) Serial numbers of the sealed containers.

(4) The articles must transit the United States in Customs bond.

(Approved by the Office of Management and Budget under control number 0579-0015)

[56 FR 63869, Dec. 6, 1991, as amended at 62 FR 56024, Oct. 28, 1997]

§95.5 Untanned hides and skins; requirements for unrestricted entry.

Untanned hides and/or skins of cattle, buffalo, sheep, goats, other ruminants, and swine which do not meet the conditions of requirements specified in any one of paragraphs (a) to (e) of this section shall not be imported except subject to handling and treatment in accordance with §95.6 after arrival at the port of entry:

(a) Hides or skins originating in and shipped directly from a region not declared by the Secretary of Agriculture to be infected with foot-and-mouth disease or rinderpest may be imported without further restriction.

(b) Hides or skins may be imported without other restriction if found upon inspection by an inspector, or by certificate of the shipper or importer satisfactory to said inspector, to be hard dried hides or skins.

(c) Abattoir hides or skins taken from animals slaughtered under national government inspection in a region[1] and in an abattoir in which is maintained an inspection service determined by the Secretary of Agriculture to be adequate to assure that they have been removed from animals found at time of slaughter to be free from anthrax, foot-and-mouth disease, and rinderpest, and to assure further the identity of such materials until loaded upon the transporting vessel, may be imported without other restriction if accompanied by a certificate bearing the seal of the proper department of such national government and signed by an official veterinary inspector of such region showing that the therein described hides or skins were taken from animals slaughtered in such specified abattoir and found free from anthrax, foot-and-mouth disease, and rinderpest.

(d) Hides or skins may be imported without other restriction if shown upon inspection by an inspector, or by certificate of the shipper or importer satisfactory to said inspector, to have been pickled in a solution of salt containing mineral acid and packed in barrels, casks, or tight cases while still wet with such solution.

(e) Hides or skins may be imported without other restriction if shown upon inspection by an inspector, or by certificate of the shipper or importer satisfactory to said inspector, to have been treated with lime in such manner and for such period as to have become dehaired and to have reached the stage of preparation for immediate manufacture into products ordinarily made from rawhide.

(Approved by the Office of Management and Budget under control number 0579-0015)

[28 FR 5981, June 13, 1963, as amended at 48 FR 57472, Dec. 30, 1983; 62 FR 56024, Oct. 28, 1997]

§95.6 Untanned hides and skins; importations permitted subject to restrictions.

Hides or skins offered for importation which do not meet the conditions or requirements of §95.5 shall be handled and treated in the following manner after arrival at the port of entry:

[1] Names of regions of this character will be furnished upon request to the Animal and Plant Health Inspection Service, Veterinary Services, National Center for Import-Export, 4700 River Road Unit 38, Riverdale, Maryland 20737-1231.

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equivalent of 4.25 gallons of 100 percent ethyl acetate. It is used in accordance with good feeding practices in ruminant feed supplements as a source of added energy.

[46 FR 52333, Oct. 27, 1981]

§ 584.700 Hydrophobic silicas.

(a) *Product.* Amorphous fumed hydrophobic silica or precipitated hydrophobic silica (CAS Reg. No. 68611–0944–099, silane, dichlorodimethyl-, reaction products with silica).

(b) *Conditions of use.* An anticaking/free-flow agent in vitamin preparations for animal feed.

(c) *Limitations.* Not to exceed 5 percent in the vitamin preparation. It shall be used in accordance with good manufacturing or feeding practices. It must be of purity suitable for intended use, and it must comply with the following specifications:

(i) Amorphous fumed hydrophobic silica: Not less than 99.0 percent silicon dioxide after ignition. Not more than 3 ppm arsenic. Not more than 0.003 percent heavy metals (as lead). Not more than 10 ppm lead. Not more than 2.5 percent loss on drying. Not more than 2 percent loss on ignition after drying. Not more than 1 percent insoluble substances. Not more than 50 parts per million dichlorodimethylsilane.

(ii) Precipated hydrophobic silica: Not less than 94.0 percent silicon dioxide after ignition. Not more than 3 ppm arsenic. Not more than 0.003 percent heavy metals (as lead). Not more than 10 ppm lead. Not more than 7 percent loss on drying. Not more than 8.5 percent loss on ignition after drying. Not more than 5 percent soluble ionizable salts (as sodium sulfate). Not more than 1 percent insoluble substances. Not more than 50 parts per million dichlorodimethylsilane.

[61 FR 43453, Aug. 23, 1996]

PART 589—SUBSTANCES PROHIBITED FROM USE IN ANIMAL FOOD OR FEED

Subpart A—General Provisions

Sec.

Subpart B—Listing of Specific Substances Prohibited From Use in Animal Food or Feed

AUTHORITY: 21 U.S.C. 321, 342, 343, 348, 371.

Subpart A—General Provisions

§ 589.1 Substances prohibited from use in animal food or feed.

(a) The substances listed in this part have been prohibited from use in animal food or feed by the Food and Drug Administration because of a determination that they present a potential risk to the public health or have not been shown by adequate scientific data to be safe for use in such food or feed. Use of any of these substances in violation of this part causes the animal food or feed involved to be adulterated and in violation of the Act.

(b) This part includes only a partial list of substances prohibited from use in animal food or feed; it is for easy reference purposes and is not a complete list of substances that may not lawfully be used in such animal food or feed. No substance may be used in animal food or feed unless it meets all applicable requirements of the Act.

(c) The Food and Drug Administration either on its own initiative or on behalf of any interested person who has submitted a petition, may publish a proposal to establish, amend, or repeal a regulation under this part on the basis of new scientific evaluation or information. Any such petition shall include an adequate scientific basis to support the petition, shall be the form set forth in § 571.1 of this chapter, and will be published in the FEDERAL REGISTER for comment if it contains reasonable ground.

[45 FR 28319, Apr. 29, 1980]

Subpart B—Listing of Specific Substances Prohibited From Use in Animal Food or Feed

§ 589.1000 Gentian violet.

The Food and Drug Administration has determined that gentian violet has

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not been shown by adequate scientific data to be safe for use in animal feed. Use of gentian violet in animal feed causes the feed to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (the act), in the absence of a regulation providing for its safe use as a food additive under section 409 of the act, unless it is subject to an effective notice of claimed investigational exemption for a food additive under § 570.17 of this chapter, or unless the substance is intended for use as a new animal drug and is subject to an approved application under section 512 of the act or an effective notice of claimed investigational exemption for a new animal drug under part 511 of this chapter.

[56 FR 40507, Aug. 15, 1991]

§ 589.1001 Propylene glycol in or on cat food.

The Food and Drug Administration has determined that propylene glycol in or on cat food has not been shown by adequate scientific data to be safe for use. Use of propylene glycol in or on cat food causes the feed to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (the act), in the absence of a regulation providing for its safe use as a food additive under section 409 of the act, unless it is subject to an effective notice of claimed investigational exemption for a food additive under § 570.17 of this chapter, or unless the substance is intended for use as a new animal drug and is subject to an approved application under section 512 of the act or an effective notice of claimed investigational exemption for a new animal drug under part 511 of this chapter.

[61 FR 19544, May 2, 1996]

§ 589.2000 Animal proteins prohibited in ruminant feed.

(a) *Definitions*—(1) *Protein derived from mammalian tissues* means any protein-containing portion of mammalian animals, excluding: Blood and blood products; gelatin; inspected meat products which have been cooked and offered for human food and further heat processed for feed (such as plate waste and used cellulosic food casings); milk products (milk and milk proteins); and any product whose only mammalian protein consists entirely of porcine or equine protein.

(2) *Renderer* means any firm or individual that processes slaughter byproducts, animals unfit for human consumption, or meat scraps. The term includes persons who collect such materials and subject them to minimal processing, or distribute them to firms other than renderers (as defined here) whose intended use for the products may include animal feed. The term includes renderers that also blend animal protein products.

(3) *Blender* means any firm or individual which obtains processed animal protein from more than one source or from more than one species, and subsequently mixes (blends) or redistributes an animal protein product.

(4) *Feed manufacturer* includes manufacturers of complete and intermediate feeds intended for animals, and includes on-farm in addition to off-farm feed manufacturing and mixing operations.

(5) *Nonmammalian protein* includes proteins from nonmammalian animals.

(6) *Distributor* includes persons who distribute or transport feeds or feed ingredients intended for animals.

(7) *Ruminant* includes any member of the order of animals which has a stomach with four chambers (rumen, reticulum, omasum, and abomasum) through which feed passes in digestion. The order includes, but is not limited to, cattle, buffalo, sheep, goats, deer, elk, and antelopes.

(b) *Food additive status.* The Food and Drug Administration has determined that protein derived from mammalian tissues for use in ruminant feed is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act (the act). The use or intended use in ruminant feed of any material that contains protein derived from mammalian tissues causes the feed to be adulterated and in violation of the act, unless it is the subject of an effective notice of claimed investigational exemption for a food additive under § 570.17 of this chapter.

(c) *Requirements for renderers that are not included in paragraph (e) of this section.* (1) Renderers that manufacture products that contain or may contain

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protein derived from mammalian tissues and that are intended for use in animal feed shall take the following measures to ensure that materials identified in paragraph (b) of this section are not used in the feed of ruminants:

(i) Label the materials as follows: "Do not feed to cattle or other ruminants"; and

(ii) Maintain records sufficient to track the materials throughout their receipt, processing, and distribution, and make the copies available for inspection and copying by the Food and Drug Administration.

(2) Renderers described in paragraph (c)(1) of this section will be exempted from the requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section if they:

(i) Use exclusively a manufacturing method that has been validated by the Food and Drug Administration to deactivate the agent that causes transmissible spongiform encephalopathy (TSE) and whose design has been made available to the public;

(ii) Use routinely a test method that has been validated by the Food and Drug Administration to detect the presence of the agent that causes TSE's and whose design has been made available to the public. Renderers whose products test positive for agents that cause TSE's must comply with paragraphs (c)(1)(i) and (c)(1)(ii) of this section. Records of the test results shall be made available for inspection by the Food and Drug Administration; or

(iii) Use exclusively a method for controlling the manufacturing process that minimizes the risk of the TSE agent entering the product and whose design has been made available to the public and validated by the Food and Drug Administration.

(3) Renderers described in paragraph (c)(1) of this section will be exempted from the requirements of paragraph (c)(1)(ii) of this section if they use a permanent method, approved by FDA, to make a mark indicating that the product contains or may contain protein derived from mammalian tissue. If the marking is by the use of an agent that cannot be detected on visual inspection, the renderer must use an agent whose presence can be detected by a method that has been validated by the Food and Drug Administration and whose design has been made available to the public.

(d) *Requirements for protein blenders, feed manufacturers, and distributors that are not included in paragraph (e) of this section.* (1) Protein blenders, feed manufacturers, and distributors that manufacture, blend, process, and distribute products that contain or may contain protein derived from mammalian tissues shall comply with paragraph (c)(1) of this section.

(2) Protein blenders, feed manufacturers, and distributors, shall be exempt from paragraphs (d)(1) of this section if they:

(i) Purchase animal products from renderers that certified compliance with paragraph (c)(2) of this section or purchase such materials from parties that certify that the materials were purchased from renderers that certified compliance with paragraph (c)(2) of this section; or

(ii) Comply with the requirements of paragraph (c)(2) of this section where appropriate.

(3) Protein blenders, feed manufacturers, and distributors, shall be exempt from paragraph (c)(1)(ii) of this section if they:

(i) Purchase animal protein products that are marked in accordance with paragraph (c)(3) of this section or purchase such materials from renderers that certified compliance with paragraph (c)(3) of this section, or purchase such materials from parties that certify that the materials were purchased from renderers that certified compliance with paragraph (c)(3) of this section; or

(ii) Comply with the requirements of paragraph (c)(3) of this section where appropriate.

(4) Pet food products that are sold or are intended for sale at retail and feeds for nonruminant laboratory animals are exempt from the labeling requirements in paragraphs (c) and (d) of this section. However, if the pet food products or feeds for nonruminant laboratory animals are sold or are intended for sale as distressed or salvage items, then such products shall be labeled in

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accordance with paragraph (c) or (d) of this section, as appropriate.

(5) Copies of certifications as described in paragraphs (d)(2) and (d)(3) of this section, shall be made available for inspection and copying by the Food and Drug Administration.

(e) *Requirements for persons that intend to separate mammalian and nonmammalian materials.* (1) Renderers, protein blenders, feed manufacturers, distributors, and others that manufacture, process, blend and distribute both products that contain or may contain protein derived from mammalian tissues or feeds containing such products, and protein products from other animal tissues or feeds containing such products, and that intend to keep those products separate shall:

(i) Comply with paragraphs (c)(1) or (d)(1) of this section as appropriate except that the labeling requirement shall apply only to products that contain or may contain protein derived from mammalian tissues or feeds containing such products;

(ii) In the case of a renderer, obtain nonmammalian or pure porcine or pure equine materials only from single-species slaughter facilities;

(iii) Provide for measures to avoid commingling or cross-contamination;

(A) Maintain separate equipment or facilities for the manufacture, processing, or blending of such materials; or

(B) Use clean-out procedures or other means adequate to prevent carry-over of products that contain or may contain protein derived from mammalian tissues into animal protein or feeds that may be used for ruminants; and

(iv) Maintain written procedures specifying the clean-out procedures or other means, and specifying the procedures for separating products that contain or may contain protein derived from mammalian tissue from all other protein products from the time of receipt until the time of shipment.

(2) Renderers, blenders, feed manufacturers, and distributors will be exempted from applicable requirements of paragraph (e)(1) of this section, if they meet the criteria for exemption under paragraphs (c)(2) or (c)(3) of this section, and (d)(2) or (d)(3) of this section.

(f) *Requirements for establishments and individuals that are responsible for feeding ruminant animals.* Establishments and individuals that are responsible for feeding ruminant animals shall maintain copies of purchase invoices and labeling for all feeds containing animal protein products received, and make the copies available for inspection and copying by the Food and Drug Administration.

(g) *Adulteration and misbranding.* (1) Animal protein products, and feeds containing such products, that are not in compliance with paragraphs (c) through (f) of this section, excluding labeling requirements, will be deemed adulterated under section 402(a)(2)(C) or 402(a)(4) of the act.

(2) Animal protein products, and feeds containing such products, that are not in compliance with the labeling requirements of paragraphs (c) through (f) of this section will be deemed misbranded under section 403(a)(1) or 403(f) of the act.

(h) *Inspection; records retention.* (1) Records that are to be made available for inspection and copying, as required by this section, shall be kept for a minimum of 1 year.

(2) Written procedures required by this section shall be made available for inspection and copying by the Food and Drug Administration.

[62 FR 30976, June 5, 1997]

EFFECTIVE DATE NOTE: At 62 FR 30976, June 5, 1997, § 589.2000 was added. Paragraph (e)(1)(iv) of this section contains information collection and recordkeeping requirements and will not become effective until approval has been given by the Office of Management and Budget.

PARTS 590–599 [RESERVED]

Bundesinstitut für Arzneimittel und Medizinprodukte BfArM

[German Federal Institute for Drugs and Medical Products]

Notification on the Marketing Authorisation and registration of drugs

Measures to avert risks associated with drugs, stage II

(Finished drugs which require Marketing Authorisation or registration for which the BfArM is responsible and which contain material derived from bovine liver, pancreas, lung, jejunum, distal colon, bone marrow, thymus, peripheral nerves, nasal mucous membrane, heart, uterus, skeletal muscle, tendons, bones, cartilage, connective tissue, skin, tallow, hair, salivary glands, thyroid gland, mammary glands, kidneys, ovaries, testicles, prostate gland, seminal vesicles, semen, blood, saliva, bile, milk, urine, faeces, foetal tissue or other bovine organs or tissue, with the exception of the finished drugs stated in the notification of 25 September 1995[1])

28 March 1996

On 25 September 1995 (Federal Bulletin, page 11604), a notification was issued which ordered restrictive measures to be taken to reduce the risk of BSE transmission for drugs containing material derived from bovine brain etc. or spleen etc.

As a consequence of the notification by the Bundesgesundheitsamt (BGA) "Notification on the safety requirements for drugs produced from body parts of cattle, sheep or goats, for prevention of the risk of transmission of BSE or scrapie" (Federal Bulletin, page 1851) of 16 February 1994, most pharmaceutical companies have already taken individual measures to reduce the risk of BSE transmission - with the aforementioned drugs. The following directive is now issued to ensure the complete regulation of relevant drugs which contain bovine body material, including those with a lower risk of infectivity and which may not have been covered before.

Notice

1. The Marketing Authorisation for drugs that contain material derived from:

- liver, pancreas, lung, jejunum, distal colon, bone marrow, thymus, peripheral nerves, nasal mucous membrane

as well as from

- heart, uterus, skeletal muscle, tendons, bones, cartilage, connective tissue, skin, tallow, hair, salivary glands, thyroid gland, mammary glands, kidneys, ovaries,

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[1] cf. Notification of German Bundesgesundheitsamt of 12 August 1991 (BAnz., page 5541) and Notification of BfArM of 11 December 1995 (BAnz. 1996, page 1545)

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testicles, prostate gland, seminal vesicles, semen, blood, saliva, bile, milk, urine, faeces, of cattle of any age as well as

- any type of foetal tissue

derived from cattle will be suspended until 30 September 1997, and the drugs concerned will be recalled. The recall will become effective 4 weeks after publication of this notice.

2. For registered homeopathic drugs that correspond to the drugs mentioned under 1. with regard to the body parts of cattle they contain the registration will be cancelled until 30 September 1997 and the drugs concerned will be recalled. The recall will become effective 4 weeks after publication of this notice.

3. Drugs are exempt from the directives contained in 1. and 2. if they are manufactured in such a way (and are placed on the market with product information to this effect) that, when used as directed, the risk to patients of becoming infected with the pathogens of bovine spongiform encephalopathy (BSE) is very probably less than the risk of contracting the corresponding spongiform encephalopathy, Creutzfeldt-Jakob disease, which occurs "naturally" in man, i.e. according to the prevailing level of scientific knowledge, if the risk of BSE infection caused by the drug concerned is not greater than 1 : 1 million.

   This requirement can only be considered to have been fulfilled if, in accordance with the analysis presented in the Appendix, the exponent sum of the safety calculation that a BSE infection will not be transmitted is at least 20.

4. Insofar as this has not already been effected, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) must be separately notified for each individual drug affected by 3. that the required safety level is guaranteed according to the criteria mentioned. This must be demonstrated by submitting the documents mentioned in the Appendix (Part C). This directive must be complied with immediately and no later than 2 weeks after publication of this notice.

5. Pharmaceutical companies that have already assessed their drugs on the basis of the aforementioned notification published by the Bundesgesundheitsamt (BGA) in February 1994 and have submitted documents to the BGA/BfArM are requested to determine which obligations they have to fulfil to meet the altered safety criteria and requirements presented in this notice.

6. The directive contained in 1. is immediately enforceable in accordance with paragraph 30, section 3, clause 2 and the directive contained in 5. in respect of registered drugs is immediately enforceable in accordance with paragraph 28, section 3c, clause 2 of the AMG (German Drug Law).

   Immediate enforcement is decreed for the directives contained in 2. and 5. in respect of registered homeopathic drugs and for the recall according to 1. and 2. in accordance with paragraph 80, section 2, No. 4 of the VwGO (Administrative Court Ordinance).

7. Further limiting measures by the EU Commission or by legal regulations shall not be affected by this.

8. The measures described in 1. to 6. shall not be applicable to drugs produced according to the provisions made in the aforementioned 3. notification of 11 December 1995 on gelatin and lactose if these ingredients are used only as excipients.
9. Nor shall the measures described in 1. to 6. be currently applicable to drugs - except for those stated in 8. - if the aforementioned ingredients are used only as excipients.
   A separate regulation will be issued for these drugs.

Reasoning

1. Legal principles

This directive is based on the provisions of paragraph 30, section 1 in conjunction with paragraph 25, section 2, No. 5; paragraph 28, sections 1 and 3c; paragraph 39, section 1; and paragraph 69, section 1, clause 3 of the German Drug Law of 24 August 1976, which was last amended by the Fifth Amendment the Drug Law of 9 August 1994 (Federal Bulletin I, page 2071, of the AMG). This was deemed necessary, based on the available scientific knowledge and taking into account the statements received after publication of the aforementioned notification, in order to invalidate the reasonably founded suspicion of potentially lethal effects connected with the use of the aforementioned drugs, which are associated with the risk of bovine spongiform encephalopathy (BSE) pathogens being transmitted to patients.

Since there is reasonable cause, according to current medical scientific knowledge, to suspect harmful effects from drugs that do not fulfil the safety requirements, in the sense of showing a sufficiently low theoretical potential for the transmission of pathogens, the suspension of the Marketing Authorisation of these drugs had to be decreed in accordance with paragraph 30, section 1, clauses 1 and 3 in conjunction with paragraph 25, section 2, No. 5 of the AMG. Suspension, a milder measure than revocation, makes it possible for the pharmaceutical company to fulfil the safety requirements, for example by technical advances or other measures. The term proposed of approximately 1½ years appears to be adequate and appropriate for this purpose. If the safety requirements can be fulfilled within a shorter period, it is possible to apply for the suspension directive to be revoked.

The temporary suspension of the registration of homeopathic drugs that do not fulfil the safety requirements is implemented in accordance with paragraph 3, section 1 and section 3, clause 2 of the directive on homeopathic drugs of 15 March 1978 (Federal Bulletin I, page 401) in conjunction with paragraph 39, section 2, No.4 of the AMG, since there is reasonable cause to suspect a potential (over and above the clinically acceptable) lethal risk for the registered drugs. The suspension is equivalent to that imposed for drugs with Marketing Authorisation. In accordance with immediate implementation regulations as stipulated in paragraph 30, section 3 of the AMG, immediate suspension is to be decreed in accordance with paragraph 80, section 2, No. 4 of the VwGO as further use of the drugs during the term required for appeals proceedings may lead to irreversible damage to health or to death. The public interest in preventing such hazards outweighs the economic interests of the pharmaceutical manufacturers concerned.

The provision of paragraph 28, section 3c of the AMG, newly introduced by the Fifth Amendment to the AMG, empowers the competent higher federal authority to issue directives for reasons of risk prevention to ensure that specific requirements are complied with and specific measures and procedures are applied in the production and control of drugs and their starting materials that are of biological origin. This empowerment was implemented here in order to reduce, as far as possible, the risks connected with the use of the drugs mentioned. Because the pathogenicity of the pathogens of bovine spongiform encephalopathy (BSE) in humans cannot be ruled out and because of the life-threatening nature of the disease in the event of infection, all precautionary measures must be taken to prevent such pathogens being transmitted to patients receiving treatment with these drugs. Compliance with the requirements mentioned under No. 3 of this notice, with appropriate proof by submitting the documents mentioned in the Appendix, Part C, is required in order to be able to assume that the use of such drugs is harmless according to the prevailing level of scientific knowledge.

Insofar as the drugs concerned are registered homeopathic drugs, the amendment of paragraph 28, section 3c of the AMG does not apply in accordance with paragraph 39, section 1 of the AMG, so that the directives are based on paragraph 30, section 1, No. 25, section 2, No. 5, and 28, section 1 of the AMG in conjunction with paragraph 36 of the VwVfG (German Administrative Procedural Law). Less severe measures than cancellation, they are justified and necessary in order to prevent serious health hazards as a result of the use of drugs that do not fulfil the safety requirements mentioned.

At the same time, for those drugs for which compliance with the safety requirements in accordance with No. 3 of this notice has not been demonstrated, it was necessary to decree their recall in accordance with paragraph 69, section 1, clause 3 of the AMG and the immediate enforcement of this measure in accordance with paragraph 80, section 2, No. 4 of the VwGO by the appropriate higher federal authority. Because severe consequences from the use of such drugs cannot be ruled out, in the interest of effective prevention of health hazards, any drugs that are already on the market must not be allowed to be used unintentionally. It is therefore necessary that such drugs be returned to the pharmaceutical company within the term stated under No. 1 and 2 of this notice. It is not possible to wait for the period required for appeals proceedings, which might take many years, since infections with lethal risks must be avoided at all costs.

2. Requirement to take action

The specifications here set out for determining the risk of contamination of drugs with BSE pathogens, the risk of BSE pathogen transmission via medicinal products, and the measures to be taken for effectively reducing the risk of such transmission are based on currently available medical data.

Dissemination of BSE

Initial concern over the possible contamination of animal material-based medicinal products with BSE pathogens was triggered by the BSE epidemic in the UK in the

late 80s. This disease had previously not been observed in cattle, and was probably a result of transmission to cattle of the spongiform encephalopathy (SE) pathogen causing scrapie in sheep and goats. It is postulated that the cattle were originally infected by being fed fodder which contained meal made of scraps remaining after the slaughter of sheep (ACF) infected with scrapie, and which was processed under conditions which did not fully inactivate the very heat resistant SE pathogen. At the same time as the incidence of BSE was increasing in cattle in the UK, there were also increasing reports of cases of SE disease in British domestic cats and in large cats in British zoos. Shortly thereafter, cases of BSE were reported in other countries; these were mainly (perhaps exclusively) in animals imported from the UK or which had been fed animal material fodder originating from the UK. Individual cases of scrapie and of BSE in cattle imported from Great Britain have also occurred in the Federal Republic of Germany.

Risks for humans

Humans must be regarded as being at risk of this SE epidemic in cattle for several reasons:

- Transmissible SE diseases are also found in man. Creutzfeldt-Jakob disease (CJD), and the related biochemical and histological alterations in the brain, cannot be differentiated, in terms of symptoms, from related diseases occurring in animals. Following several years of incubation, CJD causes extensive organic and functional damage to the CNS, and will prove fatal, as far as current medical data has shown, several months after becoming manifest. At present, the disease is impossible to diagnose during the incubation period or to treat following manifestation.

- Man is exposed to animal materials derived from cattle in the form of both foodstuffs and medicinal products. The risk of transmission of SE pathogens via parenterally administered drugs (here, classes APL-0 to APL-4) is far greater than the risk of transmission via the route by which the disease has actually been transmitted between animals.

- It was previously believed that it was impossible for the pathogen causing scrapie in sheep to infect cattle. As this transmission has apparently taken place, the question arises of whether an animal SE disease is also transferable to man, particularly in view of the fact that a possible genetic predisposition in individuals has not yet been fully examined.

- SE pathogens which have been transmitted from one animal species to another have been found to more readily infect a third species. There is thus the possibility that, although the scrapie pathogen may not (or with a very low risk) be transmitted from sheep to man, it may more easily be transmitted from cattle to man as the species barrier will have altered. This postulate is supported by the fact that the BSE pathogen can be far more easily transmitted to the cat than can the scrapie pathogen.

- It has proved possible, under experimental conditions, to transmit SE pathogens from ruminants to monkeys.

- Over the past few years (and particularly over the past few months) in the UK, several reports of SE disease in man (some of which were fatal) have been attributed by British scientists (and on 19 March 1996 by the British government) to possible infection with BSE. The SE disease in these cases occurred in young patients and was both clinically and histopathologically different from the sporadic and well-known CJD. As this type of SE disease in man has been reported only in the UK, a causal connection with the BSE epidemic in the UK has been established.

On the basis of current data, it is impossible to state, with anything approaching certainty, how high the risk of transmission of BSE or scrapie infections is to man. However, taking into account the serious nature of the disease, and the extent of exposure to possible carriers, it is essential that effective measures be taken, as specified in this notification, to reduce the risk of possible transmission.

3. Intention of adequate and defined measures to guarantee a minimal risk of infection

3.1 Orientation towards the incidence of Creutzfeldt-Jakob disease

The requirement that the risk of BSE transmission must be below 1 : 1 million, even under the most unfavourable conditions, derives from the incidence of spontaneously occurring CJD in humans, which is 1 : 1 million persons per year. By relating the safety requirements to this value, the commensurability of the decreed measures is preserved in the sense that any possible disadvantage from restriction is accepted only in the interest of the advantage of reducing a risk that is still of consequence even in relation to an unavoidable risk of the same type.

3.2 Orientation towards animal experiments

The decision on which measures were necessary was also based on the assumptions that a) patients are not protected by a species barrier against BSE pathogens and that b) humans will contract the disease in the event of exposure to BSE pathogens which are possibly pathogenic to humans with a probability as great as that found for experimental animal SE transmission in especially sensitive animals (infection of mice and hamsters with scrapie pathogens adapted to these species). This is justified by the fact that no findings are currently available that reliably prove the opposite. There is therefore no factual argument for estimating the risk of infection to be lower by any specific magnitude than in mice or hamsters following homologous administration. If there is a species barrier and humans are less susceptible to BSE pathogens, this will have the effect of being an additional safety factor.

4. Instructions for the determination of the safety of every individual drug and corresponding modifications, where necessary

The Appendix includes a detailed table for analysis of the BSE transmission potential of individual drugs, which includes all relevant factors for risk determination, and thus provides maximal flexibility for the required modifications.

Note:

All documents to be submitted according to 5. must state the Marketing Authorisation or registration number, or entry or filing number, and clearly state the reference "BSE notice" in the covering letter and on the outer envelope.

We would like to explicitly point out that this graduated plan procedure also concerns those homeopathic drugs which, according to the regulations in paragraph 38, section 1 of the AMG, are released from the obligation of registration providing less than 1000 packs are marketed annually.

It is considered necessary that the pharmaceutical companies concerned conduct the stipulated safety measures for these drugs also. Compliance with the requirements will be supervised by the respective responsible official authority.

Instructions on available legal remedies

You have the right to raise an objection against this notice within 4 weeks of publication. Any objection should be registered with, or sent in writing to, the Bundesinstitut für Arzneimittel und Medizinprodukte, Seestraße 10, 13353 Berlin.

Berlin, 28 March 1996
GV7-A 309-10113/96

Bundesinstitut für Arzneimittel und Medizinprodukte
PP
Prof. Dr. F.W.Hefendehl

Quantitative classification of the safety of individual medicinal products and the measures to be carried out, where necessary, to minimise the risk of transmission

This description is subdivided into sections:

- instructions for use in determining the potential infectivity of BSE for an individual drug
- an accompanying explication with reference to scientific publications
- a list of the required documents for information, including
- a tabular schedule for obtaining a rapid general idea of the safety characteristics of a drug.

A Instructions to determine the safety and safety deficiencies concerning potential infectivity of individual drugs by BSE. This is accomplished through analysis and classification of risk-related characteristics

A 1 Principle

The following schedule must be followed to determine whether the safety of a drug, regarding its potential BSE infectivity, is adequate. Firstly, the "actual value" for the safety of the drug (dependent on the production process and the chosen route of application) is quantified. Potential hazard is qualified on the basis of six of the most important risk-determining parameters:

1. Country of origin and keeping of animals (including country, herd and fodder)
2. Type of starting material used (organs, tissue)
3. Methods used to inactivate or remove potential SE pathogens
4. Quantities of animal starting material required to produce one daily dose of the product
5. Number of daily doses
6. Route of administration.

A logarithmic scale for each of these parameters is divided into sections, each with an exponent of 10. The scale thus reflects reduction of risk or increase in safety. The start of the scale represents the worst case which could be realistically assumed for a drug (0 safety), and further sections represent other determinants in connection with production or use of the medication which will reduce the risk of transmission (increase safety).

Sections representing actual product characteristics are termed "classes", and these are identified by a three letter abbreviation for the parameter, and by a number which is the exponent of 10 representing the relative decrease in risk (increase in safety) this class represents in comparison with the start of the scale.

In order to evaluate a product in terms of its potential risk, it will be "classified" on each of the six scales. The class exponents expressing the relative safety of the product for each of the six aspects are then added together as an exponent sum,

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and the result will show by what exponent of 10 the product is probably safer overall in comparison with the worst case.

(The exponent sum total must be at least 20 before the product can be assumed to comply with the specifications for safety in use stipulated in the notice.)

A 2 Method of classification

Preliminary remarks

a) All of the starting materials discussed here may be used for drug production only if the meat and the by-products from slaughtering are obtained in accordance with the meat hygiene regulations, and if the animals' bodies and the by-products from slaughtering are examined and judged to comply with regulations.

b) In the case of drugs containing several different constituents affected by this notice (e.g. from various organs or tissues) or several similar types of constituents which were produced according to different methods, each individual one of these components must be separately classified. For a final assessment of the finished drug, see section A 3.

c) The classification of drugs in relation to the last three parameters of the aforementioned list refers to the indication bearing the highest risk (i.e. the smallest exponent), as results from the Marketing Authorisation or registration status. If there is interdependence between various characteristics of application (for example, if different daily doses relate to particular indications or times of administration), then the constellation with the lowest levels of safety limited by the sum of these characteristics, e.g. with the smallest partial sum of the exponents (for the indication-related parameters), must be established.

A 2.1 Parameter: Origin and keeping of cattle (HRK)

Drugs are allocated to classes within this parameter based on information about the cattle used for their production. The exponents express the probabilities, based on substantiated estimations, that the animals are infected with BSE pathogens because of their origin and keeping. They represent each of the negative values, rounded down to the next smaller whole number, for the exponents of the calculated and/or estimated prevalence of infected animals in their country or in their herds. Theoretically, a class with a zero exponent would apply to manifest BSE diseased cattle (prevalence = 1), a class with the exponent 1 (HRK-1) would apply to animals from a stock with an infection prevalence of 1 : 10 to 1 : 99. HRK classes with exponents of 2 and 3 are not explicitly itemised here, since the corresponding countries are currently unknown; however, they must be included, where appropriate.

In the HRK classes with an exponent of up to 4, the exponent must be established from the prevalence of BSE infected cattle for the stated countries (see above). This is calculated as the product of the mean BSE incubation period of approximately 4.5 years and the annual incidence of disease in cattle older than two years. The latter is to be calculated as the quotient of the number of cases of BSE that have occurred, which is made public for each calendar year by e.g. the Office International des Epizooties in Paris (OIE) and other agencies, and the size of the cattle stocks in the

corresponding countries, which can be obtained by enquiring at the Food and Agricultural Organisation (FAO) in Rome and other agencies. The disease incidence or prevalence on which this is based should be the highest recorded in the past 3 whole calendar years.

The class with the highest risk (the smallest exponent) applies to animals which have spent the course of their lives in several countries or have been kept under varying conditions.

Class HRK-1

Country of origin with prevalence of BSE infected cattle 10^{-1} to 10^{-2}; country of origin unknown.

Class HRK-4

Country of origin with prevalence of BSE infected cattle 10^{-4} to 10^{-5} (1993: Switzerland, Ireland).

Class HRK-5

Country of origin with prevalence of BSE infected cattle less than 10^{-5} with certainty, but which has reported one or several cases (< 10) of BSE infection in the past 3 calendar years, and for which evidence was not provided that these cattle originated from the UK.
Also included: country without known case of BSE in the past 3 calendar years, but in which there was no legal obligation to report cases of BSE during this period.

Class HRK-6

Country of origin without any known case of BSE, or in which only one case/individual cases (< 10) involving a bovine or group of cattle known to have been imported from the UK have been reported, and in which a legal obligation to report cases of BSE has existed for at least the last 3 years, and in which a ban on the import of breeding cattle from the UK has been in existence since at least 1990 (see Commission decision 90/261/EWG).

Class HRK-7

Country of origin as class HRK-6 above, but with the following implemented since 1990 at the latest:

- ban on the import of animal fodder based on animal carcasses (ACF) from the UK.

or

- ban on feeding of ACFs to cattle before the commission decision 94/381/EG.

or

- ban on sale of ACFs which have not been heated during preparation to at least 133° C for 20 minutes in pressurised steam (see Commission Guidelines 90/667, appendix II, chapter II, No. 6a) or treated with other equivalently effective methods (Commission decision 94/382/EG and 95/29/EG).

Closed herds

If reliable proof exists that certain animals derive from closed herds that fulfil at least the same safety criteria as could be assumed for countries of class HRK-7, they may be classified as safer than other cattle of the same country.

This applies to cattle derived from herds with the following criteria for at least 6 years:

- close veterinarian monitoring
- no case of BSE
- no ACF or at least no ACF which was insufficiently heated, even before the Commission's decision 94/381/EG
- no addition of female cattle from herds which do not fulfil the 3 criteria mentioned above.

Such cattle may be classified by an exponent higher by three than can be obtained for the country from which the cattle derive, to a maximum of class HRK-8.

Additional absolute requirements with reference to origin and keeping of donor animals:

The following general criteria apply with respect to the use of donor animals for the starting materials concerned here:

Starting material derived from liver etc. equivalent to MAT class 5 (see A 2.2) of cattle should only be used from cattle in class HRK with an exponent less than 5 when it has proved impossible to use material from another HRK class.

A 2.2 Parameter: Starting materials (MAT)

Drugs are classified here according to the biological type of the animal-derived starting materials used for their production, on which the content of BSE pathogens depends in the event that an infected animal was once found among those selected for drug production.

If starting materials used are not specifically included in the material classes below, they should be classified on the basis of analogous materials and products. If this is not possible from a practical point of view, it may be necessary to perform individual experiments to determine the relative infectivity of the materials derived from infected animals.

Class MAT-5

Liver, pancreas, lung, jejunum, distal colon, bone marrow, thymus, peripheral nerves, nasal mucous membrane

Class MAT-7

Foetal tissue of any type (does not include the foetal part of the placenta; cf. Notification of 25 September 1995 section A 2.2), all organs and tissues listed under class Mat-5 derived from animals up to six months old.

Class MAT-8

Heart, uterus, skeletal muscle, tendons, bones, cartilage, connective tissue, skin, tallow, hair, salivary glands, thyroid gland, mammary glands, kidneys, ovaries, testicles, prostate gland, seminal vesicles, semen, blood, saliva, bile, milk, urine, faeces of cattle of all ages.

If, in the case of a starting material, contamination with material from a lower class (including that specified in the notification of 25 September 1995) cannot be reliably excluded, then an estimation of the extent of contamination substantiated to the greatest extent possible is to be submitted (see section C 2) and the contamination concerned is to be classified separately and included in the overall evaluation as if the drug were a combination preparation (see section A 2)

A 2.3 Parameter: Methods used to inactivate or remove infectious pathogens (ABR)

Products are classified for this parameter on the basis of whether, and to what extent, methods are used to inactivate or remove potential SE pathogens during processing of starting materials, irrespective of the effort made to acquire starting materials from safe animals.

The classes are defined in terms of the extent (quotient) to which the potential number of infectious pathogens (expressed as the LD_{50}, i.e. the dose with a 50% probability of transmitting SE infection, which is assumed to be 100% fatal) in a specified quantity of starting material has been reduced in the resultant quantity of the finished product.

Class ABR-0

Quotient (number of pathogens in starting material / number of pathogens in finished product) $\geq 10^0$ and $< 10^1$

Class ABR-1

Quotient $\geq 10^1$ and $< 10^2$

Class ABR-2

Quotient $\geq 10^2$ and $< 10^3$

Class ABR-3

Quotient $\geq 10^3$ and $< 10^4$
etc.

All methods used to inactivate or remove SE pathogens, in as far as these are required to comply with A 3, must be validated. It must be demonstrated that the methods are effective in removing infectious pathogens under the specific conditions of production of the medication between the first and last steps taken to reduce the pathogen content.

If a product requires processing to inactivate or reduce contamination by 10^4 potential SE pathogens or greater, and this is to be achieved in several process stages, each process stage used must be individually validated. Validation of methods used must be carried out in realistic models relating to the actual production processes, with addition of known infected material ("spikes"). Spikes must be added to starting materials, or one or several intermediate products, while the infectivity of the material must be investigated in suitable animal trials. The spikes used as test material must contain concentrations of pathogen which are, as far as possible, and taking into account the technical methods available and using a representative sample of the material (e.g. intermediate product), analogous to those in the product material at the stage of processing. If the methods used are successful in reducing maximal contamination levels of SE pathogens to below detection thresholds, it should be determined at what stage of processing this actually occurs.

Supposed cumulative effects of individual process stages must be validated. It should be assumed that the greater the similarity of the methods, the less likely cumulative effects are to occur (for requirements in connection with demonstrating cumulative effects, see section C 3.2)

An inactivation capacity of 10^6 can be assumed for a 20 minute autoclaving treatment at 133° C under pressurised steam and for a one hour treatment with 1 N NaOH at 20° C without any validation based on animal experiments. However, it must be demonstrated with certainty in both cases that the exact conditions are achieved in all parts of the product to be treated.

A method may be considered to be validated when it has already been validated in animal trials in another context, and it is clear that an equivalent inactivation capacity will be achieved in the material in question.

It cannot be assumed that methods used to increase concentrations of the active agent obtained from the animal starting material will necessarily cause an equivalent decrease in concentrations of potential SE pathogens. Evidence of any such decrease must be provided.

A 2.4 Parameter: Quantities of animal materials required to provide one daily dose of the product (APT)

This classification is based on the quantity of starting material required to provide the highest recommended daily dose (DD) of the product (or highest daily total of doses if a number of single doses are required).

For medicinal products designed to be applied to the skin (healthy or damaged) and for which no absolute daily dose can be established, a DD of 1 g will be assumed. For products designed to be applied to mucous membrane (see below, class APL-4), a DD of 0.1 g will be assumed. The APT quantity is the quotient of the largest quantity of starting material required for a batch divided by the number of DDs obtained therefrom.

If it is impossible to determine what quantity of animal starting material - or a preparation produced therefrom is required to produce the amount of an active or adjuvant substance contained in a daily dose of the product, this quantity will be assumed to be 1 kg (as class APT-0).

Please note that dilution of homogenates or solutions which cannot be necessarily assumed to reduce SE pathogen concentrations, and which cannot therefore be taken into account for the purposes of ABR classification, will, in as far as such dilution results in a reduction of daily dose, result in the classification of the medicinal product in an APT class with a higher exponent (relevant e.g. for homeopathic medicines).

The exponent for each class on the scale below is based on the logarithm (base 10) of the quotient of 1 kg and the upper threshold for the APT region of that class. If the APT quantity is greater than 1 kg, the scale must be extrapolated backwards to classes with negative exponents (e.g. the exponent for the APT class covering ≤ 10 kg to > 1 kg would be "minus 1").

Class APT-0

≤ 1 kg and > 100 g

Class APT-1

≤ 100 g and > 10 g

Class APT-2

≤ 10 g and > 1 g

Class APT-3

≤ 1 g and > 100 mg
etc.

A 2.5 Parameter: Number of daily doses (ANZ)

Classification here will be based on the highest number of days on which the drug is likely to be required annually by the patient. This is calculated on the basis of product information sheets and on the basis of realistic estimates, taking into account the likelihood of relapse of the disorder in question.

Class ANZ-0

Long-term or permanent administration: 100 - 365 DDs annually

Class ANZ-1

Medium-term continuous use, or long-term use with several days' interval: 10 - 99 DDs annually

Class ANZ-2

Short-term use or single dose: 1 - 9 DDs annually

A 2.6 Parameter: Route of administration (APL)

Classification should be based on the route of administration recommended in the product information which involves the highest potential risk of transmission (smallest exponent).

Class APL-0

Products administered directly into the CNS (intracisternal, intralumbal region etc.)

Class APL-1

Products administered directly into blood vessels

Class APL-2

Parenterally administered products (other than those in classes APL-0 and -1) and those used on open wounds, including ulcer preparations

Class APL-4

Insulins administered s.c., i.c.; products requiring administration on mucous membranes (excluding products in class APL-5), e.g. conjunctival, intranasal, intrabronchial, rectal, intravaginal, intravesical; products required to remain in the mouth (buccal, sublingual)

Class APL-5

Oral products to be swallowed

Class APL-6

Products to be applied to undamaged external skin (excluding those covered by APL-7)

Class APL-7

Products to be applied to undamaged external skin, with a note in the user information sheet that contact with damaged skin or mucous membrane should be avoided.

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A 3 Evaluation of overall safety of a product and methods which will be required to increase safety

In order to ascertain to what extent all product characteristics and methods used during processing determine the overall safety of the medicinal product, the exponents of each of the six classes in which the product has been categorised should be added together (see section C 7). If there is interdependence between recommended daily dose, duration of therapy, and route of administration, the smallest possible partial sum ascertainable for the constellation will be used (see section A 2). For combined preparations, the lowest exponent sum for all individual constituents will be used. This is generally applicable to the whole drug. If a product contains five or more constituents to which the lowest exponent sum has been attributed, then the overall exponent sum for the product will be reduced by 1.

The product can be assumed to comply with the specified objective for safety in use as set out in the directive - i.e. a high probability that the patient's risk of acquiring SE is not significantly increased by the use of the drug - when the exponent sum totals 20 or more (see remarks in section B 3).

If this is not the case for a particular product, then the matrix of the six scales should be used to decide if, and how, the risk can be further reduced to achieve the required specifications (see also section C 7).

A 4 Effects of changes in the manufacturing process or in the conditions of administration

If methods of inactivation or removal of SE pathogens are adopted which were not previously taken into account in the product dossier, or if information on dosage or on route and duration of administration are altered to reduce the risk of transmission, then the Ministry must be informed - in the corresponding notification or the application for an administrative decision - describing to what extent specific product characteristics and product efficacy (if assumed for the product) are likely to be altered by the changes.

B Comments on methods of safety analysis described in section A

B 1 Principle

The concept chosen here, which uses analysis of the various aspects and risks of products in order to establish their overall safety and the measures which could be taken to improve this safety, allows considerable flexibility in the choice of methods to ensure any necessary reduction of risk without compromising the aim.

It is in accordance with EU guidelines (III/3298/91 and III/8115/89), the zoonosis guidelines (Notification of 15 August 1991 - BAnz, page 6120), scientific publications (1,2) and the suggestions made by the pharmaceutical manufacturers and distributors themselves (who placed great value on being allowed freedom to choose between various alternatives), in the context of the graduated plan procedure. Their suggestion to include evaluation of potential risk based on dosage, route of administration, and duration of administration has also been taken into account. On the other hand, the suggestion that the pooling of starting materials can be

considered a factor which reduces risk has been rejected. As is pointed out in one of the publications referred to here (2), the influence which the number of donor animals may have on the risk of contamination is "unclear".

The use of analogous scales with the same orientation and subdivisions for the assessment of relevant characteristics not only allows an overall evaluation of the safety in use of a product, but also provides for equivalence of the means taken to increase safety (reduce risk), where this is necessary. The scales are designed so that the risk potential of the next class is, for reasons of safety, lower or higher by one or several indices of ten (orders of magnitude), as the effects of characteristics or methods on the potential infectivity of a material or product can be estimated only approximately. Relevant publications, on the whole, do not use more exact methods of assessing risk.

On the combination of individual safety characteristics following addition of class exponents, and the relevance of the exponent sum to the absolute risk of infection, see section B 3.

B 2 Classification

Data to be used in the classification of individual products are heterogeneous with respect to source and validity. Thus, data required to classify the product for the parameters APT and ANZ can be calculated using simple arithmetic, while data required to classify the product for the parameter ABR must be determined experimentally. In contrast, the risk potentials represented by the various MAT and APL classes have been estimated mainly on the basis of published data. The HRK classification is based partly on data provided by the OIE and FAO (to exponent 4), partly on published data in connection with dissemination of BSE infections (2), and partly on the Ministry's own estimates of the influence of risk factors. However, the degree to which estimated data is used, in relationship to the required exponent sum total of 20 for the specified safety factor, is relatively small.

The requirement that each constituent of combined preparations should be initially assessed individually takes into account the fact that these will often have to be placed in different MAT and APT classes, and may also, depending on the stage of production in which the materials are combined, have to be placed in different HRK or ABR classes.

B 2.1 Country of origin and keeping of animals

The main criteria for assessing whether only animals or animal parts which are not infected with SE pathogens are used in the production of medicines are already specified in the zoonosis and EC guidelines. These also formed the basis for determining the parameters for the HRK classes in this notice.

The criterion "country of origin" had been chosen in preference to "region" to comply with the two guidelines above and the form adopted in OIE records, as regulations covering aspects such as obligation to report disease, regulations on the use of animal products, and import restrictions usually apply to a country rather than merely

to a region. Thus, a safety bonus is given to animals from closed herds with a proven particularly low risk of SE infection compared to the country in which they are kept (see below).

For animals of unknown origin, a class with a low safety exponent of 1 is assumed, as it is possible that such animals may originate from a herd with a high incidence of SE cases.

Countries reporting isolated cases of BSE or scrapie are assessed with the safety exponent 5, not on the basis of calculation of risk, but on the basis of an informed estimate (see Danner; 2). An additional safety bonus factor of one order of magnitude is given to countries which have not reliably had a manifest case of animal SE (no reported cases despite obligation) or at least only isolated reports from cattle which were definitely imported from the UK, as this is assessed as an indicator for a very low prevalence of infectivity. The restrictions on imports from the UK, and the ban on feeding of ACFs (at least inadequately heated ACFs) to cattle, assessed as particularly relevant in the zoonosis and EC guidelines, has also been taken into account here as an additional safety factor and rewarded with an increased HRK exponent, as has the keeping of animals in closed herds with minimal risk of contact with SE infected animals.

In the sense of the EU directive, the additional selection criteria formulated with regard to the parameters Origin and Keeping of Animals represent a special priority consideration.

B 2.2 Starting materials

The classes MAT-5 and MAT-8 are approximately equivalent to the animal body part groups 3 and 4 of the zoonosis guidelines. The numbers 5 and 8 represent the differences, in indices of ten, in the concentration of SE pathogens from that estimated for group 1 (i.e. 9) and the equivalent exponents from groups 3 and 4 (i.e. 4 and 1). They thus reflect the relationship between safety and different starting materials.

The infectivity of class MAT-8 starting materials, which would theoretically contain 10^1 pathogenic units per gram, has not actually been measured experimentally. This limit represents the lowest currently known detection threshold for SE agents (for rodent-adapted SE pathogens) which has not been exceeded by inoculation of material from the listed body parts and products. Although the concentrations of pathogens in foetal tissue are also below this threshold, due to the possibility of contamination with placental tissue, this material has been classified with an exponent which is lower by one (i.e. 7).

B 2.3 Methods used to inactivate or remove SE pathogens

The requirement that the effectiveness of methods used for decontamination must be demonstrated by the results of animal trials results from the fact that no reliable *in vitro* method of testing biological materials for SE infectivity has been developed to date.

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The methods must be validated experimentally under conditions which are analogous to those of the production processes, as it is all too easy to misinterpret results of tests because of variations between test conditions and production conditions, and the possibility of this happening must be reduced to the minimum for this highly-resistant and dangerous pathogen.

Each step in processes which, it is claimed, will inactivate or reduce SE pathogens by a factor of 10^4 must be individually validated, as this will allow a better overall assessment of the method. Moreover, this will also provide a guideline to the efficacy of methods used in later stages of production where the infectivity of material is below the detection threshold. Appropriate spikes contaminated with known concentrations of pathogens are to be used to validate later inactivation processes, as experience has shown that the concentrations in intermediate products, which will have undergone several processing stages, are more difficult to determine than in native, or relatively unprocessed, starting materials. It is essential that the spikes used are appropriate to the material under investigation to ensure that the efficacy of the later decontamination processes is not overrated.

The requirement for adequate evidence of a cumulation of efficacy from risk-reducing measures, if such a requirement is claimed, is raised by findings demonstrating that an inactivation method for SE pathogens can be less effective under certain circumstances if another has preceded it. It has been shown (3) that a formaldehyde treatment of SE pathogens actually enhanced their resistance to 100° C heat. That similar types of reduction or inactivation methods can have a cumulative effect should also always initially be regarded as improbable (e.g. it is normally to be assumed of pathogens which have not been retained by filters with a specific pore size that the majority of them can also pass through other such filters). Therefore, in the event that a cumulation of efficacy is claimed for very similar methods, the requirement placed on the documentation must be especially high.

Even though infectivity can be reduced by 10^7 - 10^8 under certain circumstances by treating animal material containing SE pathogens with 1 N NaOH for 1 hour or with pressurised steam at 133° C for 20 minutes, more recent investigations have raised doubts about the reliability of this high figure (4, 5, 6), so that a figure of only 10^6 can be assumed without any further testing of this capacity (2). If a higher efficacy is asserted, the results of appropriate validation studies must be presented.

B 2.4 Quantities of animal starting material required to produce one daily dose of the product

There are considerable variations in relative risk in connection with this parameter. The daily dose has been chosen as the smallest unit, as the probability of SE pathogen transmission seems to correlate with the dose of SE pathogens received per day: if the same quantity of material is inoculated over several days, instead of on one day, the infection potential is markedly reduced (7).

The definition of the APT parameter covers that total quantity of body parts in which potentially infectious SE pathogens could be present in the DD of the final product. It may seem, on the whole, unlikely that methods used to increase the concentrations of active agents or auxiliary substances in medicinal products will also increase concentrations of pathogens, but this has actually been found to be the case e.g. in the preparation of ferritin. Unqualified statements to the effect that the proportion of infectious pathogens in the starting material which will be found in the final product is only equivalent to the aliquot which the dry weight of the end product represents to the dry weight of the starting material cannot be accepted as true. Any documented relative reduction in pathogen concentrations accompanying concentration of the active agent, however, may be taken into account for purposes of ABR classification.

B 2.5 Number of daily doses

Here it is assumed that the risk of SE transmission correlates directly with the number of days on which a patient is exposed to potentially infected materials, and that the risk will vary by multiples of ten where duration of use varies by multiples of ten. No specific class has been created for products which are used for periods of longer than one year, as the question of whether a medicinal product is used for one or even ten years is not so much dependent on its formulation or indication range, but more on the individual characteristics of the patient and illness. For this reason, treatment periods of more than one year are generally not classified in product information sheets. The period of one year was chosen to correlate with published data on the incidence of CJD, which is used as the target for the risk-reducing measures discussed here.

B 2.6 Route of administration

The relative risks represented by classes APL-0 to APL-4, i.e. administration in the CNS, blood stream, or other parenteral forms of administration, are in accordance with data quoted in publications (1, 2, 8). Subcutaneous administration was placed in class APL-4, however, only for insulins, as it can be assumed that a standard short cannula technique is used here, making injection into muscles or blood vessels very unlikely. Products for intracutaneous administration or application on mucous membrane have been included in class APL-4, as no corneal epidermal layer separates the product from subcutical layers following administration. Oral drugs to be swallowed are classified as APL-5 in accordance with published data documenting a risk of infection following intracerebral administration which is five orders of magnitude greater when compared with oral administration (1, 2, 8). The fact that swallowing a product involves less risk than subcutaneous administration may be a result of the proteolysis of protein elements in the SE pathogens in the stomach and intestines. Epicutaneous administration is seen as only one or two exponent classes safer than oral administration - assuming correct application of the product - because of the possibility that patients will not recognise, or will ignore, small areas of skin damage or will inadvertently apply the product to mucous membrane.

B 3 Evaluation of overall safety of a product and methods which will be required to increase safety

It is assumed that the six parameters all determine risk of infection, but are all unrelated in that respect. As the class exponents represent rounded down indices of ten as an expression of the relative safety of a product (base 10 logarithm), their addition represents a multiplication of the various risk factors, which should indicate the relative overall safety or otherwise of the product in comparison with the worst case.

The exponent sum total indicating compliance with the specification stated, i.e. risk of infection with SE pathogens less than 1 in 10^6, has been calculated on the basis of tests using animal material of a known transmission potential. In order to establish the relationship between the exponent sum total and the absolute numbers of infectious pathogens, one of the tests on which the specifications on potential infectivity of animal material in the zoonosis guidelines are based (and on which the MAT classes here are based) was selected. Data (see zoonosis guidelines and 2, 8) indicates that 1 gram homogenate of native brain obtained from a hamster with manifest SE symptoms contains enough infectious material to theoretically infect a further 10^9 hamsters with 50% probability following a single intracerebral injection. Thus the 1 gram of material contains 10^9 LD_{50}s (following i.c. injection).

Classification of this material produces the following result:

Parameter	Test parameter	Class
Origin and keeping: probable animal material infection	SE infected (100%)	HRK-0
Starting material	brain	MAT-0
Inactivation, removal	none	ABR-0
Relative quantity of starting material	1 g	APT-3
No. of daily doses	one	ANZ-2
Route of administration	intracerebral	APL-0
Exponent sum		5

Thus inoculation of material with an SE transmission potential of 10^9 (LD_{50}) has an exponent sum total of 5. Inactivation or removal of infectious pathogens in this material by nine indices of ten would result in a pathogen content of $10^{9-9} = 10^0 = 1$ LD_{50}/g. Even with such material there is a 50% probability that an individual could be infected. If this probability is to be reduced to the specified maximum of 10^{-6}, the risk needs to be reduced by a further six indices of ten, i.e. by a total of fifteen indices of ten compared with the original starting material. This would increase the exponent sum total to 5 + 15 = 20. Products classified with an exponent sum total of at least 20 are thus associated with a maximum 10^{-6} risk of transmission, with a 50% probability of an infectious dose of SE pathogens. They would thus comply with the specifications assuming a worst case scenario (no species-specific barrier; predisposition to infection identical to that of predisposed laboratory animals), and not increase the "natural" risk of incidence of infection in man.

It is essential that the lowest exponent sum for dosage, duration of use and route of administration classes is selected in the case of products in which these parameters are interrelated, to ensure that the risk is calculated on the basis of the least favourable realistic situation.

Combination preparations must be classified on the basis of the constituent with the lowest exponent sum, as it is this constituent which determines the overall risk the product represents.

B 4 Consequences of alteration of processes

It is clear that any new processes adopted or any adaptation of current manufacturing processes may influence product quality and efficacy in some way. Methods which effectively remove infectious SE pathogens, in particular, very often have an effect on the pharmaceutical and pharmacological properties of animal materials and products. For this reason, the Ministry specifically requests the applicant to submit a declaration on this aspect.

B 5 References

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C Data and information required in connection with assessing the risk of transmission of SE pathogens during drug use

For correct assessment of the risk of transmission of SE pathogens via products, all relevant details pertaining to the production processes, including details of origin of materials, must be submitted. The following list gives an overview of those areas which will require to be documented, where possible, by submitting information or declarations with the appropriate validation. In cases where documents cannot be submitted, a reason must be given.

In cases in which the processing of starting material commences with the supplier of a drug ingredient, the documentation listed under sections 1 to 3 inclusive must be obtained from that supplier (where these are active agents, the European Drug Master File procedure must be complied with; see Notification of 7 May 1993, BAnz., page 5622).

Numerical data should be quoted, wherever possible, as mean values, as extreme values, and with a suitable scale for range of scatter. All documentation in languages other than German or English must be provided with an authorised translation. The documentation dossier should be organised in accordance with the following list and table, and consist of detailed data (with summaries) and figures where necessary, on all aspects. In the summaries, reference should be made to the section of the

dossier in which the detailed data are to be found, including, if necessary, page number and line number.

C 1 Country of origin and keeping

C 1.1 Country/countries of origin

1. Country of birth, where kept, where slaughtered, country where starting materials were obtained
2. Type of data and sources of documentation in this respect.

C 1.2 Numbers of BSE cases in the country/countries specified in section 1.1

1. Absolute numbers and numbers of two-year-old cattle affected in every year since 1988
2. Information on origin of infected animals (imported from the UK?)
3. Type of data and documentation (e.g. OIE report or report by national authorities on the number of animals affected, and a report by the FAO on the total number of animals over two years old in the country concerned).

C 1.3 Official data on safety measures taken in the country/countries specified in section 1.1 (description, responsibility, date introduced, type of documentation)

1. Obligation to report BSE cases
2. Veterinary monitoring
3. Anti-scrapie programmes
4. Import ban on cattle and cattle body parts from the UK
5. Restrictions on cattle and body parts imported from the UK
6. Ban on feeding of ACFs to cattle
7. Methods of processing ACFs to reduce potential risk of transmission (maximum particle size, heating temperature and duration, steam pressure?)
8. Type of data and sources of documentation.

C 1.4 For animals in open herds: registration of the herd

1. Proof of non-infection with BSE; other diseases
2. Contact with other herds/exchange with other herds; risk-relevant characteristics of these herds if applicable
3. Veterinary monitoring
4. Feeding practice and regulations, particularly with respect to ACFs (origin and methods of processing of ACFs if used)
5. Type of data and sources of documentation.

C 1.5 For animals in closed herds: risk-relevant characteristics of the herd

1. Country, region, keeper, herd registration code
2. Proof of non-infection with BSE; other diseases
3. Veterinary monitoring
4. Feeds (types, content of AFC if applicable; source, whether heat-treated and packing declaration)

5. Closed herd? (date on which last animal was included from another herd, safety codes of this herd, documentation that this herd has had no contact with BSE infected animals or received ineffectively heated ACFs)
6. Type of data and sources of documentation.

C 2 Starting materials

1. Ages of donor animals
2. Organs, tissues used in detail
3. Reproducibility of combination of starting materials
4. Assessment of probability of contamination of lower-risk material with higher-risk material (e.g. during slaughter with CNS materials, or for anatomical reasons e.g. vertebrae/spinal cord)
5. Corresponding test results (e.g. of macroscopic, microscopic or biochemical tests)
6. Certification of the suitability of the slaughtered animal and body parts
7. Type of data and sources of documentation.

C 3 Inactivation and removal of BSE pathogens

C 3.1 Type of starting material

Quantity per batch, homogeneity, water content, content of constituent to be concentrated

C 3.2 Type and efficacy of removal and inactivating steps for SE pathogens

Individual steps

1. Flow diagram showing all processing stages in overview, with statement of efficacy of each stage (expressed as a base 10 logarithm if possible)
2. Description of each stage of production which may reduce the potential concentration of SE pathogens in the starting material
3. Efficacy of each stage in terms of removal of SE pathogens
4. Any similarity of stages in terms of technical methods and the expected biochemical effects
5. Any cumulative effects of individual stages; cumulation
6. Production stage at which the SE pathogen contamination falls below the detection threshold in material to which a spike with maximum concentration has been added to the starting material, if applicable
7. Inactivation capacity of any methods used after the stage at which SE pathogen contamination falls below the detection threshold, if applicable
8. Concentration of active agent or auxiliary at individual production steps.

Process overview

1. Protocols and results of overall testing of production processes; test of the final product following addition of a spike with maximum contamination to the starting material
2. Estimated total capacity of the methods used to inactivate and remove SE pathogens, taking into account each stage, cumulative effects, overall test.

C 3.3 Evidence of reliability of inactivation and removal capacity of methods used

C 3.3.1 Validation of methods adopted by the manufacturer in appropriately designed animal trials using a contaminated spike

1. Suitability of the trial model in representing the original method
2. Type of spike used (pathogen type and concentration, biological and biochemical characteristics of the material, suitability of test material in relation to starting material or spiked intermediate product)
3. Method(s) used to determine spike infectivity and contamination of the spiked material which has been subjected to the process to be validated (animal species, number of animals, route of administration, incubation period, analysis methods etc.).

C 3.3.2 Methods with known high efficacy (autoclave with pressurised steam and treatment with 1 N NaOH)

1. Results of validation trials, showing which maximum of temperature (worst case conditions) will reach all areas of a sample body (i.e. also internal regions of a larger particle), duration of maximal temperature and highest content of humidity in the vapour phase
2. Results of validation trials, showing the worst case condition of alkali treated materials (i.e. internal regions of a larger particle), including maximal pH (and minimal duration of period) and temperature
3. Maximal particle size.

C 3.3.3 Method validation conducted by a third party (e.g. licenser); comments on the three points listed in section 3.3.1

1. Body conducting the original validation
2. Suitability of the original validation method in respect of the processes to be used by the company referring to the original validation
3. Type and suitability of the spikes used (pathogen concentration, biological/biochemical comparability with the spiked starting material or intermediate product)
4. Animal trial models tested for infectivity.

C 4 Starting material per daily dose

1. Recommended maximum daily dose of product (where necessary, total of individual doses daily)
2. Number of animals used, weight of starting materials used to produce one product batch
3. Number of daily doses, including maximum daily dose, obtained from one product batch
4. APT quotient = the largest quantity of starting material required for a batch divided by the number of DDs obtained therefrom.

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C 5 Numbers of daily doses

and

C 6 Route of administration

1. Realistic estimation of number of days the drug is applied within a year, if necessary in relation to doses and route of administration, based on claimed indication, including relapses
2. Constellation of use-related characteristics - daily dose (APT), duration and frequency of administration (ANZ), and route of administration (APL) - which represents the greatest risk (i.e. with the smallest exponent sum); documentation in the form of product information sheets
3. Presentation of the latest instructions for use and data sheet for the finished drug.

C 7 Determination of the safety in use of individual drugs with respect to their potential BSE infectivity

Parameter	Brief description of classes and exponents (for details see section A)										Class exponent
HRK	unknown	prevalence $\leq 10^{-4}$	isolated cases	no cases	no AFCs	closed herd					
	1	4	5	6	7	4-8					
MAT	liver etc.	foetus	heart etc.								
	5		7		8						
ABR	Log_{10} reduction of infectivity										
	0	1	2	3	4	5	6	7	8	etc.	
APT	e.g. batch weight/maximum No. of DDs				≤ 1 kg	≤100g	≤ 10g	≤ 1 g	≤ 0.1 g etc.		
				0	1	2	3	4 etc.			
ANZ	Long term use: ≥ 100 DDs annually			short term use: ≥ 10 DDs annually			occasional use: 1-9 DDs annually				
	0			1			2				
APL	in CNS	in blood vessels	other parenteral application	s.c. insulin/ on mucous membrane	oral to be swallowed	epicutan.	Epicutan. plus instructions				
	0	1	2	4	5	6	7				
Total exponent sum (ES) as an expression of safety in use											
Extent to which risk still has to be improved (in indices of ten): 20-ES											

(b)(4) Testing-52 pages removed

TEST METHOD REPORT

Drapeability for Bilayer Wound Dressing

Prepared By:

(b)(4) [redacted]

CONFIDENTIAL

Test Method Report:
Drapeability for Bilayer Wound Dressing

May 1, 2002

1. Purpose:

The Bilayer Wound Dressing must be sufficiently pliable to conform to the contour of the wound bed. Thus, testing was performed to determine the ability of the Bilayer Wound Dressing to conform to both concave and convex curved surfaces.

2. Materials:

Bilayer Wound Dressing Lot number:
R200100
R200200
(b)(4) [redacted]

3. Method:

Samples of Bilayer Wound Dressing (b)(4) [redacted] were placed in PBS prior to testing. The sample was draped over the rod such that the two free ends of the sample were hanging freely from each side of the rod as shown in *Figure 1*. Rods with different diameters were chosen to simulate the different wound contours that may be encountered in clinical use. Each sample was tested in two configurations, with the silicone layer adjacent to the rod surface or with the silicone layer away from the rod. The sample was examined, and it was visually verified that the sample was in contact with the rod surface over the entire contour. The distance between the free ends of the sample (W) was measured and verified that it did not exceed the rod diameter (D) by more than 10 percent.

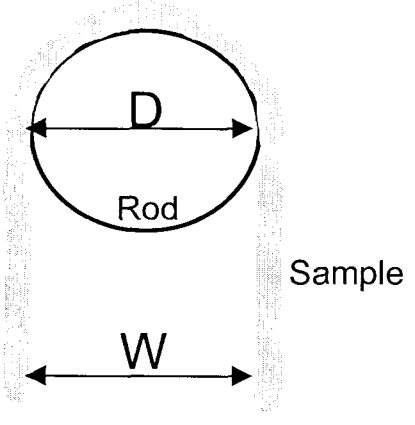

Figure 1: Setup for drapeability test

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(b)(4) Testing

5. Conclusions:

The results of the testing demonstrate that samples of BILAYER WOUND DRESSING were sufficiently pliable to conform to the surface of rods (b)(4) centimeters in diameter, regardless of whether the samples were tested with silicone against or away from the rod. For all samples tested, the width (W) between the free ends was always less than the diameter of the rod (D), indicating that the sample had conformed to rod contour.

Prediction of Shelf Life of Bilayer Matrix Wound Dressing by Accelerated Aging

Summary: The use of accelerated data is justified based upon an examination of degradation mechanisms and the effect of temperature upon those mechanisms. This is presented in Table 1 (below), which examines the mechanisms of degradation and suggests that the mechanisms do not change with temperature even though rates of degradation do change. Degradation mechanisms follow zero- and first-order kinetics and hence a (b)(4) is entirely acceptable for use with this product. For product aged at (b)(4) degrees above the indicated storage temperature, aging will occur (b) times as fast as at room temperature.

Regulatory Background

Accelerated aging studies are widely utilized in the study of medical devices and are often referenced in guidelines for devices with issued guidance documents. No published general guideline from the Agency exists which defines an approach suitable for devices for which no specific guidelines have been published. Device regulations place the burden upon the applicant to determine the need for shelf life dating of a device and, where dating is needed, the development of a rationale for testing.

Clark compiled a compilation of shelf life guidelines in 1991[1]. He advises drug-testing guidelines as a starting point to develop a testing program for medical devices. In 21 CFR 211.166 ...(b) "An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted."

The Drug Guidance from FDA[2] advises "At the time of a drug application approval, the applicant has probably not yet manufactured the subject drug product repeatedly on a production scale or accrued full long-term data. The expiration dating period granted in the original application is based on acceptable accelerated data, statistical analysis of available long-term data, and other supportive data for an NDA, or an acceptable accelerated data for an ANDA. It is often derived from pilot-scale batches of a drug product or from less than full long-term stability data. An expiration dating period assigned in this manner is considered tentative until confirmed with full long-term stability data from at least three product batches..."

[1] Shelf Life of Medical Devices (April 1991), G. Clark, Div. Small Manuf. Asistance, CDRH, FDA.
[2] Guidance for Industry, Stability Testing of Drug Substances and Drug Products (June 1998), FDA, CDER/CBER.

Other guidance documents also support the use of accelerated testing in support of initial product dating.

> The Glove Guidance Manual suggests[3], "In the past, expiration dates were based on real time studies by manufacturers. FDA has drafted guidance that allows manufacturers to make a shelf life claim based on accelerated aging techniques and it will be placed on the CDRH web site. Such claims must be verified by real time studies".
>
> The Guidance for Contact Lenses[4] outlines shelf life dating methodologies: "In general, the manufacturer should demonstrate the stability of the parameters of the finished lens over time as packaged and stored under the proposed storage conditions. However, the aging of the lens in its container can be extrapolated to e proposed storage temperature. Assuming first order kinetics, every 10°C increase for the tested temperature above the normal storage temperature will enhance the expiration date by a factor of two."

Like Bilayer Matrix Wound Dressing, both gloves and contact lenses are composed of complex cross-linked polymeric systems whose structural integrity is critical to their intended function. Thus, accelerated aging models are likely to be equally valid in all three devices.

Based upon critical assessment of the materials and potential degradation pathway for the product, Integra LifeSciences has developed a shelf life program for Bilayer Matrix Wound Dressing. This program utilizes a combination of laboratory assessment of stability, accelerated aging and real time stability studies to assign a [redacted] month shelf life and to provide shelf life extension and confirmation when data become available.

[3] Guidance for Industry and FDA, Medical Glove Guidance Manual (July 30th, 1999), CDRH, DSMA, OHIP.

[4] Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses (May 1994), Contact Lens Branch, Div. Ophthalmic Devices, ODE, CDRH.

(b)(4) Testing-2 pages removed

Proposed label

Foil Pouch
10.0 cm x 12.5 cm

DRAFT

LOT xxxxxxx

xxxxxx

Bilayer Matrix Wound Dressing

10.0 cm x 12.5 cm
4 in x 5 in

Contents: One Wound Dressing

Non-Pyrogenic

Do not Resterilize

Avoid excessive heat
Do Not Freeze

REF. XXXXX
HRI. XXXXX

(b)(4) [redacted]

Manufactured by: Integra LifeSciences Corporation, Plainsboro, NJ 08536 USA

US Pat. No. xxxxx, xxxxxx, xxxxx, and other patents pending.

RMS #

L0001

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Proposed label

Tyvek Pouch
10.0 cm x 12.5 cm

DRAFT

LOT xxxxxxx

xxxxxx

Bilayer Matrix Wound Dressing

10.0 cm x 12.5 cm
4 in x 5 in

Contents: One Wound Dressing

Non-Pyrogenic

Do not Resterilize

Avoid excessive heat

Do Not Freeze

REF. XXXXX
HRI. XXXXX

(b)(4) [redacted]

Manufactured by: Integra LifeSciences Corporation, Plainsboro, NJ 08536 USA

US Pat. No. xxxxxx, xxxxxx, xxxxxx, and other patents pending.

RMS #

L0002

Proposed label

Dispenser Box
10.0 cm x 12.5 cm

DRAFT

LOT xxxxxxx

xxxxxx

Bilayer Matrix Wound Dressing

10.0 cm x 12.5 cm
4 in x 5 in

Contents: Wound Dressing (5 units)

Non-Pyrogenic

Do not Resterilize

Avoid excessive heat

Do Not Freeze

REF. XXXXX
HRI. XXXXX

(b)(4) [redacted]

Manufactured by: Integra LifeSciences Corporation, Plainsboro, NJ 08536 USA

US Pat. No. xxxxxx, xxxxxx, xxxxxx, and other patents pending.

RMS #

L0003

Bilayer Matrix Wound Dressing

Package Insert

DESCRIPTION

Bilayer Matrix Wound Dressing is an advanced woundcare device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. The semi-permeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth.

INDICATIONS

Bilayer Matrix Wound Dressing is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

CONTRAINDICATONS

- This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials.
- The device is not indicated for use in third degree burns.

PRECAUTIONS

- **Do not resterilize.** Discard all opened and unused portions of Bilayer Matrix Wound Dressing.
- Device is sterile if the package is unopened and undamaged. Do not use if the package seal is broken.
- Discard device if mishandling has caused possible damage or contamination.
- Bilayer Matrix Wound Dressing should not be applied until excessive exudate, bleeding, acute swelling and infection are controlled.
- Debridement or excision must be done thoroughly to remove any remaining necrotic tissue that may cause infection.
- The following complications are possible with the use of wound dressings. If any of the conditions occur, the device should be removed: infection, chronic inflammation (initial application of wound dressings may be associated with transient, mild, localized inflammation), allergic reaction, excessive redness, pain or swelling.

INSTRUCTIONS FOR USE

Application

1. **Always handle Bilayer Matrix Wound Dressing using aseptic technique.**
2. Rinse the product free of storage buffer by immersion in sterile saline for 1-2 minutes.
3. Prepare wound bed using standard methods to ensure wound is free of debris and necrotic tissue. If necessary, surgically debride the wound to ensure the wound edges contain viable tissue.
4. Cut the device to size and apply immediately following wound bed preparation.
5. Note: It is critical that the collagen layer be in direct contact with the prepared wound. The silicone layer, identified by the black threads, must be placed *out* (away from the wound bed). *Do not apply upside down; the black threads must be clearly visible.*
6. Bilayer Matrix Wound Dressing should be firmly secured using surgical tapes, or other mechanical means. Any air bubbles should be carefully removed by moving them to the edge of the sheet.
7. After application, use appropriate secondary dressings to maintain dressing adherence and protect the wound area. The optimum secondary dressing is determined by wound location, size, depth and user preference.

Post-Application

1. Change the secondary dressing as needed. Frequency of secondary dressing change will be dependent upon volume of exudate produced, type of dressing used and the clinician's need to inspect the wound bed for signs of infection or healing.

Note: If hematoma or excess exudate collect under the sheet, small openings can be cut in the sheet to allow fluid to drain.

Removal

1. If edges are loose before full healing has occurred, the silicone can be trimmed away from the loose areas until the entire wound has healed.
2. Remove the silicone layer of the Bilayer Matrix Wound Dressing when the tissue underneath is healed, typically 14 to 28 days. The dressing may be loose in spots.
3. Remove by starting at one corner and pull gently. The silicone layer will peel off healed tissue relatively easily.
   Caution: if bleeding occurs, or if patient complains of excessive pain, stop and wait 1 to 2 additional days. Forced removal may result in wound reinjury.

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HOW SUPPLIED
Bilayer Matrix Wound Dressing is supplied sterile, in single use, double peel packages containing phosphate buffer. Bilayer Matrix Wound Dressing is available in the following sizes:

Product Codes	Size:	Quantity
xxxxxx	4 inch x 5 inch (10 cm x 12.5 cm)	1 unit/box
xxxxxx	4 inch x 5 inch (10 cm x 12.5 cm)	5 units/box
xxxxxx	4 inch x 10 inch (10 cm x 25 cm)	1 unit/box
xxxxxx	4 inch x 10 inch (10 cm x 25 cm)	5 units/box
xxxxxx	8 inch x 10 inch (20 cm x 25 cm)	1 unit/box
xxxxxx	8 inch x 10 inch (20 cm x 25 cm)	5 units/box

STORAGE
Store flat at room temperature. Avoid excessive heat (greater than 40°C). Avoid freezing.

CAUTION: Federal law restricts this device to sale by or on the order of a physician or practitioner.

SYMBOLS USED ON LABELING

 Expiration date

LOT Lot number

If there are any questions, a technical representative will be available to speak with you at 1-800-423-5850.

(b)(4) [redacted]

Manufactured By:

INTEGRA LIFESCIENCES CORPORATION
Plainsboro, NJ 08536
U.S. PAT. NOS.
5,489,304
5,833,665
5,837,226
5,629,191
AND PATS. PENDING

(b)(4) [redacted]

1/00

RMS #51000-1204-5

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REVISED:3/14/95

THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).

"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K 021792

Reviewer: Sam Anepalli

Division/Branch: DBRND / PRSB

Device Name: Bilayer Matrix Wound Dressing

Product To Which Compared (510(K) Number If Known): K993948

		YES	NO	
1.	Is Product A Device	X		If NO = Stop
2.	Is Device Subject To 510(k)?	X		If NO = Stop
3.	Same Indication Statement?	X		If YES = Go To 5
4.	Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NE
5.	Same Technological Characteristics?		X	If YES = Go To 7
6.	Could The New Characteristics Affect Safety Or Effectiveness?		X	If YES = Go To 8
7.	Descriptive Characteristics Precise Enough?	X		If NO = Go To 10 If YES = Stop SE
8.	New Types Of Safety Or Effectiveness Questions?			If YES = Stop NE
9.	Accepted Scientific Methods Exist?			If NO = Stop NE
10.	Performance Data Available?			If NO = Request Data
11.	Data Demonstrate Equivalence?			Final Decision:

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

1. Intended Use: See memo

2. Device Description: Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. Is the device life-supporting or life sustaining? Is the device implanted (short-term or long-term)? Does the device design use software? Is the device sterile? Is the device for single use? Is the device over-the-counter or prescription use? Does the device contain drug or biological product as a component? Is this device a kit? Provide a summary about the devices design, materials, physical properties and toxicology profile if important.

EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. Explain why not a device: It is a medical device
2. Explain why not subject to 510(k): subject to 510(k)
3. How does the new indication differ from the predicate device's indication: Same indications for use
4. Explain why there is or is not a new effect or safety or effectiveness issue: Similar material and identical indications for use
5. Describe the new technological characteristics: The subject device contains bone collagen crosslinked with glycosaminoglycans.
6. Explain how new characteristics could or could not affect safety or effectiveness: none
7. Explain how descriptive characteristics are not precise enough: descriptive characteristics are precise enough
8. Explain new types of safety or effectiveness questions raised or why the questions are not new: none
9. Explain why existing scientific methods can not be used: ~~none~~ N/A
10. Explain what performance data is needed: none
11. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

GB

ATTACH ADDITIONAL SUPPORTING INFORMATION

7

(b)(4) Review 5 pages removed

SCREENING CHECKLIST
FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS

510(k) Number: K02 1792

The cover letter clearly identifies the type of 510(k) submission as (Check the appropriate box):

☐ Special 510(k) - Do Sections 1 and 2

☐ Abbreviated 510(k) - Do Sections 1, 3 and 4

☒ Traditional 510(k) or no identification provided - Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present	Inadequate or Missing
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510)] Manual.	✓	
Table of Contents.	✓	
Truthful and Accurate Statement.	✓	
Device's Trade Name, Device's Classification Name and Establishment Registration Number.	✓	
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).	✓	
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510)] Manual.	✓	
Statement of Indications for Use that is on a separate page in the premarket submission.	✓	
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510)] Manual.	✓	
510(k) Summary or 510(k) Statement.		
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.	✓	
Identification of legally marketed predicate device. *		
Compliance with performance standards. * [See Section 514 of the Act and 21 CFR 807.87 (d).]		N/A
Class III Certification and Summary. **		N/A
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)]		N/A
510(k) Kit Certification ***		

* - May not be applicable for Special 510(k)s.

** - Required for Class III devices, only.

*** - See pages 3-12 and 3-13 in the Premarket Notification [510)] Manual and the Convenience Kits Interim Regulatory Guidance.

Section 2: Required Elements for a SPECIAL 510(k) submission: N/A

	Present	Inadequate or Missing
Name and 510(k) number of the sponsor's own, unmodified predicate device.	NA	
A description of the modified device and a comparison to the sponsor's predicate device.		
A statement that the intended use(s) and indications of the modified device, as described in its labeling, are the same as the intended uses and indications for the sponsor's unmodified predicate device.		
A statement that the modification has not altered the fundamental technology of the sponsor's predicate device.		
A Design Control Activities Summary that includes the following elements (a-e):		
a. Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.		
b. Based on the Risk Analysis, an identification of the required verification and validation activities, including the methods or tests used and the acceptance criteria to be applied.		
c. A Declaration of Conformity with design controls that includes the following statements:		
A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results of the activities demonstrated that the predetermined acceptance criteria were met. This statement is signed by the individual responsible for those particular activities.		
A statement that the manufacturing facility is in conformance with the design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review. This statement is signed by the individual responsible for those particular activities.		

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Section 3: Required Elements for an ABBREVIATED 510(k)* submission: NA

	Present	Inadequate or Missing
For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type. (If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.)	NA	
For a submission, which relies on a recognized standard, a declaration of conformity [For a listing of the required elements of a declaration of conformity, SEE **Required Elements for a Declaration of Conformity to a Recognized Standard**, which is posted with the 510(k) boilers on the **H drive.**]		
For a submission, which relies on a recognized standard without a declaration of conformity, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has not been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device and any additional information requested by the reviewer in order to determine substantial equivalence.		
Any additional information, which is not covered by the guidance document, special control, recognized standard and/or non-recognized standard, in order to determine substantial equivalence.		

* - When completing the review of an abbreviated 510(k), please fill out an Abbreviated Standards Data Form (located on the H drive) and list all the guidance documents, special controls, recognized standards and/or non-recognized standards, which were noted by the sponsor.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:	✓	
b) Sterilization and expiration dating information:	✓	
i) sterilization process	✓	
ii) validation method of sterilization process	✓	
iii) SAL		
iv) packaging		
v) specify pyrogen free		
vi) ETO residues		
vii) radiation dose		
c) Software Documentation:		

Items with checks in the "Present but Deficient" column require additional information from the sponsor. Items with checks in the "Missing" column must be submitted before substantive review of the document.

Passed Screening ✓ Yes ___ No
Reviewer: [signature]
Concurrence by Review Branch: [signature]

Date: 8/8/02

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

Internal Administrative Form

	YES	NO
1. Did the firm request expedited review?		✓
2. Did we grant expedited review?		✓
3. Have you verified that the Document is labeled Class III for GMP purposes? NA		
4. If, not, has POS been notified?		
5. Is the product a device?	✓	
6. Is the device exempt from 510(k) by regulation or policy?		✓
7. Is the device subject to review by CDRH?	✓	
8. Are you aware that this device has been the subject of a previous NSE decision?		✓
9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?	NA	
10. Are you aware of the submitter being the subject of an integrity investigation?		✓
11. If, yes, consult the ODE Integrity Officer.		
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.	NA	

(b)(4) Review 23 pages removed

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service
Food and Drug Administration

8/8/02

Memorandum

m: Reviewer(s) - Name(s) Sam Haapalainen DXK

Subject: 510(k) Number K021792

To: The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☐ Requires additional information (other than refuse to accept).
- ☒ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
  - De Novo Classification Candidate? ☐ YES ☐ NO
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Postmarket Surveillance?	☐ YES	☒ NO
Is this device subject to the Tracking Regulation?	☐ YES	☒ NO
Was clinical data necessary to support the review of this 510(k)?	☐ YES	☒ NO
Is this a prescription device?	☒ YES	☐ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☒ NO
Special 510(k)?	☐ YES	☒ NO
Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers	☐ YES	☒ NO

This 510(k) contains:

Truthful and Accurate Statement ☐ Requested ☒ Enclosed
(required for originals received 3-14-95 and after)

- ☒ A 510(k) summary OR ☐ A 510(k) statement
- ☐ The required certification and summary for class III devices N/A
- ☒ The indication for use form (required for originals received 1-1-96 and after)
- Material of Biological Origin ☒ YES ☐ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

☐ No Confidentiality ☐ Confidentiality for 90 days ☒ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: 79 FRO, Dressing, unclassified

Additional Product Code(s) with panel (optional):

Review: Anthony D. Watson, Acting Bc (HFS-3) — (Branch Chief) — (Branch Code) — 8/14/02 (Date)

Final Review: Steph Ruddy — (Division Director) — 8/14/02 (Date)

Revised:8/17//99

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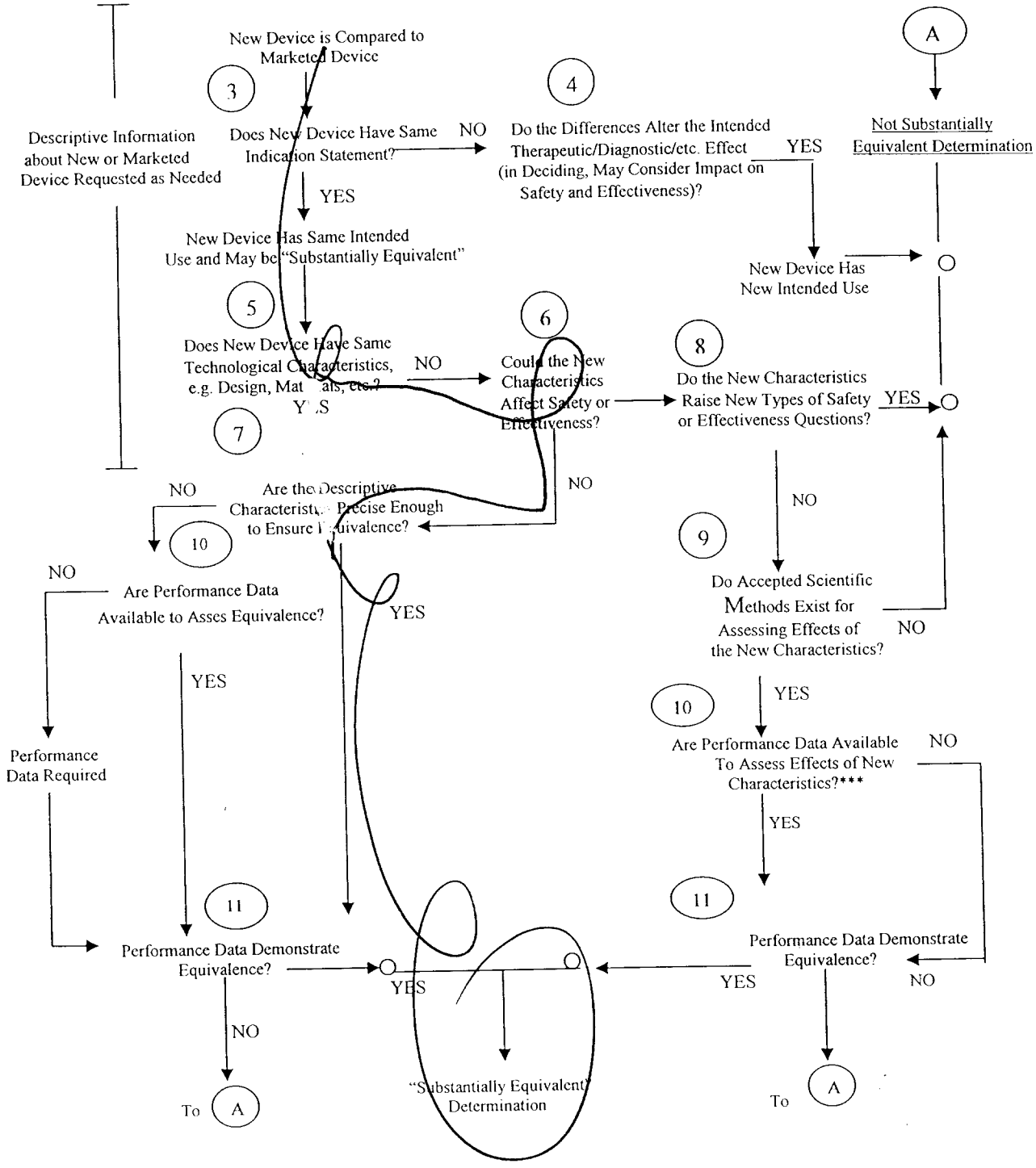
510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



❖ 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

❖❖ This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

❖❖❖ Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.