CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-832/S-008

Name: ChloraPrep with Tint
(Chlorhexidine Gluconate 2% w/v and
Isopropyl Alcohol 70% w/v)

Sponsor: Medi-Flex, Inc.

Approval Date: May 3, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-832/S-008

Medi-Flex, Inc.
Attention: Linda McBride, R.Ph.
Director, Regulatory Affairs
11400 Tomahawk Creek Parkway, Suite 310
Leawood, Kansas 66211

Dear Ms. McBride:

Please refer to your supplemental new drug application dated July 6, 2004, received July 7, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ChloraPrep with Tint (2% chlorhexidine gluconate w/v and 70% isopropyl alcohol v/v solution).

We acknowledge receipt of your submissions dated December 31, 2004, and January 25, May 2 and May 3, 2005.

Your submission of December 31, 2004 constituted a complete response to our November 5, 2004 action letter.

This supplemental new drug application proposes a newly-designed applicator with a sponge tip (pledget) impregnated with FD&C Green #3 dye for preoperative skin preparation.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert dated May 3, 2005, immediate container (lidding) labeling dated May 2, 2005, and Applicator Barrel labeling dated May 2, 2005), and must be formatted in accordance with the requirements of 21 CFR 201.66.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-832/S-008.**" Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Acting Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

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/s/

Curtis Rosebraugh
5/3/05 02:21:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

NOT APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-832/S-008

Medi-Flex, Inc.
Attention: Linda McBride, R.Ph.
Director, Regulatory Affairs
11400 Tomahawk Creek Parkway, Suite 310
Leawood, Kansas 66211

Dear Ms. McBride:

Please refer to your supplemental new drug application dated July 6, 2004, received July 7, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ChloraPrep with Tint 26-mL Applicator (2% chlorhexidine gluconate w/v and 70% isopropyl alcohol v/v solution).

We acknowledge receipt of your submissions dated July 22 and September 9, 2004.

This supplemental new drug application proposes a newly-designed applicator with a sponge tip (pledget) impregnated with FD&C Green #3 dye for preoperative skin preparation.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. Conduct the Patient Pre-operative Skin Preparation (efficacy) study using the tinted formulation versus the clear formulation that was described for you in our September 3, 2004 facsimile on this subject.

2. Conduct a skin coverage study to assure that the product may be used safely according to the labeled directions. Follow the advice we provided in facsimiles sent to you on September 3 and September 23, 2004.

We recommend that you submit your protocol for the Patient Pre-operative Skin Preparation study to the IND for review and feedback before you initiate the study.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Deputy Director
Division of Over-the-Counter Drug Products
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
11/5/04 03:25:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

LABELING

Part # 6-786800

26-mL ChloraPrep Applicator Lidding

FPO
DOES NOT PRINT
DASHED BOX ONLY REPRESENTS
LIVE AREA

Cat. No. 260800 NDC #054365-400-05 DIN #02160757

ChloraPrep® With Tint

Chlorhexidine Gluconate 2% w/v
and Isopropyl Alcohol 70% v/v
Patient Preoperative Skin Preparation
26-mL Applicator

WARNING: FLAMMABLE.
KEEP AWAY FROM FIRE OR FLAME.
DO NOT USE WITH ELECTROCAUTERY PROCEDURES.

Drug Facts

Active Ingredients	Purpose
Chlorhexidine gluconate 2% w/v	Antiseptic
Isopropyl alcohol 70% v/v	Antiseptic

Use for the preparation of the patient's skin prior to surgery.

Warnings

For external use only

Flammable, keep away from fire or flame

- Solution contains alcohol and gives off flammable vapors while drying - allow to dry 3 minutes on skin.
- Do not use with electrocautery procedures
- Do not allow to solution to pool
- Remove solution-soaked materials from prep area

Do not use

- in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption
- on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol
- for lumbar puncture or in contact with the meninges
- on open skin wounds or as a general skin cleanser

When using this product keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a physician.

Stop use and ask a doctor if irritation, sensitization, or allergic reaction occurs. These may be signs of a serious condition.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

- **Maximal treatment area for one applicator is approximately 1126 cm² (approx. 13.2 in. x 13.2 in.). Discard the applicator after a single use.**
- pinch the wings on the applicator to break the ampule and release the antiseptic. Do not touch the sponge. Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin.
- **dry surgical sites** (such as abdomen or arm) Use repeated back-and-forth strokes of the sponge for approximately **30 seconds.** Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately **three (3) minutes.** Do not blot or wipe away.
- **moist surgical sites** (such as the inguinal fold) Use repeated back-and-forth strokes of the sponge for approximately **2 minutes.** Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately **three (3) minutes.** Do not blot or wipe away.

Other Information

- Store between 20–25 °C (68–77 °F)
- Avoid freezing and excessive heat above 40 °C (104 °F)

Inactive ingredients ■ USP purified water
■ Pledget contains FD&C green #3 dye

Questions?
Call 1-800-523-0502 (M-F 8 a.m.–5 p.m. CST)
www.chloraprep.com

Single Use
Applicator is STERILE if package is intact

Medi-Flex, Inc.
Leawood, KS 66211

9.5" high

2.35" wide

Ingredients:
6 pt AntiqueOlive Bold

Title:
14 pt helvetica black oblique

Headings:
8 pt helvetica black oblique,
left justified

0.5 point hairline

Subheadings:
6 pt helvetica
black,
left justified

Bullet:
5 pt zapf
dingbats,
solid square

2.5 point
box barline

Body Text:
6 pt helvetica
regular,
6.5 leading,
left justified

heading:
8 pt helvetica
black oblique

text:
6 pt helvetica
black

8-188800
26ml Chloraprep With Tint Applicator Cliche Film

0 50mm [illegible]mm

WARNING - FLAMMABLE
Keep away from fire or flame.
To reduce the risk of fire:
- Solution contains alcohol and gives off flammable vapors while drying - allow to dry 3 minutes on skin.
- Do not use with electrocautery procedures.
- Do not allow solution to pool.
- Remove solution-soaked material from prep area.

[illegible]mm

mm

63.941mm

WARNING - FLAMMABLE
Keep away from fire or flame.
To reduce the risk of fire:
- Solution contains alcohol and gives off flammable vapors while drying - allow to dry 3 minutes on skin.
- Do not use with electrocautery procedures.
- Do not allow solution to pool.
- Remove solution-soaked material from prep area.

Arial Black 8pt
Arial Black 8pt
Arial Bold 7pt

24.308mm

Text box in this area is [illegible]mm from the top edge and [illegible]mm from the left edge of the [illegible]mm x [illegible]mm frame reference
NOTE: Text box center points ,both vertically and horizontally are used to place the text box in correct position

Part # 6-775825 insert
Insert Sheet - Labeling Format (100%) for ChloraPrep® One-Step
Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v
Patient Preoperative Skin Preparation • 26-mL Applicator

Date	Rev	CAF #	What was changed
8/25/05	A	2005-08-17	Create.

6" wide

Numbers:
9 pt antique olive roman

Title:
19 pt antique olive nord

Heading:
13pt antique olive roman

Formulation:
9 pt antique olive roman

Body Text:
8 pt CI Helvetica Condensed

Sub heading
8 pt antique olive roman

Bullet:
8 pt Round CI Helvetica Condensed

Statement:
9 pt CI Helvetica Condensed

9" high

Cat No. 260825 NDC 054365-400-05 DIN 02160757

ChloraPrep® With Tint

Patient Preoperative Skin Preparation

Chlorhexidine Gluconate 2% (w/v) • Isopropyl Alcohol (70% v/v) • 26-mL Applicator

STERILE EO | Do Not Reuse | External Use Only | Professional Use Only | Sterile Contents:* Applicator(1) Cotton Swabs (2)

Lot No.: **Exp. Date:**

* Sterility of contents guaranteed unless package is damaged or open.

See Drug Facts for full drug labeling information

⚠ WARNING

- ChloraPrep solution contains alcohol and is flammable while drying.
- To prevent fires, follow instructions in this insert!

Medi-Flex recommends all users participate in a product in-service training prior to use. In-servicing is available from your Medi-Flex sales representative.

ChloraPrep is a fast-acting, broad spectrum, persistent antiseptic that significantly reduces the number of microorganisms on intact skin.

To Prevent Fire:
- Do not use with electrocautery procedures.
- Do not drape until prepped area is completely dry.
- Allow preparation to completely dry:
  - if the prepped area is to be extended, or
  - if prepping for an additional procedure, or
  - if re-application of skin preparation is required.
  - drying time for dry surgical sites is approximately three (3) minutes.
  - drying time for moist surgical sites is approximately three (3) minutes.
- Whenever prepping the neck area, place towels under each side to absorb excess solution. Remove the towels before draping.
- Do not allow the solution to pool.
- Remove any soaked materials, drapes, and gowns before draping.
- Avoid getting preparation into hair. If solution gets into hair, wipe hair with towel and allow more time for solution to completely dry.

Directions for Use:
Prepare Patient for ChloraPrep Solution:
- When hair removal is necessary, the preferred method is to use a surgical clipper on the morning of the surgery.
- Preparation should be applied to clean, dry, residue-free, intact skin.
- When applying the solution, start at the incision site and apply the solution in a back and forth or up and down motion.

After ChloraPrep Is Applied:
- Allow solution to completely dry prior to draping.

While Waiting for ChloraPrep to Dry:
- Do not drape.
- Check for pooled preparation. Use sterile gauze to absorb pooled solution. Do not blot. Allow solution to dry.
- Remove all solution-soaked materials.

When ChloraPrep Solution Is Dry:
- Begin draping only after solution is dry and all solution-soaked materials are removed.
- If incise drapes are used, apply directly to dry prepped area.

Questions or Comments?
- (800) 523-0502 (M-F 8 a.m.-5 p.m. CST) • www.chloraprep.com

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

LABELING REVIEWS

LABELING REVIEW OF NDA SUPPLEMENT

NDA: 20-832
SUPPLEMENT: SCF-008/BL

Submission Date: 09/09/04
Received: 09/13/04
Review Date: 11/01/04

Applicant: Medi-Flex, Inc.

Applicant's Representative: Cynthia T. Crosby
Vice President, Clinical Affairs
913-451-0880

Drug: ChloraPrep With Tint 26-mL Applicator
chlorhexidine gluconate 2%

Pharmacologic Category: Health Care Antiseptic Patient Preoperative Skin Preparation

Submitted: 1. Color package labeling and insert for the 26-mL tinted antiseptic applicator
2. "Flammability Study of Alcohol-Based Products"

Background:

The sponsor has submitted an amendment to a "Prior Approval Supplement" (SCF-008), dated September 9, 2004, for a 26-mL tinted antiseptic applicator for the Chloraprep product line of patient preoperative skin preparations.

In a September 2, 2004 teleconference with FDA, the sponsor agreed to withdraw the modified labeling submitted in Prior Approval Supplement SCF-008 submitted on July 6, 2004, which included a change in the "Directions" section of the "Drug Facts" box. The sponsor notes that this amendment includes labeling with directions for use that are identical (except for the coverage area) to the labeling for the ChloraPrep One-Step 10.5 mL Applicator submitted in Supplement SLR-006, which was approved on June 10, 2004

(see last approved labeling in Tab A). This amendment also includes a study

comparing the ChloraPrep product to two currently marketed, alcohol-based preoperative skin preparations (DuraPrep and Prevail-FX) when exposed to both an electrocautery scalpel and direct flame.

Reviewer's Comments:

1. The bulleted statement "[redacted]" has been added under the "Directions" section of the Drug Facts label. This is acceptable.

2. Under the "Directions" section of the Drug Facts label, the "maximal treatment area for one applicator has been revised from "...approximately 457 cm2 (approximately 8.4 x 8.4 inches)." to "[redacted]" Because the skin coverage study that was submitted was unacceptable and no new study was provided, this change is unacceptable.

3. Under the Inactive Ingredient section of the Drug Facts label, the bulleted statement "Pledget contains FD&C green #3 dye" has been added. This is acceptable.

4. The product name on the insert has been changed from "ChloraPrep One-Step" on the approved 10.5 ml product to "ChloraPrep with Tint" for the 26 ml applicator. This is acceptable.

5. The bulleted statement "[redacted]" has been added to the insert. This is acceptable.

6. The bulleted statement "When applying the solution, start at the incision site and apply the solution in a back and forth or up and down motion." has been added to the insert. This is acceptable.

7. The catalogue and NDC numbers on the insert are changed to reflect the new product size. This is acceptable.

8. A latex-free symbol has been added to the insert. This is acceptable.

9. The proposed labeling conforms to the last approved labeling for ChloraPrep One-Step and meets the content and format requirements of 21 CFR 201.66 in all other respects. This is acceptable.

Recommendations:

1. Based on the directions for use, the submitted labeling cannot be approved. The sponsor must provide data to support the proposed directions for use.

Robert Sherman, B.S.
Biologist, HFD-560

Debbie Lumpkins, B.S.
Team 3 Leader, HFD-560

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-832
HFD-560Div Files
HFD-560:Ganley/Rosebraugh
HFD-560:Lumpkins/Sherman/Frazier
HFD-520:Bostwick
R/D-RSherman/11/1/04
DocID:LABELING REVIEW NDA SUPP SCF-008(20-832)

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/s/

Robert Sherman
11/2/04 03:37:56 PM
INTERDISCIPLINARY

Debbie Lumpkins
11/2/04 05:34:46 PM
INTERDISCIPLINARY

LABELING REVIEW OF NDA SUPPLEMENT (AMENDED)

NDA: 20-832
SUPPLEMENT: SCF-008/BL

Submission Date: 09/09/04
Received: 09/13/04
Review Date: 04/25/05

Applicant: Medi-Flex, Inc.

Applicant's Representative: Cynthia T. Crosby
Vice President, Clinical Affairs
913-451-0880

Drug: ChloraPrep With Tint 26-mL Applicator
chlorhexidine gluconate 2%

Pharmacologic Category: Health Care Antiseptic Patient Preoperative Skin Preparation

Submitted: 1. Color package labeling, applicator barrel labeling, and insert for the 26-mL tinted antiseptic applicator
2. "Flammability Study of Alcohol-Based Products"

Background:

The sponsor submitted an amendment to a "Prior Approval Supplement" (SCF-008), dated September 9, 2004, for a 26-mL antiseptic applicator for a tinted Chloraprep product line of patient preoperative skin preparations. The amendment includes labeling with directions for use that are identical (except for the coverage area) to labeling for the ChloraPrep One-Step 10.5 mL Applicator (Supplement SLR-006), approved on June 10, 2004.

This amendment was originally reviewed by HFD-560 on November 1, 2004. The reviewer noted that under the "Directions" section of the Drug Facts label, the maximal treatment area for one applicator was revised from

"...approximately 457 cm2 (approximately 8.4 x 8.4 inches)." to "[redacted]" The reviewer stated that because the submitted skin coverage study was unacceptable and because data were needed to support the directions for use, the proposed labeling could not be approved.

This review provides amended and additional labeling comments based on a review by The Division of Anti-Infective Drug Products (HFD-520).

Reviewer's Comments:

1. HFD-520's review stated that even though the labeling included the warning "Do not use with electrocautery procedures," the danger of spark introduction would be present in a large number of cases. The reviewer stated that it may be more realistic to delete this warning, but noted that additional warning language would be needed if this was done.

However, the TFM currently recommends this warning. In addition, the sponsor has no objection to including the warning in the product's labeling, and no data have been provided to support a change in our position that the warning should be included. Therefore, we will leave the warning as is.

2. The original HFD-560 review stated that the bulleted statement "[redacted] had been added under the "Directions" section of the Drug Facts label and on the package insert, and that this change was acceptable.

However, HFD-520's review stated that no data were provided to support the use of [redacted] with this product and that this change is unacceptable without supporting data. HFD-520 recommended that the statement be deleted from the Drug Facts label on the packaging and that the insert not be used.

However, on June 10, 2004, HFD-560 approved the insert for the ChoraPrep One-Step 10.5 ml Applicator. The insert provides important additional information about reducing the risk of fire. Rather than removing the insert entirely, the statement regarding the use of [redacted]

should be deleted from the insert and from the "Directions" section of the Drug Facts label on the outer package.

We concur with the following recommendations in HFD-520's review and the sponsor should include them in the labeling:

3. Based on a review of studies submitted to support the maximal coverage area, under the "Directions" section the bulleted statement "Maximal treatment area for one applicator is approximately [redacted]" should be deleted.

4. Under the "Directions" section, the first bullet "[redacted]" should be deleted and replaced with "Maximal treatment area for one applicator is approximately 1126 cm2 (approx. 13.2 x 13.2 in.). Discard the applicator after a single use." in boldface type.

5. The drying time for both dry and moist surgical sites should be 3 minutes, rather than [redacted].

6. Under the "Warnings" section, the following statement should be added: "Solution contains alcohol and gives off flammable vapors while drying - allow to dry 3 minutes on the skin."

7. Because the labeling on the applicator barrel can be seen at the point of use, the following information should be added (first two lines in boldface type followed by the bulleted statements below):

WARNING - FLAMMABLE
Keep away from fire or flame. ·To reduce fire risk:

- Solution contains alcohol and gives off flammable vapors while drying - allow to dry for 3 minutes on skin.
- Do not use with electrocautery procedures.
- Do not allow solution to pool
- Remove solution-soaked material from prep area.

8. The proposed labeling conforms to the last approved labeling for ChloraPrep One-Step and meets the content and

format requirements of 21 CFR 201.66 in all other respects. This is acceptable.

Recommendations:

The sponsor should be informed that the submitted labeling can be approved with the following revisions:

1. The bulleted statement [redacted] should be deleted from the package labeling and the insert.

2. Under the "Directions" section the bulleted statement "Maximal treatment area for one applicator is approximately [redacted] " should be deleted.

3. Under the "Directions" section, the first bullet [redacted]' should be deleted and replaced (in boldface type) with "Maximal treatment area for one applicator is approximately 1126 cm2 (approx. 13.2 x 13.2 in.). Discard the applicator after a single use."

4. The drying time for both dry and moist surgical sites should be revised to "3 minutes" and should be in bold face type.

5. Under the "Warnings" section of the Drug Facts label, the following statement should be added: "Solution contains alcohol and gives off flammable vapors while drying - allow to dry 3 minutes on the skin."

6. The following information should be added to the labeling on the applicator barrel (first two lines in boldface type followed by the bulleted statements below):

WARNING - FLAMMABLE
Keep away from fire or flame. To reduce fire risk:

- Solution contains alcohol and gives off flammable vapors while drying - allow to dry for 3 minutes on skin.
- Do not use with electrocautery procedures.

- Do not allow solution to pool.
- Remove solution-soaked material from prep area.

Robert Sherman, B.S.
Biologist, HFD-560

Debbie Lumpkins, B.S.
Team 3 Leader, HFD-560

cc: NDA 20-832
HFD-560Div Files
HFD-560:Ganley/Rosebraugh/Johnson
HFD-560:Lumpkins/Sherman/Frazier
HFD-520:Bostwick
R/D-RSherman/04/25/05
DocID:LABELING REVIEW (AMENDED) 20-832, SCF-008BL

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/s/

Robert Sherman
5/3/05 03:41:08 PM
INTERDISCIPLINARY

Debbie Lumpkins
5/3/05 03:48:58 PM
INTERDISCIPLINARY

OTC DRUG LABELING REVIEW

Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products

SUBMISSION/REVIEW DATES:	Received by CDER: August 4, 2005 Received by Reviewer: January 9, 2006 Review Completed: January 31, 2006
SUBMISSION TYPE:	NDA: 20-832/SLR-008/FA
SPONSOR:	Medi-Flex, Inc. 11400 Tomahawk Creek Parkway, Suite 310 Leawood, KS 66211
CONTACT:	Linda McBride, R.Ph. Director Regulatory Affairs (913) 345-3562
DRUG PRODUCT:	ChloraPrep® With Tint 10.5-mL Applicator
ACTIVE INGREDIENT:	2% chlorhexidine gluconate (w/v) 70% isopropyl alcohol (v/v)
PHARMACOLOGICAL CATEGORY:	Antiseptic
DOSAGE FORM:	Sponge applicator
PROVIDING FOR:	patient preoperative skin preparation
MATERIAL REVIEWED:	Labeling: Immediate Container (lidding) Drug Facts labeling, Applicator Barrel labeling (Side A), Applicator Barrel labeling (Side B), and shipping label
PROJECT MANAGER:	Laura Shay, C.R.N.P., M.S.
REVIEWER:	Michelle M. Jackson, Ph.D.

Background on the Current Application

FDA issued an approval letter on May 3, 2005, requesting final printed labeling identical to the approved draft labeling and, as such, in accordance with the labeling requirements of 21 CFR 201.66, when available. In response to FDA's approval letter, the sponsor submitted an electronic version of the final printed labeling for its ChloraPrep® With Tint 26-mL Applicator product.

Reviewer's Comments:

1. The submitted final printed labels for the immediate container (lidding) labeling, and applicator barrel labeling (side A) are identical to the draft labels submitted on May 2, 2005.

2. The sponsor has provided additional labeling for its ChloraPrep® With Tint 26-mL Applicator product. They have included an applicator barrel labeling (side B), which has not been included in the May 3, 2005, approval letter. The additional labeling for the applicator barrel (side B) for the ChloraPrep® With Tint 26-mL Applicator product is acceptable.

3. A package insert for the product was approved separately. No final printed labeling has been submitted for the product. The sponsor should be reminded that they will need to provide final printed labeling for this.

RECOMMENDATIONS FOR THE SPONSOR:

1. The final printed labels submitted for the immediate container (lidding) labeling, and Applicator Barrel labeling (side A) for the ChloraPrep® With Tint 26-mL Applicator, are acceptable.

2. You should be reminded to submit final printed labeling for the package insert, since this was approved separately. It must be identical to the draft labeling dated May 3, 2005.

3. The additional labeling for the applicator barrel (side B) for the ChloraPrep® With Tint 26-mL Applicator product is acceptable.

Michelle M. Jackson, Ph.D. – 2/27/06
IDS Microbiology Reviewer
Office of Nonprescription Products

Debbie Lumpkins
Team Leader
Office of Nonprescription Products
Concurrence – 2/28/06

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/s/

Michelle Jackson
2/28/2006 12:54:34 PM
MICROBIOLOGIST

Debbie Lumpkins
2/28/2006 01:54:52 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

CHEMISTRY REVIEW

Chemistry Review # 1	**1. Division** HFD-560	**2. NDA Number** 20-832
3. Name and Address of Applicant Medi-Flex Hospital Products, Inc. 8717 West 110th Street, Suite 750 Overland Park, KS 66210 Contact: Linda McBride, Director, Regulatory Affairs Phone: 913-451-0880		**4. Supplement** **Number:** SCF-008 **Letter Date:** 7/06/04 **Stamp Date:** 7/07/04 **User Fee Due Date:** 11/07/04
5. Name of Drug Chloraprep	**6. Nonproprietary Name** Chlorhexidine digluconate	
7. Supplement Provides for: A 26 mL applicator with two 13 mL ampoules and green tint in the pledget to mix with the chlorhexidine gluconate solution at the time of application		**8. Amendment(s)** N/A
9. Pharmacological Category Patient Preoperative Skin Preparation	**10. How Dispensed** OTC	**11. Related Documents** N/A
12. Dosage Form Solution (Topical)	**13. Potency(ies)** 2% w/v	
14. Chemical Name and Structure see USAN 1,6-di(4-chlorophenyl-diguaniodo)hexane		

15. Comments **Changes Being Effected in 30 Days**

This supplement provides for a larger 26 mL applicator with two 13 mL size ampoules and green tint in the pledget to mix with the chlorhexidine gluconate s(CHG) 2% solution at the time of application.

It was indicated that the materials used in the applicator remain unchanged from those used in the current applicators.

The submission included a four months of stability data at 25°C and 6 months at 40°C on one production scale batch, and two months of supporting stability data at 40°C on one production scale batch, and 12 months of stability data on commercial scale "prototype" batch of 26 mL applicator. The supplement also included the supporting stability data on three pilot scale batches of a non-approved — mL ampoule size for up to 36 months at 25°C and for 6 months at 40°C.

The submitted sterilization validation report was found adequate by the OPS microbiologist Dr. Bryan Riley.

16. Conclusions and Recommendations
This supplement is recommended for approval.
This supplement contains labeling. Action letter will be issued by HFD-560.

17. Name	**Date**
Rao Puttagunta, Ph.D., Reviewer	11/04/04

18. Concurrence
John Smith, Ph.D., Team Leader

Review Notes

The currently approved ampoule sizes under NDA 20-832 contain CHG volume of 1.1 mL, 1.5 mL, 3.0 mL, and 10.5 mL. The proposed CHG volume in the new ampoules is 13 mL each with a combined volume of 26 mL. It was indicated that all the materials used in the applicator remain unchanged from those used in the current applicators, except for the addition of green tint to the pledget.

The applicator consists of two sealed glass (Type I Borosilicate Glass, USP) ampoules, containing 13.0 mL each of 2% (w/v) CHG solution in 70% (v/v) isopropyl alcohol, enclosed in a molded HDPE plastic handle. The handle is sealed at one end with a ——— pledget that is impregnated with the green dye (FD&C Green #3) and laminated to a ——— foam. After ampoulization, the formulation remains in contact with glass only. The submitted batch records reflect the proposed changes.

The CHG 2% solution within the ampoules will be untinted. However, at the time of application, when the ampoules are broken, the solution flows through the pledget and extracts the green dye.

Therefore the proposed "formulation change" occurs at the time of application of the CHG solution, not at the time of ampoulization. The estimated maximum concentration of the green tint was stated to amount to ——% w/v in the CHG solution. FD&C Green #3 is widely used in CDER approved drug products. Moreover, the dye does not come in contact with the CHG solution until at the time of usage. Therefore it is not likely to affect the safety or the quality of the product. ***OK.***

Stability Data: ***Adequate***

The submission included a four months of stability data at 25°C and 6 months at 40°C on one production scale batch, and two months of supporting stability data at 40°C on one production scale batch, and 12 months of stability data on commercial scale "prototype" batch of 26 mL applicator. The supplement also included the supporting stability data on three pilot scale batches of a non-approved — mL ampoule size for up to 36 months at 25°C and for 6 months at 40°C.

Evaluation:

The submitted stability data is well within the established acceptance criteria. The submitted primary stability data did not show any clear trends.

In a t-con on 10/19/04 the applicant (Ms. Linda McBride of Regulatory Affairs) was asked if they have any information on whether there were any changes in dye elution from the pledget on storage. Ms. McBride responded stating that they did not think there would be any adverse changes on storage in dye elution and therefore did not see any need for further investigation. Since the dye does not come in contact with the CHG solution until at the time of usage, and it is widely used in CDER approved products, we did not see any serious safety concerns.

The proposed changes do not affect the protective properties of the container/closure system and therefore are not likely to adversely affect the product quality. ***Adequate.***

Stability Commitment: ***Adequate***

The applicant committed to place first three commercial batches and annual batches thereafter according the current stability protocol. Stability protocol was also included in this supplement.

Sterilization Validation: ***Adequate***

The submitted sterilization validation report was evaluated by Dr. Bryan Riley of the OPS Microbiology team and found adequate (see microbiology review dated 11/04/04 in DFS).

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/s/

Rao Puttagunta
11/4/04 02:15:50 PM
CHEMIST

John Smith
11/4/04 03:01:58 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review
Review for HFD-550

3 NOVEMBER 2004

NDA: 20-832/SCF-008

Drug Product Name
Proprietary: Chloraprep
Non-proprietary: chlorhexidine gluconate 2%
Drug Product Priority Classification: N/A

Review Number: 1

Subject of this Review
Submission Date: 6 July 2004
Receipt Date: 7 July 2004
Consult Date: 13 October 2004
Date Assigned for Review: 25 October 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Medi-Flex Hospital Products
Address: 8717 W 110th, Suite 750, Overland Park, KS 66210
Representative: Diane Beatty (Beckloff Associates)
Telephone: 913-451-3955

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** Prior Approval

2. **SUPPLEMENT PROVIDES FOR:** A new size container

3. **MANUFACTURING SITE:** [redacted]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Topical Applicator, 2% solution

5. **METHOD(S) OF STERILIZATION:** ————————

6. **PHARMACOLOGICAL CATEGORY:** Pre-operative Skin Disinfectant

B. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:** N/A

filename: N020832S008R1.doc

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ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product is [redacted]

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Microbiology Supervisor

C. CC Block
N/A

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Product Quality Microbiology Assessment

The applicant proposes to market the approved product (2% chlorhexidine gluconate) in a 26 mL applicator (contains 2 × 13 mL ampoules). The applicators are sterilized using [redacted] and the new size applicator will use the same [redacted] process as the previously approved applicators (0.67, 1.1, 1.5, 3.0 and 10.5 mL). The validation approach for the new applicators was the same as that used for the previously approved applicators [redacted]

ADEQUATE

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/s/

Bryan Riley
11/4/04 01:37:07 PM
MICROBIOLOGIST

David Hussong
11/4/04 01:48:44 PM
MICROBIOLOGIST
approval

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 1
Consultation for HFD-560

NDA: 20-832/SN008 **Date Completed: November 4, 2004**

Applicant:
Mediflex Hospital Products
11400 Tomahawk Creek Parkway
Suite 310
Leawood, KS 66211
913-451-0880

Contact:
Beckloff Associates, Inc.
7400 West 110th Street
Suite 300
Overland Park, KS 66210
913-451-3955

Chem/Ther. Type: Antimicrobial

Submission Reviewed: NDA 20-832 SN008

Providing for: Patient Preoperative Skin Preparation

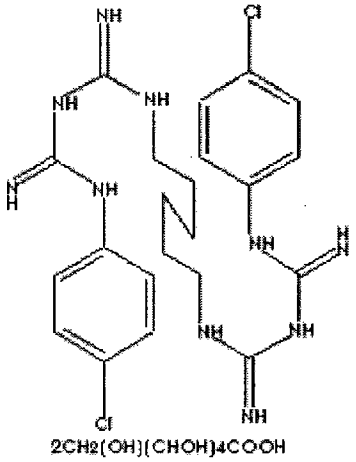
Product Names:
Proprietary: ChloraPrep with Tint
Non-proprietary/USAN: Chlorhexidine Gluconate

Chemical Names: 1-6-di(4-chlorophenyl-diguanido)hexane

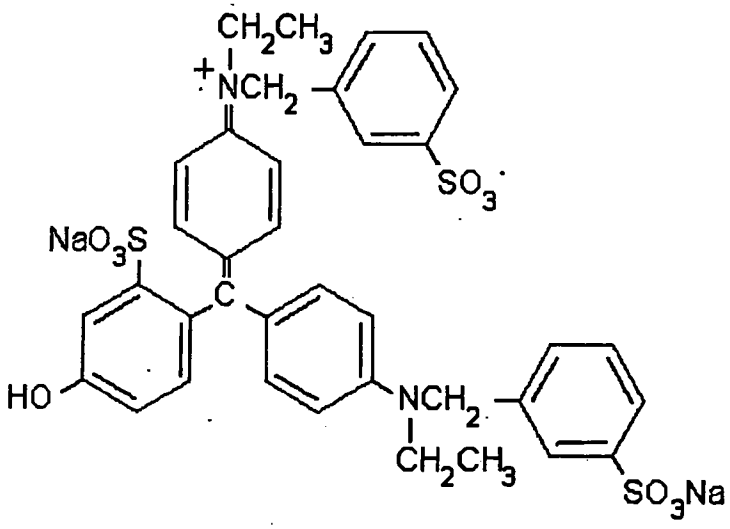
Molecular Formulae: Chlorhexidine Gluconate: $C_{22}H_{30}Cl_2N_{10}\bullet 2C_6H_{12}O_7$
Fast Green FCF: $C_{37}H_{34}N_2Na_2O_{10}S_3$

Structural Formulae: Chlorhexidine Gluconate and Fast Green FCF

CHG



Fast Green FCF



Dosage Form: 2% solution

Route of Administration: Chlorhexidine Gluconate 2% (w/v) Topical Solution, 20mL, 22mL, and 26mL applied for 30 seconds and —minutes

Pharmacological Category: Antiseptic

Dispensed: Rx_____ OTC__X___

Initial Submission Dates

Received by CDER: January 15, 1997 (volumes 1.1, 1.3. and 1.9)
Received by Reviewer: January 23, 1997
Review Completed: January 30, 1998

Supplements/Amendments:

Received by CDER: August 8, 1997 (volumes 1.2 and 2.2)
Received by Reviewer: August 20, 1997
Review Completed: January 30, 1998

Initial Resubmission:

Received by CDER: January 13, 2000 (volumes 1 through 11)
Received by Reviewer: January 13, 2000
Review Completed: July 11, 2000

Supplement Resubmission:

Received by CDER: February 2, 2000
Received by Reviewer: February 2, 2000
Review Completed: July 11, 2000

Supplement SMC004 Resubmission:

Received by CDER: August 7, 2002
Received by Reviewer: October 28, 2002
Review Completed: November 6, 2002

Supplement SMC004 Resubmission:

Received by CDER: January 30, 2003
Received by Reviewer: January 31, 2003
Review Completed: February 5, 2003

Supplement Submission:

Received by CDER: July 15, 2004
Received by Reviewer: July 22, 2004
Review Completed: November 9, 2004

Related Documents: IND-46,243

Remarks:

On July 14, 2000, the FDA approved NDA 20-832 for Chlorhexidine Gluconate 2% (w/v) Topical Solution in the 3-mL Applicator for the indication of patient preoperative skin preparation. With this submission, the Applicant requests approval for a larger-sized, tinted antiseptic applicator for the ChloraPrep product line (ChloraPrep® With Tint 26-mL Applicator). The currently approved sizes of ChloraPrep One-Step (non-tinted antiseptic) include 1.1-ml (Frepp®), 1.5-mL (Frepp), 3.0-mL, and 10.5-mL.

The Agency provided a study design outlining unresolved clinical issues in the facsimile dated May12, 2003. A Type-A meeting was held on June 11, 2003 at which time the Agency stated its position that the clinical study requested in the May 12, 2003, facsimile was necessary to support the safety of the 26-mL ChloraPrep One-Step Applicator.

On [redacted], which requested approval for a [redacted] was withdrawn.
As with the approved sizes of Chlorhexidine Gluconate 2% (w/v) Topical Solution applicators, the ChloraPrep with Tint 26-mL Applicator will be used for the approved indication of patient preoperative skin preparation but will treat a maximal area of approximately [redacted]

The ChloraPrep with Tint 26-mL Applicator is similar to the 3.0- and 10.5-mL Applicators in design and packaging component materials and contains the same Chlorhexidine Gluconate 2% (w/v) Topical Solution as approved in NDA No. 20-832 for all the approved sizes. The ChloraPrep with Tint 26-mL Applicator employs two 13-mL glass ampoules which are slightly larger than the single ampoule found in the 10.5-mL Applicator. FD&C Green #3 dye has been added to the pledget so that the coverage area is well defined during application of the ChloraPrep Solution. The similarities and differences between the 3.0-, 10.5-, and 26-mL Applicators are summarized in the Chemistry, Manufacturing, and Controls section of the current submission.

This supplement proposes an applicator for pre-operative prepping that delivers 26 mL of ChloraPrep with Tint. This review describes the findings and the recommendations of the Microbiology Reviewer from the Division of Anti-infective Drug Products (HFD-520). These recommendations are for evaluation by the Division Director for Over the Counter Drug Products to identify and comment upon any microbiology concerns and the proposed surface coverage study found in the submission reviewed.

Recommendations:
From the data presented by the Applicant, the Microbiology Reviewer makes the following recommendations:

1. The Applicant failed to meet the Technical Final Monograph (TFM) criteria for *in vitro* spectrum of activity testing. Too few microbial isolates were tested against the product. The TFM presents a list of 21 microorganisms to which a product is to be tested. The TFM also states that the product is to be tested against 25 clinical isolates and 25 laboratory strains of the individual organisms on this list. The Applicant did not present MICs for 25 fresh clinical isolates and 25 laboratory strains of each organism on the list in the TFM. In addition, the Applicant did not differentiate clinical isolates from laboratory strains in the MIC data presented. It is not clear from the data how many clinical isolates or laboratory strains were tested. Thus, the Applicant should differentiate the MIC data based upon these criteria. Also, the Applicant should be aware that the MIC_{90}s presented in Table 1 are tentative MIC_{90}s since in many cases, less than 100 isolates were used in the determination of those MIC_{90}s.

2. Time-kill kinetics data for all 21 organisms on the TFM *in vitro* testing list against the test product are useful in determining the fast-acting ability of the test product. This Reviewer recommends these data be provided by the Applicant. Due to the limited number of organisms tested, and lack of data from the neutralizer validation for the

time kill studies, it is not possible to determine if the test product, CHG+colorant, is fast-acting.

3. No information was presented on the mechanism of action of the drug product. The Applicant should present studies or literature which demonstrates the mechanism of action.

4. No information or data was submitted on the mechanism of resistance to the drug product. Resistance mechanisms may limit the effectiveness of an antimicrobial drug in clinical settings. Therefore, characterization of the mechanisms mediating resistance and their distribution within the proposed target pathogens may delineate the potential clinical usefulness of the drug under investigation. Two approaches may be taken. First, the determination of the evolution of a point mutation by the sequential passage of an organism through increasing concentration of the antimicrobial included in the culture medium. The second approach is a thorough survey of the published literature to determine whether resistance has been reported for the antimicrobial ingredient.

5. The results of the clinical simulation studies indicate that the product does not meet the TFM criterion for a two- $\log_{10}$ reduction after ten minutes in a dry skin site. According to the TFM, both ChloraPrep and ChloraPrep with Tint fail to meet the two- $\log_{10}$ threshold for a dry skin site, normally the abdomen.

6. There are several deficiencies in the protocol for the clinical simulation. These deficiencies include: the lack of a positive control, the lack of a negative control, only one study was conducted, baseline counts were too low, and only a dry anatomical site was tested, namely the back (a dry site). The Reviewer recommends that all of these deficiencies be addressed in future protocol submissions.

7. On September 3, 2004, a facsimile was sent to the Applicant addressing the Skin Coverage Study. The Microbiology Reviewer concurs with the findings of the Medical Officer, Mr. David Bostwick regarding this study. In that facsimile, the Applicant was asked to conduct the following two clinical studies:

A. Skin Coverage Study:

The study submitted in support of this supplemental application ("Evaluation of the Area Covered by a Preoperative skin Preparation") is deficient in that the product was applied for a 30 second period rather than the maximum 2 minute application period recommended in the approved labeling. Since it is the intent of this study to determine the potential for product runoff and pooling when used for the longest possible time, you need to conduct another skin coverage study to support approval of the larger applicator.
(i). We presume that the preferred additional applicator size is 26- mL. Therefore, all test subjects should be tested using this size. Skin area coverage should be determined using a total of at least 20 applicators on adult volunteers of varying heights and weights. The average amount (weight/volume) of product used in the applications should be recorded.
(ii). The protocol should specifically instruct that the directions for application for a two-minute prep as presented in the approved labeling will be used. The report should

specifically state whether product runoff and/or pooling occurred for each test subject. You can use the same format for the skin coverage report that you used for the July 6, 2004 submission.

B. Patient Pre-operative Skin Preparation Study:

(i). Bacterial reductions in a representative number of test subjects should be determined. We recommend that the following outline be utilized:

(a). Data from 20 evaluable subjects should be available. Ten subjects should have been prepped with the "new" (tinted) formulation, and ten should have been prepped with the "old" (untinted) formulation.

(b). The procedure should approximate that recommended in the Tentative Final Monograph for Health-Care Antiseptic Drug Products for "dry" surgical sites. That is, the abdomen should be used for testing, the subjects should have at least a 3 log baseline bacterial count, and bacterial reductions should be determined at 10 minutes and 6 hours after prepping. A 30-second prep as recommended in the approved labeling should be used.

(ii). We strongly recommended that you submit the protocol for testing to the IND for review and feedback before you initiate the study.

Table of Contents

Introduction

The purpose of this supplement to NDA No. 20-832 is to provide data supporting approval of a 26-mL Applicator for ChloraPrep with Tint and propose appropriate labeling. ChloraPrep with Tint 26-mL Applicator is very similar to the currently approved ChloraPrep One-Step Applicators approved in NDA 20-832 except for the larger size, inclusion of FD&C Green #3 dye in the pledget, and inclusion of ———— ————————————. The dye allows for better visualization of the coverage area when the solution is applied, highlighting the area which might be under-treated as well as areas of pooling, solution runoff, or solution-soaked drapes. The visual effects presented by the tinted solution suggest that the addition of the tinting element is a significant contribution to the product's overall safety. The currently approved sizes of ChloraPrep One-Step include 1.1-ml (FreppR), 1.5-mL (Frepp), 3.0-mL, and 10.5-mL Applicators. The 1.1-mL Frepp is not currently marketed.

As with the approved sizes, the ChloraPrep with Tint 26-mL Applicator will be used for the approved indication of patient preoperative skin preparation but will treat a maximal area of approximately ————————————. The ChloraPrep with Tint 26-mL Applicator contains the same chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (w/v) topical solution as approved in NDA No. 20-832 for the ChloraPrep One-Step Applicators. The similarities and differences between applicators and information to support the addition of the ChloraPrep with Tint 26-mL Applicator are provided in the Chemistry, Manufacturing, and Controls section of the current submission. No changes have been made to the drug substance, Chlorhexidine Gluconate 20%, as previously approved in this NDA, as a result of this change.

Mechanism of Action

The Applicant presents no information on the mechanism of action for either CHG or isopropanol.

Antimicrobial Spectrum of Activity

Table 1 summarizes the *in vitro* activity of Medi-flex CHG +/- Colorant and its vehicles against 714 microorganisms. Appendix A of the submission provides line listings of individual strains and results.

Table 1. MICs for Products tested (μg/mL).

organism	N	product	geomean	range	MIC_{50}	MIC_{90}
All aerobic strains combined	547	CHG-Colorant MIC	7.25	0.78-100	8	32
		CHG MIC	6.48	0.4-100	8	32
		Hibiclens MIC	5.1	0.11	8	32
		Isopropanol MIC	--	4.4-70	128	128
		Povidone Iodine Solution MIC	--	390->12500	8192	16384
All aerobic Gram-negative strains combined	265	CHG-Colorant MIC	14.24	0.78-100	32	32
		CHG MIC	12.83	0.4-100	16	32
		Hibiclens MIC	10.27	0.1-100	16	32
		Isopropanol MIC	--	4.4-70	128	128
		Povidone Iodine Solution MIC	--	390-12500	8192	8192
All aerobic Gram-positive strains combined	282	CHG-Colorant MIC	3.58	0.78-25	4	16
		CHG MIC	3.15	0.4-25	4	16
		Hibiclens MIC	2.44	0.2-25	2	16
		Isopropanol MIC	--	17.5-70	128	128
		Povidone Iodine Solution MIC	--	390->12500	4096	8192
Acinetobacter baumannii	17	CHG-Colorant MIC	18.79	6.25-50	32	32
		CHG MIC	18.79	6.25-50	32	32
		Hibiclens MIC	11.52	3.12-25	16	32
		Isopropanol MIC	67.2	35-70	128	128
		Povidone Iodine Solution MIC	6000.29	3125-12500	8192	8192
Acinetobacter calcoaceticus	9	CHG-Colorant MIC	10.72	3.12-25	16	32
		CHG MIC	9.92	3.12-25	16	32
		Hibiclens MIC	7.29	3.12-25	8	32
		Isopropanol MIC	60.01	35-70	128	128
		Povidone Iodine Solution MIC	3936.55	390-6250	8192	8192
Acinetobacter lwoffii	15	CHG-Colorant MIC	5.19	0.78-25	8	32
		CHG MIC	5.2	0.4-25	8	32
		Hibiclens MIC	2.99	0.1-25	2	32
		Isopropanol MIC	53.07	4.47	128	128
		Povidone Iodine Solution MIC	3759.05	390-6250	4096	8192
Bacteroides cepacia	18	CHG-Colorant MIC	28.06	12.5-100	32	128
		CHG MIC	27	12.5-100	32	128
		Hibiclens MIC	17.7	0.1-100	32	128
		Isopropanol MIC	37.83	4.4-70	64	128
		Povidone Iodine Solution MIC	4252.01	390-6250	8192	8192
Enterobacter aerogenes	14	CHG-Colorant MIC	20.51	6.25-50	32	32
		CHG MIC	18.57	6.25-50	32	32
		Hibiclens MIC	17.68	6.25-25	32	32
		Isopropanol MIC	70	70-70	128	128
		Povidone Iodine Solution MIC	6900.56	6250-12500	8192	16384

organism	N	product	geomean	range	MIC_{50}	MIC_{90}
Enterobacter cloacae	15	CHG-Colorant MIC	13.09	3.12-25	16	32
		CHG MIC	10.88	3.12-25	16	32
		Hibiclens MIC	11.94	3.12-25	16	32
		Isopropanol MIC	70	70-70	128	128
		Povidone Iodine Solution MIC	6250	6250-6250	8192	8192
Escherichia coli	20	CHG-Colorant MIC	2.13	1.56-13	2	4
		CHG MIC	1.86	1.56-6	2	4
		Hibiclens MIC	1.73	0.78-6	2	4
		Isopropanol MIC	56.86	35-70	128	128
		Povidone Iodine Solution MIC	6470.41	6250-12500	6250	6250
All enterococci combined	61	CHG-Colorant MIC	5.51	1.56-13	8	16
		CHG MIC	6.04	1.56-13	8	16
		Hibiclens MIC	4.7	0.78-13	8	8
		Isopropanol MIC	66.89	35-70	128	128
		Povidone Iodine Solution MIC	5453.32	3125-6250	8192	8192
Enterococcus faecalis vancomycin resistant	15	CHG-Colorant MIC	9.92	3.12-13	16	16
		CHG MIC	9.92	6.25-13	16	16
		Hibiclens MIC	6.86	6.25-13	8	16
		Isopropanol MIC	60.94	35-70	128	128
		Povidone Iodine Solution MIC	5967.76	3125-6250	8192	8192
Enterococcus faecalis vancomycin sensitive	15	CHG-Colorant MIC	6.86	3.12-13	8	16
		CHG MIC	7.18	3.12-13	8	16
		Hibiclens MIC	5.7	1.56-13	8	8
		Isopropanol MIC	70	70-70	128	128
		Povidone Iodine Solution MIC	5698.27	3125-6250	8192	8192
Enterococcus faecium vancomycin resistant Linezolid-R	4	CHG-Colorant MIC	4.42	3.12-6	ND	ND
		CHG MIC	6.25	6.25-6	ND	ND
		Hibiclens MIC	5.26	3.12-6	ND	ND
		Isopropanol MIC	70	70-70	ND	ND
		Povidone Iodine Solution MIC	5255.6	3125-6250	ND	ND
Enterococcus faecium vancomycin resistant	11	CHG-Colorant MIC	3.77	1.56-3	4	8
		CHG MIC	5.17	1.56-3	8	8
		Hibiclens MIC	4.28	1.56-3	8	8
		Isopropanol MIC	70	70-70	128	128
		Povidone Iodine Solution MIC	5173.46	3125-6250	8192	8192
Enterococcus faecium vancomycin sensitive	16	CHG-Colorant MIC	3.56	1.56-13	4	8
		CHG MIC	3.56	1.56-13	4	8
		Hibiclens MIC	2.86	0.78-6	4	8
		Isopropanol MIC	67.03	35-70	128	128
		Povidone Iodine Solution MIC	5032.78	3125-6250	8192	8192
Enterococcus hirae ATCC strain	1	CHG-Colorant MIC	3.13	3.00	ND	ND
		CHG MIC	3.13	3.00	ND	ND
		Hibiclens MIC	1.56	1.56-2	ND	ND
		Isopropanol MIC	70	70	ND	ND
		Povidone Iodine Solution MIC	6250	6250	ND	ND

organism	N	product	geomean	range	MIC_{50}	MIC_{90}
Haemophilus influenzae	48	CHG-Colorant MIC	19	12.50-25	32	32
		CHG MIC	15.98	12.5-25	16	32
		Hibiclens MIC	14.44	12.5-25	16	32
		Isopropanol MIC	36.55	35-70	64	64
		Povidone Iodine Solution MIC	6072.07	3125-6250	8192	8192
Klebsiella oxytoca	5	CHG-Colorant MIC	16.49	12.5-25	ND	ND
		CHG MIC	14.36	6.25-25	ND	ND
		Hibiclens MIC	10.88	6.25-13	ND	ND
		Isopropanol MIC	70	70	ND	ND
		Povidone Iodine Solution MIC	9473.23	6250-12500	ND	ND
Klebsiella pneumoniae ESBL+	16	CHG-Colorant MIC	20.13	3.12-50	32	32
		CHG MIC	18.46	6.25-25	32	32
		Hibiclens MIC	16.93	6.25-25	32	32
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	6250	6250	8192	8192
Micrococcus luteus ATCC Strain	1	CHG-Colorant MIC	3.13	3.12-3	ND	ND
		CHG MIC	3.13	3.12-3	ND	ND
		Hibiclens MIC	3.13	3.12-3	ND	ND
		Isopropanol MIC	70	70	ND	ND
		Povidone Iodine Solution MIC	3125	3125	ND	ND
Pseudomonas aeruginosa	13	CHG-Colorant MIC	17.21	6.25-25	32	32
		CHG MIC	14.67	6.25-25	16	32
		Hibiclens MIC	11.24	6.25-25	16	32
		Isopropanol MIC	66.37	35-70	128	128
		Povidone Iodine Solution MIC	8159.45	6250-12500	8192	16384
Pseudomonas aeruginosa Ciprofloxacin resistant	5	CHG-Colorant MIC	14.36	6.25-25	ND	ND
		CHG MIC	14.36	6.25-25	ND	ND
		Hibiclens MIC	10.88	6.25-25	ND	ND
		Isopropanol MIC	53.04	35-70	ND	ND
		Povidone Iodine Solution MIC	7179.36	6250-12500	ND	ND
Pseudomonas fluorescens/ Pseudomonas putida	12	CHG-Colorant MIC	7.87	3.12-25	8	16
		CHG MIC	7.02	3.12-25	8	16
		Hibiclens MIC	5.57	3.12-25	8	16
		Isopropanol MIC	52.47	4.4-70	128	128
		Povidone Iodine Solution MIC	8342.75	6250-12500	8192	16384
Proteus mirabilis	10	CHG-Colorant MIC	23.33	3.12-50	32	64
		CHG MIC	20.3	1.56-50	32	32
		Hibiclens MIC	18.94	1.56-50	32	64
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	6698.58	6250-12500	8192	8192
Proteus vulgaris	15	CHG-Colorant MIC	21.76	12.5-50	32	64
		CHG MIC	18.09	12.5-50	16	32
		Hibiclens MIC	13.71	6.25-25	16	32
		Isopropanol MIC	58.19	35-70	128	128
		Povidone Iodine Solution MIC	6545.59	6250-12500	8192	8192

organism	N	product	geomean	range	MIC_{50}	MIC_{90}
Serratia marcescens	15	CHG-Colorant MIC	27.42	6.25-50	32	64
		CHG MIC	27.42	6.25-50	32	64
		Hibiclens MIC	23.87	6.25-50	32	64
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	6250	6250	8192	8192
All Staphylococci combined	145	CHG-Colorant MIC	2.16	0.78-6	2	4
		CHG MIC	1.75	0.4-6	2	4
		Hibiclens MIC	1.13	0.2-6	1	2
		Isopropanol MIC	68.35	17.5-70	128	128
		Povidone Iodine Solution MIC	--	390-6250	4096	4096
Staphylococcus aureus methicillin resistant	21	CHG-Colorant MIC	3.12	1.56-6	4	4
		CHG MIC	2.32	1.56-3	4	4
		Hibiclens MIC	1.61	0.78-6	2	2
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	3450	3125-6250	4096	8192
Staphylococcus aureus methicillin susceptible	20	CHG-Colorant MIC	3.02	1.56-3	4	4
		CHG MIC	1.79	1.56-3	2	4
		Hibiclens MIC	1.41	0.78-3	2	2
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	3125	3125	4096	4096
Staphylococcus epidrmidis methicillin resistant	20	CHG-Colorant MIC	2.54	1.56-6	4	8
		CHG MIC	1.92	1.56-6	2	4
		Hibiclens MIC	1.27	0.78-3	1	4
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	2451.43	390-6250	4096	4096
Staphylococcus epidermidis methicillin susceptible	21	CHG-Colorant MIC	1.9	1.56-3	2	4
		CHG MIC	1.84	1.56-3	2	4
		Hibiclens MIC	1.05	0.78-3	1	2
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	2830.21	1562-6250	4096	4096
Staphylococcus haemolyticus methicillin resistant	5	CHG-Colorant MIC	2.72	1.56-3	ND	ND
		CHG MIC	2.37	1.56-3	ND	ND
		Hibiclens MIC	1.56	0.78-3	ND	ND
		Isopropanol MIC	70	70	ND	ND
		Povidone Iodine Solution MIC	2061.34	1562-3125	ND	ND
Staphylococcus haemolyticus methicillin susceptible	11	CHG-Colorant MIC	2.14	0.78-3	4	4
		CHG MIC	1.89	1.56-3	2	4
		Hibiclens MIC	1.14	0.20-3	2	2
		Isopropanol MIC	61.74	17.50-70	128	128
		Povidone Iodine Solution MIC	1213.57	390-3125	2048	4096
Staphylococcus hominis	15	CHG-Colorant MIC	1.56	0.78-3	2	4
		CHG MIC	1.36	0.4-2	2	2
		Hibiclens MIC	0.78	0.2-2	1	2
		Isopropanol MIC	60.94	35-70	128	128
		Povidone Iodine Solution MIC	619.32	390-3125	512	4096

organism	N	product	geomean	range	MIC_{50}	MIC_{90}
Staphylococcus saprophyticus	16	CHG-Colorant MIC	1.15	0.78-2	2	2
		CHG MIC	1.15	0.78-2	2	2
		Hibiclens MIC	0.63	0.2-1	1	1
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	1939.74	390-3125	2048	2048
Staphylococcus simulans	16	CHG-Colorant MIC	2.02	1.56-6	2	8
		CHG MIC	1.63	0.78-3	2	4
		Hibiclens MIC	1.15	0.78-3	1	4
		Isopropanol MIC	70	70	128	128
		Povidone Iodine Solution MIC	2865.24	390-6250	4096	8192
Stenotrophomonas maltophilia	16	CHG-Colorant MIC	15.52	1.56-50	32	64
		CHG MIC	14.23	1.56-50	32	64
		Hibiclens MIC	8.46	0.78-25	16	32
		Isopropanol MIC	58.86	35-70	128	128
		Povidone Iodine Solution MIC	4819.41	3125-6250	8192	8192
All streptococci combined	76	CHG-Colorant MIC	6.66	0.78-25	16	16
		CHG MIC	5.76	0.40-25	16	16
		Hibiclens MIC	6.25	0.78-25	16	16
		Isopropanol MIC	39.41	17.5-70	64	128
		Povidone Iodine Solution MIC	>12500	1562->12500	>12500	>12500
Streptococcus agalactiae	15	CHG-Colorant MIC	3.76	3.12-6	4	8
		CHG MIC	2.85	1.56-3	4	4
		Hibiclens MIC	3.43	3.12-6	4	8
		Isopropanol MIC	46.18	35-70	64	128
		Povidone Iodine Solution MIC	7874.51	6250-12500	8192	8192
Streptococcus pneumoniae	46	CHG-Colorant MIC	12.88	1.56-25	16	32
		CHG MIC	12.5	0.78-25	16	32
		Hibiclens MIC	12.13	6.25-25	16	16
		Isopropanol MIC	37.14	35-70	64	64
		Povidone Iodine Solution MIC	>12500	6250->12500	>12500	>12500
Streptococcus pyogenes	15	CHG-Colorant MIC	1.56	0.78-6	2	4
		CHG MIC	1.08	0.40-6	1	4
		Hibiclens MIC	1.49	0.78-3	2	4
		Isopropanol MIC	40.2	17.5-70	64	128
		Povidone Iodine Solution MIC	4123.29	1562->12500	4096	8192
All anaerobic strains combined	92	CHG-Colorant MIC	4.15	0.10-50	8	16
		CHG MIC	4.09	0.20-50	8	16
		Hibiclens MIC	3.84	0.20-50	4	16
		Isopropanol MIC	27.2	4.4-70	64	64
		Povidone Iodine Solution MIC	UR	390-3125	4096	UR
Bacteroides distansonis	6	CHG-Colorant MIC	11.14	6.25-25	ND	ND
		CHG MIC	11.14	6.25-25	ND	ND
		Hibiclens MIC	12.5	6.25-25	ND	ND
		Isopropanol MIC	UR	0	ND	ND
		Povidone Iodine Solution MIC	UR	0	ND	ND

organism	N	product	geomean	range	MIC_{50}	MIC_{90}
Bacteroides fragilis	18	CHG-Colorant MIC	10.31	6.25-25	16	16
		CHG MIC	10.31	6.25-25	16	16
		Hibiclens MIC	10.31	6.25-25	16	16
		Isopropanol MIC	UR	UR	UR	UR
		Povidone Iodine Solution MIC	UR	UR	UR	UR
Bacteroides ovatus	7	CHG-Colorant MIC	12.5	6.25-50	ND	ND
		CHG MIC	12.5	6.25-50	ND	ND
		Hibiclens MIC	12.5	6.25-50	ND	ND
		Isopropanol MIC	UR	UR	ND	ND
		Povidone Iodine Solution MIC	UR	UR	ND	ND
Bacteroides thetoiotaomicron	16	CHG-Colorant MIC	8.84	6.25-50	8	32
		CHG MIC	9.23	3.12-50	8	32
		Hibiclens MIC	10.51	3.12-50	16	32
		Isopropanol MIC	UR	UR	UR	UR
		Povidone Iodine Solution MIC	UR	UR	UR	UR
Clostridium difficile	11	CHG-Colorant MIC	3.54	0.78-12.5	4	16
		CHG MIC	4.86	1.56-12.5	8	16
		Hibiclens MIC	3.12	0.78-12.5	4	16
		Isopropanol MIC	12.37	8.75-17.5	16	32
		Povidone Iodine Solution MIC	781.57	390-1562	1024	1024
Eubacterium lentum ATCC strain	1	CHG-Colorant MIC	6.25	6.25	ND	ND
		CHG MIC	6.25	6.25	ND	ND
		Hibiclens MIC	6.25	6.25	ND	ND
		Isopropanol MIC	--	UR	ND	ND
		Povidone Iodine Solution MIC	--	UR	ND	ND
Prevotella bivia	16	CHG-Colorant MIC	3.56	0.40-6.25	4	8
		CHG MIC	3.13	0.40-6.25	4	8
		Hibiclens MIC	3.56	0.40-6.25	4	8
		Isopropanol MIC	UR	UR	UR	UR
		Povidone Iodine Solution MIC	UR	1562	UR	UR
Propionibacterium acnes	17	CHG-Colorant MIC	0.37	0.10-0.40	1	1
		CHG MIC	0.38	0.20-0.40	1	1
		Hibiclens MIC	0.49	0.40-0.78	1	1
		Isopropanol MIC	UR	UR	UR	UR
		Povidone Iodine Solution MIC	UR	782-1562	UR	UR
All yeast strains combined	75	CHG-Colorant MIC	4.32	1.56-25	4	8
		CHG MIC	4.01	1.56-25	4	8
		Hibiclens MIC	3.3	0.20-25	4	16
		Isopropanol MIC	27.78	4.40-70	64	64
		Povidone Iodine Solution MIC	2720.35	390-3125	4096	4096
Candida albicans	14	CHG-Colorant MIC	6.25	1.56-12.50	8	16
		CHG MIC	5.13	1.56-12.50	8	8
		Hibiclens MIC	3.63	0.20-12.5	4	16
		Isopropanol MIC	24.76	4.4-35	64	64
		Povidone Iodine Solution MIC	2001.11	390-3125	4096	4096

organism	N	product	geomean	range	MIC_{50}	MIC_{90}
Candida glabrata	14	CHG-Colorant MIC	5.95	3.12-6.25	8	8
		CHG MIC	6.25	3.12-12.5	8	8
		Hibiclens MIC	7.62	3.12-12.5	8	16
		Isopropanol MIC	30.17	17.50-35	64	64
		Povidone Iodine Solution MIC	2973.98	1562-3125	4096	4096
Candida krusei	17	CHG-Colorant MIC	3.83	3.12-6.25	4	8
		CHG MIC	3.53	3.12-6.25	4	8
		Hibiclens MIC	2.65	1.56-3.13	4	4
		Isopropanol MIC	29.73	17.50-35	64	64
		Povidone Iodine Solution MIC	3125	3125	4096	4096
Candida parapsilosis	18	CHG-Colorant MIC	3.25	1.56-25	4	16
		CHG MIC	2.89	1.56-25	4	16
		Hibiclens MIC	1.97	0.78-25	2	16
		Isopropanol MIC	28.87	17.50-70	64	128
		Povidone Iodine Solution MIC	2678.79	1562-3125	4096	4096
Candida tropicalis	12	CHG-Colorant MIC	3.51	3.12-6.25	4	8
		CHG MIC	3.51	1.56-6.25	4	8
		Hibiclens MIC	3.31	1.56-6.25	4	8
		Isopropanol MIC	24.75	17.50-35	32	64
		Povidone Iodine Solution MIC	2949.53	1562-3125	4096	4096

Aerobic Strains. The MICs of Medi-flex CHG + Colorant were similar to those obtained with CHG without colorant (geomeans of 7.25 and 6.48 µg/ml respectively) and slightly less effective than Hibiclens (97.25 vs. 510 µg/ml, respectively, Table 1). The differences in geomeans for the CHG + Colorant vs. CHG without colorant were less than one log2 dilution (i.e. 0.77 log). This is to be expected since the active ingredient in both formulations is chlorhexidine gluconate. The differences in geomeans for the CHG+Colorant vs. Hibiclens were more than two log2 dilutions (2.15 logs). Medi-flex CHG + Colorant was slightly more active against Gram-positive strains as compared to Gram-negative strains (geomeans of 3.58 vs. 14.24 µg/ml, respectively). The same trend was seen with Hibiclens (2.44 vs. 10.27). The MIC_{50}s were ≤32 µg/ml for all strains tested and the MIC_{90}s were ≤64 µg/ml for the vast majority of species. Only *B. cepacia* had a MIC_{90} of 128 µg/ml. There were no species with MIC_{90}s >128 µg/ml (including anaerobes and yeasts). Since the concentration of the undiluted product is approximately 3000 times greater than the MIC_{90} of 64 µg/ml for the majority of strains tested, it is anticipated that Medi-flex CHG + Colorant would be effective in inhibiting the growth of nearly all bacteria and yeasts. If the MIC_{90} were to be adjusted to the actual concentration rather than the next highest even log2 value, then the dilution factor would be even greater. The MIC_{50} and MIC_{90} were not calculated for species with less than nine strains tested.

Anaerobic Bacteria. The MIC_{90}s of the Medi-flex CHG + Colorant preparation were mostly ≤16 µg/ml (Table 1). The geomeans for Medi-flex CHG with or without Colorant were essentially identical for all anaerobic species combined (i.e. 4.15 vs. 4.09 µg/ml, respectively) and only slightly less active than Hibiclens (4.15 vs. 3.84 µg/ml, respectively) as shown in Table 1. Since only one strain of *E. lentum* (a Gram-positive anaerobe was tested, there could be no comparison of the effectiveness of Medi-flex CHG + Colorant on Gram-positive vs. Gram-negative strains. At 32 µg/ml, the MIC_{90} for *B. thetaiotaomicron* was one dilution higher than the other *Bacteroides* species as well as for all anaerobic strains combined. The 17 strains of *P. acnes* were more susceptible than the other anaerobes tested. The majority of the strains were unreadable when the Brucella broth + lysed horse blood was combined with either isopropyl alcohol or povidone iodine solution.

Candida spp. The susceptibility of *Candida* spp. to the Medi-flex CHG + Colorant preparations varied extremely little among the different species. MICs generally ranged from 1.56 to 12.5 µg/ml (Table 1). *C. albicans* and *C. parapsilosis* were slightly less susceptible than the other species, but only by one doubling dilution (= 16 µg/ml vs. 8 µg/ml for other species).

Antimicrobial Resistant Strains. Comparisons of methicillin-resistant vs. –susceptible staphylococci, vancomycin-resistant vs. –susceptible enterococci, and ciprofloxacin-resistant vs. –susceptible *P. aeruginosa* showed no significant differences or trends in Medi-flex CHG + Colorant MICs (Table 1).

Reviewer's comments: To demonstrate the *in vitro* spectrum of activity of the product, the Applicant presents MIC values for the product against a wide variety of microorganisms. These microorganisms were tested against five different products which included: CHG+colorant, CHG, Hibiclens, Isopropanol and Povidone Iodine Solution. The test product, CHG+colorant, shows similar activity to CHG alone.

However, the Applicant fails to meet the TFM criteria for *in vitro* spectrum of activity testing. Too few microbial isolates were tested against the product. The TFM presents a list of 21 microorganisms to which a product is to be tested. The TFM also states that the product is to be tested against 25 clinical isolates and 25 laboratory strains of the individual organisms on this list. The Applicant did not present MICs for 25 clinical isolates and 25 laboratory strains of each organism on the list in the TFM. In addition, the Applicant did not differentiate clinical isolates from laboratory strains in the MIC data presented in Table 1. It is not clear from the data how many clinical isolates or laboratory strains were tested. Thus, the Applicant should differentiate the MIC data based upon these criteria.

Validation of Neutralizer in MIC Studies

The microorganisms studied in this phase of the evaluation were *E. coli* ATCC 11229 and *S. aureus* ATCC 6538. The composition of the sampling solution containing neutralizers was as follows: 0.4g KH_2PO_4, 10.1g Na_2HPO_4, 1.0mL Triton X-100, 10.0mL Polysorbate 80, 3.0 g Lecithin, and 10.0g Tamol per liter deionized water. The neutralizer was not toxic to either of these two strains for up to 30 minutes (Table 2, Tubes B). The neutralizing solution was effective in completely neutralizing the test solution when the solution was diluted 1:10 prior to use (Table 2, Tubes A). Preliminary experiments indicated that the neutralizer could not completely neutralize the test solution at full, undiluted concentrations. Un-neutralized
Medi-flex CHG + Colorant solution was 100% effective at killing both organisms at a 1:10 dilution in water after 30 minutes (Table 2, Tubes D). The disinfectant was 99.2% effective at killing *S. aureus* and 100% effective at killing *E. coli* when the samples were taken immediately after inoculating the microorganisms into the disinfectant.

Table 2. Neutralizer Validation.									
time			Set 1		Set 2		Set 3		Mean
			plate A	plate B	plate A	plate B	plate A	plate B	CFU/mL
Organism #1 ***S. aureus* 6538**									
Tube A Neutralization Effectiveness	0 min.	TSA	16	11	9	13	7	3	9.8
		TSA+N	23	20	9	6	7	4	11.5
	30 min.	TSA	16	15	0.4	12	8	2	9.5
		TSA+N	21	28	11	11	3	9	13.8
Tube B Toxicity of Neutralizer	0 min.	TSA	16	8	9	10	4	6	8.8
		TSA+N	60	100	10	13	4	4	31.8
	30 min.	TSA	16	14	9	12	5	4	10
		TSA+N	100	23	7	12	8	5	25.8
Tube C Viability of test strains	0 min.	TSA	19	14	7	11	7	3	10.2
		TSA+N	60	70	11	11	3	2	26.2
	30 min.	TSA	15	16	12	15	5	11	12.3
		TSA+N	40	9	10	20	6	6	15.2
Tube D Effectiveness or activity of disinfectant	0 min.	TSA	1	0	3	0	0	1	0.8
		TSA+N	8	10	3	6	1	1	4.8
	30 min.	TSA	0	0	0	0	0	0	0
		TSA+N	0	0	0	0	0	0	0
Organism #2 ***E. coli 11229***									
Tube A Neutralization Effectiveness	0 min.	TSA	11	7	6	4	6	6	6.7
		TSA+N	8	11	3	8	6	1	6.2
	30 min.	TSA	12	14	3	5	1	6	6.8
		TSA+N	3	10	6	6	5	7	6.2
Tube B Toxicity of Neutralizer	0 min.	TSA	8	7	6	7	3	2	5.5
		TSA+N	7	5	7	7	3	1	5
	30 min.	TSA	2	8	10	5	3	6	5.7
		TSA+N	8	0	8	9	4	5	5.7
Tube C Viability of test strains	0 min.	TSA	7	5	5	2	5	9	5.5
		TSA+N	5	5	12	9	5	6	7
	30 min.	TSA	4	6	3	10	1	6	5
		TSA+N	7	6	6	4	5	4	5.3
Tube D Effectiveness or activity of disinfectant	0 min.	TSA	0	0	0	0	0	0	0
		TSA+N	0	0	0	0	0	0	0
	30 min.	TSA	0	0	0	0	0	0	0
		TSA+N	0	0	0	0	0	0	0

Time-Kill Kinetic Studies

All test strains grew well in this phase of the evaluation with the exception of *M. luteus* ATCC 7468 which had an inoculum size of approximately 10^4 CFU/mL. This strain has performed poorly in previous studies that were similar to this one. The results for the time-kill portion of the study are presented in Table 3. For all organisms, Medi-flex CHG + Colorant was successful in achieving a $\geq$ 99.9% (i.e. $\geq$ 3 log2) kill within the three minute sampling interval. At a starting dilution of 1:10 and final working dilution of 1:100, Medi-flex CHG + Colorant killed $\geq$ 99.9% of the cells in $\leq$ 3 minutes (Table 3, Tube A). The majority of the strains were killed upon immediate exposure to the compound. At the same dilution factor, i.e. 1:100 final dilution, Hibiclens achieved $\geq$ 99.9% (i.e. $\geq$ 3 log2 reduction in CFU/mL) of the cells in $\leq$ 3 minutes with the single exception of *M. luteus* ATCC 7468, which never achieved a full three log reduction in CFU/mL (Table 3, Tube B). Hibiclens was not tested at the higher dilution. Since both Medi-flex CHG + Colorant and Hibiclens were able to achieve $\geq$ 99.9% kill in $\leq$ 3 minutes at a 1:10 final dilution, it is concluded that the activity of both compounds in nearly identical. The non-inferiority of Medi-flex CHG + Colorant as compared to Hibiclens has been demonstrated.

Reviewer's comments: The Applicant conducted time-kill kinetic studies on the effects of the product against ten organisms, five Gram-positive and five Gram-negative laboratory bacterial strains. The product and Hibiclens were tested at a dilution of 1:10; in addition the product was tested at a dilution of 1:100. At a dilution of 1:100, the test product caused a three log reduction within three minutes for six of the organisms, *S. aureus* 6538, *S. aureus* 29213, *S. epidermidis* 12228, *E. coli* 11229, *E. coli* 25922, and *P. aeruginosa* 27853. Three of these organisms are Gram-positive, three are Gram-negative organisms. Very little and no useable data were generated from the Hibiclens the test product (both diluted 1:10), respectively.

While it is not required by the TFM, time-kill kinetics data for all 21 organisms on the TFM *in vitro* testing list against the test product are very useful in determining the fast-acting ability of the test product. Due to the limited number of organisms tested, it is not possible to determine if the test product, CHG+colorant, is fast-acting.

The Applicant does not present data for validation of the neutralizer for the organisms tested in the time-kill kinetics studies. Thus, the results of the time-kill kinetics studies are not validated. Consequently, no determination of fast-acting for the test product can be made.

Table 3. Time-Kill Kinetic Studies in Gram-Positive Organisms.

organism	count time (min.)	Tube A (CHG+Colorant diluted 1:10 in PBS)	Tube B (CHG+Colorant diluted 1:100 in PBS)	Tube C (Hibiclens diluted 1:10 in PBS)	Tube D PBS Viability Control
S. aureus **6538**	0	0	1.0×10^6	0	6.6×10^5
	3	0	2.5×10^3	0	8.3×10^5
	6	0	1.3×10^3	0	8.0×10^5
	9	0	4.0×10^2	0	6.6×10^5
	12	0	0	0	6.5×10^5
	15	0	0	0	5.6×10^5
	20	0	0	0	5.3×10^5
	30	0	0	0	5.0×10^5
S. aureus **29213**	0	0	1.0×10^6	4.6×10^3	6.0×10^5
	3	0	8.4×10^3	0	6.1×10^5
	6	0	2.6×10^3	0	4.3×10^5
	9	0	6.0×10^3	0	6.5×10^5
	12	0	4.5×10^2	0	5.5×10^5
	15	0	3.0×10^2	0	4.6×10^5
	20	0	0	0	5.6×10^5
	30	0	0	0	4.6×10^5
E. faecalis **29212**	0	0	TNTC	0	3.2×10^5
	3	0	3.0×10^5	0	5.8×10^5
	6	0	1.9×10^4	0	3.3×10^5
	9	0	4.2×10^3	0	4.0×10^5
	12	0	4.5×10^2	0	4.5×10^5
	15	0	1.5×10^2	0	3.1×10^5
	20	0	5.0×10^1	0	2.5×10^5
	30	0	0	0	3.8×10^5
S. epidermidis **12228**	0	0	9.2×10^3	0	3.1×10^5
	3	0	0	0	2.8×10^5
	6	0	0	0	3.0×10^5
	9	0	0	0	4.0×10^5
	12	0	0	0	3.5×10^5
	15	0	0	0	4.0×10^5
	20	0	0	0	4.8×10^5
	30	0	0	0	2.4×10^5
M. luteus **7468**	0	0	2.4×10^4	5.1×10^3	2.0×10^4
	3	0	2.5×10^4	0	4.0×10^4
	6	0	1.7×10^4	0	1.0×10^4
	9	0	1.5×10^4	0	1.0×10^4
	12	0	1.1×10^4	0	1.0×10^4
	15	0	8.6×10^3	0	2.5×10^4
	20	0	5.8×10^3	0	3.5×10^4
	30	0	2.4×10^3	0	1.0×10^4

Table 3. Time-Kill Kinetic Studies in Gram-Negative Organisms.

organism	count time (min.)	Tube A (CHG+Colorant diluted 1:10 in PBS)	Tube B (CHG+Colorant diluted 1:100 in PBS)	Tube C (Hibiclens diluted 1:10 in PBS)	Tube D PBS Viability Control
E.coli **11229**	0	0	4.8×10^3	0	6.8×10^5
	3	0	0	0	6.5×10^5
	6	0	0	0	7.8×10^5
	9	0	0	0	3.0×10^6
	12	0	0	0	7.0×10^5
	15	0	0	0	7.3×10^5
	20	0	0	0	7.4×10^5
	30	0	0	0	7.6×10^5
E. coli **25922**	0	0	2.0×10^5	0	6.7×10^5
	3	0	2.0×10^2	0	6.2×10^5
	6	0	0	0	5.9×10^5
	9	0	4.5×10^2	0	6.0×10^5
	12	0	0	0	6.8×10^5
	15	0	0	0	5.9×10^5
	20	0	0	0	5.5×10^5
	30	0	0	0	7.5×10^5
P. aeruginosa **15422**	0	0	5.9×10^4	0	1.2×10^6
	3	0	1.3×10^3	0	1.1×10^6
	6	0	0	0	9.1×10^5
	9	0	0	0	8.4×10^5
	12	0	0	0	8.6×10^5
	15	0	0	0	9.4×10^5
	20	0	0	0	5.7×10^5
	30	0	0	0	6.3×10^5
P. aeruginosa **27853**	0	0	1.3×10^4	5.0×10^1	1.3×10^6
	3	0	0	0	1.0×10^6
	6	0	0	0	1.2×10^6
	9	0	0	0	9.7×10^5
	12	0	0	0	1.0×10^6
	15	0	0	0	1.0×10^6
	20	0	0	0	5.8×10^5
	30	0	0	0	6.2×10^5
S. marcescens **14756**	0	6.9 X 103	TNTC	0	1.1×10^6
	3	0	TNTC	0	1.2×10^6
	6	0	1.8×10^4	0	1.4×10^6
	9	0	6.3×10^3	0	1.1×10^6
	12	0	2.0×10^3	0	1.2×10^6
	15	0	0	0	1.2×10^6
	20	0	0	0	1.1×10^6
	30	0	0	0	1.0×10^6

Validation of Neutralizer in Time-Kill Kinetic Studies
No data are presented on the validation of the neutralizer in the time-kill kinetic studies.

Mechanism of Resistance Studies
Neither data nor literature is presented on the mechanism of resistance.

Conclusions
Inhibitory Phase: Of the 714 organisms tested, 689 (96.5%) were inhibited by ≤ 25 µg/ml of Medi-Flex CHG + Colorant solution and 712 (99.7%) were inhibited by a concentration of ≤ 50 µg/ml. For Medi-flex CHG without Colorant, a total of 694 (97.2%) were inhibited by ≤ 25 µg/ml and 712 (99.7%) were inhibited by a concentration of ≤ 50 µg/ml. It is concluded the colorant has no appreciable effect on the activity of the CHG compound. For Hibiclens, a total of 700 (98.0%) were inhibited by ≤ 25 µg/ml and 712 (99.7%) were inhibited by a concentration of ≤ 50 µg/ml. The two strains with MICs > 50 µg/ml for all three compounds were both *B. cepacia.* The concentration of 50 ug/ml represents a 1:400 dilution of the 2% topical solution, and thus most organisms would appear to be highly susceptible to this agent. The highest concentration tested was 200 µg/ml and all results were on-scale.

Neutralization of Activity: A neutralizing suspension consisting of 10% polysorbate 80, 3% lecithin, and 0.3% sodium thiosulfate effectively neutralized the activity of a 1:10 dilution of Medi-flex CHG + Colorant and had no discernible toxicity to the two test strains over a 30 minute exposure period.

Time-Kill Kinetics: Medi-flex CHG + Colorant successfully achieved a ≥ 99.9% reduction in viable cells in ≤ 3 minutes for all strains tested when used at a final dilution of 1:10. These results are comparable to those achieved with Hibiclens (4% CHG).

Clinical Efficacy
The Applicant conducted a clinical simulation study (————————————) to estimate the area covered (and the runoff determined) by different applicators containing different volumes of ChloraPrep and ChloraPrep with Tint. Two groups of subjects were evaluated. Group A contained at least forty subjects and was used to evaluate the area covered on different section of the volunteer's back only. Group B contained at least twenty subjects and was used to evaluate the area covered on different sections of the volunteer's back. In addition, antimicrobial efficacy was determined on volunteers in this group. Antimicrobial efficacy was assessed by the reduction in the number of viable bacteria recovered from intact skin. The antimicrobial efficacy data was generated for the Applicant's internal use only.

A total of sixty subjects were treated with the test articles. Thirty subjects were treated with ChloraPrep and thirty subjects were treated with ChloraPrep with Tint. Each test article had three different volume configurations, 20 mL, 22 mL, and 26 mL. Within each group of thirty treated subjects, ten subjects were treated with each volume configuration. Of the sixty total subjects, forty were evaluated for area coverage (Group

A). Twenty subjects were evaluated for area coverage and antimicrobial efficacy at 30 seconds and ten minutes post application.

Detailed results of the study are presented in Tables 1-8, Appendix VII, of the submission.

Table 4. Log reductions for test articles.

label identification	volume of applicator	avg. dosage rate (g/cm^2)	30 seconds		10 minutes	
			avg. log reduction	avg.	avg. log reduction	avg.
ChloraPrep with Tint	20 mL	0.0033	1.62	1.65	1.92	1.85
	22 mL	0.0034	1.64		1.93	
	26 mL	0.0030	1.71		1.71	
ChloraPrep	20 mL	0.0035	1.5	1.54	1.77	1.58
	22 mL	0.0037	1.59		1.33	
	26 mL	0.0032	1.54		1.64	

Reviewer's comments: The Applicant presents data from the clinical efficacy studies for three different volume configurations, 20 mL, 22 mL, and 26 mL. The studies present log reduction data for two products tested: ChloraPrep and ChloraPrep with Tint. Ten subjects were treated with each volume configuration. Twenty subjects were evaluated for antimicrobial efficacy on the back at 30 seconds and ten minutes. The average log reduction at ten minutes for ChloraPrep and ChloraPrep with Tint was 1.58 $\log_{10}$ and 1.85 $\log_{10}$, respectively.

The results of the clinical simulation studies indicate that the product does not meet the TFM criterion for a two- $\log_{10}$ reduction after ten minutes in a dry skin site. According to the TFM, both ChloraPrep and ChloraPrep with Tint fail to meet the two- $\log_{10}$ threshold for a dry skin site, normally the abdomen.

In addition, there are several deficiencies in the protocol. These deficiencies include: the lack of a positive control, the lack of a negative control, only one study was conducted, baseline counts were too low, and only a dry anatomical site was tested, namely the back (a dry site).

Validation of Neutralizer

An *in vitro* neutralization assay is performed (Appendix II, Section 4.3—Clinical Final Report). This assay is based on the American Society for Testing and Materials (ASTM) Standard E1054-02, "Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents." The microorganism (*Staphylococcus aureus* ATCC #12228) is added to the neutralizer prior to the addition of test product showing that neutralizer is capable of neutralizing the carry-over of concentrated CHG. The neutralization assay is performed with 1.5 times the amount of test article determined to be applied to the skin-sampling site (the area covered by the sampling ring.) Testing is performed to evaluate

the neutralizing efficiency of the scrub solution and the neutralizing efficiency of the first dilution prepared from the scrub sample.

The composition of the sampling solution containing neutralizers was as follows: 0.4g KH_2PO_4, 10.1g Na_2HPO_4, 1.0mL Triton X-100, 10.0mL Polysorbate 80, 3.0 g Lecithin, and 10.0g Tamol per liter deionized water.

The report on testing performed to demonstrate the effectiveness of the neutralizers used in this study is shown in Appendix V of the submission.

For both Tables 5 and 6, results are expressed as average colony forming units (CFU) recovered from three replicates per tube per contact time.

Table 5. Neutralizer Effectiveness.

DS No.	Tube No.	Contact time	Avg. CFU	Log $_{10}$ value
6510 (TSA+**)	1	immediate	46.2	1.66
		30 minutes	48.3	1.68
	2	immediate	47.2	1.67
		30 minutes	49	1.69

Table 6. Neutralizer Toxicity.

Plating Media	Tube No.	Contact Time	Avg. CFU	Log $_{10}$ value
TSA*	1	immediate	45.3	1.66
		30 minutes	43	1.63
	2	immediate	45.8	1.66
		30 minutes	43.2	1.64
TSA+**	1	immediate	46	1.66
		30 minutes	41.3	1.62
	2	immediate	46.8	1.67
		30 minutes	42	1.62
Test Article Control	1	immediate	0	NA
		30 minutes	0	NA
Numbers Control	1	immediate	48.7	1.69
		30 minutes	45.8	1.69

TSA*=Tryptic Soy Agar
TSA**=Tryptic Soy Agar containing 0.5% polysorbate 80 and 0.07% lecithin

Data is evaluated according to ASTM Standard E1054-02, "Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents." The average number of surviving challenge microorganisms is determined for each replicate of each control test. The number of survivors is converted to $\log_{10}$ values.

No statistically significant difference is found between the mean $\log_{10}$ values for the Numbers Control and the mean $\log_{10}$values for the Neutralizer Effectiveness Control

using the ChloraPrep Tint (DS No. 6510). Since there is no recovery in the Test Article Controls, the results are considered statistically less than the Numbers Control. No statistically significant difference is found between the recovery population of the Neutralizer Toxicity Control and the test organism population of the Numbers Control. Therefore, these results indicate the neutralizer is effective and non-toxic.

References

21 CFR 333.470 Tentative Final Monograph for Topical Antimicrobial Drug Products, Federal Register, Volume 59, No. 116, June 17, 1994.

American Society for Testing and Materials (ASTM) Standard E1054-02, "Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents."

Recommendations:

From the data presented by the Applicant, the Microbiology Reviewer makes the following recommendations:

8. The Applicant failed to meet the Technical Final Monograph (TFM) criteria for *in vitro* spectrum of activity testing. Too few microbial isolates were tested against the product. The TFM presents a list of 21 microorganisms to which a product is to be tested. The TFM also states that the product is to be tested against 25 clinical isolates and 25 laboratory strains of the individual organisms on this list. The Applicant did not present MICs for 25 fresh clinical isolates and 25 laboratory strains of each organism on the list in the TFM. In addition, the Applicant did not differentiate clinical isolates from laboratory strains in the MIC data presented. It is not clear from the data how many clinical isolates or laboratory strains were tested. Thus, the Applicant should differentiate the MIC data based upon these criteria. Also, the Applicant should be aware that the MIC_{90}s presented in Table 1 are tentative MIC_{90}s since in many cases, less than 100 isolates were used in the determination of those MIC_{90}s.

9. Time-kill kinetics data for all 21 organisms on the TFM *in vitro* testing list against the test product are useful in determining the fast-acting ability of the test product. This Reviewer recommends these data be provided by the Applicant. Due to the limited number of organisms tested, and lack of data from the neutralizer validation for the time kill studies, it is not possible to determine if the test product, CHG+colorant, is fast-acting.

10. No information was presented on the mechanism of action of the drug product. The Applicant should present studies or literature which demonstrates the mechanism of action.
11. No information or data was submitted on the mechanism of resistance to the drug product. Resistance mechanisms may limit the effectiveness of an antimicrobial drug in clinical settings. Therefore, characterization of the mechanisms mediating resistance and their distribution within the proposed target pathogens may delineate

the potential clinical usefulness of the drug under investigation. Two approaches may be taken. First, the determination of the evolution of a point mutation by the sequential passage of an organism through increasing concentration of the antimicrobial included in the culture medium. The second approach is a thorough survey of the published literature to determine whether resistance has been reported for the antimicrobial ingredient.

12. The results of the clinical simulation studies indicate that the product does not meet the TFM criterion for a two- $\log_{10}$ reduction after ten minutes in a dry skin site. According to the TFM, both ChloraPrep and ChloraPrep with Tint fail to meet the two- $\log_{10}$ threshold for a dry skin site, normally the abdomen.

13. There are several deficiencies in the protocol for the clinical simulation. These deficiencies include: the lack of a positive control, the lack of a negative control, only one study was conducted, baseline counts were too low, and only a dry anatomical site was tested, namely the back (a dry site). The Reviewer recommends that all of these deficiencies be addressed in future protocol submissions.

14. On September 3, 2004, a facsimile was sent to the Applicant addressing the Skin Coverage Study. The Microbiology Reviewer concurs with the findings of the Medical Officer, Mr. David Bostwick regarding this study. In that facsimile, the Applicant was asked to conduct the following two clinical studies:

A. Skin Coverage Study:

The study submitted in support of this supplemental application ("Evaluation of the Area Covered by a Preoperative skin Preparation") is deficient in that the product was applied for a 30 second period rather than the maximum 2 minute application period recommended in the approved labeling. Since it is the intent of this study to determine the potential for product runoff and pooling when used for the longest possible time, you need to conduct another skin coverage study to support approval of the larger applicator.
(i). We presume that the preferred additional applicator size is 26- mL. Therefore, all test subjects should be tested using this size. Skin area coverage should be determined using a total of at least 20 applicators on adult volunteers of varying heights and weights. The average amount (weight/volume) of product used in the applications should be recorded.
(ii). The protocol should specifically instruct that the directions for application for a two-minute prep as presented in the approved labeling will be used. The report should specifically state whether product runoff and/or pooling occurred for each test subject. You can use the same format for the skin coverage report that you used for the July 6, 2004 submission.

B. Patient Pre-operative Skin Preparation Study:

(i). Bacterial reductions in a representative number of test subjects should be determined. We recommend that the following outline be utilized:
(a). Data from 20 evaluable subjects should be available. Ten subjects should have been prepped with the "new" (tinted) formulation, and ten should have been prepped with the "old" (untinted) formulation.
(b). The procedure should approximate that recommended in the Tentative Final Monograph for Health-Care Antiseptic Drug Products for "dry" surgical sites.

That is, the abdomen should be used for testing, the subjects should have at least a 3 log baseline bacterial count, and bacterial reductions should be determined at 10 minutes and 6 hours after prepping. A 30-second prep as recommended in the approved labeling should be used.
(ii). We strongly recommended that you submit the protocol for testing to the IND for review and feedback before you initiate the study.

Peter Coderre, Ph.D.
Microbiology Reviewer

Cc: Original NDA No. 20-832/S008
Microbiologist, HFD-520
File name: N20832/S008.FIN

Acting TLMicro/FMarsik
Finalized 1/5/05 FJM

DepDir/LGavrilovich

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/s/

Peter Coderre
1/4/05 09:29:32 AM
MICROBIOLOGIST

Frederic Marsik
1/4/05 11:02:34 AM
MICROBIOLOGIST

Lillian Gavrilovich
1/12/05 05:47:07 PM
MEDICAL OFFICER

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 2
Consultation for HFD-560

NDA: 20-832/SN008 A003 **Date Completed:** March 29, 2005

Applicant:
Mediflex Hospital Products
11400 Tomahawk Creek Parkway
Suite 310
Leawood, KS 66211
913-451-0880

Contact:
Beckloff Associates, Inc.
7400 West 110th Street
Suite 300
Overland Park, KS 66210
913-451-3955

Chem/Ther. Type: Antimicrobial

Submission Reviewed: NDA 20-832 SN008 A003

Providing for: Patient Preoperative Skin Preparation

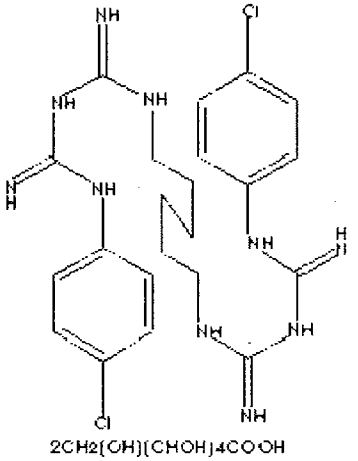
Product Names:
Proprietary: ChloraPrep with Tint
Non-proprietary/USAN: Chlorhexidine Gluconate

Chemical Names: 1-6-di(4-chlorophenyl-diguanido)hexane

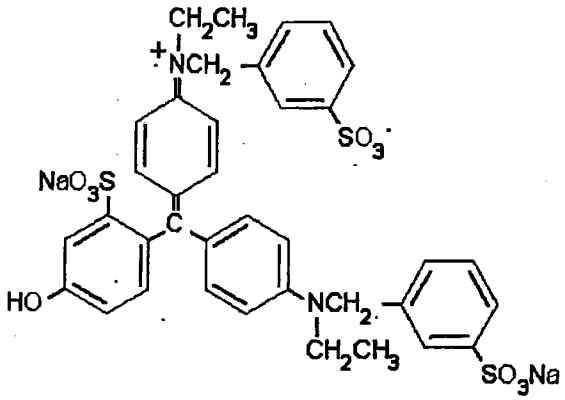
Molecular Formulae: Chlorhexidine Gluconate: $C_{22}H_{30}Cl_2N_{10}\bullet 2C_6H_{12}O_7$
Fast Green FCF: $C_{37}H_{34}N_2Na_2O_{10}S_3$

Structural Formulae: Chlorhexidine Gluconate and Fast Green FCF

CHG



Fast Green FCF



Dosage Form: 2% solution

Route of Administration: Chlorhexidine Gluconate 2% (w/v) Topical Solution, 26mL applied for 30 seconds and two minutes for dry and moist surgical sites, respectively over a —— cm^2 area; allow to dry for ——————————for dry and moist surgical sites, respectively.

Pharmacological Category: Antiseptic

Dispensed: Rx_____ OTC__X____

Supplement Submission:
Received by CDER: July 15, 2004

Received by Reviewer: July 22, 2004
Review Completed: November 9, 2004

Amendment Submission:
Received by CDER: January 3, 2005
Received by Reviewer: February 1, 2005
Review Completed: March 29, 2005

Related Documents: IND-46,243

Remarks:
On July 14, 2000, the FDA approved NDA 20-832 for Chlorhexidine Gluconate 2% (w/v) Topical Solution in the 3-mL Applicator for the indication of patient preoperative skin preparation. With this submission, the Applicant requests approval for a larger-sized, tinted antiseptic applicator for the ChloraPrep product line (ChloraPrep® With Tint 26-mL Applicator). The currently approved sizes of ChloraPrep One-Step (non-tinted antiseptic) include 1.1-ml (Frepp®), 1.5-mL (Frepp), 3.0-mL, and 10.5-mL.

The Agency provided a study design outlining unresolved clinical issues in the facsimile dated May12, 2003. A Type-A meeting was held on June 11, 2003 at which time the Agency stated its position that the clinical study requested in the May 12, 2003, facsimile was necessary to support the safety of the 26-mL ChloraPrep One-Step Applicator.

On ——— NDA ——— which requested approval for a ———
——————————————— was withdrawn.
As with the approved sizes of Chlorhexidine Gluconate 2% (w/v) Topical Solution applicators, the ChloraPrep with Tint 26-mL Applicator will be used for the approved indication of patient preoperative skin preparation but will treat a maximal area of approximately ———————————————

The ChloraPrep with Tint 26-mL Applicator is similar to the 3.0- and 10.5-mL Applicators in design and packaging component materials and contains the same Chlorhexidine Gluconate 2% (w/v) Topical Solution as approved in NDA No. 20-832 for all the approved sizes. The ChloraPrep with Tint 26-mL Applicator employs two 13-mL glass ampoules which are slightly larger than the single ampoule found in the 10.5-mL Applicator. FD&C Green #3 dye has been added to the pledget so that the coverage area is well defined during application of the ChloraPrep Solution. The similarities and differences between the 3.0-, 10.5-, and 26-mL Applicators are summarized in the Chemistry, Manufacturing, and Controls section of submission #8 (SN008).

This submission provides the Agency with the reports for the "Test for Preoperative Skin Preparations" and the "Evaluation of the Area Covered by a Preoperative Skin Preparation" to remedy the deficiencies cited by the Clinical and Microbiology Reviewers from the Division of Anti-infective Drug Products (HFD-520) in the review of NDA 20-832 SN008. This review describes the findings and the recommendations of the Microbiology Reviewer. These recommendations are for evaluation by the Division

Director for Over the Counter Drug Products to determine if the NDA for ChloraPrep with Tint be approved.

Conclusions:
From the Microbiology perspective, the Applicant has conducted the clinical simulation study and the skin coverage study to the satisfaction of this Reviewer. ***This Reviewer recommends that the NDA 20-832 for ChloraPrep with Tint is approvable contingent upon the following change to the label:***

> **Maximal treatment area for one applicator is approximately 1126 cm^2 (approx. 13.2 in. x 13.2 in.) Discard the applicator after a single use.**

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INTRODUCTION

The purpose of this supplement to NDA No. 20-832 is to provide data supporting approval of a 26-mL Applicator for ChloraPrep with Tint and propose appropriate labeling. ChloraPrep with Tint 26-mL Applicator is very similar to the currently approved ChloraPrep One-Step Applicators approved in NDA 20-832 except for the larger size, inclusion of FD&C Green #3 dye in the pledget, and [redacted]. The dye allows for better visualization of the coverage area when the solution is applied, highlighting the area which might be under-treated as well as areas of pooling, solution runoff, or solution-soaked drapes. The visual effects presented by the tinted solution suggest that the addition of the tinting element is a significant contribution to the product's overall safety. The currently approved sizes of ChloraPrep One-Step include 1.1-ml (FreppR), 1.5-mL (Frepp), 3.0-mL, and 10.5-mL Applicators. The 1.1-mL Frepp is not currently marketed.

As with the approved sizes, the ChloraPrep with Tint 26-mL Applicator will be used for the approved indication of patient preoperative skin preparation but will treat a maximal area of approximately [redacted]. The ChloraPrep with Tint 26-mL Applicator contains the same chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (w/v) topical solution as approved in NDA No. 20-832 for the ChloraPrep One-Step Applicators. The similarities and differences between applicators and information to support the addition of the ChloraPrep with Tint 26-mL Applicator are provided in the Chemistry, Manufacturing, and Controls section of the current submission. No changes have been made to the drug substance, Chlorhexidine Gluconate 20%, as previously approved in this NDA, as a result of this change.

The purpose of this amendment (NDA 20-832 SN008 A003) is to provide the Agency with the reports for the "Test for Preoperative Skin Preparations" and the "Evaluation of the Area Covered by a Preoperative Skin Preparation."

On September 3, 2004, a facsimile was sent to the Applicant addressing the Skin Coverage Study. The Microbiology Reviewer concurs with the findings of the Medical Officer, Mr. David Bostwick regarding this study. In that facsimile, the Applicant was asked to conduct the following two clinical studies:

Skin Coverage Study:
The study submitted in support of the supplemental application ("Evaluation of the Area Covered by a Preoperative Skin Preparation") was deficient in that the product was applied for a 30 second period rather than the maximum two minute application period recommended in the approved labeling. Since it is the intent of this study to determine the potential for product runoff and pooling when used for the longest possible time, the Applicant should conduct another skin coverage study to support approval of the larger applicator.

1. The Agency presumes that the preferred additional applicator size is 26- mL. Therefore, all test subjects should be tested using this size. Skin area coverage

should be determined using a total of at least 20 applicators on adult volunteers of varying heights and weights. The average amount (weight/volume) of product used in the applications should be recorded.

2. The protocol should specifically instruct that the directions for application for a two-minute prep as presented in the approved labeling will be used. The report should specifically state whether product runoff and/or pooling occurred for each test subject. The Applicant may use the same format for the skin coverage report that was used for the July 6, 2004 submission.

Patient Preoperative Skin Preparation Study:

1. Bacterial reductions in a representative number of test subjects should be determined. The Agency recommends that the following outline be utilized:

a. Data from 20 evaluable subjects should be available. Ten subjects should have been prepped with the "new" (tinted) formulation, and ten should have been prepped with the "old" (untinted) formulation.

b. The procedure should approximate that recommended in the Tentative Final Monograph for Health-Care Antiseptic Drug Products for "dry" surgical sites. That is, the abdomen should be used for testing, the subjects should have at least a 3 log baseline bacterial count, and bacterial reductions should be determined at 10 minutes and 6 hours after prepping. A 30-second prep as recommended in the approved labeling should be used.

2. The Agency strongly recommends that the Applicant submit the protocol for testing to the IND for review and feedback before initiation of the study.

What follows is the data and review of these two studies.

Clinical Simulation Study

In the current submission, the Applicant presents data from the clinical simulation study performed at [redacted] In this study, the reductions achieved by the test and reference products at the 2-minute, 10-minute, and 6-hour sampling intervals for the groin site and 30-second, 10-minute, and 6-hour for the abdomen sites are evaluated. All time points per site are compared to the treatment day baseline count only.

Prepping Technique. The Applicant presents the prepping technique for the application of the test product for both the abdomen and the groin.

Abdomen. The applicator is pressed into the bottle chamber until locked. The bottle is inverted and squeezed to dispense the solution into the applicator sponge. Using the applicator, the solution is applied within the designated treatment area using a *continuous scrubbing motion* of the sponge for *30 seconds* so that a thin even coat is applied. The designated treatment area is not given. The area is allowed to *air-dry for 30 seconds* prior to the initiation of the contact times.

Groin. The applicator is pressed into the bottle chamber until locked. The bottle is inverted and squeezed to dispense the solution into the applicator sponge. Using the applicator, the solution is applied within the designated treatment area using a *continuous scrubbing motion* of the sponge for *two minutes* so that a thin even coat is applied. The designated treatment area is not given. The area is allowed to *air-dry for one minute* prior to the initiation of the contact times.

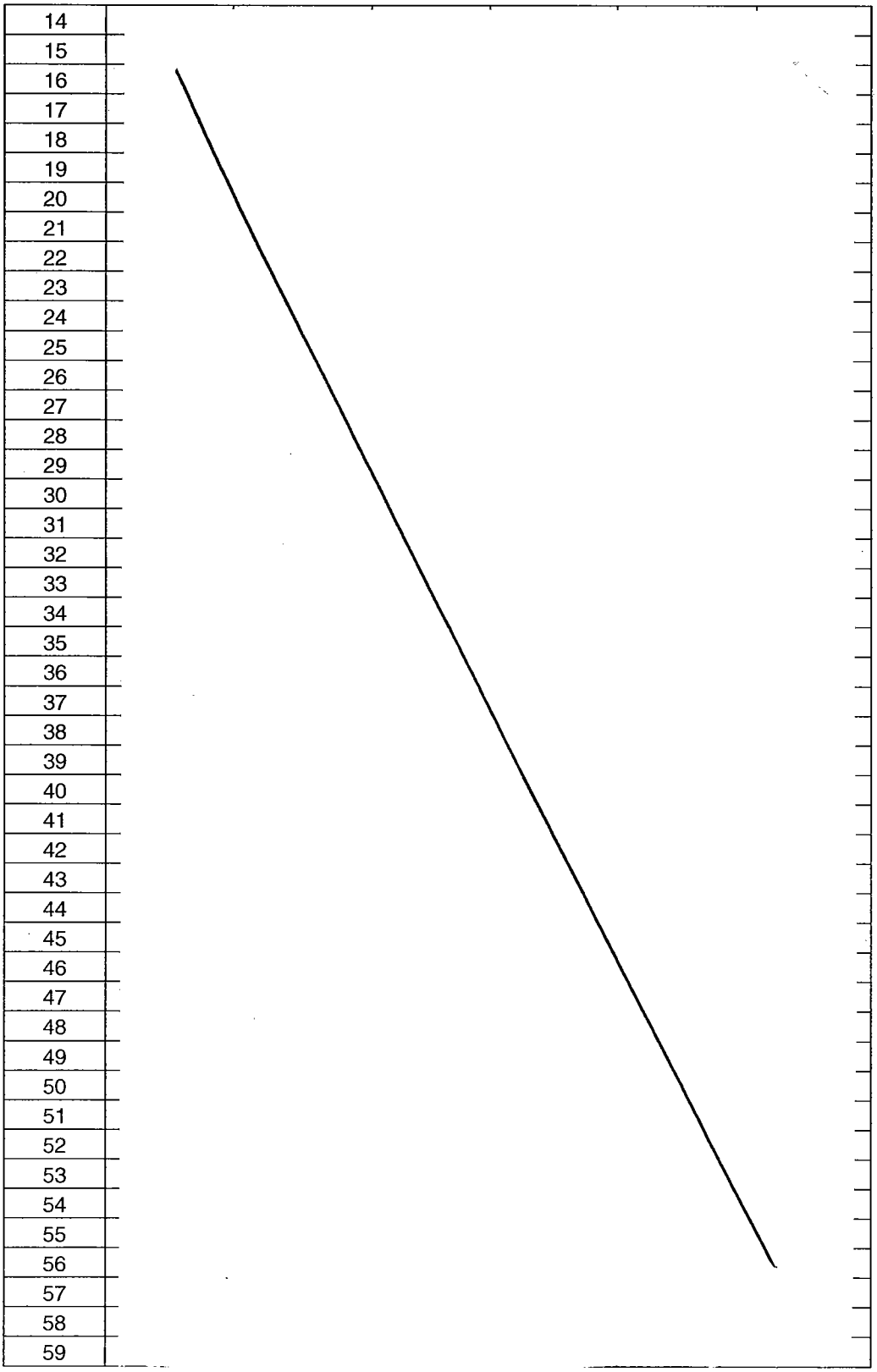
Results. The average $\log_{10}$ reductions achieved for each test article per sampling interval per site are tabulated in Table 1 (p11, clinical simulation report, volume 1 of this submission). In addition, the $\log_{10}$ reductions for each individual subject are presented in Table 2 (Appendix 7, volume 1 of this submission).

Table 1. Bacterial Log Reductions—Clinical Simulation.

Groin Site--Average $\log_{10}$ Reduction (using test-day baseline)			
Sampling interval	**ChloraPrep w/tint**	**ChloraPrep**	**Scrub Care® Preoperative Skin Prep Tray**
2 minutes	4.27	4.01	3.44
10 minutes	4.69	4.53	4.38
6 hours	4.37	4.3	4.37
Abdomen Site--Average $\log_{10}$ Reduction (using test-day baseline)			
Sampling interval	**ChloraPrep w/tint**	**ChloraPrep**	**Scrub Care® Preoperative Skin Prep Tray**
2 minutes	2.68	2.64	2.18
10 minutes	3	3.12	3.02
6 hours	2.46	2.54	2.33

Table 2. Log Reductions by Subject.

	Abdomen			**Groin**		
Subject #	**ChlorPrep w/Tint**	**ChloraPrep**	**Scrub Care**	**ChlorPrep w/Tint**	**ChloraPrep**	**Scrub Care**
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						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60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean	**3.00**	**3.33**	**3.22**	**4.69**	**4.99**	**4.53**
passed	27/30	31/32	31/32	27/30	33/33	27/31
%	**90**	**96.9**	**96.9**	**90**	**100**	**87.1**

X=not done

Reviewer's comments: The Applicant meets the $\log_{10}$ reductions for both the groin and abdomen sites at all three time points. Reductions of more than 4- $\log_{10}$ and 3- $\log_{10}$ are achieved for the groin and abdomen sites, respectively. The percentage of subjects that satisfied the TFM criteria for bacterial reductions ranged from 87.1% (Scrub Care, groin) to 100% (ChloraPrep, groin). These percentages are higher than the percentages achieved in previous NDA applications including NDA applications submitted for DuraPrep and CHG towelette.

Validation of Neutralizer—Clinical Simulation

In the current submission, the Applicant presents data to validate the neutralizer from the present study performed at [redacted]. Both neutralizer effectiveness and toxicity are examined. Results of the neutralizer effectiveness and neutralizer toxicity are presented in Table 3 and Table 4, respectively.

Table 3. Neutralizer Effectiveness.

Test Agent	Tube No.	Contact time	Avg. CFU	Log $_{10}$ value
ChloraPrep With Tint	1	immediate	76.3	1.66
		30 minutes	76.3	1.88
	2	immediate	73.8	1.87
		30 minutes	73	1.86
Scrub Care® Preoperative Skin Prep Tray	1	immediate	74.7	1.87
		30 minutes	73.2	1.86
	2	immediate	77.5	1.89
		30 minutes	74.3	1.87

Results expressed as average colony forming units (CFU) recovered from three replicates per tube per contact time.

Table 4. Neutralizer Toxicity.

Plating Media	Tube No.	Contact Time	Avg. CFU	Log $_{10}$ value
TSA*[1]	1	immediate	78	1.89
		30 minutes	78.5	1.89
	2	immediate	86.3	1.94
		30 minutes	83.3	1.92
TSA+**[1]	1	immediate	75.3	1.88
		30 minutes	74	1.87
	2	immediate	81.7	1.91
		30 minutes	80.8	1.91
TSA*[2]	1	immediate	74.3	1.87
		30 minutes	75.8	1.88
	2	immediate	85.2	1.93
		30 minutes	86.2	1.94
TSA+**[2]	1	immediate	72	1.86
		30 minutes	73.7	1.87
	2	immediate	83.2	1.92
		30 minutes	85.7	1.93
ChloraPrep With Tint	1	immediate	0	NA
		30 minutes	0	NA
Scrub Care® Preoperative Skin Prep	1	immediate	0	NA
		30 minutes	0	NA
Numbers Control	1	immediate	72.5	1.86
		30 minutes	75.5	1.88

TSA*=Tryptic Soy Agar
TSA**=Tryptic Soy Agar containing 0.5% polysorbate 80 and 0.07% lecithin.
1=Scrub solution and dilution fluid containing 1% polysorbate, 0.3% lecithin, and 1% tamol used specific for ChloraPrep.
2= Scrub solution and dilution fluid containing 0.2% sodium thiosulfate used specific for Scrub Care® Preoperative Skin Prep Tray.
Results expressed as average colony forming units (CFU) recovered from three replicates per tube per contact time.

Method and Results of Statistical Analysis

Data is evaluated according to ASTM Standard E1054-02, "Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents." The average number of surviving challenge microorganisms is determined for each replicate of each control test. The number of survivors is converted to $\log_{10}$ values.

No statistically significant difference is found between the mean $\log_{10}$ values for the Numbers Control and the mean $\log_{10}$ values for the Neutralizer Effectiveness Control using the ChloraPrep With Tint (DS No. 6913). No statistically significant difference is found between the mean $\log_{10}$ values for the Numbers Control and the mean $\log_{10}$ values for the Neutralizer Effectiveness Control using Scrub Care Preoperative Skin Prep Tray (DS No. 6949). Since there is no recovery in the Test Article Controls, the results are considered statistically less than the Numbers Control. No statistically significant

difference is found between the recovery population of the Neutralizer Toxicity Control and the test organism population of the Numbers Control.

The results indicate the neutralizer is effective and non-toxic.

Skin Coverage Study

Rationale for Experimental Design. Prior to surgery or other invasive procedure, the skin is treated with antimicrobial products to prevent infections by reducing the number of microorganisms on the skin. The purpose of this protocol is to study the proficiency of an FDA approved preoperative skin preparation (ChloraPrep) and a preoperative skin preparation under development (ChloraPrep with Tint 26ml Applicator) in a single use, foam applicator, which is designed to control the flow of the solution deliverable to the skin. The solution will be delivered in prototype applicator containing 26ml solution and will be applied to the corresponding coverage area of 2432 cm^2.

The test agent ChloraPrep with Tint 26ml Applicator is applied to a 2432 cm^2 surface area on the backs of 20 adult human volunteers of varying heights and weights (Attachment II: Prepping Technique, p12, volume 2, current submission). The drying time, surface area covered, amount of product used (wt/vol), and observations of pooling and runoff are documented.

Prepping Technique. The applicator is pressed into the bottle chamber until locked. The bottle is inverted and squeezed to dispense the solution into the applicator sponge. Using the applicator, the solution is applied within the designated treatment area beginning in the center of the back moving outward using vertical (up and down) strokes for two minutes so that a thin even coat is applied.

> ***Reviewer's comments:*** The question arises, whether the top and bottom of the designated area will receive more product than the skin located in the center of the area of application. This would result in a higher dosage to the peripheral skin area.

Results. Result tables of the study are presented in Appendix IV, volume 2 of this submission. An abbreviated table from this table is shown below in Table 5.

Table 5. ChlorPrep with Tint Dosage and Dry Times.

Subject #	Dosage g/cm^2	Average Dry Time (Seconds)
1	0.0033	93
2	0.0034	61
3	0.0043	90
4	0.0044	75
5	0.0036	117
6	0.0036	108
7	0.0047	95
8	0.0047	97
9	0.0056	52
10	0.0047	92
11	0.0046	67
12	0.0033	78
13	0.004	87
14	0.0037	71
15	0.0041	68
16	0.0035	93
17	0.005	71
18	0.0042	104
19	0.0033	99
20	0.0036	88
Avg.	**.0041**	**85.3**

Reviewer's comments: The study was conducted with 20 subjects using the procedure designated by the Agency. The average applied dosage and dry time were 0.0041 g/cm^2 and 85 seconds, respectively. The applied dosage ranged from 0.0033 to 0.0056 g/cm^2 while the drying time ranged from 52 to 117 seconds (approximately two minutes). These data suggest a minimum dry time of two minutes. No pooling on the body was observed and no run-off on the surgical drapes was observed. No sample calculation of the dosage was presented. This Reviewer concludes that the 26ml volume of drug product can cover an area approximating 19 inches by 19 inches (361 in^2 or 2432 cm^2) of human skin without pooling.

In regards to the coverage study, the Microbiology Reviewer is concerned that the volume and thus concentration delivered to the skin be consistent with the pre-approved products, that is, the 3ml and 10.5ml applicators. For the 3ml applicator, the approved maximal skin coverage area is 4.5 in. x 4.5 in. equivalent to 20.25 in.^{2} (130 cm^2). For the 10.5ml applicator, the approved maximal skin coverage area is 8.4 in. x 8.4 in. equivalent to 70.56^2 in. (454 cm^2).

The Applicant desires labeling for the 26ml applicator allowing for the coverage of [redacted]. Data of actual volumes of product applied in the skin coverage study were not supplied in the submission. Instead, the Applicant submitted weights rather than volumes. Therefore, this Reviewer assumes that the entire volume of the applicator was applied.

The approved applicator configuration of 3ml demonstrates efficacy over an area of 4.5 in. x 4.5 in. or 20.25 in.^{2} (130 cm^2). By delivery of the entire contents, 0.231 ml of product is delivered to each square centimeter.

Calculation: 3ml total volume of product/130 cm^2 of skin surface area prepped = 0.0231 ml of product per square centimeter.

Similarly, the approved applicator configuration of 10.5ml demonstrates efficacy over an area of 21.3 in. x 21.3 in. or 70.5 $in.^2$ (455 cm^2). By delivery of the entire contents, 0.231 ml of product is delivered to each square centimeter.

Calculation: 10.5ml total volume of product/455 cm^2 of skin surface area prepped = 0.0231 ml of product per square centimeter.

Now, using the volume and use directions of the new product configuration, it is possible to determine if the volume of the new product configuration supplies a sufficient dosage to cover the proposed area. The directions suggest a [redacted] may be covered by the 26ml of product.

Calculation: 26ml total volume of product/ [redacted] cm^2 of skin surface area prepped = [redacted] ml of product per square centimeter.

Clearly, the dosage of product delivered per square centimeter is only [redacted] % ([redacted] ml /0.0231 ml) of the volume per square centimeter in the two previously approved product configurations. The 26ml configuration use directions suggests preparation of the skin surface area with a volume that is *less than half* that is approved for preoperative skin preparation with the 3ml and 10.5ml configurations. This is unacceptable given that no clinical simulation trails were performed to show that this proposed volume is acceptable.

To determine the appropriate area of skin to be prepped, the total volume of the 26ml product is divided by the desired total volume (and thus concentration) per square centimeter (0.0231 ml/cm^2) to determine the area that could be covered which is consistent with the dosages in the previously approved products (3ml and 10.5ml configurations). The total surface area is determined to be no greater than 1126 cm^2 which is equivalent to 174 in. This would cover an area of 13.2 in. by 13.2 in., not [redacted] in. as desired by the Applicant.

Calculation: 26ml total volume of product/0.0231 ml/cm^2 approved dosage of product = 1126 cm^2 of surface area.

Thus, to reflect these findings, the label should be rewritten to read:

Maximal treatment area for one applicator is approximately 1126 cm^2 (approx. 13.2 in. x 13.2 in.) Discard the applicator after a single use.

REFERENCES

21 CFR 333.470 Tentative Final Monograph for Topical Antimicrobial Drug Products, Federal Register, Volume 59, No. 116, June 17, 1994.

American Society for Testing and Materials (ASTM) Standard E1054-02, "Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents."

Conclusions:
From the Microbiology perspective, the Applicant has conducted the clinical simulation study and the skin coverage study to the satisfaction of this Reviewer. ***This Reviewer recommends that the NDA 20-832 for ChloraPrep with Tint is approvable contingent upon the following change to the label:***

> **Maximal treatment area for one applicator is approximately 1126 cm^2 (approx. 13.2 in. x 13.2 in.) Discard the applicator after a single use.**

Peter Coderre, Ph.D.
Microbiology Reviewer

Cc: Original NDA No. 20-832/S008/A003
Microbiologist, HFD-520
File name: N20832.S008.A003.FIN

TLMicro/HFD-520/FMarsik, Ph.D.
Finalized 31 Mar 05 FJM

DepDir/HFD-520/LGavrilovich, M.D.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Peter Coderre
4/20/05 01:42:41 PM
MICROBIOLOGIST

Frederic Marsik
4/20/05 01:54:23 PM
MICROBIOLOGIST

Lillian Gavrilovich
4/20/05 07:02:04 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 20-832 SUPPL # 008 HFD # 560

Trade Name ChloraPrep With Tint 26-mL Applicator

Generic Name Established name: 2% chlorhexidine gluconate and 70% isopropyl alcohol

Applicant Name Medi-Flex

Approval Date, If Known NDA approved July 14, 2000

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☐ NO ☒

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This supplement provides for (1) an enlargement of container size such that an increased amount of solution per treatment is applied and (2) the addition of a green dye to the solution for better visualization of already-prepped skin surfaces.

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 19-258 Cida-Stat (2% chlorhexidine gluconate) solution

NDA# NDA 19-422 Exidine (2% chlorhexidine gluconate) solution

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. Clinical Simulation Study Test for Pre-Operative Skin Preparation (Protocol 371.09.07.04)
2. Evaluation of the Area Covered by a Pre-Operative Skin Preparation (Protocol 371.1.09.07.04)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Clinical Simulation Study Test for Pre-Operative Skin Preparation (Protocol 371.09.07.04)
2. Evaluation of the Area Covered by a Pre-Operative Skin Preparation (Protocol 371.1.09.07.04)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 46,243	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 46,243	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Tia Frazier
Title: Regulatory Project Manager
Date: April 13, 2005

Name of Office/Division Director signing form:

Curtis Rosebraugh, M.D.
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tia Frazier
4/18/05 11:58:37 AM
CSO

Curtis Rosebraugh
4/18/05 01:08:28 PM
MEDICAL OFFICER

Consultative Review of NDA Supplement
NDA 20-832/S-008

Date of Consult Request: July 15, 2004

Date DAIDP Received: July 21, 2004

Date Assigned to Reviewer: July 21, 2004

Date Review Initiated: November 4, 2004

Consult Initiator: Tia Frazier, R.N.
Division of OTC Drug Products

Drug: ChloraPrep One-Step Antiseptic (2% chlorhexidine gluconate/ 70% isopropyl alcohol).

Sponsor: Medi-Flex
Leawood, KS 66210

Dates of Correspondence: Supplement S-008 was submitted on July 6, 2004. Amendments were filled on July 22 and September 9, 2004.

Purpose of Consult Request: The sponsor wishes to market the product in a 26 mL container (the largest size presently approved is 10.5 mL). The original supplement proposed revised Directions for Use for the product as well as the new package size and the addition of a green tint to the formulation.

Background: The product is approved for use as a patient preoperative skin preparation. The supplement contained manufacturing control information, revised labeling and a report of a skin area coverage study which was requested by FDA because of concerns that the relatively large amount of the product might run off the body of a patient who is being prepared for surgery, resulting in pooling of solution or saturation of drapes and subsequent ignition if electrocautery or laser devices are used in the vicinity of this product. The study also contained results of a comparison of the tinted and presently marketed untinted formulations in their ability to remove bacteria from the skin.

On July 22, 2004 the sponsor submitted additional reports concerning the *in vitro* activity of the product and its irritation potential.

On September 2, 2004, a teleconference was held with the sponsor to discuss issues which arose during the preliminary review of the supplement. These were (in summary):

- The skin coverage study employed a 30-second scrub, rather than the requested 2-minute scrub time required for moist site skin preparation, thus potentially minimizing the chance that the product would pool or run off the skin.

- The test preparations (tinted and the original nontinted version) exhibited log reductions between 1.85 and 1.58 at the test site, triggering questions about the product's ability to achieve the log reductions required by the TFM. Both the colored and non-colored products failed to meet the required log reductions at 10 minutes.

- The supplement included a revision to the changes in directions for use. The application time for "dry" sites was extended from 30 seconds to [redacted] without data to support the change.

A fax conveying FDA comments was sent to the sponsor on September 3, 2004. On September 15, 2004, the sponsor submitted a new protocol for the skin area and bacterial reduction studies. On September 23, 2004 the sponsor was sent a fax with the following comment on that protocol:

> We have received the new skin coverage protocol (submission of Sept 15, 2004 to IND 46, 243). The new protocol is satisfactory with one addition: Presently, drying time is estimated by one individual. It is recommended that drying time be estimated (separately) by 3 qualified persons, including at least one person with operating room experience, if possible. The estimated drying times should then be averaged.

Review: It now appears that the required study will not be submitted before the due date for the supplement (November 5, 2004). Therefore, the Division of Over-the-Counter Drug Products has determined that the supplement is "not approvable". It should be noted that the sponsor has withdrawn the proposed labeling change, so that the supplement provides only for the new size and the addition of a green tint to the formulation. The following language is recommended concerning the deficiencies in the application.

1. Conduct the Patient Pre-operative Skin Preparation (efficacy) study using the tinted formulation versus the clear formulation that was described for you in our September 3, 2004 facsimile on this subject.

2. Conduct a skin coverage study to assure that the product may be used safely according to the labeled directions. Follow the advice we provided in facsimiles sent to you on September 3 and September 23, 2004.

David Bostwick

Jean Mulinde, MD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Bostwick
11/4/04 02:19:00 PM
MEDICAL OFFICER

Jean Mulinde
11/4/04 02:24:08 PM
MEDICAL OFFICER

Janice Soreth
11/5/04 02:43:55 PM
MEDICAL OFFICER

Consultative Review of NDA Supplement
NDA 20-832/S-008

Date of Consult Request: January 12, 2005

Date DAIDP Received: January 12, 2005

Date Assigned to Reviewer: January 12, 2005

Date Review Initiated: January 24, 2005

Consult Initiator: Tia Frazier, R.N.
Division of OTC Drug Products
(HFD-560)

Drug: ChloraPrep One-Step Antiseptic (2% chlorhexidine gluconate/70% isopropyl alcohol [IPA])

Dates of Correspondence: Supplement S-008 was submitted on July 6, 2004. The amendments reviewed here are dated September 9 and December 31, 2004.

Purpose of Consult Request: The sponsor wishes to market the product in a 26 mL container (the largest size presently approved is 10.5 mL). The supplement also provides for the addition of a green tint to the formulation.

Background: This product is approved for use as a patient preoperative skin preparation. The larger container is requested so that the product may conveniently be used in surgeries requiring extensive skin decontamination (e.g. cardiac surgery). Because there is concern that the relatively large amount of the product might run off of the body of a patient who is being prepared for surgery, resulting in pooling of solution with possible risk of ignition, the Agency required a study to determine what the recommended skin area coverage for the product should be, and whether excessive runoff is observed using standard application procedures. The Agency also requested a small study to determine whether use of the green tint might affect the antimicrobial effectiveness of the drug.

Following is a brief history of interactions concerning this supplement. In March, 2003, the sponsor submitted a supplement (S-005) for a 26 mL applicator. Because there was insufficient safety data accompanying the supplement, the OTC Drug Division refused to file it on April 9, 2003. On May 12, 2003, FDA sent comments concerning the safety deficiencies. Specifically, a study to approximate the skin area covered by a container of this size in normal use was requested. After a meeting with the sponsor to discuss the subject (June 11, 2003), the sponsor submitted a protocol for the necessary study on October 1, 2003. The protocol was reviewed by Mr. Bostwick on October 22, 2003, and found to be generally satisfactory, though it was noted that the application method to be used required a more detailed description.

A revised protocol was submitted on December 11, 2003, and reviewed by HFD-520 on February 19, 2004. The review noted that the application time to be used was 30 seconds, while approved directions for use for "wet" surgical sites specified 2 minutes of application. The review requested that the study be performed using the 2 minute application time and include an evaluation of the drying time necessary for the product. This information was transmitted in a telecon between Mr. Bostwick and Mr. Wayne Vallee of Beckloff Associates, representing the sponsor, Medi-Flex, on March 10, 2004.

The supplement S-008 was submitted on July 6, 2004. In a preliminary review it was noted that the application time used was 30 seconds, rather than 2 minutes. It was also noted that a small bacterial reduction study resulted in log reductions which were less than those specified in the Tentative Final Monograph (TFM) for Health-Care Antiseptics for patient preoperative skin preps. A telecon was held with the sponsor on September 2, 2004, to discuss these problems. The sponsor committed to perform a new skin area coverage, drying time, and bacterial reduction study. However, they were not able to complete the study prior to the review goal date of November 7, 2004. Therefore, the supplement was made "not approvable" on November 5, 2004. The December 31, 2004, amendment submits the required study.

The Agency also requested that a study be performed to evaluate the flammability of the product, since it has a high alcohol content. This study was submitted on September 9, 2004.

This review will consist of four parts. Part A will concern the bacterial reduction study, Part B will concern the skin area coverage and drying time study, Part C will concern the flammability study, and Part D will concern the proposed labeling for the product.

Review

A. Bacterial reduction study

Study Title: Test for Preoperative Skin Preparations (Protocol No. 371.2.09.07.04)

Investigator: [redacted] MD

Study Dates: October 24 – December 12, 2004

Study Objectives: The following is taken directly from the protocol:

To evaluate the antimicrobial effectiveness potential of ChloraPrep with Tint and ChloraPrep, each of which contains chlorhexidine gluconate, and a reference product, Scrub Care Preoperative Skin Prep Tray, that contains povidone-iodine.

Method:

1. Study design: This study compared the original ChloraPrep untinted, ChloraPrep containing a green dye, and a povidone-iodine preparation (Scrub Care) which contains 10% povidone-iodine. Fifty-one subjects completed the study, which employed methodology based on the TFM. Test product applications were bilateral with two of the three test products used on each subject in random fashion.

2. Inclusion criteria: The following is taken directly from the protocol:

> Potential subjects may be included in this study if they meet the following requirements:
> Male and/or females, ≥18 years of age and ≤65 years of age.
> Are cooperative and willing to answer questionnaires and sign a consent form (to be provided prior to study initiation).
> Is in general good health.
> Have skin within 6 inches of the test sites that is free of tattoos, dermatoses, abrasions, cuts, lesions, or other skin disorders.

Additionally, subjects must have had baseline bacterial counts of at least 5 logs at the groin site and/or 3 logs at the abdomen site to enter the study.

3. Exclusion criteria: The following is taken directly from the protocol:

> An individual cannot be enrolled in the study if they:
> Have been exposed to topical or systemic antimicrobials during the two-week pretest-conditioning period. This restriction includes, but is not limited to, shampoos, lotions, soaps, body powders, and material such as solvents, acids, or alkalis.
> Have been medically diagnosed as having a medical condition, which would preclude participation such as: diabetes, hepatitis, an organ transplant, a medical surgical implant or an immune compromised system.
> Have any medical condition that in the opinion of the Investigator would preclude participation.
> Have bathed in chemically treated pools or hot tubs two weeks prior to any microbial sampling.
> Have used UV tanning lamps two weeks prior to any microbial sampling.
> Have bathed or showered less than 48 hours prior to any microbial sampling.
> Have a known sensitivity to CHG, povidone-iodine, and 70% Isopropanol.
> Have a known sensitivity to latex products.
> Have a known sensitivity to fragrances.
> Are pregnant or nursing.
> Are not willing to fulfill the requirements of the protocol.

4. Dosage and duration of therapy: This study was performed using a modified protocol for testing patient preoperative skin preparations suggested in the TFM. Test subjects were screened for minimum bacterial counts as outlined in Inclusion criteria, above. Each test subject was assigned 2 of the 3 test materials in a random fashion. The treatment areas were 2 x 5 inches at the groin and 5 x 5 inches at the abdomen. Each treatment area was divided into subsites for microbial sampling at baseline and sampling at 2 and 10 minutes and 6 hours (groin) or 30 seconds, 10 minutes, and 6 hours (abdomen). The test sites were covered with a gauge bandage after the 10 minute sample to minimize contamination from external sources. The prep procedures used were as follows for the ChloraPrep applicators: at the abdomen, a "continuous scrubbing motion" of the sponge to the designated treatment area was used. The same technique was used at the groin. The duration of scrubbing was 30 seconds at the abdomen and 2 minutes at the groin. Drying time allowed was 30 seconds at the abdomen and 1 minute at the groin. The prep procedure for the povidone-iodine product was as follows: a "scrub" solution (formulation not given) on a prepared sponge was applied to the test area for 3 minutes. A second "scrub" sponge was then applied for the same length of time, followed by blotting with a sterile towel. A "paint" solution (formulation not specified) was then used for an unspecified length of time.

5. Additional information: There was a 2 week washout period prior to the test during which no antimicrobial products were to be used by the test subjects. They were not to shave the test area for 5 days prior to the test and were not to bathe in the 48 hours before the test began. All subjects were sampled for sufficient baseline bacteria 72 hours before the test began. A final baseline sample was taken on the day of testing. Subjects were admitted to the study only for those anatomical sites where sufficient baseline bacteria were present.

6. Effectiveness parameters: The TFM standards for patient preoperative skin preparations are a mean decrease of 2 logs in the baseline microbial counts at a dry test site (abdomen) within 10 minutes of drug application, with the count not to exceed baseline for at least 6 hours. The requirement is similar for a wet test site (groin), though the 10 minute reduction is to be 3 logs, rather than 2.

7. Safety: Adverse events were recorded and compared between the treatment groups.

Results:

1. Evaluability: 60 subjects were entered into the study. Of these, 51 met screening requirements at the abdomen and/or groin. This resulted in 102 possible test sites for evaluation. As noted above, 2 of the 3 test materials were utilized for each

subject. For various reasons (usually missed samples), the number of evaluable test sites varied. The following table present the number of test sites evaluated for each test article. The numbers of sites was the same for each time interval (2 minutes, 10 minutes, and 6 hours for the groin and 30 seconds, 10 minutes, and 6 hours for the abdomen).

Table 1: Sample Sizes by Product

Test Product	Abdomen	Groin
ChloraPrep with Tint	30	30
ChloraPrep (plain)	32	33
Povidone-Iodine	32	31

2. Demographics: The demographics presented are for the 60 subjects who entered the study. There were 44 Caucasians, 10 Asians, and 3 each Black and Hispanic.

3. Efficacy results: Results will be presented for all time intervals, though the 30 second interval applies to the indication patient preinjection skin preparation, and the 2 minute interval is not applicable to any TFM indication. These data have not been audited by this reviewer except for the tables of log reduction (Tables 7-12 in the study report). Results are those reported by the test laboratory. The reductions are calculated by subtracting the log counts found at the various time points from the test day baseline log counts.

Table 2: Mean Log Reductions at Groin Site

Sampling Interval	Test Article Identification		
	ChloraPrep with Tint	ChloraPrep	Povidone-Iodine
Baseline Mean	5.56	5.58	5.54
2 minute	4.27	4.01	3.44
10 minute	4.69	4.53	4.38
6 hour	4.37	4.30	4.37

Table 3: Mean Log Reductions at Abdominal Site

Sampling Interval	Test Article Identification		
	ChloraPrep with Tint	ChloraPrep	Povidone-Iodine
Baseline Mean	3.44	3.51	3.41
30 second	2.68	2.65	2.18
10 minute	3.00	3.12	3.02
6 hour	2.46	2.54	2.33

Reviewer's comment: The statistical analysis presented indicates that there are no significant differences between the groups in bacterial reduction at the TFM time points (10 minutes and 6 hours). The positive control included in this study (povidone-iodine) is included in the TFM as a Category I product for the patient preoperative skin preparation indication and is therefore acceptable.

This is a successful study in that it provides evidence that addition of a tint to ChloraPrep does not materially affect its ability to lower microbial counts on human skin. All 3 test products met the TFM requirements for a patient preoperative skin preparation (and for a patient preinjection skin preparation).

B. Skin area coverage and drying time study

Study Title: Evaluation of the Area Covered by a Preoperative Skin Preparation (Protocol No. 371-108)

Investigator: [redacted]. MD

Study Dates: October 19 – 24, 2004

Study Objectives: The following is taken from the protocol:

> The study was designed to evaluate the area covered by antimicrobial skin compounds for use as preoperative skin preparations and injection site preparations. The study was also designed to estimate the area covered (and the runoff determined) by the applicators containing 26 mL of ChloraPrep with Tint. Twenty (20) subjects were used to evaluate the area covered on their backs.

Method:

1. Study design: This study was intended to establish a) whether using the 26 mL applicator as directed resulted in pooling on the body or runoff of the product to the surrounding area and b) what the observed drying time for the product was. Twenty applicators were used on the 20 test subjects.

2. Testing parameters: A predetermined surface area was treated with a surgical marker on the backs of the test subjects. This area was 2432 cm^2, or about 19 by 19 inches. The prepping technique used was as follows:

> Using the applicator, the solution will be applied within the designated treatment area beginning in the center of the back, moving outward using vertical (up and down) strokes for two minutes so that a thin even coat is applied.

The same technician made all applications. The containers were weighed before and after the procedure to determine the volume used. The drying time was observed, apparently by only one person.

Results:

1. Demographics: There were 9 males and 11 females in the test subject population. There were 9 Caucasians and 11 Asians, with a mean age of 34 years.

2. Pooling and runoff observations: The investigator states that no pooling on the body was observed, and there was no runoff onto the drapes. However, the results tables indicate that the product "ran off" the treatment site in 10 of the 20 subjects, though this runoff did not apparently reach the drapes. The draping technique/location is not described in the protocol.

3. Amount used: The average amount used was 0.0041 g/cm^2.

4. Drying time: The estimated drying times ranged from 52-117 seconds (average 85 seconds).

Reviewer's Comment: Since there have been reports of ignition of excess alcohol in similar products marketed in relatively large containers, it seems necessary to estimate the possibility of similar occurrences with ChloraPrep. The fact that no pooling was seen is not surprising, since the body surface used was the back. Reports of ignition with other products have not described pooling on the body as a problem compared to pooling under the body (from runoff) or in the surgical drapes used during the procedure. The runoff observed in 10 of the 20 subjects indicates that this could be a concern during normal use.

The recommended drying time for the product based on these observations is 3 minutes.

C. Flammability study

Study Title: Flammability Study of Alcohol-Based Products (Protocol No. 371-107)

Investigator: _____, MD
_____
_____

Study Dates: August 9, 2004

Study Objectives: The following is taken from the protocol:

> To determine the potential for alcohol-based pre-operative skin preparations to remain flammable after application to skin.

Method:

1. Study design: This is an engineering study rather than a clinical study.

Approximately an 18 x 24 inch segment of pig skin was used for testing. Three test products were examined: ChloraPrep, DuraPrep (which contains 70% IPA and 0.7% iodine), and Prevail-FX which also contains 70% IPA and an unknown amount of iodine. The products were applied for 30 seconds or 2 minutes and levels of IPA vapors were observed 30 seconds, 1 minute, and 2 minutes later. Additionally, the protocol called for the investigator to attempt to cause a fire by operating an electrocautery device and a cigarette lighter next to the prepped pigskin.

Results:

1. Vapor readings: These values are presented as percentages of the lower explosive limit for IPA. The lower explosive limit is not stated in the protocol. The flammability limits for IPA published by NIOSH is 2-12.7% or 20,000-127,000 ppm by volume. The experiment was done twice. The following table presents the lower explosive limit percentages observed at each time point. NA means the reading was not taken because the previous reading was 0.

Table 4: % of Lower Explosive Limit for IPA
30 second application

Product	Drying Time		
	30 seconds	60 seconds	120 seconds
ChloraPrep (1)	9	0	NA
ChloraPrep (2)	10	0	NA
DuraPrep (1)	14.5	4	0
DuraPrep (2)	15	10	0
Prevail-FX (1)	8	0	NA
Prevail-FX (2)	18	4	0

Table 2: % of Lower Explosive Limit for IPA
2 minute application

Product	Drying Time		
	30 seconds	60 seconds	120 seconds
ChloraPrep (1)	5	0	NA
ChloraPrep (2)	6	0	NA
DuraPrep (1)	20	0	NA
DuraPrep (2)	7	2	0
Prevail-FX (1)	36	9	0
Prevail-FX (2)	11	0	NA

2. Flame and spark evaluations: These evaluations are presented as positive (a spark was seen upon operation of the electrocautery device, or a flame was supported by the test preparation when the cigarette lighter was operated) or negative.

Table 6: Spark and Flame Occurrences
30 second application

Product	Drying Time					
	30 seconds		60 seconds		120 seconds	
	Spark	Flame	Spark	Flame	Spark	Flame
ChloraPrep (1)	Yes	Yes	No	No	NA	NA
ChloraPrep (2)	Yes	Yes	No	No	NA	NA
DuraPrep (1)	Yes	Yes	Yes	Yes	No	No
DuraPrep (2)	Yes	Yes	Yes	No	No	NA
Prevail-FX (1)	Yes	Yes	No	No	NA	NA
Prevail-FX (2)	Yes	Yes	No	No	NA	NA

There were no spark or flame observations for ChloraPrep after the 2 minute application. Observations at 2 minutes for the other test articles are presented below.

Table 7: Spark and Flame Occurrences
2 minute application

Product	Drying Time					
	30 seconds		60 seconds		120 seconds	
	Spark	Flame	Spark	Flame	Spark	Flame
DuraPrep (1)	Yes	No	No	NA	NA	NA
DuraPrep (2)	Yes	No	No	NA	NA	NA
Prevail-FX (1)	Yes	Yes	No	No	NA	NA
Prevail-FX (2)	No	No	NA	NA	NA	NA

Reviewer's Comment: This information supports the utility of a 3 minute drying time for ChloraPrep. Under the conditions of this study, both DuraPrep and Prevail-FX demonstrate a greater propensity for vapor presence after product use. Since the methodology used here has not been validated, no conclusions should be drawn concerning the likelihood of ignition of the products in clinical use.

D. Labeling review

The sponsor submitted labeling on July 6, 2004 and revised labeling on September 9, 2004. This review concerns the label submitted September 9, 2004.

Review of the labeling for this product is complicated by the large size of the new container and by reports of ignition of similar products in containers of comparable size which resulted in serious burns to the patient being prepped. The reports most often involved pooling of the IPA-containing preparation on or under the patient's body, with fire resulting when use of an electrocautery device caused a spark which ignited the preparation.

In this case, the Warnings section of the labeling contains the statement, "Do no use with electrocautery procedure", which should minimize flammability incidents. However, discussions concerning similar products have revealed that most surgical procedures do involve use of electrocautery at some point. Therefore, it seems prudent to label the product with the assumption that in a large number of cases, the danger of spark introduction in the surgical field will take place, even with the above noted Warning. It may be more realistic to delete the electrocautery warning from the label, though if this is done, additional warning language to that proposed below will be necessary. This issue is best resolved by the Division of OTC Drug Products. If the warning is deleted, it would be contrary to the recommendations for the labeling of IPA when used as a patient preop in the present draft of the TFM.

The sponsor has submitted the following labeling pieces for the ChloraPrep 26 mL container:

A. Applicator barrel label. This is submitted in the July 6, 2004 submission only.

B. Insert sheet. This label apparently is used in conjunction with a package that contains the 26 mL applicator [redacted].

C. Lidding label. Presumably this is the label used on the container which holds the 26 mL applicator.

The labeling pieces will be commented on individually:

A. Applicator barrel label. This label presently bears only identifying information (drug name, lot no., etc.). Because this is the only label that will positively be seen by the user, it should contain additional safety information, to read as follows:

WARNING – FLAMMABLE
Keep away from fire or flame. To reduce the risk of fire:

- Solution contains alcohol and gives off flammable vapors while drying – allow to dry 3 minutes on skin.
- Do not use with electrocautery procedures.
- Do not allow solution to pool.
- Remove solution-soaked material from prep area.

B. Insert sheet. This label and packaging should not be used. Approval of this configuration including [redacted] as a dosage form, which has not taken place.

C. Lidding label. The following changes in this label are necessary:

1. The statement, "Solution contains alcohol and gives off flammable vapors while drying – allow to dry 3 minutes on skin" should be added to the Warnings section.

2. In the Directions section:

a. Delete the first bullet, reading " [redacted] " and replace it with the following:
   - Discard any portion of the solution which is not required to cover the recommended area. The maximal treatment area for one applicator is approximately [redacted] cm^2. Discard the applicator after a single use.

b. Delete the present third bullet, concerning use of the [redacted].

c. The drying time for both dry and moist surgical sites should be 3 minutes (rather than [redacted]).

David Bostwick

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: September 2, 2004
TIME: 10:35-10:55AM
LOCATION: 9201 Corporate Blvd., Rockville, MD 20817
Teleconference line: 1-800-[redacted]
APPLICATION: NDA 20-832/S-008
DRUG NAME: ChloraPrep with Tint 26-mL Applicator

TYPE OF MEETING: Type C

MEETING CHAIR: Dr. Curtis Rosebraugh, M.D., M.P.H.

MEETING RECORDER: Tia Frazier, R.N., M.S.

FDA ATTENDEES:

Name of FDA Attendee	Title	Division Name and HFD#
1. Tia Frazier, R.N., M.S.	Regulatory Project Manager	Division of Over-the-Counter Drug Products HFD-560
2. David Bostwick	Clinical Reviewer	Division of Anti-infective Drug Products HFD-520
3. Dr. Curtis Rosebraugh, M.D., M.P.H.	Deputy Director	Division of Over-the-Counter Drug Products HFD-560

EXTERNAL CONSTITUENT ATTENDEES:

Attendee Name	Title	Affiliation
1. Lyle Clayton	President and CEO	Medi-Flex, Inc.
2. Cynthia T. Crosby	Director, Clinical Affairs	Medi-Flex, Inc.
3. Scott Tufts	Vice President, Research and Development	Medi-Flex, Inc.
4. Orlando Cordova	Vice President, Quality Assurance	Medi-Flex, Inc.
5. [redacted]	Scribe	Medi-Flex, Inc.
6. [redacted]	Scribe	Medi-Flex, Inc.

BACKGROUND:

Originally, sponsor sought approval of a 26-mL applicator with no colorant, via a "Changes Being Effected" application submitted on March 11, 2003. On April 9, 2003, FDA issued an "Unacceptable for filing" (UN) letter because the change required clinical data for approval, and because the change required a user fee.

FDA met with the applicant on June 11, 2003, to explain what types of clinical data might support their development plans for the proposed 26-mL applicator. FDA met with the applicant on November 12, 2003 to provide consultation on the design of a clinical study to support the proposed applicator.

On December 11, 2003, Medi-Flex submitted the proposed study protocol for the ChloraPrep applicator impregnated with green dye to IND 46,243. The stated purpose of the study was to determine the area of skin that the applicator would cover. FDA had the following questions and advice on the proposed study:

- Did the applicant intend to market the green formulation?
- The product must be scrubbed onto the skin for 2 minutes (as the labeling directs for "wet" surgical sites) in order to ascertain whether or not pooling or run-off of the solution would occur.
- How would drying time be measured?

The applicant completed their study on December 23, 2003, before receiving the FDA feedback outlined above.

FDA requested this meeting to address filing and review issues associated with its initial review of the supplement, which was submitted on July 6, 2004.

FDA communicated that the following review issues were noted upon completing its initial cursory review of the application:

- The skin coverage study conducted at ——— employed a 30-second scrub, rather than the requested 2-minute scrub time required for moist site skin preparation, thus potentially minimizing the chance that the product would pool or run off the skin.

- Both preparations exhibited log reductions between 1.85 and 1.58 at the back site, triggering questions about the product's ability to achieve the log reductions required by TFM. Both the colored and non-colored products failed to meet the required log reductions at 10 minutes.

- The supplement included a revision to the changes in directions for use. The application time for "dry" sites was extended from 30 seconds to ——— without data to support the change.

MEETING OBJECTIVES:

Medi-Flex, Inc. requested this meeting to understand the potential filing issues and review issues that FDA had identified in its initial review of their application.

DISCUSSION POINTS:

- FDA explained that the applicant's decision to change the approved directions for the product's application required supportive data not submitted in this application. FDA further explained that it could not file the application without data to review that supported the proposed change in directions for use.

- Medi-Flex inquired if FDA would review the application if they withdrew the proposed change in directions from the supplement in question.

- FDA confirmed that the supplement could be filed as a chemistry supplement if the proposed change in directions for use was withdrawn. We also discussed initial impressions regarding possible limitations to the data that may limit approval (see below).

- FDA conveyed the following review issues that were initial identified as possible problems that may not lead to an approval action

Review Issues:

1. The sponsor performed a 30 second scrub on four different quadrants of the back instead of the two minute scrub. This may not be sufficient safety data for approval. The sponsor stated that they may consider performing a second skin coverage study to supplement the data in this submission.

2. It was noted that the medication did not meet the required bacterial log reductions for patient pre-operative skin preparations as described in the June 14, 1994 Tentative Final Monograph for Healthcare Antiseptic Drug Products.

- FDA clarified that if Medi-Flex sought to change its directions for use, a second efficacy study involving at least 30 subjects would need to be conducted to support the change.

- Medi-Flex inquired about the trajectory for FDA's review of the supplement if it did not include a change in the directions for use. FDA responded that it would regard this supplement as a chemistry supplement and would review it with a 4-month PDUFA review clock.

DECISIONS (AGREEMENTS) REACHED:

Medi-Flex agreed to notify FDA of its decision about whether or not to pursue a change in directions for use for this product on or before September 3, 2004.

ACTION ITEMS:

FDA advised that Medi-Flex submit the efficacy protocol to the IND for FDA review and comment sufficiently ahead of the November 7, 2004 goal date for this submission.

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/s/

Curtis Rosebraugh
9/20/04 12:02:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-832/S-008

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-832/S-008

PRIOR APPROVAL SUPPLEMENT

Beckloff Associates, Inc.
Attention: Wayne F. Vallee, R.Ph., RAC
Director, Regulatory Affairs
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Mr. Vallee:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ChloraPrep with Tint 26-mL Applicator (2% chlorhexidine gluconate w/v and 70% isopropyl alcohol v/v solution)

NDA Number: 20-832

Supplement number: 008

Review Priority Classification: Standard (S)

Date of supplement: July 6, 2004

Date of receipt: July 7, 2004

This supplemental application proposes a newly-designed applicator with a sponge tip (pledget) impregnated with FD&C Green #3 dye for preoperative skin preparation.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 5, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 7, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

David Hilfiker, M.S.
Chief, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

David Hilfiker
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END OF DOCUMENT INFORMATION PAGE

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: September 3, 2004

To: Linda McBride, R.Ph. Director, Regulatory Affairs	**From:** Tia Frazier Project Manager
Company: Medi-Flex	Division of Over-the-Counter Drug Products
Fax number: 913-451-8509	**Fax number:** 301-827-2315
Phone number: 913-451-0880	**Phone number:** 301-827-2271

Subject: Discipline Review Completed for NDA 20-832/S-008
Clinical studies

Total no. of pages including cover: 3

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: **YES** ☑ **NO**

Message: Please refer to the clinical studies submitted on July 6, 2004 to NDA 20-832, Supplement 008, for ChloraPrep with Tint 26-mL Applicator. We wish to provide the following comments and requests for clinical information to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified.

Conduct the following two clinical studies:

Skin Coverage Study:

The study submitted in support of this supplemental application ("Evaluation of the Area Covered by a Preoperative skin Preparation") is deficient in that the product was applied for a 30 second period rather than the maximum 2 minute application period recommended in the approved labeling. Since it is the intent of this study to determine the potential for product runoff and pooling when used for the longest possible time, you need to conduct another skin coverage study to support approval of the larger applicator.

1. We presume that the preferred additional applicator size is 26-mL. Therefore, all test subjects should be tested using this size. Skin area coverage should be determined using a total of at least 20 applicators on adult volunteers of varying heights and weights. The average amount (weight/volume) of product used in the applications should be recorded.

2. The protocol should specifically instruct that the directions for application for a two-minute prep as presented in the approved labeling will be used. The report should specifically state whether product runoff and/or pooling occurred for each test subject. You can use the same format for the skin coverage report that you used for the July 6, 2004 submission.

Patient Pre-operative Skin Preparation Study:

1. Bacterial reductions in a representative number of test subjects should be determined. We recommend that the following outline be utilized:

> A. Data from 20 evaluable subjects should be available. Ten subjects should have been prepped with the "new" (tinted) formulation, and ten should have been prepped with the "old" (untinted) formulation.
>
> B. The procedure should approximate that recommended in the Tentative Final Monograph for Health-Care Antiseptic Drug Products for "dry" surgical sites. That is, the abdomen should be used for testing, the subjects should have at least a 3 log baseline bacterial count, and bacterial reductions should be determined at 10 minutes and 6 hours after prepping. A 30-second prep as recommended in the approved labeling should be used.

2. We strongly recommended that you submit the protocol for testing to the IND for review and feedback before you initiate the study.

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/s/

Tia Frazier
9/3/04 11:24:55 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

SNDA 20-832/S-008

Medi-Flex, Inc
Attention: Lisa McBride, R.Ph.
Director, Regulatory Affairs
11400 Tomahawk Creek Parkway
Suite 310
Leawood, Kansas

Dear Ms. McBride:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ChloraPrep with Tint 26-mL applicator (2% chlorhexidine gluconate w/v and 70% isopropyl alcohol v/v solution).

We also refer to the teleconference meeting between representatives of your firm and the FDA on September 2, 2004. The purpose of the meeting was to discuss filing issues.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

Dr. Curtis Rosebraugh, M.D., M.P.H.
Deputy Director Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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/s/

Curtis Rosebraugh
9/20/04 12:02:21 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: April 26, 2005

To: Linda McBride	**From:** Tia Frazier
Company: Medi-Flex	Division of Over-the-Counter Drug Products
Fax number: 913-451-8509	**Fax number:** 301-827-2315
Phone number: 913-451-0880	**Phone number:** 301-827-2271

Subject: Labeling Revisions

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

Please refer to your July 6, 2004 submission proposing a 26-mL Applicator with a sponge tip (pledget) impregnated with FD&C Green #3 dye for preoperative skin preparation. Reference is made to the labeling you submitted on September 9, 2004. We also refer to the resubmission dated December 31, 2004, and to the labeling submitted on January 25, 2005.

We recommend that you incorporate the following revisions to the labeling proposed in this supplement.

In terms of the timing for submission of revised labeling, we remind you that we must review and act on this new drug application, with or without an amendment, on or before May 3, 2005.

Drug Facts Labeling Revisions:

1. Under ***Directions***, revise the labeling to incorporate the following changes:

   a. Delete the first bullet, reading "[redacted]' and replace it with the following:

      - **Maximal treatment area for one applicator is approximately 1126 cm2 (approx. 13.2 in. x 13.2 in.) Discard the applicator after a single use.**

   b. Delete the present third bullet, concerning [redacted]. Alternatively, you must provide data to support the use of this product with [redacted]
   c. The drying time for both dry and moist surgical sites should be 3 minutes (rather than [redacted]).
   d. Delete the last bulleted statement that reads "maximal treatment area for one applicator is approximately [redacted]."

2. Under ***Warnings*** add the following statement:
   "Solution contains alcohol and gives off flammable vapors while drying – allow to dry 3 minutes on skin".

3. Applicator Barrel Labeling Revisions: I

Add the following information into the labeling for the applicator barrel:

WARNING – FLAMMABLE
Keep away from fire or flame. To reduce the risk of fire:

- Solution contains alcohol and gives off flammable vapors while drying
  -allow to dry 3 minutes on skin.
- Do not use with electrocautery procedures.
- Do not allow solution to pool.
- Remove solution-soaked material from prep area.

4. Package Insert Revision:

The package insert sheet provides directions concerning [redacted]. Provide data to support the use of this product [redacted] or withdraw directions pertaining to the use of [redacted] from the labeling for this product.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Tia Frazier
4/26/05 06:04:32 PM
CSO

Debbie Lumpkins
4/26/05 06:08:29 PM
INTERDISCIPLINARY

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: May 2, 2005

To: Linda McBride	**From:** Tia Frazier
Company: Medi-Flex	Division of Over-the-Counter Drug Products
Fax number: 913-451-8509	**Fax number:** 301-827-2315
Phone number: 913-451-0880	**Phone number:** 301-827-2271

Subject: Labeling Negotiation

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ **YES** ☑ **NO**

Please refer to your May 2, 2005 labeling submission received today by facsimile for NDA 20-832, Supplement 008. We recommend that you incorporate the following additional revisions to the labeling proposed in this supplement. Please send your labeling revisions for our consideration by facsimile and by electronic mail, if possible.

In terms of the timing for submission of revised labeling, we remind you that we must review and act on this new drug application, with or without an amendment, on or before May 3, 2005.

Drug Facts Labeling Revisions:

1. Under ***Directions***, revise the labeling to incorporate the following changes in bold print:

    - **Maximal treatment area for one applicator is approximately 1126 cm2 (approx. 13.2 in. x 13.2 in.) Discard the applicator after a single use.**

2. Under ***Directions***, revise the labeling so that the phrase "three (3) minutes" in the third and fourth bulleted statements appears in bold print.

APPEARS THIS WAY
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/s/

Tia Frazier
5/2/05 03:04:45 PM
CSO

MEDI-FLEX

August 3, 2005

Charles J. Ganley, M.D., Director
Division of Nonprescription Clinical Evaluation, HFD-560
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Room 560
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: FPL for approved supplement NDA 20-832/S-008

Dear Dr. Ganley:

Reference is made to NDA No. 20-832, ChloraPrep® With Tint (chlorhexidine gluconate 2% (w/v)) Topical Solution for the indication of patient preoperative skin preparation which was approved on May 3, 2005 (Supplement No. 008).

The purpose of this submission is to provide the Center with an electronic version of the final printed labeling (FPL) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* as requested. The FPL is approximately 261KB and is virus free as confirmed using Symantec Antivirus Corporate Edition 9.0 Software to detect viruses. The final printed labeling for the barrel, lidding and shipper are identical to the submitted labeling referenced in the approval letter for the ChloraPrep With Tint.

Please do not hesitate to contact me at (913)345-3562 should you have any questions regarding this submission or require additional information.

Sincerely,

Linda McBride, R.Ph.
Director, Regulatory Affairs

cc: Ms. T. Frazier; FDA (cover only)

www.medi-flex.com
ISO 9001-2000 & ISO 13488; 1996 Certified

Corporate Offices
11400 Tomahawk Creek Parkway, Suite 310 • Leawood, KS 66211
(800) 523-0502 • fax (913) 451-8509

Manufacturing Facility
1550 Northwestern Drive • El Paso, TX 79912
(800) 742-0473 • fax (915) 778-6425

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-832/S-008

Medi-Flex, Inc.
Attention: Linda McBride, R.Ph.
Senior Director, Regulatory Affairs
11400 Tomahawk Creek Parkway, Suite 310
Leawood, Kansas 66211

Dear Ms. McBride:

We acknowledge receipt of your May 3, 2006 submission containing final printed labeling in response to our May 3, 2005 letter approving your supplemental new drug application for ChloraPrep® (2% chlorhexidine gluconate (w/v) topical solution) with tint 26-mL applicator.

We also refer you to our April 14, 2006 letter approving the final printed label for the immediate container and applicator barrel for supplement 008.

We have reviewed the labeling for the package insert that you submitted in accordance with our May 3, 2005 and April 14, 2006 letters and we find it acceptable.

If you have any questions, call Laura Shay, Regulatory Project Manager, at 301-796-0994.

Sincerely,

{See appended electronic signature page}

Susan Johnson, Ph.D.
Associate Director
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Susan Johnson
8/15/2006 05:58:35 PM