CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208288Orig1s000

OTHER REVIEW(S)

Target Product Labeling Review for SoluPrep™ Film-Forming Sterile Surgical Solution
Draft Labeling

SUBMISSION DATES:	July 6, 2015; August 25, 2015; November 6, 2015; March 3, 2017; August 1, 2018
NDA/SUBMISSION TYPE:	208288/Original
ACTIVE INGREDIENTS:	2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol, 10.6 mL and 26 mL
DOSAGE FORMS:	Solution
SPONSOR:	3M Health Care Business 3M Center, Bldg. 0275-05-W-06 Saint Paul, MN 55144-1000 Dianne L. Gibbs, RAC Regulatory Affairs Director (651) 737-0844
REVIEWER:	Michelle M. Jackson, PhD IDS Microbiologist, DNDP, ODEIV
TEAM LEADER:	Francisco Martínez-Murillo, PhD Team Leader, DNDP, ODEIV
PROJECT MANAGER:	Celia Peacock, RDN, MPH, DNDP, ODEIV Senior Regulatory Project Manager

I. BACKGROUND

On July 6, 2015, 3M Health Care submitted NDA 208288 SoluPrep™ film-forming sterile patient preoperative skin preparation as an orginal new NDA. The Sponsor proposes a sterile antiseptic surgical solution containing the active ingredients, chlorhexidine gluconate and isopropyl alcohol in solution with an inactive ingredient 3M film-forming copolymer and other inactive ingredients. Once the solution is applied to the skin, the copolymer would produce a water-insoluble film. (b) (4) Three different applicators are proposed, 10.5 mL "Brite Green" (tinted solution), 10.5 mL "Clear" (nontinted solution), and 26 mL "Brite Green." On March 3, 2017, the Sponsor submitted a revised Target Product Information (TPI) package insert. In response to the Agency's information requests (IRs) dated July 30, 2018 and July 31, 2018, the Sponsor submitted a revised and updated TPI sheet on August 1, 2018, addressing all our revisions.

Submitted Target Product Information Labeling for NDA 208288	
Type of Labeling	**Date**
Target Product Information (Clean copy)	August 1, 2018
Target Product Information (Track changes)	August 1, 2018
Target Product Information (Annotated text)	August 1, 2018

II. REVIEWER'S COMMENTS

1. Indications and Usage

3M™ SoluPrep™ Film-Forming Sterile Surgical Solution (3M CHG/IPA Prep) is indicated for use as a patient preoperative skin preparation, for preparation of the skin prior to surgery, and to help reduce bacteria that can potentially cause skin infection.

> ***Reviewer's comments:*** *The Sponsor should include the statement "(3M CHG/IPA Prep)" to come after the descriptor statement "Film-Forming Sterile Surgical Solution" since this term has been used throughout the TPI. There should be a comma placed between the word "surgery" and word "and". The Sponsor should revise the statement to read: 3M™ SoluPrep™ Film-Forming Sterile Surgical Solution (3M CHG/IPA Prep) is indicated for use as a patient preoperative skin preparation, for preparation of the skin prior to surgery, and to help reduce bacteria that can potentially cause skin infection.*

Agency's Recommendation (IR: July 30, 2018):

Revise the statement to read: *3M™ SoluPrep™ Film-Forming Sterile Surgical Solution* (3M CHG/IPA Prep) is indicated for use as a patient preoperative skin preparation, for preparation of the skin prior to surgery, and to help reduce bacteria that can potentially cause skin infection.

> ***Reviewer's comments:*** *In accordance with the Agency's request, the Sponsor has revised the statement to read: 3M™ SoluPrep™ Film-Forming Sterile Surgical Solution (3M CHG/IPA Prep) is indicated for use as a patient preoperative skin preparation, for preparation of the skin prior to surgery, and to help reduce bacteria that can potentially cause skin infection. These changes are acceptable.*

2. Dosage and Administration

Single use topical application:

10.5 mL applicator (Clear/Tint)

- For head, neck and small prep areas
- Sterile solution
- Applicator is sterile if package is intact
- Solution volume 10.5 mL / 0.36 fl. oz.
- Maximal treatment area for one applicator is approximately 13 in. x 13 in. (178.8 in^2)

26 mL applicator (Tint)

- For large prep areas below the neck
- Sterile solution
- Applicator is sterile if package is intact
- Solution volume 26 mL / 0.9 fl. oz.
- Maximal treatment area for one applicator is approximately 19.5 in. x 19.5 in. (387.5 in^2)

Reviewer's comment: *The Sponsor will need to adjust the spacing between the word "approximately" and "13 in." and "19.5 in."*

Agency's Recommendation (IR: July 30, 2018):
Adjust the spacing between the word "approximately" and "13 in." and "19.5 in."

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has adjust the spacing between the word "approximately" and "13 in." and "19.5 in." This is acceptable.*

Directions (follow all directions for use)

- Discard the applicator after a single use along with any portion of the solution not required to cover the prepped area. It is not necessary to use the entire amount available.

Getting patient ready for solution:

- Use in well-ventilated area.
- Do not microwave or heat the solution applicator.
- Apply to clean, completely dry, residue-free, intact skin.
- When hair removal is necessary, use a surgical clipper on the morning of surgery. If a wet shave is used, thoroughly remove all soap residues.

Activating the applicator:

- Remove applicator from package; do not touch sponge.
  For 26 mL Applicator:
- With sponge face parallel to the floor, press the cap end of the applicator. Solution will begin to flow into the sponge.
- Wait for fluid level to reach indicator line of applicator barrel.
  For 10.5 mL Applicator:
- Grasp product by wrapping hand and fingers around the labeled portion of the applicator. Place thumb on the lever.
- With sponge face parallel to the floor, snap lever. Allow all fluid to flow into sponge.

When applying solution:

- Completely wet the treatment area with antiseptic.
- Dry surgical sites (e.g., abdomen or arm): Use repeated back-and-forth strokes for 30 seconds.
- Moist surgical sites (e.g., inguinal fold): Use repeated back-and-forth strokes for 2 minutes.
- Maximal treatment area for one 26- mL applicator is approximately 19.5 in x 19.5 in.
- Maximal treatment area for one 10.5- mL applicator is approximately 13 in. x 13 in.

Reviewer's comment: *The Sponsor will need to remove the hyphen in "26 mL" and "10.5 mL".*

Agency's Recommendation (IR: July 30, 2018):
Remove the hyphen in "26 mL" and "10.5 ml".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the hyphen in "26 mL" and "10.5 mL". These changes are acceptable.*

- Do not allow solution to pool; tuck prep towels to absorb solution, and then remove.
- Clean umbilicus with enclosed swabs when applicable. (Moisten swabs by pressing against solution-soaked sponge applicator.) (26- mL applicator only).

Reviewer's comment: *The Sponsor will need to remove the hyphen in "26 mL".*

Agency's Recommendation (IR: July 30, 2018):
Remove the hyphen in "26 mL".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the hyphen in "26 mL". This change is acceptable.*

- Avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry.
- When prepping skin folds, toes, or fingers, use a sterile-gloved hand to hold skin apart until completely dry. Otherwise, skin may adhere to itself.

After applying solution:
- To reduce the risk of fire, wait until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair.

While waiting for solution to completely dry:
- Do not drape or use ignition source (e.g., cautery, laser).

Reviewer's comment: *The Sponsor will need to include a period in the bulleted statement.*

Agency's Recommendation (IR: July 30, 2018):
Include a period in the bulleted statement.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has included a period in the bulleted statement. This change is acceptable.*

- Check for pooled solution. Use sterile gauze to soak up pooled solution. Do not blot because it may remove solution from skin.
- Remove wet materials from prep area. Replace if necessary.

After solution is completely dry:
- To reduce risk of fire, begin draping and/or using cautery only after solution is completely dry and all wet materials are removed.
- If incise drapes are used, apply directly to dry prep.
- Apply dressing following standard practices.

Other information for product with tint:
- The tint will slowly fade from the skin over time postoperatively. Alcohol may be used to remove the tint if desired.

3 Dosage Forms and Strengths
Antiseptic solution for topical delivery.

Active ingredients:
Chlorhexidine gluconate (CHG) 2% w/v
Isopropyl alcohol (IPA) 70% v/v

Reviewer's comment: *This is acceptable.*

4 Contraindications

Do not use:

- on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product.
- for lumbar puncture or in contact with the meninges.
- on open skin wounds or as a general skin cleanser.

Reviewer's comment: *The Sponsor will need to include a period after each bulleted statement.*

Agency's Recommendation (IR: July 30, 2018):

Include a period after each bulleted statement.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has included a period in the three bulleted statements. These changes are acceptable.*

5 Warnings and Precautions

FOR EXTERNAL USE ONLY. FLAMMABLE, KEEP AWAY FROM FIRE OR FLAME.

~~For external use only.~~

Flammable, keep away from fire or flame.

Reviewer's comment: *The Sponsor will need to capitalize the statements so that it is prominent to the user.*

Agency's Recommendation (IR: July 30, 2018):

Capitalize the statements so that it is prominent to the user.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has capitalized the statements. These changes are acceptable.*

To reduce risk of fire; PREP CAREFULLY:

- Do not use 26-mL applicator for head and neck surgery.

Reviewer's comment: *The Sponsor will need to remove the hyphen in "26 mL".*

Agency's Recommendation (IR: July 30, 2018):

Remove the hyphen in "26 mL".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the hyphen in "26 mL". This change is acceptable.*

- Do not use on an area smaller than 13 in. x 13 in. Use a smaller applicator instead. (b) (4)

Reviewer's comment: *The Sponsor will need to remove the statement* (b) (4) *the meaning is confusing.*

Agency's Recommendation (IR: July 30, 2018):
Remove the statement (b) (4) the meaning is confusing.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the statement* (b) (4) *This change is acceptable.*

- Solution contains alcohol and gives off flammable vapors.
- Avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry.
- Do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair).
- Do not allow solution to pool.
- Remove wet materials from prep area.

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 doctor.
- Use with care in premature infants or infants under 2 months of age. These products may cause irritation and chemical burns. See Clinical Pharmacology section 12 regarding possible cutaneous absorption.

Reviewer's comments: *The Sponsor will need to include the statement "See Clinical Pharmacology section 12 regarding possible cutaneous absorption." This was recommended by Medical Officer Reviewer Dr. Teresa Podruchny.*

Agency's Recommendation (IR: July 30, 2018):
Include the statement "See Clinical Pharmacology section 12 regarding possible cutaneous absorption." The bulleted statement should be revised to read: "Use with care in premature infants or infants under 2 months of age. These products may cause irritation and chemical burns. See Clinical Pharmacology section 12 regarding possible cutaneous absorption."

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised the statement to read: "Use with care in premature infants or infants under 2 months of age. These products may cause irritation and chemical burns. See Clinical Pharmacology section 12 regarding possible cutaneous absorption." This change is acceptable.*

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.

6 Adverse Reactions

Exclusion criteria in trials included known hypersensitivity. Adverse events reported in the development program were typically related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. A total of (b) (4) subjects received at least one treatment (b) (4) pivotal studies (one pivotal study was discontinued early due to technical and quality issues), the persistence study, the ~~2~~two

coverage area and dry time studies, the ~~2~~two drape adhesion clinical studies and the ~~3~~three safety challenge studies [redacted]). All adverse results resolved [redacted]

Reviewer's comments: *The Sponsor will need to include the statement "Exclusion criteria in trials included known hypersensitivity." Revise the number [redacted]. Include the statement "(One pivotal study was discontinued early due to technical and quality issues)". Revise the number "2" and "3" to the word "two" and "three". This was recommended by Medical Officer Reviewer Dr. Teresa Podruchny.*

Agency's Recommendation (IR: July 30, 2018):

Include the statement "Exclusion criteria in trials included known hypersensitivity." Revise the number [redacted]. Include the statement "(One pivotal study was discontinued early due to technical and quality issues)". Revise the number "2" and "3" to the word "two" and "three". The paragraph should be revised to read: "Exclusion criteria in trials included known hypersensitivity. Adverse events reported in the development program were typically related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. A total of [redacted] subjects received at least one treatment for [redacted] pivotal studies (one pivotal study was discontinued early due to technical and quality issues), the persistence study, the two coverage area and dry time studies, the two drape adhesion clinical studies and the three safety challenge studies [redacted]. All adverse results resolved [redacted]

Please note that the [redacted] and the skin irritation assessment are still currently under review. We will provide you an update.

Reviewer's comments: *Medical Officer Reviewer Dr. Teresa Podruchny has additional edits to convey to the Sponsor. The Sponsor will need to relocate the statement "Exclusion criteria in trials included known hypersensitivity" to come after the statement "…safety challenge studies…" Relocate the statement "Adverse events reported in the development program were typically related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product." to come after the statement "Thirty-one (31) AEs (2%) were reported." Revise the statement "A total of [redacted] subjects received at least one treatment [redacted] pivotal studies (one pivotal study was discontinued early due to technical and quality issues), the persistence study, the two coverage area and dry time studies, the two drape adhesion clinical studies and the three safety challenge studies [redacted] to read: "A total of 1544 subjects received at least one treatment in the studies supporting approval: pivotal studies (one of the studies, a study of 169 subjects, was discontinued early due to technical and quality issues), the persistence study, the two coverage area and dry time studies, the two drape adhesion clinical studies and the three safety challenge studies." Include the statement "Nine moderate adverse events occurred in studies designed to evaluate safety in more under exaggerated conditions (see Section 14, Human Safety Studies). Seven discontinuations occurred secondary to adverse events in the Human Safety Studies. A few [Sponsor to fill in #] adverse events required treatment." to come after the statement "Adverse events reported in the development program were typically related to the skin, mild to moderate in severity*

and similar to typical adverse events associated with this type of product." Revise the statement "All adverse results resolved (b) (4) *." to read "All adverse results resolved or stabilized."*

Agency's Recommendation (IR: July 31, 2018):

Revise the Adverse Reaction section to read: A total of 1544 subjects received at least one treatment in the studies supporting approval: pivotal studies (one of the studies, a study of 169 subjects, was discontinued early due to technical and quality issues), the persistence study, the toe coverage area and dry time studies, the two drape adhesion clinical studies and the three safety challenge studies. Exclusion criteria in trials included known hypersensitivity. Thirty-one (31) AEs (2%) were reported. Adverse events reported in the development program were typically related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. Nine moderate adverse events occurred in studies designed to evaluate safety in more under exaggerated conditions (see Section 14, Human Safety Studies). Seven discontinuations occurred secondary to adverse events in the Human Safety Studies. A few [Sponsor to fill in #] adverse events required treatment. All adverse results resolved or stabilized.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised this section to read: "A total of 1544 subjects received at least one treatment in the studies supporting approval: pivotal studies (one of the studies, a study of 169 subjects, was discontinued early due to technical and quality issues), the persistence study, the toe coverage area and dry time studies, the two drape adhesion clinical studies and the three safety challenge studies. Exclusion criteria in trials included known hypersensitivity. Thirty-one (31) AEs (2%) were reported. Adverse events reported in the development program were typically related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. Nine moderate adverse events occurred in studies designed to evaluate safety in more under exaggerated conditions (see Section 14, Human Safety Studies). Seven discontinuations occurred secondary to adverse events in the Human Safety Studies. A few (12) adverse events required treatment. All adverse results resolved or stabilized." These changes are acceptable.*

Skin irritation scores of 0 to 3 for categories of erythema, edema, rash and dryness were collected for many of the clinical studies. A skin irritation rating of 3 represented significant irritation and qualified as an adverse event. There was no skin irritation rating of 3 in any clinical study. Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product.

Reviewer's comments: *The Sponsor will need to include the statement "Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product." This was recommended by Medical Officer Reviewer Dr. Teresa Podruchny.*

Agency's Recommendation (IR: July 31, 2018):

Include the sentence at the end of the paragraph: "Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product."

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has included the statement "Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product." This change is acceptable.*

7 Drug Interactions

Not applicable.

8 Use in Specific Populations

Pediatric Use:
Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns or be detectable in the blood of infants, (b) (4) See section 12.

Reviewer's comments: *The Sponsor will need to include the statement "or be detectable in the blood of infants,* (b) (4) *See section 12." This was recommended by Medical Officer Reviewer Dr. Teresa Podruchny.*

Agency's Recommendation (IR: July 30, 2018):
Include the statement "or be detectable in the blood of infants, (b) (4) See section 12." The paragraph should be revised to read: "Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns or be detectable in the blood of infants, (b) (4) See section 12."

Reviewer's comments: *Medical Officer Reviewer Dr. Teresa Podruchny had additional revisions to this section. She requested that the Sponsor delete the statement "…* (b) (4)

Agency's Recommendation (IR: July 31, 2018):
Revise the Use in Specific Populations section to read: "Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns or be detectable in the blood of infants. See section 12."

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised this section to read: "Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns or be detectable in the blood of infants. See section 12." These changes are acceptable.*

9 Drug Abuse and Dependence

Not applicable.

10 Overdosage

Not applicable.

11 Description

3M™ SoluPrep™ Film-Forming Sterile Surgical Solution is an antimicrobial skin preparation containing ~~2~~two active ingredients, 2% weight/volume (w/v) Chlorhexidine gluconate (CHG) and 70% volume/volume (v/v) Isopropyl alcohol (IPA), in combination with an acetyltri-n-butyl citrate, acrylate copolymer and purified water. The tinted solution also contains FD&C Blue #1 and FD&C Yellow #5.

Reviewer's comment: *The Sponsor will need to replace the number "2" with the word "two".*

Agency's Recommendation (IR: July 30, 2018):
Replace the number "2" with the word "two".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has replaced the number "2" with the word "two." This change is acceptable.*

3M™ SoluPrep™ Surgical Solution provides (b) (4) fast acting, broad-spectrum antimicrobial activity, and persistence up to (b) (4) 6-hours post-prep.

Reviewer's comment: *The Sponsor will need to revise the word (b) (4) to read: "fast" and revise the "(b) (4) hours" to read: "6 hours".*

Agency's Recommendation (IR: July 30, 2018):
Revise the word (b) (4) to read: "fast". Revise the "(b) (4) hours" to read: "6 hours".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised the word (b) (4) to read: "fast" and revised the "(b) (4) hours" to read "6 hours". These changes are acceptable.*

3M™ SoluPrep™ Surgical Solution is a film-forming, sterile patient preoperative skin preparation. Each 7130 unit dose applicator contains 0.9 fl oz (26 mL) of solution which covers 19.5 in x 19.5 in area (approximately from shoulder to groin in an average full size adult).

For procedures requiring less coverage, a smaller applicator is available (7133-Tinted or 7134-Clear). The smaller applicator size contains 0.36 fl oz (10.5 mL) of solution which covers an approximate 13 in. x 13 in. area.

12 Clinical Pharmacology

Chlorhexidine is a cationic biguanide that exhibits broad-spectrum antimicrobial activity, which is thought to be related to its ability to disrupt cell membranes of bacterial cells. Isopropyl alcohol is a secondary aliphatic alcohol that, at the proposed concentration of 70%, also exhibits antiseptic properties, most likely resulting from protein denaturation.

(b) (4)

~~n~~No clinical pharmacokinetic or pharmacodynamic studies ~~were~~ have been conducted with the drug product formulation.

It is generally recognized that chlorhexidine is not or is only minimally absorbed through mature intact adult skin. Literature publications, generally of small numbers of subjects and generally of neonates, have demonstrated detectable CHG blood levels after topical exposure to CHG containing products for either bathing or catheter antisepsis[1,2,3,4]. The clinical significance is not known.

(b) (4)

The systemic absorption of chlorhexidine after topical application of 3M CHG/IPA Prep was evaluated following a single application to 24 female and male adult subjects. Plasma concentrations of chlorhexidine were all below the level of quantitation (<1 ng/mL) following a topical application of four 26 mL 3M CHG/IPA Prep applicators to approximately 1550 in^2 (10,000 cm^2) surface area of intact skin.

The systemic absorption of isopropyl alcohol after topical application of 3M CHG/IPA Prep was not studied. Isopropyl alcohol is slightly absorbed approximately 1% of the amount applied to the intact skin. In a published study, a different product containing 49.8% (w/w) isopropyl alcohol was applied to subjects aged 1 month to 23 years for a preoperative skin preparation resulting in detectable blood concentration of isopropyl alcohol ranging from 0.83 to 12.25 mg/L 1 hour after application.

> ***Reviewer's comments:*** *The Sponsor will need to revise this section accordingly. The first paragraph was included by Pharmacologist-Toxicologist Reviewer Dr. Charles Thompson. He also revised the first sentence and recommended removing the last three sentences. Medical Officer Reviewer Dr. Teresa Podruchny has included the statement "…adult skin. Literature publications, generally of small numbers of subjects and generally of neonates, demonstrated detectable CHG blood levels after topical exposure to CHG containing products for either bathing or catheter antisepsis. The clinical significance is not known." Clinical Pharmacologist Reviewer Dr. Sojeong Yi has included the last two paragraphs.*

Agency's Recommendation (IR: July 30, 2018):

Revise this section accordingly. This section should be revised to read:

Chlorhexidine is a cationic biguanide that exhibits broad-spectrum antimicrobial activity, which is thought to be related to its ability to disrupt cell membranes of bacterial cells. Isopropyl alcohol is a secondary aliphatic alcohol that, at the proposed concentration of 70%, also exhibits antiseptic properties, most likely resulting from protein denaturation.

No clinical pharmacokinetic or pharmacodynamic studies have been conducted with the drug product formulation.

It is generally recognized that chlorhexidine is not or is only minimally absorbed through mature intact adult skin. Literature publications, generally of small numbers of subjects and generally of neonates, have demonstrated detectable CHG blood levels after topical exposure to CHG containing products for either bathing or catheter antisepsis[1,2,3,4]. The clinical significance is not known.

The systemic absorption of chlorhexidine after topical application of 3M CHG/IPA Prep was evaluated following a single application to 24 female and male adult subjects. Plasma concentrations of chlorhexidine were all below the level of quantitation (<1 ng/mL) following a topical application of four 26 mL 3M CHG/IPA Prep applicators to approximately 1550 in^2 (10,000 cm^2) surface area of intact skin.

The systemic absorption of isopropyl alcohol after topical application of 3M CHG/IPA Prep was not studied. Isopropyl alcohol is slightly absorbed, approximately 1% of the amount applied to the intact skin. In a published study[5], a different product containing 49.8% (w/w) isopropyl alcohol was applied to subjects aged 1 month to 23 years for a preoperative skin preparation resulting in detectable blood concentration of isopropyl alcohol ranging from 0.83 to 12.25 mg/L 1 hour after application.

> ***Reviewer's comments:*** *In accordance with the Agency's request, the Sponsor has revised this section to read: "Chlorhexidine is a cationic biguanide that exhibits broad-spectrum antimicrobial activity, which is thought to be related to its ability to disrupt cell membranes of bacterial cells. Isopropyl alcohol is a secondary aliphatic alcohol that, at the proposed concentration of 70%, also exhibits antiseptic properties, most likely resulting from protein denaturation.*
>
> *No clinical pharmacokinetic or pharmacodynamic studies have been conducted with the drug product formulation.*
>
> *It is generally recognized that chlorhexidine is not or is only minimally absorbed through mature intact adult skin. Literature publications, generally of small numbers of subjects and generally of neonates, have demonstrated detectable CHG blood levels after topical exposure to CHG containing products for either bathing or catheter antisepsis[1,2,3,4]. The clinical significance is not known.*
>
> *The systemic absorption of chlorhexidine after topical application of 3M CHG/IPA Prep was evaluated following a single application to 24 female and male adult subjects. Plasma concentrations of chlorhexidine were all below the level of quantitation (<1 ng/mL) following a topical application of four 26 mL 3M CHG/IPA Prep applicators to approximately 1550 in^2 (10,000 cm^2) surface area of intact skin.*
>
> *The systemic absorption of isopropyl alcohol after topical application of 3M CHG/IPA Prep was not studied. Isopropyl alcohol is slightly absorbed, approximately 1% of the amount applied to the intact skin. In a published study[5], a different product containing 49.8% (w/w) isopropyl alcohol was applied to subjects aged 1 month to 23 years for a preoperative skin preparation resulting in detectable blood concentration of isopropyl alcohol ranging from 0.83 to 12.25 mg/L 1 hour after application." These changes are acceptable.*

13 Nonclinical Toxicology

Chlorhexidine gluconate and isopropyl alcohol both have long histories of (b) (4) use (b) (4)

No studies addressing the mutagenicity, carcinogenicity, or development/ reproductive toxicity of the drug product formulation or its active ingredients were conducted in support of marketing of this drug product.

(b) (4)

Reviewer's comments: *The Sponsor will need to revise this section accordingly. This section was revised by Pharmacologist-Toxicologist Reviewer Dr. Charles Thompson. This section will only have the following statements: "Chlorhexidine gluconate and isopropyl alcohol both have long histories of use. No studies addressing the mutagenicity, carcinogenicity, or development/ reproductive toxicity of the drug product formulation or its active ingredients were conducted in support of marketing of this drug product."*

Agency's Recommendation (IR: July 30, 2018):
Revise this section accordingly. This section should be revised to read: "Chlorhexidine gluconate and isopropyl alcohol both have long histories of use. No studies addressing the mutagenicity, carcinogenicity, or development/reproductive toxicity of the drug product formulation or its active ingredients were conducted in support of marketing of this drug product."

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised this section to read: "Chlorhexidine gluconate and isopropyl alcohol both have long histories of use. No studies addressing the mutagenicity, carcinogenicity, or development/reproductive toxicity of the drug product formulation or its active ingredients were conducted in support of marketing of this drug product." These changes are acceptable.*

14 Clinical Studies

Pivotal Studies:
Three pivotal studies were conducted to evaluate the safety and antimicrobial efficacy of 3M CHG/IPA Prep on the abdominal and inguinal regions. One of these studies was discontinued prematurely due to technical and data quality issues (b) (4) efficacy data were not (b) (4) ted.

Reviewer's comment: *The Sponsor will need to remove the word (b) (4) " and revise the word " (b) (4) " to read: "evaluated".*

Agency's Recommendation (IR: July 30, 2018):
Remove the word (b) (4) and revise the word (b) (4) to read: "evaluated".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the word (b) (4) and revised the word (b) (4) to read: "evaluated". These changes are acceptable.*

In the pivotal randomized, third-party blind studies, efficacy was assessed from analyses of bacterial counts of cultures obtained from test sites on the abdominal and inguinal regions. The results from two pivotal studies are summarized in the table below.

Study 1

	3M CHG/IPA Prep, 10.5 mL, tinted	3M CHG/IPA Prep, 26 mL, tinted	Saline
Abdominal Region			
N	205	201	62
Responder rate*, % (95% CI)	81.5 (76.1, 86.8)	87.1 (82.4, 91.7)	0
Bacterial Count Reduction	2.66	2.74	0.64

Mean (SD)**	(0.71)	(0.64)	(0.49)
Difference in Mean Compared to Saline***	1.96 (1.8, 2.12)	2.07 (1.91, 2.23)	
Inguinal Region			
N	204	203	59
Responder rate*, % (95% CI)	82.4 (77.1, 87.6)	79.8 (74.3, 85.3)	6.8 (0.4, 13.2)
Bacterial Count Reduction Mean (SD)**	3.98 (1.03)	3.89 (0.93)	1.34 (1.10)
Difference in Mean Compared to Saline***	2.64 (2.35, 2.93)	2.55 (2.27, 2.94)	

*Responder defined as a subject with 2-$\log_{10}/cm^2$ (abdominal region) and 3-$\log_{10}/cm^2$ (inguinal region) bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours
** $\log_{10}/cm^2$ scale
*** This is the average treatment effect of test drug compared to saline. It is estimated from a linear regression of final bacterial count on treatment and baseline bacterial count

Study 2

	3M CHG/IPA Prep, 10.5 mL, clear	3M CHG/IPA Prep,10.5 mL with HEDTA	Saline
Abdominal Region			
N	196	202	59
Responder rate*, % (95% CI)	81.1 (75.6, 86.6)	81.7 (76.3, 87.0)	8.5 NA
Bacterial Count Reduction Mean (SD)**	2.78 (0.94)	2.73 (1.00)	0.76 (0.81)
Difference in Mean Compared to Saline***	1.99 (1.73, 2.26)	2.03 (1.76,2.29)	
Inguinal Region			

N	208	209	61
Responder rate*, % (95% CI)	38.9 (32.3, 45.6)	46.9 (40.1, 53.7)	1.6 (NA)
Bacterial Count Reduction Mean (SD)**	2.84 (1.19)	2.99 (1.13)	1.01 (0.67)
Difference in Mean Compared to Saline***	1.9 (1.59, 2.2)	1.72 (1.42, 2.03)	

*Responder defined as a subject with 2-$\log_{10}/cm^2$ (abdominal region) and 3-$\log_{10}/cm^2$ (inguinal region) bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours
** $\log_{10}/cm^2$ scale
*** This is the average treatment effect of test drug compared to saline. It is estimated from a linear regression of final bacterial count on treatment and baseline bacterial count

(b) (4)

[redacted]

Reviewer's comments: *The Statistician Reviewer Dr. Joo-Yeon Lee has revised the written text to be in form of an easy to read table. She has included the statistical results to include results using the success rate (responder rate) of the test product be significantly higher than 70 percent. She has also included FDA's updated analysis (82 FR 60474; December 20, 2017) to assess whether the average treatment effects across subjects meet indication-specific conditions of superiority and non-inferiority.*

Agency's Recommendation (IR: July 30, 2018):

Revise the written text to be in form of an easy to read table. We have included the statistical results to include results using the success rate (responder rate) of the test product being significantly higher than 70 percent. We have also included FDA's updated analysis (82 FR 60474; December 20, 2017) to assess whether the average treatment effects across subjects meet indication-specific conditions of superiority and non-inferiority.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised the written text to be in form of an easy to read table. These changes are acceptable.*

In the two pivotal studies to support safety and efficacy, no adverse events were reported in one study. In the other study, (b) (4) AEs reported were related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. All AEs resolved without sequelae.

Reviewer's comments: *The Medical Officer Reviewer Teresa Podruchny has provided edits to the adverse events for the clinical simulation studies. She requested that the Sponsor included the statement "In the two pivotal studies to support safety and efficacy, no adverse events were reported in one study. In the other study," and removed the statements* (b) (4)

Agency's Recommendation (IR: July 30, 2018):

Revise this section accordingly. This paragraph should be revised to read: "In the two pivotal studies to support safety and efficacy, no adverse events were reported in one study. In the other study, (b) (4) AEs reported were related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. All AEs resolved without sequelae."

Reviewer's comments: *The Medical Officer Reviewer Teresa Podruchny has provided additional edits to this paragraph. She requested that the Sponsor remove the word* (b) (4) *after the deleted statement* (b) (4) *. She also requested that the Sponsor included the statement "…though [Sponsor to populate] subjects required treatment."*

Agency's Recommendation (IR: July 31, 2018):

Revise this section accordingly. This paragraph should be revised to read: "In the two pivotal studies to support safety and efficacy, no adverse events were reported in one study. In the other study, AEs reported were related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. All AEs resolved without sequelae though [Sponsor to populate] subjects required treatment."

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised this paragraph to read: "In the two pivotal studies to support safety and efficacy, no adverse events were reported in one study. In the other study, (b) (4) AEs reported were related to the skin, mild to moderate in severity and similar to typical adverse events associated with this type of product. All AEs resolved without sequelae though one subject required treatment." These changes are acceptable.*

Skin irritation scores for 0 to 3 for categories of erythema, edema, rash and dryness were collected prior to collection of the baseline, 10-minute and 6-hour post prep samples for the 3 pivotal studies. A skin irritation rating of 3 represented significant irritation and qualified as an adverse event. There was no skin irritation rating of 3 in any of the pivotal studies. Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product.

Reviewer's comment: *The Medical Officer Reviewer Teresa Podruchny has requested that the Sponsor to include the statement "Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product."*

Agency's Recommendation (IR: July 30, 2018):

Included the statement "Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product." The paragraph should be revised to read:

Skin irritation scores for 0 to 3 for categories of erythema, edema, rash and dryness were collected prior to collection of the baseline, 10-minute and 6-hour post prep samples for the three pivotal studies. A skin irritation rating of 3 represented significant irritation and qualified as an adverse event. There was no skin irritation rating of 3 in any of the pivotal studies. Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised the statement to read: "Skin irritation scores for 0 to 3 for categories of erythema, edema, rash and dryness were collected prior to collection of the baseline, 10-minute and 6-hour post prep samples for the three pivotal studies. A skin irritation rating of 3 represented significant irritation and qualified as an adverse event. There was no skin irritation rating of 3 in any of the pivotal studies. Under wet conditions in one of the studies of drape adhesion, moderate reactions of erythema were seen with all surgical preparations including this NDA product." This is change acceptable.*

(b) (4)

[redacted]

Reviewer's comments: *The Sponsor provided a persistence efficacy study entitled "Assessment of the Persistent Antimicrobial Efficacy of 3M CHG/IPA Film-Forming Preoperative Skin Preparation against Resident Human Skin Flora on the Abdominal and Inguinal Regions." The study was to evaluate the antimicrobial*

persistence of 3M CHG/IPA with HEDTA on the abdomen and groin at 48 hours and 72 hours post treatment. In order to demonstrate persistence for a patient preoperative skin preparation claim, FDA requires that the level of resident microorganisms remain below baseline for the 6-hour time point. We have been advising sponsors if it wishes to obtain a claim with an associated time-frame greater than 6 hours, then it is necessary to show clinical benefit with clinically meaningful outcomes, not just log reductions. Therefore, the persistence efficacy study the Sponsor submitted in the submission was not reviewed. This was also noted in a memorandum to the IND file dated May 26, 2015 in DARRTS. The Sponsor will need to remove this section from the TPI.

Agency's Recommendation (IR: July 30, 2018):
In order to demonstrate persistence for a patient preoperative skin preparation claim, FDA requires that the level of resident microorganisms remain below baseline for the 6-hour time point. We have been advising sponsors that, if they wish to obtain a claim with an associated time-frame greater than 6 hours, then it is necessary to show clinical benefit with clinically meaningful outcomes, not just log reductions. Therefore, the persistence efficacy study you submitted in the submission was not reviewed. You will need to remove this section from the TPI.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed this section from the TPI. This is acceptable.*

Coverage Area and Dry Time Studies:
Two open-label clinical studies, one using the tinted 3M CHG/IPA Prep 10.5-mL applicator and the other using the tinted 3M CHG/IPA Prep 26-mL applicator, evaluated the treatment area coverage, dry time, IPA vapor dissipation (in the 3M CHG/IPA Prep 26-mL applicator study only), ease of removability, and safety of tinted 3M CHG/IPA Prep when applied to areas of the back, arms and legs of healthy subjects. Each study included 16 – 20 subjects.

Reviewer's comment: *The Medical Officer Reviewer Teresa Podruchny has included the statement "Each study included 16 – 20 subjects."*

Agency's Recommendation (IR: July 30, 2018):
Include the statement "Each study included 16 – 20 subjects."

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has included the statement "Each study included 16 – 20 subjects." at the end of the paragraph. This change is acceptable.*

For both applicators sizes, the mean coverage per gram of product was similar, approximately 50 in^2/g. The mean dry time for both applicator sizes was under 2 minutes. Removability of 3M CHG/IPA Prep was considered moderate for 25 (73.5%) subjects and difficult for 9 (26.5%) subjects.

- The mean coverage area with the 26- mL applicator was 387.5 (31.96) in^2 or 2499.8 (206.2) cm^2. The mean dry time was 1.54 (0.79) minutes.
- The mean (SD) coverage area with the 10.5- mL applicator was 178.8 (16.8) in^2 or 1153.7 (108.7) cm^2. The mean (SD) dry time was 1.80 (0.48) minutes.

Collection of IPA vapor in the 3M CHG/IPA Prep 26 mL study yielded a mean maximum alcohol concentration of 18.6 ppm; all individual values were well below the lower flammability limit (LFL) of 23,000 ppm.

(b) (4)

Reviewer's comments: *The Medical Officer Reviewer Teresa Podruchny requested that the Sponsor delete the statement* (b) (4)

Agency's Recommendation (IR: July 30, 2018):
Revise the section according to the edits. Remove the last statement (b) (4)

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the statements "* (b) (4) *" These changes are acceptable.*

A laboratory study was performed to determine the dry time of 3M CHG/IPA Prep (from 10.5- mL) and 26- mL applicators) on human hair (using mannequins), as well as vapor dissipation values and ignition potential. Twelve human hair mannequins were used in this study that was performed under surgical suite conditions.

The mean weight of prep delivered was:
- 2.95 g for the 10.5- mL applicator
- 9.16 g for the 26- mL applicator

The mean dry time of prep was:
- 29.17 minutes for the 10.5- mL applicator
- 40.83 minutes for the 26- mL applicator

Collection of IPA vapor yielded a mean maximum IPA concentration of:
- 1097.8 ppm for the 10.5- mL applicator
- 4117.3 ppm for the 26- mL applicator

Reviewer's comment: *The Sponsor will need to remove the hyphen in "26 mL" and "10.5 mL".*

Agency's Recommendation (IR: July 30, 2018):
Remove the hyphen in "26 mL" and "10.5 ml".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the hyphen in "26 mL" and "10.5 mL". These changes are acceptable.*

All individual maximum values for both applicator size was well below the LFL of 23,000 ppm.

For each applicator size, a mannequin head with dried prep was tested for ignition capability; on each of these heads, the hair did not ignite with multiple attempts using a sparking device.

(b) (4)

Reviewer's comment: *The Medical Officer Reviewer Teresa Podruchny requested that the Sponsor remove the Drape Adhesion studies from the TPI because this was not a required study and the safety information is already reported in other sections of the TPI.*

Agency's Recommendation (IR: July 30, 2018):
Remove the Drape Adhesion studies from the TPI because this was not a required study and the safety information is already reported in other sections of the TPI.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the Drape Adhesion studies section from the TPI. This change is acceptable.*

In vitro studies:
Two in vitro studies using a modified time-kill procedure were conducted to examine microbial activity with and without the presence of serum, and ~~1~~ one in vitro study was conducted to examine the potential of antimicrobial resistance.

Reviewer's comment: *The Sponsor will need to revise the number "1" to read the word "one".*

Agency's Recommendation (IR: July 30, 2018):
Revise the number "1" to read: the word "one".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has revised the number "1" to read: the word "one". This change is acceptable.*

In the first **time-kill study** (Table 1), both tinted and colorless 3M CHG/IPA Prep products (at full strength and at 50% strength) showed >5 $\log_{10}$ reductions at both the 3-minute and 5-minute time points for all microorganisms tested, thus meeting the efficacy criterion of a 3 $\log_{10}$ or greater reduction required by the FDA.

In the second **time-kill study** (Table 2), **in the presence of a serum challenge**, both tinted and colorless 3M CHG/IPA Prep products showed >5 $\log_{10}$ reductions at both the 3-minute and 5-minute timepoints for all microorganisms tested, again meeting the efficacy criterion of a 3 $\log_{10}$ or greater reduction.

The development of antimicrobial resistance study (Table 3) was designed to detect the potential for development of resistance to the test product (tinted 3M CHG/IPA Prep) and a control product (2% aqueous CHG) by the sequential passage of several clinically relevant microorganisms (42 isolates) through increasing concentrations of the antimicrobial included in the culture media. If the microorganisms were able to acclimate to at least a 4-fold increase in the initial MIC of the test product or control product and maintain that increase after 3 serial passages on media that did not contain the antimicrobial, resistance to the product was to have been established. The MIC did not increase for any of the strains evaluated for emergence of resistance; therefore, tinted 3M CHG/IPA Prep and the control 2% aqueous CHG were not considered to have the potential for the development of resistance. In addition, an evaluation of the potential for antibiotic cross-resistance was done by comparing the MICs of several antibiotics before and after extended exposure to sublethal levels of each antiseptic. There was no indication of a change in MIC related to cross-resistance observed for any of the organism/antibiotic combinations tested.

Note: The clinical significance of in vitro data is unknown.

Table 1. Microbial Kill for 3M CHG/IPA Prep Solution (b) (4)

Full-strength Test Product and Active Control Product Average Bacterial Counts and Reductions at Specific Contact Times

Microorganism	Contact Time	3M CHG/IPA Prep, Tint			3M CHG/IPA Prep, Colorless		
		Average CFU/mL	Percent Reduction	Log Reduction	Average CFU/mL	Percent Reduction	Log Reduction
Burkholderia cepacia	3 min	1.0E+01	99.99986	5.87	1.0E+01	99.99986	5.87
	5 min	1.0E+01	99.99984	5.84	1.0E+01	99.99984	5.84
Drug-resistant *Burkholderia cepacia*	3 min	1.0E+01	99.99978	5.67	1.0E+01	99.99978	5.67
	5 min	1.0E+01	99.99981	5.74	1.0E+01	99.99981	5.74
Candida albicans	3 min	1.0E+01	99.99978	5.75	1.0E+01	99.99978	5.75
	5 min	1.0E+01	99.99977	5.75	1.0E+01	99.99977	5.75
Drug-resistant *Candida*	3 min	1.0E+01	99.99941	5.27	1.0E+01	99.99941	5.27
	5 min	1.0E+01	99.99938	5.25	1.0E+01	99.99938	5.25

albicans							
Enterococcus faecalis	3 min	1.0E+01	99.99980	5.70	1.0E+01	99.99980	5.70
	5 min	1.0E+01	99.99979	5.69	1.0E+01	99.99979	5.69
Drug-resistant *Enterococcus faecalis*	3 min	1.0E+01	99.99974	5.70	1.0E+01	99.99974	5.70
	5 min	1.0E+01	99.99976	5.73	1.0E+01	99.99976	5.73
Enterococcus faecium	3 min	1.0E+01	99.99983	5.83	1.0E+01	99.99983	5.83
	5 min	1.0E+01	99.99982	5.82	1.0E+01	99.99982	5.82
Drug-resistant *Enterococcus faecium*	3 min	1.0E+01	99.99976	5.68	1.0E+01	99.99976	5.68
	5 min	1.0E+01	99.99973	5.65	1.0E+01	99.99973	5.65
Escherichia coli	3 min	1.0E+01	3M 99.99984	5.93	1.0E+01	99.99984	5.93
	5 min	1.0E+01	99.99984	5.93	1.0E+01	99.99984	5.93
Drug-resistant *Escherichia coli*	3 min	1.0E+01	99.99974	5.64	1.0E+01	99.99974	5.64
	5 min	1.0E+01	99.99975	5.67	1.0E+01	99.99975	5.67
Klebsiella pneumoniae	3 min	1.0E+01	99.99983	5.84	1.0E+01	99.99983	5.84
	5 min	1.0E+01	99.99978	5.78	1.0E+01	99.99978	5.78
Drug-resistant *Klebsiella pneumoniae*	3 min	1.0E+01	99.99983	5.78	1.0E+01	99.99983	5.78
	5 min	1.0E+01	99.99983	5.78	1.0E+01	99.99983	5.78
Pseudomonas aeruginosa	3 min	1.0E+01	99.99978	5.81	1.0E+01	99.99978	5.81
	5 min	1.0E+01	99.99977	5.79	1.0E+01	99.99977	5.79
Drug-resistant *Pseudomonas aeruginosa*	3 min	1.0E+01	99.99987	5.92	1.0E+01	99.99987	5.92
	5 min	1.0E+01	99.99987	5.92	1.0E+01	99.99987	5.92
Serratia marcescens	3 min	1.0E+01	99.99969	5.69	1.0E+01	99.99969	5.69
	5 min	1.0E+01	99.99971	5.69	1.0E+01	99.99971	5.69
Drug-resistant *Serratia marcescens*	3 min	1.0E+01	99.99977	5.73	1.0E+01	99.99977	5.73
	5 min	1.0E+01	99.99978	5.75	1.0E+01	99.99978	5.75

Staphylococcus aureus	3 min	1.0E+01	99.99974	5.59	1.0E+01	99.99974	5.59
	5 min	1.0E+01	99.99974	5.58	1.0E+01	99.99974	5.58
Drug-resistant *Staphylococcus aureus*	3 min	1.0E+01	99.99973	5.59	1.0E+01	99.99973	5.59
	5 min	1.0E+01	99.99974	5.62	1.0E+01	99.99974	5.62
Staphylococcus epidermidis	3 min	1.0E+01	99.99988	5.97	1.0E+01	99.99988	5.97
	5 min	1.0E+01	99.99988	5.96	1.0E+01	99.99988	5.96
Drug-resistant *Staphylococcus epidermidis*	3 min	1.0E+01	99.99980	5.73	1.0E+01	99.99980	5.73
	5 min	1.0E+01	99.99978	5.67	1.0E+01	99.99978	5.67
Streptococcus pneumoniae	3 min	1.0E+01	99.99944	5.30	1.0E+01	99.99944	5.30
	5 min	1.0E+01	99.99944	5.30	1.0E+01	99.99944	5.30
Drug-resistant *Streptococcus pneumoniae*	3 min	1.0E+01	99.99968	5.57	1.0E+01	99.99968	5.57
	5 min	1.0E+01	99.99970	5.60	1.0E+01	99.99970	5.60
Streptococcus pyogenes	3 min	1.0E+01	99.99983	5.81	1.0E+01	99.99983	5.81
	5 min	1.0E+01	99.99984	5.83	1.0E+01	99.99984	5.83
Drug-resistant *Streptococcus pyogenes*	3 min	1.0E+01	99.99957	5.39	1.0E+01	99.99957	5.39
	5 min	1.0E+01	99.99953	5.34	1.0E+01	99.99953	5.34

Abbreviations: CFU = colony-forming units; E = x10 with an exponent of; min = minute

Table 2. Microbial Kill with Serum Challenge for SoluPrep Solution (b) (4)

Average Control Bacterial Counts and Test Product Bacterial Counts and Reductions at Specific Contact Times

Microorganism	ATCC No.	Contact Time	Control (Initial) Count	Tinted 3M CHG/IPA Prep			Colorless 3M CHG/IPA Prep		
			Average CFU/mL	Average CFU/mL	Percent Reduction	Log Reduction	Average CFU/mL	Percent Reduction	Log Reduction
Multidrug-resistant *Escherichia coli*	BAA-197	3 min	7.8E+06	<1.0E+01	>99.99987	>5.89	<1.0E+01	>99.99987	>5.89
		5 min	7.8E+06	<1.0E+01	>99.99987	>5.89	<1.0E+01	>99.99987	>5.89
Multidrug-resistant *Escherichia coli*	BAA-200	3 min	1.4E+07	<1.0E+01	>99.99993	>6.13	<1.0E+01	>99.99993	>6.13
		5 min	1.2E+07	<1.0E+01	>99.99992	>6.08	<1.0E+01	>99.99992	>6.08
Methicillin-resistant *S. aureus*	33591	3 min	4.6E+06	<1.0E+01	>99.99978	>5.66	<1.0E+01	>99.99978	>5.66
		5 min	4.8E+06	<1.0E+01	>99.99979	>5.68	<1.0E+01	>99.99979	>5.68
Methicillin-resistant *S. aureus*	33592	3 min	9.0E+06	<1.0E+01	>99.99989	>5.95	<1.0E+01	>99.99989	>5.95
		5 min	1.3E+07	<1.0E+01	>99.99992	>6.10	<1.0E+01	>99.99992	>6.10
Methicillin-resistant *S. epidermidis*	51625	3 min	8.5E+06	<1.0E+01	>99.99988	>5.93	<1.0E+01	>99.99988	>5.93
		5 min	1.3E+07	<1.0E+01	>99.99992	>6.10	<1.0E+01	>99.99992	>6.10
Multidrug-resistant *S. epidermidis*	700563	3 min	7.1E+06	<1.0E+01	>99.99986	>5.85	<1.0E+01	>99.99986	>5.85
		5 min	6.6E+06	<1.0E+01	>99.99985	>5.82	<1.0E+01	>99.99985	>5.82

Abbreviations: ATCC No.=the identification number of the official bacterial strain; CFU=colony-forming units; E=x10 with an exponent of; min=minute

Note: Control (initial) count was the count in the dilution blanks that were inoculated, plated, and incubated along with the test products at each time point. The $\log_{10}$ reduction was calculated by subtracting the $\log_{10}$ recovery of each test product from the $\log_{10}$ recovery of the control (initial) count at each time point.

Table 3. Antimicrobial Resistance and Cross-resistance (b) (4)

A total of 42 isolates were evaluated.

Ten repository isolates from eight species were evaluated:
• Methicillin-resistant *Staphylococcus aureus* (MRSA), ATCC 33591 • Methicillin-sensitive *Staphylococcus aureus* (MSSA), ATCC 25923 • Methicillin-resistant *Staphylococcus epidermidis* (MRSE), ATCC 51625 • Vancomycin-resistant *Enterococcus faecalis* (VRE), ATCC 51299 • *Acinetobacter baumannii*, ATCC 17904 • *Burkholderia cepacia*, ATCC 25608 • *Escherichia coli*, ATCC 11229 • *Pseudomonas aeruginosa*, ATCC 15442 • *Serratia marcescens*, ATCC 14756 • Multi-Drug Resistant (MDR) *Serratia marcescens*, ATCC 43297
Eight clinical isolate species, 2 resistant and 2 nonresistant, per species were evaluated:
• *Staphylococcus aureus* • *Staphylococcus epidermidis* • *Enterococcus faecalis* • *Acinetobacter baumannii* • *Burkholderia cepacia* • *Escherichia coli* • *Pseudomonas aeruginosa* • *Serratia marcescens*

Reviewer's comment: *The Sponsor will need to remove the study numbers "* (b) (4) *from the tables above.*

Agency's Recommendation (IR: July 30, 2018):
Remove the study numbers "(b) (4)" from the tables above.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has removed the study numbers "*(b) (4)*" from the tables above. These changes are acceptable.*

Human Safety Studies:
Three clinical safety studies were performed under exaggerated but controlled conditions to assess the cumulative irritation potential, allergic contact sensitization potential, phototoxic potential, photoallergic potential, and photoirritant potential of 3M CHG/IPA Prep compared to positive and negative controls.

The objective of the **cumulative irritation patch (21-day) with challenge trial** is to determine by repetitive epidermal contact the primary or cumulative irritation potential of the test materials compared to the positive control and a marketed active control.

For the 205 evaluable subjects over all product test sites, the individual observed erythema scores ranged from 0 (no visible erythema) to 3 (marked erythema). Individual cumulative irritation test (CIT) scores for evaluable subjects ranged from 0 to 34.5 for colorless 3M CHG/IPA Prep and 0 to 36 for tinted 3M CHG/IPA Prep. AN overall CIT score was generated for each study product by adding up the erythema scores on the product test sites for all evaluable subjects during the cumulative irritation induction phase. For evaluable subjects, colorless 3M CHG/IPA Prep and tinted 3M CHG/IPA Prep had overall CIT scores (1716.5 and 1937.0, respectively) that categorized them as products that would be probably mild in normal use.

There were 14 adverse events in 9 subjects and no serious adverse events during the clinical trial. Five adverse events in one subject were judged to be related and the other 7 adverse events in 7 subjects to be unlikely related to the investigational products or marketed active control. Of the 14 adverse events, 9 were moderate, and 5 were mild in severity. All of the events resolved. In this clinical trial, both investigational products appeared safe and well tolerated.

The objective of the clinical evaluation to assess **phototoxicity potential trial** was to determine the phototoxicity potential in human subjects of two investigational products, 3M CHG/IPA Prep colorless and tint, and a marketed active control product.

Evaluation scores remained within normal limits for the investigational products and the marketed active control throughout the clinical trial. Because observations remained within normal limits throughout the trial, there was no indication of phototoxic contact dermatitis observed at any time during the course of the trial. During the course of this study there were no adverse events and there were no clinically significant changes in vital signs. The investigational products were safe and well tolerated.

The primary objective of the clinical evaluation of **photoallergy potential trial** was to determine by repetitive epidermal contact and UV radiation, the photoallergic potential of a test material when applied to human subjects. The secondary objective of this trial is to determine by repetitive epidermal contact and UV radiation, the photo irritant potential of a test material when applied to human subjects.

The observations remained within normal limits throughout the Induction Phase and the Challenge Phase for both investigational products and for the marketed active control. The evaluation scores during the Induction Phase are consistent with the twice the minimum erythema dose (MED) of UV full spectrum irradiation. Similarly, the evaluation scores during the Challenge Phase are lower, consistent with half the MED of full spectrum irradiation and 16 Joules.cm^2 of UVA radiation.

Under the conditions of this trial, the investigational products 3M CHG/IPA Prep colorless and tint, did not induce a response indicative of irritant contact dermatitis, allergic contact dermatitis, photoallergic contact dermatitis, or phototoxic contact dermatitis.

> ***Reviewer's comments:*** *Medical Officers Dr. Gary Chiang and Dr. David Kettl from the Division of Dermatological and Dental Products stated that the summary of the three dermal safety studies discussed in the above section are accurate. They find this acceptable.*

15 References

1. Garland JS, Alex CP, Uhing MR, Peterside IE, Rentz A, and Harris MC. "Pilot Trial to Compare Tolerance of Chlorhexidine Gluconate to Povidone-iodine Antisepsis for Central Venous Catheter Placement in Neonates." J Perinatol 2009; 29(12): 808–813.

2. Chapman, AK, Aucott W, Gilmore MM, Advani S, Clarke W, and Milstone AM. "Absorption and Tolerability of Aqueous Chlorhexidine Gluconate Used for Skin Antisepsis Prior to Catheter Insertion in Preterm Neonates." J Perinatol , 2013 Oct; 33 (10): 768-771.

3. Chapman, AK, Aucott, SW, and Milstone, AM. "Safety of Chlorhexidine Gluconate for Skin Antisepsis in the Preterm Infant." J Perinatol 2012 Jan; 32 (1), 4-9 (review article).

4. Lee, A, Harlan, R, Breaud, AR, Speck, K., Perl, TM, Clarke, W., and Milstone AM. "Blood Concentrations of Chlorhexidine in Hospitalized Children Undergoing Daily Chlorhexidine Bathing." Infect Control Hosp Epidemiol 2011 Apr; 32 (4): 395-7.

5. Wittman, S, Gilg, T, Grantzow, R, Pesch, O, and von Meyer, L. Isopropanol-And Acetone Serum Levels after Presurgical Disinfection with Isopropanol Containing Antiseptics. Blood Alcohol 1992 Vol 291: 326-335.

Reviewer's comments: *The Sponsor will need to include the references cited in the TPI. The Sponsor may use whatever reference format it likes.*

Agency's Recommendation (IR: July 30, 2018):

Include literature references cited in the TPI. You may use whatever reference format you like.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has included the references cited in the TPI. The Sponsor has revised the format of the references to read:*

1. *Garland JS, Alex CP, Uhing MR, Peterside IE, Rentz A, and Harris MC. Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antisepsis for central venous catheter placement in neonates. J Perinatol. 2009;29(12):808–813.*

2. *Chapman, AK, Aucott SW, Gilmore MM, et al. Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonates. J Perinatol. 2013;33:768-771.*

3. *Chapman AK, Aucott SW, and Milstone AM. Safety of chlorhexidine gluconate for skin antisepsis in the preterm infant. J Perinatol. 2012;32(1):4-9.*

4. *Lee A, Harlan R, Bread AR, et al. Blood concentrations of chlorhexidine in hospitalized children undergoing daily chlorhexidine bathing. Infect Control Hosp Epidemiol. 2011;32(4):395-397.*

5. *Wittmann S, Gilg T, Dietz HG, et al. Isopropanol and acetone serum levels after presurgical disinfection with isopropanol containing antiseptics. Blutalkohol. 1992;291:326-335.*

These changes are acceptable.

16 How Supplied/Storage and Handling

Single Use Applicator
10.5 mL applicator (Clear/Tint)

- Solution volume 10.5 ml / 0.36 fl.oz.

26 mL applicator (Tint)

- Solution volume 26 mL / 0.9 fl.oz.

Active ingredients:
Chlorhexidine gluconate (CHG) 2% w/v
Isopropyl alcohol (IPA) 70% v/v

Inactive ingredients (Tinted):
acetyltri-n-butyl citrate, acrylate copolymer, FD&C blue #1, FD&C yellow #5, purified water USP, Trisodium HEDTA

Reviewer's comments: *The Sponsor will need to include the statement "(Tinted)" after inactive ingredients. It will also need to include the inactive ingredient "Trisodium HEDTA".*

Agency's Recommendation (IR: July 30, 2018):
Include the statement "(Tinted)" after inactive ingredients. Also include the inactive ingredient "Trisodium HEDTA".

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has included the statement "(Tinted)" after the inactive ingredients. It also included the inactive ingredient "Trisodium HEDTA". These changes are acceptable.*

Inactive ingredients (Clear):
acetyltri-n-butyl citrate, acrylate copolymer, purified water USP, Trisodium HEDTA

Reviewer's comment: *The Sponsor will need to include the statements "Inactive ingredients (Clear):" and "acetyltri-n-butyl citrate, acrylate copolymer, purified water USP, Trisodium HEDTA" in this section.*

Agency's Recommendation (IR: July 30, 2018):
Include the statements "Inactive ingredients (Clear):" and "acetyltri-n-butyl citrate, acrylate copolymer, purified water USP, Trisodium HEDTA" in this section.

Reviewer's comments: *In accordance with the Agency's request, the Sponsor has included the statements "Inactive ingredients (Clear):" and "acetyltri-n-butyl citrate, acrylate copolymer, purified water USP, Trisodium HEDTA" in this section. These changes are acceptable.*

Storage and Handling:

- Store between 15-30ºC (59-86ºF)
- Avoid freezing and excessive heat above 40ºC (104ºF)

17 Patient Counseling Information

3M recommends all users participate in product in-service training prior to use. In-serving is available on video, from your 3M sales representative, or at the 3M website (www.3M.com).

III. RECOMMENDATIONS

Issue an APPROVAL letter to the Sponsor for the submitted SoluPrep™ Film-Forming Sterile Surgical Solution Target Product Information labeling and request final printed labeling (FPL). Request that the Sponsor submits FPL identical to the following submitted labeling (appended below):

Labeling submitted August 1, 2018

- Target Product Information

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

MICHELLE M JACKSON
08/01/2018

FRANCISCO MARTINEZ-MURILLO
08/01/2018

4th Addendum Labeling Review for SoluPrep™ Film-Forming Sterile Surgical Solution
Draft Labeling

SUBMISSION DATES:	July 6, 2015; August 25, 2015; November 6, 2015; March 3, 2017; June 6, 2017; July 5, 2018
NDA/SUBMISSION TYPE:	208288 (Original)
ACTIVE INGREDIENTS:	2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol (IPA), 10.5 mL and 26 mL
DOSAGE FORMS:	Solution
SPONSOR:	3M Health Care Business 3M Center, Bldg. 0275-05-W-06 Saint Paul, MN 55144-1000 Dianne L. Gibbs, RAC Regulatory Affairs Director (651) 737-0844
REVIEWER:	Michelle M. Jackson, PhD IDS Microbiologist, DNDP, ODEIV
TEAM LEADER:	Francisco Martínez-Murillo, PhD Team Leader, DNDP, ODEIV
PROJECT MANAGER:	Celia Peacock, RDN, MPH, DNDP, ODEIV Senior Regulatory Project Manager

I. BACKGROUND

This is an addendum to my review dated July 18, 2017. On July 6, 2015, 3M Health Care submitted NDA 208288, SoluPrep™ film-forming sterile patient preoperative skin preparation, as an orginal new NDA. The Sponsor proposes a sterile antiseptic surgical solution containing the active ingredients, chlorhexidine gluconate and isopropyl alcohol in solution with an inactive ingredient 3M film-forming copolymer and other inactive ingredients. Once the solution is applied to the skin, the copolymer would produce a water-insoluble film. Three different applicators are proposed, 10.5 mL "Brite Green" (tinted solution), 10.5 mL "Clear" (nontinted solution), and 26 mL "Brite Green." Please refer to the reviews from July 18, 2017, April 5, 2017, and March 31, 2016 for complete background information.

On July 2, 2018, the Agency requested via email a number of changes to the Sponsor's proposed labeling. On July 5, 2018, the Sponsor responded with an amendment and submitted revised labeling that identified all changes requested by the Agency. Following below is the review of the Sponsor's response from July 5, 2018. See list of submitted labeling in the table below:

Submitted Labeling July 5, 2018*	Representative of Following SKUs
10.5 mL Brite Green outer container (pouch with *Drug Facts*) clean label	NA
10.5 mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
10.5 mL Brite Green immediate container (handle) clean label	NA
10.5 mL Brite Green immediate container (handle) annotated label	NA
10.5 mL Brite Green consumer information leaflet clean label	NA
10.5 mL Brite Green consumer information leaflet annotated label	NA
10.5 mL Clear outer container (pouch with *Drug Facts*) clean label	NA
10.5 mL Clear outer container (pouch with *Drug Facts*) annotated label	NA
10.5 mL Clear immediate container (handle) clean label	NA
10.5 mL Clear immediate container (handle) annotated label	NA
10.5 mL Clear consumer information leaflet clean label	NA
10.5 mL Clear consumer information leaflet annotated label	NA
26 mL Brite Green outer container (pouch with *Drug Facts*) clean label	NA
26 mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
26 mL Brite Green immediate container (handle) clean label	NA
26 mL Brite Green immediate container (handle) annotated label	NA
26 mL Brite Green consumer information leaflet clean label	NA
26 mL Brite Green consumer information leaflet annotated label	NA

* Target Product Information will be addressed in a separate review.

II. REVIEWER'S COMMENTS

Per the Sponsor's response to the Agency's email dated July 2, 2018:

26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator

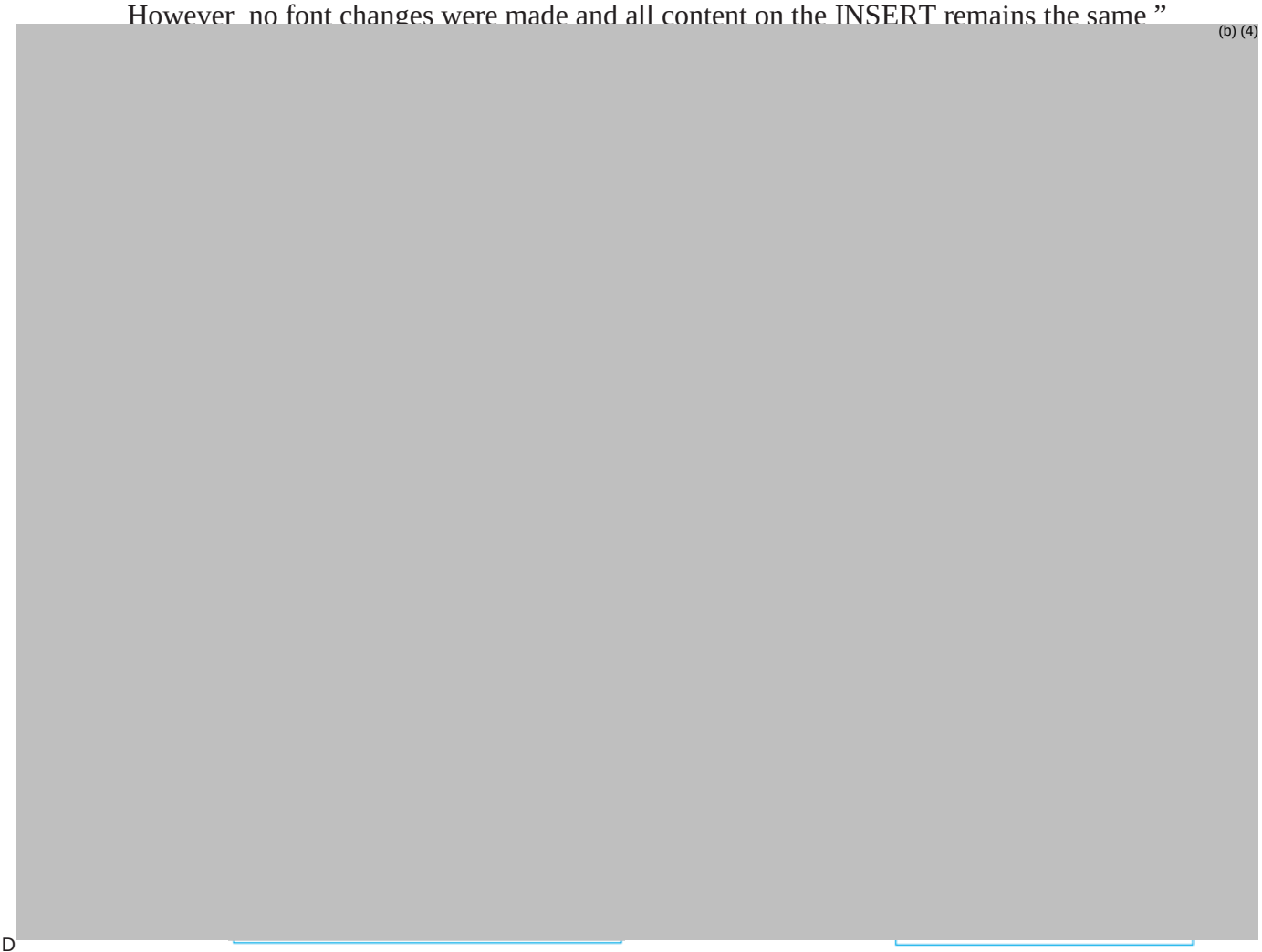
1. Agency's recommendation: Revise your principal display panel on the secondary packaging (pouch), applicator handle, and package insert include the established drug name followed by its concentration, chlorhexidine gluconate, 2% w/v and isopropyl alcohol, 70% v/v or chlorhexidine gluconate (2% w/v) and isopropyl alcohol (70% v/v).

Reviewer's comments: In accordance with the Agency's request, the established drug name followed by its concentration, chlorhexidine gluconate (2% w/v) and isopropyl alcohol (70% v/v) has been incorporated in the Drug Facts labeling for the 26 mL applicator, 10.5 mL tint applicator and 10.5 mL clear applicator on the principal display panel on the secondary packaging (pouch), applicator handle, and package insert. This change is acceptable.

Additional comment

1. The Sponsor noted that it has reduced the dimension size of the paper for the smaller size Cat. No. 7133 and 7134 (10.5 mL) INSERT. "The width of the paper for the 10.5 mL size INSERT has been reduced slightly from 3.25 in. to 2.5 in. in order to fit better side-to-side in the secondary sealed pouch package. The length of the paper INSERT has not changed and remains at 7.5 inches. Also, along with the narrowing of the paper, the placement of two graphics (the "not made with natural rubber latex" symbol and the "single use only" symbol) were moved from the bottom of the INSERT to the top right of the INSERT. However, no font changes were made and all content on the INSERT remains the same."

(b) (4)



Reviewer's comments: For the 10.5 mL Clear and Tint, the placement of the two graphics (the "not made with natural rubber latex" symbol and the "single use only" symbol) were moved from the bottom of the INSERT to the top right of the INSERT. This is acceptable.

2. The Sponsor changed the website from "www.3M.com" to "www.3M.com/Medical" on its secondary packaging (pouch) and package insert.

   Reviewer's comment: This is acceptable.

III. RECOMMENDATIONS

Issue an APPROVAL letter to the Sponsor for the submitted SoluPrep™ Film-Forming Sterile Surgical Solution labeling and request final printed labeling (FPL). Request that the Sponsor submits FPL identical to the following submitted labeling (appended below):

Labeling submitted July 5, 2018

- 10.5 mL Brite Green outer container (pouch with *Drug Facts*)
- 10.5 mL Brite Green immediate container (handle)
- 10.5 mL Brite Green consumer information leaflet
- 10.5 mL Clear outer container (pouch with *Drug Facts*)
- 10.5 mL Clear immediate container (handle)
- 10.5 mL Clear consumer information leaflet
- 26 mL Brite Green outer container (pouch with *Drug Facts*)
- 26 mL Brite Green immediate container (handle)
- 26 mL Brite Green consumer information leaflet

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

MICHELLE M JACKSON
07/30/2018

FRANCISCO MARTINEZ-MURILLO
07/31/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 25, 2017
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 208288
Product Name and Strength:	SoluPrep (Chlorhexidine Gluconate/Isopropyl Alcohol) Topical Solution, 2%/70%
Product Type:	Multi-Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	3M Healthcare Inc.
Submission Date:	March 3, 2017 and June 7, 2017
OSE RCM #:	2017-522
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA review process for SoluPrep, we reviewed the proposed container labels, carton labeling, information leaflet, and Target Product Information package insert for areas of vulnerability that could lead to medication errors.

The application had received a Complete Response on May 6, 2016. The Applicant then resubmitted their application on March 3, 2017.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The currently proposed container labels are identical to the previously reviewed container labels in our previous review from the last review cycle.[a]

Our current review of the proposed carton labeling, which contains the Drug Facts Label (DFL) identified the following notable differences in the June 7, 2017 submission when compared to the last review cycle:

- the addition of an Allergy Alert section under the Warnings section in the DFL,
- the When using this product section now includes a second bullet "to avoid skin injury, care should be taken when removing drapes, tapes, etc. ..applied over film"

[a] Jones, GP. Label and Labeling Review for SoluPrep (NDA 208288). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 21. OSE RCM No.: 2015-1596.

- the bullet “use with care in premature infants or infants under 2 months of age…” under the When using this product section was relocated to the Directions section as the first bullet, and
- the inactive ingredient, Trisodium HEDTA, was added.

Our review of the currently proposed information leaflet identified the following notable difference:

- the addition of the text: “SoluPrep™ Film-Forming Sterile Surgical Solution is an antimicrobial skin preparation. It is recommended that the Prep remain on the skin after the procedure for continued protection. The prep will gradually wear away. If however early removal is desired, use 70% isopropyl alcohol. Place alcohol soaked gauze for approximately 40 seconds on the prepped area. Lightly rub gauze over area to remove prep.”

The currently proposed Target Product Information package insert was not included in our previous review from the last review cycle.

Based on our evaluation, we find the proposed SoluPrep container labels, carton labeling, information leaflet, and Target Product Information package insert acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed SoluPrep container labels, carton labeling, information leaflet, and Target Product Information package insert are acceptable from a medication error perspective and have no further recommendations.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for SoluPrep that 3M submitted on June 7, 2017.

Table 2. Relevant Product Information for SoluPrep	
Initial Approval Date	N/A
Active Ingredient	chlorhexidine gluconate and isopropyl alcohol
Indication	patient preoperative skin preparation • for preparation of skin prior to surgery • helps reduce bacteria that potentially can cause skin infection
Route of Administration	topical solution for use by health care professionals
Dosage Form	topical solution (with an applicator)
Strength	2% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol
Dose and Frequency	single use 26 mL (0.9 fl oz) or 10.5 mL (0.36 fl oz) applicator solution delivered topically to the patient's skin prior to surgery
How Supplied	10.5 mL applicator (clear/tint): solution volume 10.5 ml/0.36 fl. oz. (coverage area 13 in. x 13 in. (178.8 in2) 26 mL applicator (tint): solution volume 26 mL/0.9 fl. oz. (coverage area 19.5 in. x 19.5 in. (387.5 in2)
Storage	store between 15-30°C (59-86°F); avoid freezing and excessive heat above 40°C (104°F)
Container Closure	packaged in (b) (4) sealed, 10.5 mL onion skin, (b) (4) glass ampules; and 26 mL (b) (4) glass ampules; each sealed ampule is housed in a plastic applicator, and sealed in a film (b) (4) pouch; two cotton-tipped swabs are provided with each 26 mL applicator

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 12, 2017, we searched the L:drive and AIMS using the terms, SoluPrep to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 Proprietary Name reviews[b,c,d] and 1 labels and labeling review[e] for SoluPrep. Our labels and labeling review concluded the proposed container labels, carton labeling, and information leaflet were acceptable.

[b] Jones, GP. Proprietary Name Review for SoluPrep IND 076549. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 3. RCM No.: 2014-39497.

[c] Jones, GP. Proprietary Name Memorandum for SoluPrep NDA 208288. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 9. RCM No.: 2015-1210657.

[d] Jones, GP. Proprietary Name Review for SoluPrep NDA 208288. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 19. RCM No.: 2017-13536820.

[e] Jones, GP. Label and Labeling Review for SoluPrep (NDA 208288). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 21. OSE RCM No.: 2015-1596.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

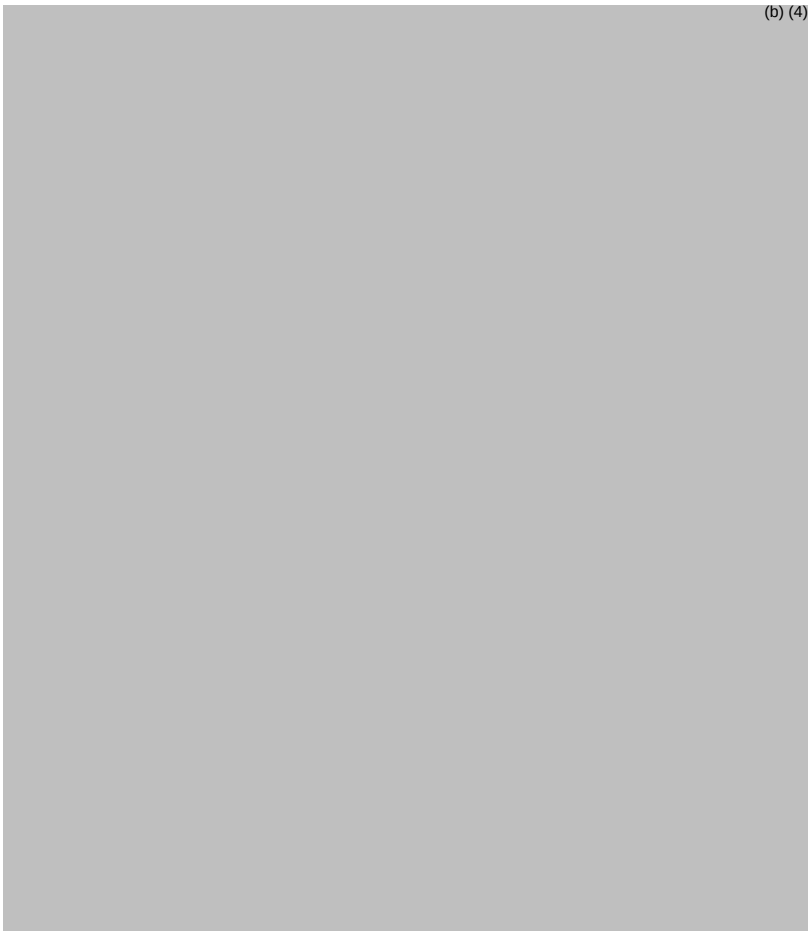
Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following SoluPrep labels and labeling submitted by 3M on June 7, 2017.

- Container labels
- Carton labeling
- Information Leaflet
- Target Product Information package insert (submitted March 3, 2017) (Image not shown)

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

G.2 Label and Labeling Images

Container Labels – shown for 26 mL Green tint (see submission for 10.5 mL clear and green tint)



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/s/

GRACE JONES
07/25/2017

CHI-MING TU
07/25/2017

3rd Addendum Labeling Review for SoluPrep™ Film-Forming Sterile Surgical Solution *Draft Labeling*

SUBMISSION DATES:	July 6, 2015; August 25, 2015; November 6, 2015; March 3, 2017; June 6, 2017
NDA/SUBMISSION TYPE:	208-288 (Original)
ACTIVE INGREDIENTS:	2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol (IPA), 10.5 mL and 26 mL
DOSAGE FORMS:	Solution
SPONSOR:	3M Health Care Business 3M Center, Bldg. 0275-05-W-06 Saint Paul, MN 55144-1000 Dianne L. Gibbs, RAC Regulatory Affairs Director (651) 737-0844
REVIEWER:	Michelle M. Jackson, PhD IDS Microbiologist, DNDP, ODEIV
TEAM LEADER:	Francisco Martínez-Murillo, PhD Team Leader, DNDP, ODEIV
PROJECT MANAGER:	Celia Peacock, RDN, MPH, DNDP, ODEIV Senior Regulatory Project Manager

I. BACKGROUND

This is an addendum to my review dated April 5, 2017. On July 6, 2015, 3M Health Care submitted NDA 208-288 SoluPrep™ film-forming sterile patient preoperative skin preparation as an orginal new NDA. The Sponsor proposes a sterile antiseptic surgical solution containing the active ingredients, chlorhexidine gluconate and isopropyl alcohol in solution with an inactive ingredient 3M film-forming copolymer and other inactive ingredients. Once the solution is applied to the skin, the copolymer would produce a water-insoluble film. (b) (4) Three different applicators are proposed, 10.5 mL "Brite Green" (tinted solution), 10.5 mL "Clear" (nontinted solution), and 26 mL "Brite Green." Please refer to the reviews from April 5, 2017 and March 31, 2016 for complete background information.

On April 5, 2017, the Agency requested via email a number of changes to the Sponsor's proposed labeling. On June 6, 2017, the Sponsor responded with an amendment and submitted revised labeling that identified all changes requested by the Agency. Following below is the review of the Sponsor's response from June 6, 2017. See list of submitted labeling in the table below:

Submitted Labeling June 6, 2017*	Representative of Following SKUs
10.5 mL Brite Green outer container (pouch with *Drug Facts*) clean label	NA
10.5 mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
10.5 mL Brite Green immediate container (handle) clean label	NA
10.5 mL Brite Green immediate container (handle) annotated label	NA
10.5 mL Brite Green consumer information leaflet clean label	NA
10.5 mL Brite Green consumer information leaflet annotated label	NA
10.5 mL Clear outer container (pouch with *Drug Facts*) clean label	NA
10.5 mL Clear outer container (pouch with *Drug Facts*) annotated label	NA
10.5 mL Clear immediate container (handle) clean label	NA
10.5 mL Clear immediate container (handle) annotated label	NA
10.5 mL Clear consumer information leaflet clean label	NA
10.5 mL Clear consumer information leaflet annotated label	NA
26 mL Brite Green outer container (pouch with *Drug Facts*) clean label	NA
26 mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
26 mL Brite Green immediate container (handle) clean label	NA
26 mL Brite Green immediate container (handle) annotated label	NA
26 mL Brite Green consumer information leaflet clean label	NA
26 mL Brite Green consumer information leaflet annotated label	NA

* Target Product Information will be addressed in a separate review.

II. REVIEWER'S COMMENTS

Per the Sponsor's response to the Agency's email dated April 5, 2017:

26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator

1. Agency's recommendation: On February 2, 2017, FDA sent a Changes Being Effected (CBE) Supplement Request letter to the Sponsor requesting labeling revisions. The Agency determined that a class labeling change was warranted for chlorhexidine gluconate (CHG) topical antiseptic drug products. Currently, the Drug Facts Labeling warnings for CHG products are not consistent, regarding allergy to CHG, across the various CHG drug Products that are approved for use.

   Include the allergy alert warning to read as follows:

Warnings

For external use only. Flammable: Keep away from fire or flame.

To reduce risk of fire; PREP CAREFULLY:

- do not use 26-mL applicator for head and neck surgery
- do not use on an area smaller than (b) (4) Use a smaller applicator instead
- solution contains alcohol and gives off flammable vapors
- avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry.
- do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair)
- do not allow solution to pool
- remove wet materials from prep area

Allergy Alert: This product may cause a severe allergic reaction. Symptoms may include:

• wheezing/difficulty breathing • shock • facial swelling • hives • rash

If an allergic reaction occurs, stop use and seek medical help right away.

(Wrap around format)

Allergy Alert: This product may cause a severe allergic reaction. Symptoms may include:

- wheezing/difficulty breathing
- shock
- facial swelling
- hives
- rash

If an allergic reaction occurs, stop use and seek medical help right away.

(Vertical alignment format)

According to 21 CFR 201.66(d)(4), "Bullets shall be presented in the same shape and color throughout the labeling. The first bulleted statement on each horizontal line of text shall be either left justified or separated from an appropriate heading or subheading by at least two square "ems" (i.e., two squares of the size of the letter "M"). If more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement shall be separated from the beginning of the next bulleted statement by at least two square "ems" and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line." Therefore you may either use the wrap around bulleted statements (if spacing is an issue) or vertically align the bulleted statements in accordance with 21 CFR 201.66(d)(4).

Reviewer's comment: *In accordance with the Agency's request, the CHG allergy alert warning has been incorporated in the Drug Facts labeling for the 26 mL applicator, 10.5 mL tint applicator and 10.5 mL clear applicator. This change is acceptable.*

10.5 mL Tint Applicator and 10.5 mL Clear Applicator

2. Agency's recommendation: Revise the statement under the subheader **Do not use:** "● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol" to read "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product", so it is consistent with the class labeling for chlorhexidine gluconate warning labeling.

   Reviewer's comment: *In accordance with the Agency's request, the statement under the subheader* ***Do not use:*** *"● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol" has been revised to read "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product", so it is consistent with the class labeling for chlorhexidine gluconate warning labeling. This change is acceptable.*

26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator

3. Agency's recommendation: Included the "Trisodium HEDTA" in the inactive ingredients listing in accordance with section 502(e)(1) of the Food, Drug, and Cosmetic Act, as amended by section 412(c) of the Food and Drug Administration Modernization Act of 1997, and 21 CFR 201.66.

   Reviewer's comment: *In accordance with the Agency's request, the inactive ingredient "Trisodium HEDTA" has been included in the inactive ingredients listing in accordance with section 502(e)(1) of the Food, Drug, and Cosmetic Act, as amended by section 412(c) of the Food and Drug Administration Modernization Act of 1997, and 21 CFR 201.66. This is change is acceptable.*

26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator

4. Agency's recommendation: Bold and increase the size of the pharmacological category "Patient Preoperative Skin Preparation" to be the same size as the established name or half the size of the most prominent display of the tradename (SoluPrep™) in accordance with 21 CFR 201.61(c). This applies to the Drug Facts (secondary packaging - lidding), applicator barrel handle, and the consumer information leaflet.

   Reviewer's comment: *In accordance with the Agency's request, the size of the pharmacological category "Patient Preoperative Skin Preparation" has been bolded and increased to be the same size as the established name or half the size of the most prominent display of the tradename (SoluPrep™) in accordance with 21 CFR 201.61(c). This change is acceptable.*

26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator

5. Agency's recommendation: Remove the statement "● use with care in premature infants or infants under 2 months of age. The products may cause irritation or chemical burns." from under the subheader **When using this product** and place it under ***Directions*** as the first bulleted statement.

   On October 21, 2011, FDA sent a CBE Supplement Request letter to sponsors (products containing chlorhexidine gluconate) requesting labeling revisions. FDA has determined that a class labeling change was warranted for chlorhexidine gluconate (CHG) topical antiseptic drug products. At that time, the Drug Facts label warnings for CHG products

were not consistent regarding use in infants, across the various CHG drug products that are approved for use. In order to reduce the incidence of skin irritation and burns in infants, and in the interest of clear and uniform labeling, FDA is requiring that all CHG topical antiseptic product labels include language regarding this. Even labels that already state "Do not use in infants" should be revised so that they will be consistent with all other CHG product labels. Therefore, the same labeling was required to be consistent across single ingredient CHG products and combination CHG/IPA products. FDA requested sponsor to include the infant warning statement "● use with care in premature infants or infants under 2 months of age. The products may cause irritation or chemical burns." to be placed as the first bulleted statement under ***Directions***.

Reviewer's comment: *In accordance with the Agency's request, the statement "● use with care in premature infants or infants under 2 months of age. The products may cause irritation or chemical burns." has been removed from under the subheader* ***When using this product*** *and placed under* ***Directions*** *as the first bulleted statement. This change is acceptable.*

26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator

6. Agency's recommendation: Include the statement "● to avoid skin injury, care should be taken when removing drapes, tapes, etc…applied over film" under the subheader **When using this product**. This statement is currently included in the DuraPrep Surgical Solution labeling. Both the SoluPrep Film-Forming Sterile Surgical Solution and DuraPrep Surgical Solution are film-forming antiseptic products.

Reviewer's comment: *In accordance with the Agency's request, the statement "● to avoid skin injury, care should be taken when removing drapes, tapes, etc…applied over film" has been included under the subheader* ***When using this product****. This change is acceptable.*

26 mL Tint Applicator

7. Agency's recommendation: Include a barcode for the 26 mL Tint applicator for the consumer information leaflet to be consistent with the 10.5 mL Tint and Clear applicator consumer information leaflet and so that it is in accordance with 21 CFR 201.25(c).

Reviewer's comment: *In accordance with the Agency's request, a barcode for the 26 mL Tint applicator for the consumer information leaflet has been included to be consistent with the 10.5 mL Tint and Clear applicator consumer information leaflet and so that it is in accordance with 21 CFR 201.25(c). This change is acceptable.*

10.5 mL Clear Applicator

8. Remove the statement "● the tint will slowly fade from the skin. Alcohol may be used to remove the tint if desired." for the 10.5 mL Clear applicator, because there is no tint in the solution.

Reviewer's comment: *In accordance with the Agency's request, the statement "● the tint will slowly fade from the skin. Alcohol may be used to remove the tint if desired." has been removed for the 10.5 mL Clear applicator, because there is no tint in the solution. This change is acceptable.*

III. RECOMMENDATIONS

Issue an APPROVAL letter to the Sponsor for the submitted SoluPrep™ Film-Forming Sterile Surgical Solution labeling and request final printed labeling (FPL). Request that the Sponsor submits FPL identical to the following submitted labeling (appended below):

Labeling submitted June 6, 2017

- 10.5 mL Brite Green outer container (pouch with *Drug Facts*)
- 10.5 mL Brite Green immediate container (handle)
- 10.5 mL Brite Green consumer information leaflet
- 10.5 mL Clear outer container (pouch with *Drug Facts*)
- 10.5 mL Clear immediate container (handle)
- 10.5 mL Clear consumer information leaflet
- 26 mL Brite Green outer container (pouch with *Drug Facts*)
- 26 mL Brite Green immediate container (handle)
- 26 mL Brite Green consumer information leaflet

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MICHELLE M JACKSON
07/18/2017

FRANCISCO MARTINEZ-MURILLO
07/18/2017

HUMAN FACTORS, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 3, 2018
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 208288
Product Name and Strength:	SoluPrep (Chlorhexidine Gluconate/Isopropyl Alcohol) Topical Solution, 2%/70%
Product Type:	Multi-Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	3M Healthcare Inc.
FDA Received Date:	March 3, 2017, June 7, 2017, and February 9, 2018
OSE RCM #:	2017-522-1
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

As part of the NDA review process for SoluPrep, we reviewed the proposed container labels, carton labeling, information leaflet, and Target Product Information package insert for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The application received a Complete Response (CR) letter on May 6, 2016 and a second CR letter on September 1, 2017. The Applicant resubmitted their application as a Class 2 Resubmission on February 9, 2018.

We note that all product characteristics in this current February 9, 2018 submission remain the same since our last July 25, 2017 Label and Labeling Review. The Applicant did not submit any new container labels, carton labeling, information leaflet, and Target Product Information package insert in this current submission.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant did not submit any new container labels, carton labeling, information leaflet, and Target Product Information package insert in this current submission. Our previous label and labeling review found the proposed SoluPrep container labels, carton labeling, information

leaflet, and Target Product Information package insert acceptable from a medication error perspective, and we still maintain our previous assessment.[a]

As a preoperative skin preparation product, this proposed chlorhexidine gluconate/isopropyl alcohol) topical solution combination product would be used in hospital surgical room environments by healthcare professional (HCP) end users, and use of the proposed product involves opening and removing the single use applicator from the container packaging, and then pressing down on the cap end of the applicator sponge to cleanse the surgical site. The risks associated with use of this product are well understood and we have not identified any additional or unique considerations that would warrant the need for additional data at this time. Therefore, we determined that a human factors validation study is not necessary at this time.

4 CONCLUSION & RECOMMENDATIONS

We conclude that a human factors validation study is not needed for this product. In addition, the proposed SoluPrep container labels, carton labeling, information leaflet, and Target Product Information package insert are acceptable from a medication error perspective and we have no recommendations at this time.

[a] Jones, GP. Label and Labeling Review for SoluPrep (NDA 208288). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 25. OSE RCM No.: 2017-522.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for SoluPrep received on June 7, 2017 from 3M.

Table 2. Relevant Product Information for SoluPrep	
Initial Approval Date	N/A
Active Ingredient	chlorhexidine gluconate and isopropyl alcohol
Indication	patient preoperative skin preparation • for preparation of skin prior to surgery • helps reduce bacteria that potentially can cause skin infection
Route of Administration	topical solution for use by health care professionals
Dosage Form	topical solution (with an applicator)
Strength	2% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol
Dose and Frequency	single use 26 mL (0.9 fl oz) or 10.5 mL (0.36 fl oz) applicator solution delivered topically to the patient's skin prior to surgery
How Supplied	10.5 mL applicator (clear/tint): solution volume 10.5 ml/0.36 fl. oz. (coverage area 13 in. x 13 in. (178.8 in2) 26 mL applicator (tint): solution volume 26 mL/0.9 fl. oz. (coverage area 19.5 in. x 19.5 in. (387.5 in2)
Storage	store between 15-30°C (59-86°F); avoid freezing and excessive heat above 40°C (104°F)
Container Closure	packaged in (b) (4) sealed, 10.5 mL (b) (4) glass ampules; and 26 mL (b) (4) glass ampules; each sealed ampule is housed in a plastic applicator, and sealed in a (b) (4) pouch; two cotton-tipped swabs are provided with each 26 mL applicator

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 16, 2018, we searched DMEPA's previous reviews using the terms, SoluPrep. Our search identified 4 previous proprietary name reviews[b,c,d,e] and 2 labels and labeling review[f,g] for SoluPrep. Our labels and labeling review concluded the proposed container labels, carton labeling, information leaflet, and Target Product Information package insert were acceptable.

[b] Jones, G. Proprietary Name Review for SoluPrep IND 076549. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 3. RCM No.: 2014-39497.

[c] Jones, G. Proprietary Name Memorandum for SoluPrep NDA 208288. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 9. RCM No.: 2015-1210657.

[d] Jones, G. Proprietary Name Review for SoluPrep NDA 208288. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 19. RCM No.: 2017-13536820.

[e] Jones, G. Proprietary Name Memorandum for SoluPrep NDA 208288. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 03. RCM No.: 2018- 21245098.

[f] Jones, G. Label and Labeling Review for SoluPrep (NDA 208288). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 21. OSE RCM No.: 2015-1596.

[g] Jones, G. Label and Labeling Review for SoluPrep (NDA 208288). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 25. OSE RCM No.: 2017-522.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following SoluPrep labels and labeling submitted by 3M on June 7, 2017.

- Container labels
- Carton labeling
- Information Leaflet
- Target Product Information package insert (submitted March 3, 2017) (Image not shown)

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[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

GRACE JONES
07/03/2018

CHI-MING TU
07/03/2018

QUYNHNHU T NGUYEN
07/04/2018

Addendum Labeling Review for SoluPrep™ Film-Forming Sterile Surgical Solution *Draft Labeling*

SUBMISSION DATES:	July 6, 2015; August 25, 2015; November 6, 2015; March 3, 2017
NDA/SUBMISSION TYPE:	208-288 (Original)
ACTIVE INGREDIENTS:	2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol (IPA), 10.5 mL and 26 mL
DOSAGE FORMS:	Solution
SPONSOR:	3M Health Care Business 3M Center, Bldg. 0275-05-W-06 Saint Paul, MN 55144-1000 Dianne L. Gibbs, RAC Regulatory Affairs Director (651) 737-0844
REVIEWER:	Michelle M. Jackson, PhD IDS Microbiologist, DNDP, ODEIV
TEAM LEADER:	Francisco Martínez-Murillo, PhD Team Leader, DNDP, ODEIV
PROJECT MANAGER:	Celia Peacock, RDN, MPH, DNDP, ODEIV Senior Regulatory Project Manager

I. BACKGROUND

This is an addendum to my review dated March 31, 2016. On July 6, 2015, 3M Health Care submitted NDA 208-288 SoluPrep™ film-forming sterile patient preoperative skin preparation as an orginal new NDA. The Sponsor proposes a sterile antiseptic surgical solution containing the active ingredients, chlorhexidine gluconate and isopropyl alcohol in solution with an inactive ingredient 3M film-forming copolymer and other inactive ingredients. Once the solution is applied to the skin, the copolymer would produce a water-insoluble film. (b) (4) Three different applicators are proposed, 10.5 mL "Brite Green" (tinted solution), 10.5 mL "Clear" (nontinted solution), and 26 mL "Brite Green." Please refer to the March 31, 2016 review for complete background information.

On August 20, 2015, an information request sent to the Sponsor requested submission of the target product information package insert labeling layout without the annotation. The Sponsor responded on August 25, 2015, with submission of the unannotated target product information package insert labeling. On November 6, 2015, the Sponsor submitted the target product information package insert with annotation links to the modules within the submission.

On March 3, 2017, the Sponsor submitted labeling that identifies all changes and supporting annotations for the Target Product Information labeling. See list of submitted labeling in the table below:

Submitted Labeling July 6, 2015	**Representative of Following SKUs**
10.5-mL Brite Green immediate container (handle) clean label	NA
10.5-mL Brite Green immediate container (handle) annotated label	NA
10.5-mL Brite Green consumer information leaflet clean label	NA
10.5-mL Brite Green consumer information leaflet annotated label	NA
10.5-mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
10.5-mL Clear immediate container (handle) clean label	NA
10.5-mL Clear immediate container (handle) annotated label	NA
10.5-mL Clear consumer information leaflet clean label	NA
10.5-mL Clear consumer information leaflet annotated label	NA
10.5-mL Clear outer container (pouch with *Drug Facts*) annotated label	NA
26-mL Brite Green immediate container (handle) clean label	NA
26-mL Brite Green immediate container (handle) annotated label	NA
26-mL Brite Green consumer information leaflet clean label	NA
26-mL Brite Green consumer information leaflet annotated label	NA
26-mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
Target Product Information (package insert) annotated label*	NA
Submitted Labeling August 25, 2015	
Target Product Information (package insert) clean label	NA
Submitted Labeling November 6, 2015	
Target Product Information (package insert) annotated label with links	NA
Submitted Labeling March 3, 2017	
Target Product Information (package insert) clean label	NA
Target Product Information (package insert) annotated label with links	NA

* Target Product Information will be addressed in a separate review.

II. REVIEWER'S COMMENTS

SoluPrep™ 10.5-mL Brite Green, 10.5-mL Clear, and 26-mL Brite Green Film-Forming Sterile Solution Secondary Packaging

Drug Facts Labeling

a. ***Warnings***

On February 2, 2017, FDA sent a Changes Being Effected (CBE) Supplement Request letter to the Sponsor requesting labeling revisions. The Agency determined that a class labeling change was warranted for chlorhexidine gluconate (CHG) topical antiseptic drug products. Currently, the Drug Facts Labeling warnings for CHG products are not consistent, regarding allergy to CHG, across the various CHG drug Products that are approved for use. The decision to request the inclusion of a consistent warning regarding use of CHG products was based on the review of safety issues pertaining to the use of CHG topical antiseptic products. This review was based on FDA's Adverse Event Reporting System (FAERS) database, in which 43 cases of anaphylactic reaction were reported with the use of CHG topical products from 1969 through 2015. Twenty-four cases were reported after 2010. Twenty-six of the 43 cases reported the outcome as life-threatening: 12 patients were hospitalized, and 2 patients died. Hypotension in association with either skin, respiratory, or gastrointestinal allergy symptoms was reported in 39 of the 43 cases. A search of the medical literature also identified eight cases of anaphylactic reaction associated with topical chlorhexidine gluconate that were not reported to FAERS.

In order to reduce the incidence of anaphylactic reaction with CHG, and in the interest of clear and uniform labeling, the Agency is requiring that all CHG topical antiseptic product labels include the same specific language regarding this warning. Even labels that already address allergy alert under the subheaders "**Do not use"** and "**Stop use and ask a doctor if"** should be revised so that their text is consistent with all other CHG product labels. The Agency's review finds that CHG-only products, as well as CHG and alcohol combination products, can both cause severe skin and anaphylactic reactions. It is difficult to discern from postmarket data whether there are any differences in the incidence or severity of these reactions between these two types of products. Therefore, the same labeling will be required to be consistent across single ingredient CHG products and combination CHG/IPA products.

The Agency requested that the following changes in labeling be made so as to furnish adequate information for safe and effective use of the drug:

1) Add the following Warning "Allergy Alert":

   Warnings
   Allergy Alert
   This product may cause a severe allergic reaction. Symptoms may include:
   - wheezing/difficulty breathing
   - shock
   - facial swelling
   - hives
   - rash

   If an allergic reaction occurs, stop use and seek medical help right away.

2) Modify the approved "**Do no use**" and "**Stop use and ask a doctor if**" sections to read as follows:

Do not use

- if you are allergic to chlorhexidine gluconate or any other ingredients in this product

Note that, consistent with its indication, we have subsequently modified this statement to read: "on patients allergic to CHG or any other ingredient in this product".

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

Reviewer's comments: *In response to the FDA's CBE Supplement Request letter, the Sponsor stated that it is aware of the Agency's recent request for a new Warning-Allergy Alert statement in product labeling for chlorhexidine gluconate topical products, and notes that the following statement is already included in its proposed SoluPrep Drug Facts labeling: "Do not use on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product." The Sponsor stated that since the proposed labeling will be discussed with the Agency during the review of this resubmission, it has chosen to wait to make changes in relation to this CHG allergy warning until receiving direction from the Agency with regard to specific text and appropriate location in the Drug Facts labeling during final review.*

*According to 21 CFR 201.66(c)(5)(i), "**For external use only**" and 21 CFR 201.66(c)(5)(ii)(C) and 21 CFR 344.52(c)(1), "**Flammable: Keep away from fire or flame.**" these subheading should come directly under the header **Warnings**. On April 16, 2009, there was a Drug Safety Oversight Board Meeting to discuss health care antiseptics and flammability risk. There have been changes to the product labeling but fires continue to be a problem. There have been up to 100 surgical fires, 20 serious injuries, and 2 deaths from complications related to fires occurring annually. There are multiple sources of fuel, heat, and oxygen which create a perfect fire triangle in the operating room suite. On August 4, 2009, FDA sent a CBE-30 Supplement Request letter to sponsors in regards to the flammability issues on topical antiseptics containing alcohol. FDA determined that a class labeling change was warranted for alcohol-based topical antiseptic products. At that time, labeling included warnings regarding flammability and the need for the product to be completely dry before the patient is either draped for surgery or an ignition source is used. The labeling stated drying takes a "minimum of 3 minutes on hairless skin." The label also had warnings that the user should avoid getting the solution into the hair of the patient as "the solution may take much longer to dry or may not dry completely." The length of time needed for the hair to dry is not defined on the label. FDA decided to include a more specific warning regarding the length of time required for the hair to dry. See DARRTS NDA 21-586 dated August 4, 2009.*

On April 7, 2011, FDA sent another CBE Supplement Request letter to the Sponsor stating that we had reviewed the labeling requests in the letter of August 4, 2009, and determined that the requested labeling revisions were not complete and should include a more specific warning regarding the length of time required for the hair to dry. For example, "Allow the solution to completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair)." See DARRTS NDA 21-586 dated April 7, 2011.

*Therefore, FDA mandated a labeling change across the preoperative skin preparation class of drug products that are alcohol-based and the locations of such warning within the Drug Facts Labeling was below the "**For external use only**." and "**Flammable, keep away from fire or flame**."*

*On February 9, 2017, the Safety Team provided greater clarity and agreed that the new Allergy Alert warning should be placed under **Warnings,** after the "**For external use only**." warning, the "**Flammable, keep away from fire or flame**." warning, and the class flammability warning: "**To reduce risk of fire; PREP CAREFULLY:…**".*

The Sponsor should therefore revise its labeling to read as follows:

Warnings

For external use only. Flammable: Keep away from fire or flame.

To reduce risk of fire; PREP CAREFULLY:

- do not use 26-mL applicator for head and neck surgery
- do not use on an area smaller than (b) (4) Use a smaller applicator instead
- solution contains alcohol and gives off flammable vapors
- avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry.
- do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair)
- do not allow solution to pool
- remove wet materials from prep area

Allergy Alert: This product may cause a severe allergic reaction. Symptoms may include:

- wheezing/difficulty breathing • shock • facial swelling • hives • rash

If an allergic reaction occurs, stop use and seek medical help right away.

(Wrap around format)

Allergy Alert: This product may cause a severe allergic reaction. Symptoms may include:

- wheezing/difficulty breathing
- shock
- facial swelling
- hives
- rash

If an allergic reaction occurs, stop use and seek medical help right away.

(Vertical alignment format)

According to 21 CFR 201.66(d)(4), "Bullets shall be presented in the same shape and color throughout the labeling. The first bulleted statement on each horizontal line of text shall be either left justified or separated from an appropriate heading or subheading by at least two square "ems" (i.e., two squares of the size of the letter "M"). If more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement shall be separated from the beginning of the next bulleted statement by at least two square "ems" and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line." Therefore the Sponsor may either use the wrap around bulleted statements (if spacing is an issue) or vertically align the bulleted statements in accordance with 21 CFR 201.66(d)(4).

*Note that the Sponsor already has the "**Stop and ask the doctor if…"** language as recommended in the February 2nd, 2017 class labeling change. This is sufficient and acceptable.*

b. Do not use

The Sponsor proposes the following labeling:

Proposed 10.5-mL Brite Green and Clear

Note that the first bulleted statement for the 26 mL Tint applicator, "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product," is different from the first bulleted statement for the 10.5 mL Tint and 10.5 mL Clear applicators, "● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol".

Reviewer's comments*: This is not acceptable. The Sponsor will need to revise the 10.5 ml Tint and 10.5 mL Clear applicators statement: "● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol" to read: "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product", so it is consistent with the recent class labeling change for chlorhexidine gluconate allergy warning.*

c. ***Inactive ingredients***

Proposed 10.5 mL Clear

Reviewer's comments*: The Inactive ingredients sections are not acceptable. The Sponsor has not included the Trisodium HEDTA (hydroxylethyl ethylenediamine triacetic acid) as one of the inactive ingredients in the final formulation it will be using for its to-be-marketed antiseptic drug product. The Sponsor will need to include Trisodium HEDTA (hydroxylethyl ethylenediamine triacetic acid) in the inactive ingredients listing in accordance with section 502(e)(1) of the Food, Drug, and Cosmetic Act, as amended by section 412(c) of the Food and Drug Administration Modernization Act of 1997. Additionally, 21 CFR 201.66 also requires that inactive ingredients be listed and included in the Drug Facts Labeling.*

III. RECOMMENDATIONS

We currently recommend a COMPLETE RESPONSE to the Sponsor on the following labeling deficiencies:

Required Changes

1. 26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator

   On February 2, 2017, FDA sent a Changes Being Effected (CBE) Supplement Request letter to the Sponsor requesting labeling revisions. The Agency determined that a class labeling change was warranted for chlorhexidine gluconate (CHG) topical antiseptic drug products. Currently, the Drug Facts Labeling warnings for CHG products are not consistent, regarding allergy to CHG, across the various CHG drug Products that are approved for use.

   Include the allergy alert warning to read as follows:

Warnings

For external use only. Flammable: Keep away from fire or flame.

To reduce risk of fire; PREP CAREFULLY:

- do not use 26-mL applicator for head and neck surgery
- do not use on an area smaller than (b) (4) Use a smaller applicator instead
- solution contains alcohol and gives off flammable vapors
- avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry.
- do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair)
- do not allow solution to pool
- remove wet materials from prep area

Allergy Alert: This product may cause a severe allergic reaction. Symptoms may include:

• wheezing/difficulty breathing • shock • facial swelling • hives • rash

If an allergic reaction occurs, stop use and seek medical help right away.

(Wrap around format)

Allergy Alert: This product may cause a severe allergic reaction. Symptoms may include:

- wheezing/difficulty breathing
- shock
- facial swelling
- hives
- rash

If an allergic reaction occurs, stop use and seek medical help right away.

(Vertical alignment format)

According to 21 CFR 201.66(d)(4), "Bullets shall be presented in the same shape and color throughout the labeling. The first bulleted statement on each horizontal line of text shall be either left justified or separated from an appropriate heading or subheading by at least two square "ems" (i.e., two squares of the size of the letter "M"). If more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement shall be separated from the beginning of the next bulleted statement by at least two square "ems" and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line." Therefore you may either use the wrap around bulleted statements (if spacing is an issue) or vertically align the bulleted statements in accordance with 21 CFR 201.66(d)(4).

2. 10.5 mL Tint Applicator and 10.5 mL Clear Applicator
   Revise the statement under the subheader **Do not use:** "● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol" to read "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product", so it is consistent with the class labeling for chlorhexidine gluconate warning labeling.

3. 26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator
   Included the "Trisodium HEDTA" in the inactive ingredients listing in accordance with section 502(e)(1) of the Food, Drug, and Cosmetic Act, as amended by section 412(c) of the Food and Drug Administration Modernization Act of 1997, and 21 CFR 201.66.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

MICHELLE M JACKSON
04/05/2017

FRANCISCO MARTINEZ-MURILLO
04/05/2017

Labeling Review for
SoluPrep™ Film-Forming Sterile Surgical Solution
Draft Labeling

SUBMISSION DATES:	July 6, 2015; August 25, 2015; November 6, 2015
NDA/SUBMISSION TYPE:	208-288/Original
ACTIVE INGREDIENTS:	2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol, 10.6 mL and 26 mL
DOSAGE FORMS:	Solution
SPONSOR:	3M Health Care Business 3M Center, Bldg. 0275-05-W-06 Saint Paul, MN 55144-1000 Dianne L. Gibbs, RAC Regulatory Affairs Director (651) 737-0844
REVIEWER:	Michelle M. Jackson, PhD IDS Microbiologist, DNDP, ODEIV
ASSOCIATE DIRECTOR FOR LABELING:	Ruth E. Scroggs, PharmD, RPh Associate Director for Labeling, DNDP, ODEIV
PROJECT MANAGER:	Celia Peacock, RDN, MPH, DNDP, ODEIV Senior Regulatory Project Manager

I. BACKGROUND

On July 6, 2015, 3M Health Care submitted NDA 208-288 SoluPrep™ film-forming sterile patient preoperative skin preparation as an orginal new NDA. The sponsor proposes a sterile antiseptic surgical solution containing the active ingredients, chlorhexidine gluconate and isopropyl alcohol in solution with an inactive ingredient 3M film-forming copolymer and other inactive ingredients. Once the solution is applied to the skin, the copolymer would produce a water-insoluble film. (b) (4) Three different applicators are proposed, 10.5 mL "Brite Green" (tinted solution), 10.5 mL "Clear" (nontinted solution), and 26 mL "Brite Green."

On August 20, 2015, an information request sent to the sponsor requested submission of the target product information package insert labeling layout without the annotation. The sponsor responded on August 25, 2015, with submission of the unannotated target product information package insert labeling. On November 6, 2015, the sponsor submitted the target product information package insert with annotation links to the modules within the submission.

The sponsor submitted labeling that identify all changes and supporting annotations of these changes. See list of submitted labeling in the table below:

Submitted Labeling July 6, 2015	Representative of Following SKUs
10.5-mL Brite Green immediate container (handle) clean label	NA
10.5-mL Brite Green immediate container (handle) annotated label	NA
10.5-mL Brite Green consumer information leaflet clean label	NA
10.5-mL Brite Green consumer information leaflet annotated label	NA
10.5-mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
10.5-mL Clear immediate container (handle) clean label	NA
10.5-mL Clear immediate container (handle) annotated label	NA
10.5-mL Clear consumer information leaflet clean label	NA
10.5-mL Clear consumer information leaflet annotated label	NA
10.5-mL Clear outer container (pouch with *Drug Facts*) annotated label	NA
26-mL Brite Green immediate container (handle) clean label	NA
26-mL Brite Green immediate container (handle) annotated label	NA
26-mL Brite Green consumer information leaflet clean label	NA
26-mL Brite Green consumer information leaflet annotated label	NA
26-mL Brite Green outer container (pouch with *Drug Facts*) annotated label	NA
Target Product Information (package insert) annotated label*	NA
Submitted Labeling August 25, 2015	
Target Product Information (package insert) clean label*	NA
Submitted Labeling November 6, 2015	
Target Product Information (package insert) annotated label with links*	NA

*Target Product Information (package insert) label will be reviewed separately.

II. REVIEWER'S COMMENTS

A. SoluPrep™ 10.5-mL Brite Green, 10.5-mL Clear, and 26-mL Brite Green Film-Forming Sterile Solution Secondary Packaging

i. Label Outside *Drug Facts*

a. Principal Display Panel (PDP)

(b) (4)

Proposed 26-mL Brite Green

1. Proprietary Name

Reviewer's comment: Currently, the proprietary name is conditionally acceptable due to the COMPLETE RESPONSE assessment of the submission. DMEPA will conduct another review once all the deficiencies are addressed and the submission is ready for approval.

Background: The proprietary name *SoluPrep*™ was initially submitted under the IND 76,549 on September 22, 2014 for, FDA's review and comments. The Division of Medication Errors Prevention and Analysis (DMEPA) conducted a preliminary review) of the trade name to determine if there were any areas of vulnerability that could lead to medication error (refer to March 3, 2015 review in DARRTS under IND 76549). DMEPA communicated its findings to the Division of Nonprescription Drug Evaluation (DNDP) via e-mail on February 19, 2015. At that time, DMEPA also requested from DNDP, any additional information or concerns that could inform their review. In e-mail correspondence from DNDP to DMEPA on February 20, 2015, we stated that we had no additional concerns with the proposed proprietary name, *SoluPrep*. On March 13, 2015, DMEPA sent a letter to the sponsor indicating that the proprietary name *SoluPrep* was conditionally acceptable and a full complete review would be conducted once the NDA is submitted. On October 19, 2015, DMEPA sent a letter to the sponsor stating that a full review was completed and that the proprietary name *SoluPrep* was conditionally acceptable.

2. **Descriptor**
   The descriptor "Film-Forming Sterile Surgical Solution" was placed directly below the trade name. We compare to other OTC antiseptic drug products labeled with descriptors. Approved product examples include "DuraPrep" labeled with the descriptor "Surgical Solution" and "Scrub-Stat" labeled with the descriptor "Antiseptic Foam Forming Solution". This review finds the current descriptor "Film-Forming Sterile Surgical Solution" acceptable. DMEPA's review (see DARRTS March 21, 2016) concluded that the proposed container labels, carton labeling, and information leaflet for SoluPrep are acceptable from a medication error perspective.

3. **Statement of Identity**

   Reviewer's comment: *For the OTC PDP, 21 CFR 201.61 requires that the statement of identity consisting of the established name of the drug followed by a statement of the pharmacologic category follow the proprietary name and also requires that the font "shall be in a size reasonably related to the most prominent printed matter." The proposed pharmacological category "Patient Preoperative Skin Preparation" is acceptable, but must be bolded and be in a size reasonably related to the most prominent display of the trade name, i.e., half the size of the tradename (SoluPrep™) in accordance with 21 CFR 201.61(c). This will be communicated to the firm.*

   Background: The June 17, 1994, tentative final monograph (TFM) for OTC Healthcare Antiseptic Drug Products (59 FR 31402) proposes the following as acceptable statements of the pharmacology category for OTC use patient preoperative skin preparations: "antiseptic" or "patient preoperative skin preparation." The sponsor's proposed pharmacology category "patient preoperative skin preparation" appears to be more appropriate for the product, based on its indication for use. See 59 FR 31402 at 31443.

4. The statement "for head, neck and small prep area" for the 10.5 mL Tint and 10.5 mL Clear applicators and the statement "for large prep areas below the neck" for the 26 mL Tint applicator are located below the pharmacological category.

   Reviewer's comment*: The proposed statements are acceptable. Backgroiund: The sponsor has incorporated this statement* "for head, neck and small prep area" *for the 10.5 mL Tint and Clear applicators, since this is specifically used for the head, neck, and small prep areas. This is to minimize the risk of excessive saturation of the hair and drape materials, which may be associated with an increased risk of flammability when used in conjunction with electrocautery. This statement was not incorporated in the 26 mL Tint applicator label, since this use is not intended for the head, neck and small prep area, instead the statement "for large prep areas below the neck" was included. This is acceptable.*

5. The statement "Sterile Solution" and "Applicator is sterile if package is intact" are included on the PDP for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint.

   Reviewer's comment*: These statements are consistent with class labeling safety changes requested in 2013 and are acceptable.*

   Background: On November 14, 2013, FDA sent a CBE supplement request letter to sponsors requesting labeling changes for topical antiseptic drug products indicated for patient preoperative skin preparation. FDA determined that a class labeling change was warranted for patient preoperative skin preparation based on our review of safety

information. We have performed a review of safety issues pertaining to contaminated topical antiseptic products. Therefore, to help reduce the risk of contamination and subsequent infections, the FDA has requested class labeling changes for topical antiseptic drug products indicated for patient preoperative skin preparation as follows:

- *Revise product labels to indicate the sterility or non-sterility of the drug product.*
- *Secondary packaging (lidding) single use applicators that are sterilized in an enclosed package should also include a sterility statement regarding the status of the applicator. The sterility statement will inform the healthcare professionals of the sterilization status (sterile or non-sterile) of the applicator so that healthcare professionals can decide whether the product may be introduced into a sterile field. This statement should be no longer than the "Non-sterile Solution" or "Sterile Solution" statement on the PDP.*
- *An applicator that is sterilized should include the following sterility statement: "Applicator is sterile if package is intact." This statement should immediately follow the solution sterility statement, which should be at least equally prominent as the applicator statement in terms of font size and other formatting.*

6. The NDC number 17518-080-02 (for the 10.5 mL Tint), 17518-081-02 (for the 10.5 mL Clear), and 17518-080-01 (for the 26 mL Tint) is located on the upper right corner of the PDP.

   ***Reviewer's comment**: The NDC numbers are in accordance with 21 CFR 207.35(b)(i) through (iv). They are acceptable.*

7. The reference catalog numbers, 7133 (for the 10.5 mL Tint), 7134 (for the 10.5 mL Clear), and 7130 (for the 26 mL Tint) are located on the upper right corner of the PDP.

   ***Reviewer's comment**: This is acceptable.*

8. On the upper right side corner of the PDP, the sponsor has included the statement "Single Use Only" and the do not reuse symbol located below the NDC number for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint.

   ***Reviewer's comment**: This is acceptable.*

9. The net contents "0.36 fl oz ● 10.5 mL" (for the 10.5 mL Tint and Clear) and "0.9 fl oz ● 26 mL" (for the 26 mL Tint) is located at the bottom of the PDP.

   ***Reviewer's comment**: The net content is in accordance with 21 CFR 201.62. This is acceptable.*

10. The sponsor has included a green banner with the statement "Brite Green" for the 10.5 mL Tint applicator and 26 mL Tint applicator and a grey banner with the statement "Clear" for the 10.5 mL applicator to indicate the color of the surgical prep solutions. This is located above the enclosed ***Drug Facts*** box.

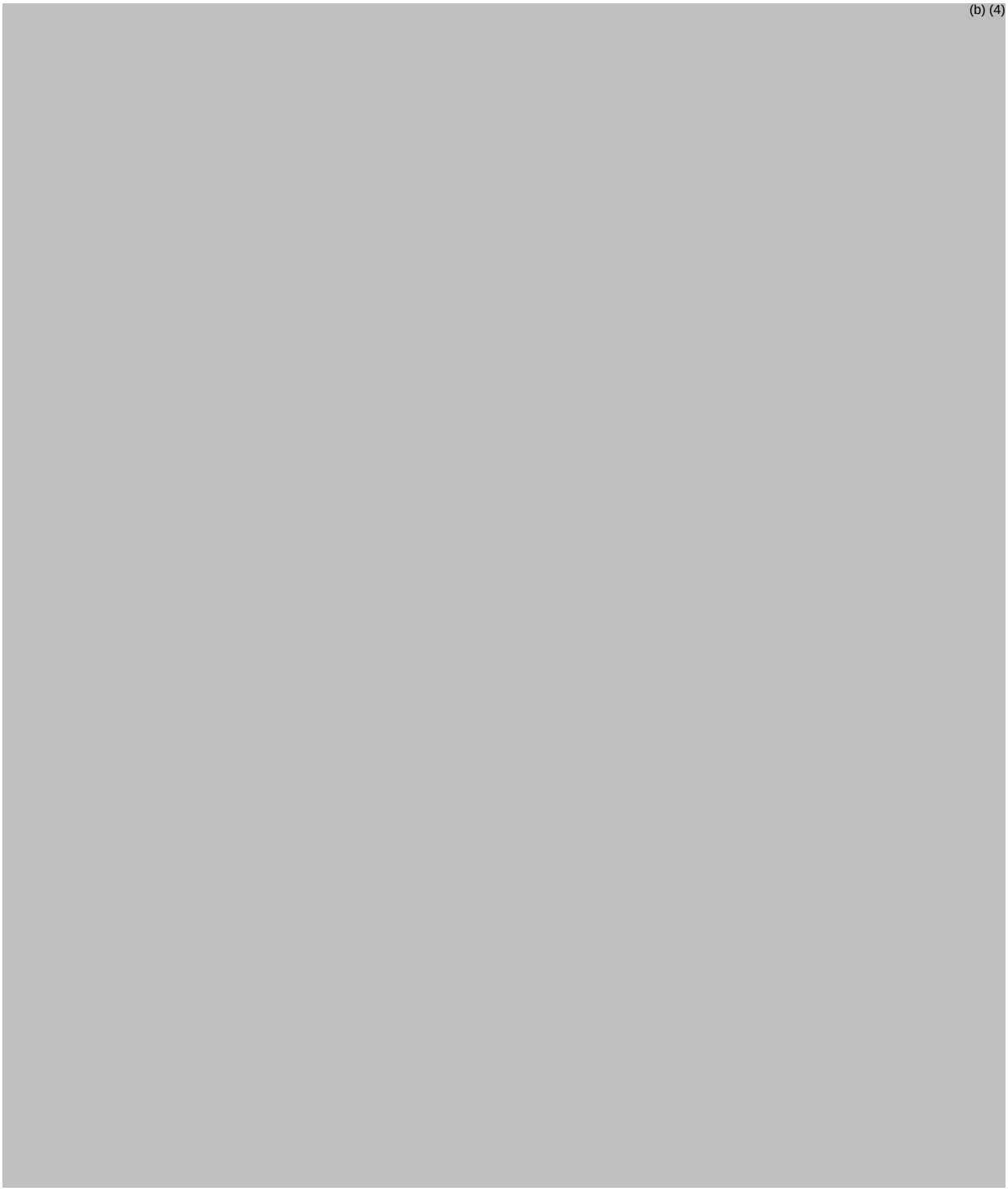
***Reviewer's comment**: This is acceptable.*

b. Outside of *Drug Facts*

1. The sponsor described that the lot number and expiration date codes is applied to the applicator barrel for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint applicators.

Reviewer's comment: *This is acceptable.*

(b) (4)



Reviewer's comment*: The sponsor has incorporated FDA's class labeling change for alcohol-based topical antiseptic products. This is acceptable.*

Background: On August 4, 2009, FDA sent a CBE-30 Supplement Request letter to sponsors requesting labeling revisions (products containing alcohol). FDA determined that a class labeling change was warranted for alcohol-based topical antiseptic products. The previous labeling had included warnings regarding flammability and the need for the product to be completely dry before the patient is either draped for surgery or an ignition source is used. The previous label had stated that drying takes a "minimum of 3 minutes on hairless skin." The previous label also had warnings that the user should avoid getting the solution into the hair of the patient as "the solution may take much longer to dry or may not dry completely." The length of time needed for the hair to dry was not defined on the previous label. FDA's decision to include a more specific regarding the length of time required for the hair to dry was based on the following:

- *The alcohol-based topical antiseptic products are associated with an increased incidence of surgical suite fires. Most of the documented fires are associated with the use of alcohol based topical antiseptics in combination with electrocautery, electrosurgery, or laser surgery, particularly when the surgical site is not completely dry after the prep is applied.*
- *Hirsute areas are particular risk factor. Recently completed studies showed extended drying times when the products are used in hirsute areas.*

FDA requested that the labeling be revised as follows:

- *Revise the statement under the Drug Facts Warnings and the boxed flammability warning to read "**To reduce risk of fires, PREP CAREFULLY:**"*
- *Revise the following bulleted statements under the subheading "**To reduce risk of fire, PREP CAREFULLY**:" to read*
  - *"● avoid getting solution into hairy areas. **Wet hair is flammable**. Hair may take up to 1 hour to dry." The statement "**Wet hair is flammable**" should be bolded and in red print.*
  - *"● do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair)."*
- *Revise the bulleted statement under the Directions: "● avoid getting solution into hairy areas. Wet hair is flammable. Hair may take up to 1 hour to dry."*

*FDA allowed the use of pictograms to improve visibility and prominence to decrease the incidence of fires in operating rooms. FDA had concerns of reports of burns which have been connected with the use of the product. On November 5, 2001, FDA requested that the sponsor (3M) improve the labeling to address the issue of flammability for the product solution containing alcohol (DuraPrep Surgical Solution). Therefore, the use of a pictogram flame improves the visibility and prominence of information relevant to the risk management of the product under **Warnings** is acceptable.*

The statement for the 26 mL Tint applicator "● do not use 26-mL applicator for head and neck surgery" and "● do not use on an area smaller than (b) (4) *. Use a smaller applicator instead." have been included in the **Warnings** section. This is acceptable. The statements for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint applicators "● do not allow solution to pool" and "● remove wet materials from prep area" have been included the **Warnings** section. This is acceptable.*

(b) (4)

The first bulleted statement for the 26 mL Tint applicator "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product" is different from the first bulleted statement for the 10.5 mL Tint and 10.5 mL Clear applicators "● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol".

Reviewer's comment*: This is not acceptable. The sponsor will need to revise the 26 mL Tint applicator statement "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product" to read "● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol" so it is consistent with the 10.5 ml Tint and 10.5 mL Clear applicators and class labeling for chlorhexidine gluconate and isopropyl alcohol labeling.*

(b) (4)

The statement "● use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." has been placed as the second bulleted statement under the warning subheading, **When using this product**, for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint applicators.

Reviewer's comment*: This section is not acceptable as is because it is not consistent with class labeling as follows:*

Inform the sponsor that the infant warning statement "● use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." be moved from under "when using this product" to under Directions as the first bulleted statement. This is consistent with class labeling.

Inform the sponsor that the warnings statement "● to avoid skin injury, care should be taken when removing drapes, tapes, etc…applied over film" be added as a second bullet under the subheading When using this product consistent with class labeling.

This statement is currently included in the DuraPrep Surgical Solution labeling. Both the SoluPrep Film-Forming Sterile Surgical Solution and DuraPrep Surgical Solution are film-forming antiseptic products.

Background: On October 21, 2011, FDA sent a CBE Supplement Request letter to sponsors (products containing chlorhexidine gluconate) requesting labeling revisions. FDA has determined that a class labeling change was warranted for chlorhexidine gluconate (CHG) topical antiseptic drug products. At that time, the Drug Facts label warnings for CHG products were not consistent regarding use in infants, across the various CHG drug products that are approved for use. The decision to request the inclusion of a consistent warning regarding use of the CHG products in infants. This review was triggered by a 15-day MedWatch report describing a case of a chemical burn sustained by a neonate on whom a CHG-containing solution had been applied. FDA found 15 additional cases of severe irritation or chemical burns in FDA's Adverse Event Reporting System involving infants less than 3 months of age, after use of products containing only CHG or combination of CHG and isopropyl alcohol.

In order to reduce the incidence of skin irritation and burns in infants, and in the interest of clear and uniform labeling, FDA is requiring that all CHG topical antiseptic product labels include language regarding this. Even labels that already state "Do not use in infants" should be revised so that they will be consistent with all other CHG product labels. Therefore, the same labeling was required to be consistent across single ingredient CHG products and combination CHG/IPA products. FDA request that the infant warning statement "● use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." to be placed as the first bulleted statement under ***Directions****.*

Therefore, the sponsor will need to remove the statement "● use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." from under the subheading ***When using this product*** *to be place as the first bulleted statement under* ***Directions****.*

This reviewer also recommends that the statement "● to avoid skin injury, care should be taken when removing drapes, tapes, etc…applied over film" be included under the subheading ***When using this product****. This statement is currently included in the DuraPrep Surgical Solution labeling. Both the SoluPrep Film-Forming Sterile Surgical Solution and DuraPrep Surgical Solution are film-forming antiseptic products.*

(b) (4)

Reviewer's comment*: This is acceptable.*

(b) (4)

Reviewer's comment*: This is not acceptable. Inform the sponsor to insert the statement "● use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." as the first bulleted statement under* ***Directions****. See discussion above under* ***When using this product****.*

(b) (4)

Reviewer's comment*: This is acceptable.*

(b) (4)

Reviewer's comment*: This is acceptable. FDA will allow the use of pictograms to improve visibility and prominence to decrease the incidence of fires in the operating rooms. FDA is concerned about reports of burns that have been connected with the use of this product. In the labeling review for DuraPrep Surgical Solution (DARRTS September 15, 2006), FDA approved the use of the no pooling pictogram. The pictogram used for the SoluPrep Film-Forming Surgical Solution is the same for the DuraPrep Surgical Solution.*

The bulleted statement "● avoid getting solution into hairy areas. ***Wet hair is flammable.*** *Hair may take up to 1 hour to dry." for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint applicators is acceptable. See discussion above under* ***Warnings****.*

(b) (4)

Reviewer's comment*: FDA has allowed the red bolding of the statement "wait until solution is completely dry" on other alcohol-based topical antiseptics (e.g., ChloraPrep). This is acceptable.*

(b) (4)

***Reviewer's comment**: This is acceptable. FDA will allow the use of pictograms to improve visibility and prominence to decrease the incidence of fires in the operating rooms. FDA is concerned about reports of burns that have been connected with the use of this product. In the labeling review for DuraPrep Surgical Solution (DARRTS September 15, 2006), FDA approved the use of the do not use with electrocautery pictogram. The pictogram used for the SoluPrep Film-Forming Surgical Solution is the same for the DuraPrep Surgical Solution.*

(b) (4)

***Reviewer's comment**: The third bulleted statement is not acceptable. The sponsor must remove the statement "● the tint will slowly fade from the skin.* (b) (4) *." for the 10.5 mL Clear applicator because there is no tint in the solution, therefore is not applicable.*

(b) (4)

***Reviewer's comment**: The Inactive ingredients sections are acceptable.*

(b) (4)

iii. Format Specifications

a. The font specifications are in accordance with 21 CFR 201.66. This is acceptable.

B. SoluPrep™ Film-Forming Sterile Solution 10.5 mL Brite Green, 10.5 mL Clear, and 26 mL Brite Green Applicator Handle (Barrel)

(b) (4)

a. The proprietary name, descriptor, and statement of identitiy information are acceptable, see section II.A.i.a.1, 2, and 3.

b. The pharmacological category "Patient Preoperative Skin Preparation" should be bolded and be in a size reasonably related to the most prominent display of the trade name, i.e., half the size of the tradename (SoluPrep™) in accordance with 21 CFR 201.61(c).

c. The statement "for head, neck and small prep area" for the 10.5 mL Tint and 10.5 mL Clear applicators and the statement "for large prep areas below the neck" for the 26 mL Tint applicator are located below the pharmacological category. This is acceptable, see section II.A.i.a.4. for detailed description.

d. The statement "Sterile Solution" and "Applicator is sterile if package is intact" are included on the PDP for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint. This is acceptable, see section II.A.i.a.5 for detailed description.

e. The NDC number 17518-080-02 (for the 10.5 mL Tint), 17518-081-02 (for the 10.5 mL Clear), and 17518-080-01 (for the 26 mL Tint) is located on the upper right corner of the PDP.

Reviewer's comment: *The NDC number is in accordance with 21 CFR 207.35(b)(i) through (iv). This is acceptable.*

f. The reference catalog number 7133 (for the 10.5 mL Tint), 7134 (for the 10.5 mL Clear), and 7130 (for the 26 mL Tint) is located on the right side of the PDP green banner.

Reviewer's comment: *This is acceptable.*

g. On the upper right side corner of the PDP, the sponsor has included the sterility statement "STERILE / EO" symbol located below the NDC number for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint.

Reviewer's comment: *This is acceptable.*

h. The net contents "0.36 fl oz ● 10.5 mL" (for the 10.5 mL Tint and Clear) is located above the pictogram of the applicator and direction for use. The net contents "0.9 fl oz ● 26 mL" (for the 26 mL Tint) is located below the statement "Applicator is sterile if package is intact".

Reviewer's comment: *The net content is in accordance with 21 CFR 201.62. This is acceptable.*

i. The sponsor included a pictogram of the applicator for the 10.5 mL Tint and Clear and 26 mL Tint along with brief directions on how to activate the applicator.

Proposed 10.5 mL Brite Green & Clear **Proposed 26 mL Brite Green**

Reviewer's comment: *This is acceptable.*

j. The statements "External use only," "Professional use only," and "Read Drug Facts information before use" for the 10.5 mL Tint and Clear and 26 mL Tint applicators is located below the pictogram of the .

Reviewer's comment: *This is acceptable.*

k. On the right side above the pictogram of the applicator, the sponsor has included the statement "Single Use Only" and the do not reuse symbol for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint applicators.

Reviewer's comment*: This is acceptable.*

ii. Applicator Handle (Barrel) Flammability Warning Box

Proposed 10.5 mL Brite Green & Clear **Proposed 26 mL Brite Green**

a. This is acceptable because FDA has allowed the use of pictograms to improve visibility and prominence to decrease the incidence of fires in the operating rooms. FDA is concerned about reports of burns that have been connected with the use of this product. In the labeling review for DuraPrep Surgical Solution (DARRTS September 15, 2006), FDA approved the use of the do not use with electrocautery pictogram. The pictogram used for the SoluPrep Film-Forming Surgical Solution is the same for the DuraPrep Surgical Solution. This is acceptable. See also section II.A.ii.c.1. for detailed description regarding the flammability warning.

C. SoluPrep™ Film-Forming Sterile Solution 10.5 mL Brite Green, 10.5 mL Clear, and 26 mL Brite Green Consumer Information Leaflet

i. Consumer Information Leaflet PDP

(b) (4)

Proposed 26 mL Brite Green

a. The proprietary name, descriptor, and statement of identity information are acceptable, see section II.A.i.a.1, 2, and 3.

b. The pharmacological category "Patient Preoperative Skin Preparation" must be bolded and be in a size reasonably related to the most prominent display of the trade name, i.e., half the size of the tradename (SoluPrep™) in accordance with 21 CFR 201.61(c) and is therefore unacceptable.The sponsor will be informed.

c. The statement "for head, neck and small prep area" for the 10.5 mL Tint and 10.5 mL Clear applicators and the statement "for large prep areas below the neck" for the 26 mL Tint applicator are located below the pharmacological category. This is acceptable, see section II.A.i.a.4. for detailed description.

d. The statement "Sterile Solution" and "Applicator is sterile if package is intact" are included on the PDP for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint. This is acceptable, see section II.A.i.a.5 for detailed description.

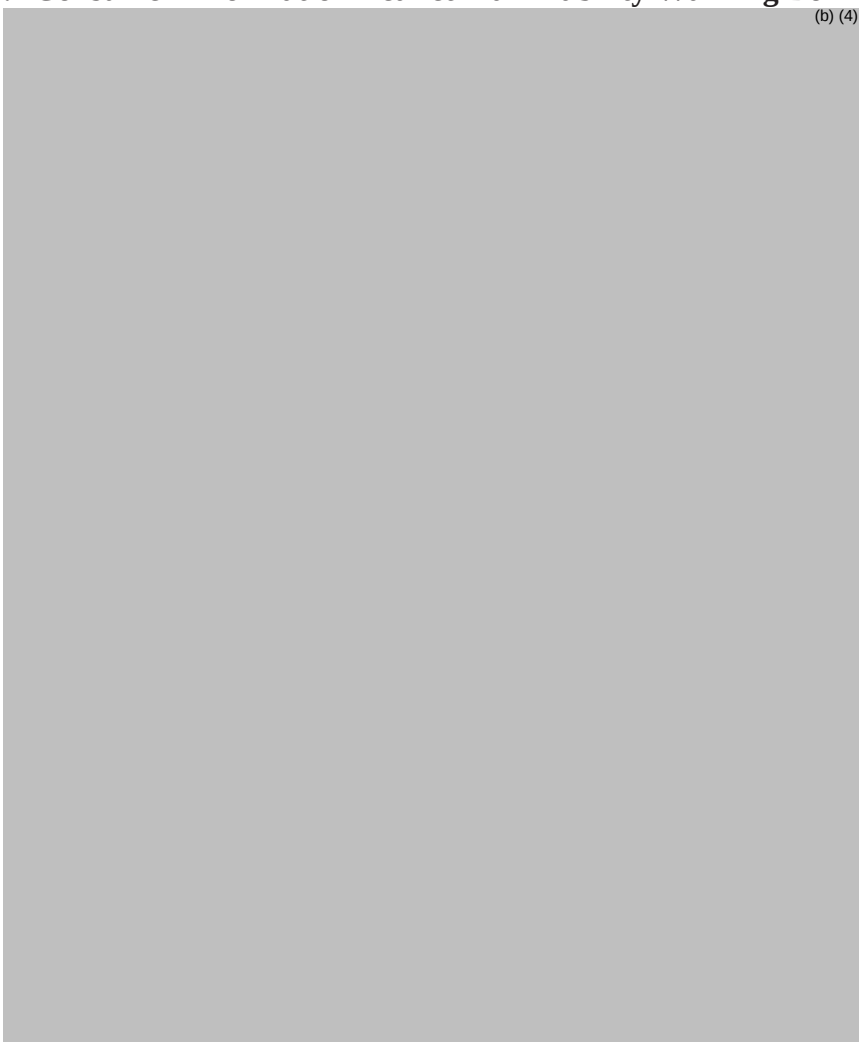
e. The NDC number 17518-080-02 (for the 10.5 mL Tint), 17518-081-02 (for the 10.5 mL Clear), and 17518-080-01 (for the 26 mL Tint) is located on the upper right corner of the PDP.

Reviewer's comment: *The NDC number is in accordance with 21 CFR 207.35(b)(i) through (iv). This is acceptable.*

f. On the upper right side corner of the PDP, the sponsor has included the sterility statement "STERILE / EO" symbol located below the NDC number for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint applicators.

Reviewer's comment: *This is acceptable.*

ii. Consumer Information Leaflet Flammability Warning Box



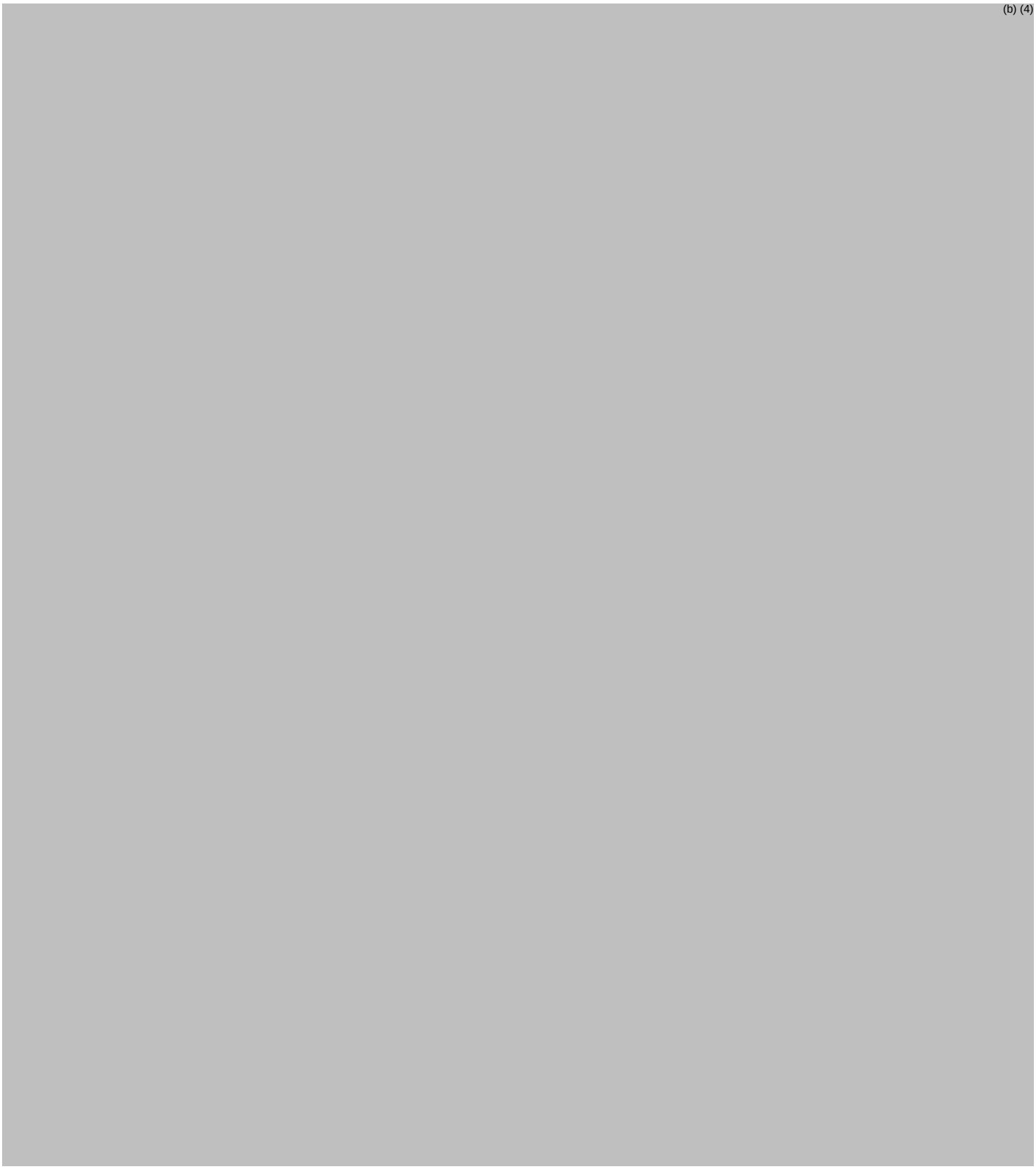
Proposed 10.5 mL Brite Green & Clear

Proposed 26 mL Brite Green

a. This is acceptable. FDA has allowed the use of pictograms to improve visibility and prominence to decrease the incidence of fires in the operating rooms. FDA is concerned about reports of burns that have been connected with the use of this product. In the labeling review for DuraPrep Surgical Solution (DARRTS September 15, 2006), FDA approved the use of the do not use with electrocautery pictogram. The pictogram used for the SoluPrep Film-Forming Surgical Solution is the same for the DuraPrep Surgical Solution. This is acceptable. See also section II.A.ii.c.1. for detailed description regarding the flammability warning.

iii. Bottom Half of Consumer Information Leaflet

(b) (4)



Proposed 26 mL Brite Green

a. On the left side below the flammability warning box, the sponsor has included the statement "Single Use Only" and the do not reuse symbol for the 10.5 mL Tint, 10.5 mL Clear, and 26 mL Tint applicators.

***Reviewer's comment**: This is acceptable.*

b. The statement "SoluPrep™ Surgical Solution is a film-forming, sterile patient preoperative skin preparation. Each unit dose applicator contains 0.36 fl oz (10.5 mL) of solution which covers a 13 in. x 13 in. area." is included on the 10.5 mL Tint and Clear applicators. The statement "SoluPrep™ Surgical Solution is a film-forming, sterile patient preoperative skin preparation. Each unit dose applicator contains 0.9 fl oz (26 mL) of solution which covers a 19.5 in. x 19.5 in. area (approximately from shoulder to groin in an average full size adult)." is included for the 26 mL Tint applicator.

***Reviewer's comment**: This is acceptable.*

c. The statement "For procedures requiring less coverage, a smaller applicator is available (7133 – Tinted or 7134 – Clear). The smaller applicator size contains 0.36 fl oz (10.5 mL) of solution which covers a 13 in. x 13 in. area. Do not use more than required for the area." is included for the 26 mL Tint applicator.

***Reviewer's comment**: This is acceptable.*

d. The statement "3M recommends all users participate in product in-service training prior to use. In-servicing is available on video, from your 3M sales representative or at the 3M website (www.3m.com)." is included for the 10.5 mL Tint and Clear and 26 mL Tint applicators.

***Reviewer's comment**: This is acceptable.*

e. The reference catalog number 7133 (for the 10.5 mL Tint), 7134 (for the 10.5 mL Clear), and 7130 (for the 26 mL Tint) is located on the left side below the 3M in-serve training statement.

***Reviewer's comment:** This is acceptable.*

f. The net contents "0.36 fl oz ● 10.5 mL" (for the 10.5 mL Tint and Clear) and "0.9 fl oz ● 26 mL" (for the 26 mL Tint) is located on the right side below the 3M in-service training statement.

***Reviewer's comment:** The net content is in accordance with 21 CFR 201.62. This is acceptable.*

g. The bar codes "(01)00317518081026" for the 10.5 mL Clear and "(01)00317518080029" for the 10.5 mL Tint applicators have been included on the consumer information leaflet. However, there was no bar code proposed for the 26 mL Tint applicator.

***Reviewer's comment:** This is not acceptable. The barcode is not in accordance with 21 CFR 201.25(c) for the 26 mL Tint applicator.*

Background: The barcode must be placed somewhere on the labeling. Since the 10.5 mL and 26 mL applicators are not packaged in a carton, then the barcode must be displayed somewhere on the secondary packaging. According to CFR 201.25(c)(2), "The bar code must appear on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act." Section 201(k) states the following: "The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information, also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper."

h. The following statements pictured below have been included on the 10.5 mL Tint and Clear and 26 mL Tint applicators.

Proposed 26 mL Brite Green, 10.5 mL Brite Green and Clear

Reviewer's comment: *This is acceptable.*

III. RECOMMENDATIONS

We currently recommend a COMPLETE RESPONSE to the sponsor on the following labeling deficiencies:

Required Changes

1. 26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator
   Bold and increase the size of the pharmacological category "Patient Preoperative Skin Preparation" to be the same size as the established name or half the size of the most prominent display of the tradename (SoluPrep™) in accordance with 21 CFR 201.61(c). This applies to the Drug Facts (secondary packaging - lidding), applicator barrel handle, and the consumer information leaflet.

2. 26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator
   Remove the statement "● use with care in premature infants or infants under 2 months of age. The products may cause irritation or chemical burns." from under the subheader **When using this product** and place it under ***Directions*** as the first bulleted statement.

   On October 21, 2011, FDA sent a CBE Supplement Request letter to sponsors (products containing chlorhexidine gluconate) requesting labeling revisions. FDA has determined that a class labeling change was warranted for chlorhexidine gluconate (CHG) topical antiseptic drug products. At that time, the Drug Facts label warnings for CHG products were not consistent regarding use in infants, across the various CHG drug products that are approved for use. In order to reduce the incidence of skin irritation and burns in infants, and in the interest of clear and uniform labeling, FDA is requiring that all CHG topical antiseptic product labels include language regarding this. Even labels that already state "Do not use in infants" should be revised so that they will be consistent with all other CHG

product labels. Therefore, the same labeling was required to be consistent across single ingredient CHG products and combination CHG/IPA products. FDA requested sponsor to include the infant warning statement "● use with care in premature infants or infants under 2 months of age. The products may cause irritation or chemical burns." to be placed as the first bulleted statement under ***Directions***.

3. 26 mL Tint Applicator, 10.5 mL Tint Applicator and 10.5 mL Clear Applicator
   Include the statement "● to avoid skin injury, care should be taken when removing drapes, tapes, etc…applied over film" under the subheader **When using this product**. This statement is currently included in the DuraPrep Surgical Solution labeling. Both the SoluPrep Film-Forming Sterile Surgical Solution and DuraPrep Surgical Solution are film-forming antiseptic products.

4. 26 mL Tint Applicator
   Revise the statement under the subheader **When using this product** "● on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product" to read "● on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol" so it is consistent with the 10.5 mL Tint and 10.5 mL Clear applicators and class labeling for chlorhexidine gluconate and isopropyl alcohol labeling.

5. 26 mL Tint Applicator
   Include a barcode for the 26 mL Tint applicator for the consumer information leaflet to be consistent with the 10.5 mL Tint and Clear applicator consumer information leaflet and so that it is in accordance with 21 CFR 201.25(c).

Recommended Changes

6. 10.5 mL Clear Applicator
   Remove the statement "● the tint will slowly fade from the skin. Alcohol may be used to remove the tint if desired." for the 10.5mL Clear applicator, because there is no tint in the solution.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MICHELLE M JACKSON
03/31/2016

RUTH E SCROGGS
03/31/2016

Clinical Inspection Summary

Date	3/18/16
From	Sharon Gershon, Pharm.D.
To	Francis Becker, Medical Team Leader Teresa Podruchny, Medical Officer Celia Peacock, Regulatory Health Project Manager Division of Non Prescription Drug Products
NDA #	208288
Applicant	3M Health Care
Drug	SoluPrep™ Film-Forming Sterile Surgical Solution
NME	No
Therapeutic Classification	Priority
Proposed Indication	Patient preoperative skin preparation, for the preparation of skin prior to surgery, and to help reduce bacteria that can potentially cause skin infection
Consultation Request Date	November 13, 2015
Summary Goal Date	April 1, 2016
Action Goal Date	April 1, 2016
PDUFA Date	May 6, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

Three clinical investigator sites were inspected, and four protocols audited in support of NDA 208288. Study EM-05-12760 (pivotal) and study EM-05-13509 (antimicrobial persistence study) was audited at Dr. Bashir's site in Sterling, Virginia (Micro Bio Test). Study EM-05-13260 (pivotal) was audited at Dr. Paulson's site in Bozeman, Montana (BioScience Laboratories). Study EM-05-12853 (irritation patch/safety study) was audited at Dr. Caswell's site (Consumer Product Testing, NJ). No regulatory violations were found at any inspected site, and all inspections were classified NAI. OSI recommends the data be considered acceptable in support of the NDA.

II. BACKGROUND

3M™ Film-Forming Sterile Surgical Solution is indicated for use as a patient preoperative skin preparation, for the preparation of the skin prior to surgery, and to help reduce bacteria that can potentially cause skin infection. The topical solution consists of two well-known active ingredients: chlorhexidine gluconate (2% w/v CHG) and isopropyl alcohol (70% v/v IPA).

The following two studies were used to demonstrate efficacy for this application:

EM-05-12760 (Pivotal study) : Assessment of the Antimicrobial Efficacy of 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation against Resident Human Skin Flora on the Abdominal and Inguinal Regions.

EM-05-13260 (Pivotal study): Assessment of the Antimicrobial Efficacy of 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation against Resident Human Skin Flora on the Abdominal and Inguinal Regions

The following two studies were conducted as supporting studies under the NDA:

EM-05-013509 (Persistence of efficacy study): Assessment of the Persistent Antimicrobial Efficacy of 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation against Resident Human Skin Flora on the Abdominal and Inguinal Regions

EM-05-12853 (Safety study): Cumulative Irritation Patch Test (21-day) with Challenge of 3M CHG/IPA Film-Forming Skin Prep Colorless and with Tint, Marketed Active Control, Positive Control, and Negative Control.

Study **EM-05-12760** was a randomized, controlled, third-party blind, single-center study (Micro Bio Test, Sterling, Virginia) in healthy volunteers to evaluate the antimicrobial efficacy of tinted 3M CHG/IPA Prep 10.5 mL and 26 mL compared with ChloraPrep and saline. Each subject received two of the four possible study products on the abdomen and/or two of the four possible study products on the groin. For the abdominal region a total of 406 subjects were randomized to 6 treatment groups and for the inguinal region a total of 391 subjects were randomized to 6 treatment groups.

Study EM-05-13260 was a randomized, controlled, third-party blind, single-center study (BioScience Laboratories, Bozeman, MT) in healthy volunteers to evaluate the antimicrobial efficacy of colorless 3M CHG/IPA Prep 10.5 mL with and without (hydroxyethyl) ethylenediaminetriacetic acid (HEDTA) compared with ChloraPrep® Patient Preoperative Skin Preparation (ChloraPrep) and saline. The formulation of 3M CHG/IPA Prep with HEDTA was used in this study to confirm that the efficacy and safety of 3M CHG/IPA was unchanged with a trace amount of HEDTA added to the formulation to prevent the formation of crystals.

Reasons for Site Selection: The Review Division selected inspections at two sites where pivotal studies EM-05-12760 and EM-05-013260 were conducted, one site where the persistence of efficacy study EM-05-013509 was conducted, and one site where the safety study EM-05-12853 was conducted. For the two pivotal studies, the Review Division raised several questions: 1) why the test product and active control always failed to meet the 70% responder rate in the groin region at BioSciences Laboratories (Bozeman, Montana), whereas both the test products and active control met the 70% responder rate in the same region at Micro Bio Test (Sterling, Virginia); and 2) why Micro Bio Test had fewer screen failures for each anatomic site (20-24%) compared to BioScience Laboratories (45%).

III. RESULTS (by site):

Name of CI, Address	Protocol # , Site #, and # of Subjects	Inspection Dates	Final Classification
M. Hamid Bashir Micro Bio Test Sterling, VA 20164	EM-05-12760 Screened: 511 Enrolled: 489 EM-05-013509 Screened: 35 Enrolled: 27	11/23/2015 – 12/2/2015	NAI NAI
Daryl S. Paulson BioScience Laboratories Bozeman, MT 59718	EM-05-13260 Screened: 1035 Enrolled: 632	11/30/2015 – 12/10/2015	NAI
Michael Caswell, Ph.D., Consumer Product Testing Company Fairfield, NJ 07004	EM-05-12853 Screened: 235 Enrolled: 205	2/2 – 4/2016	NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. M. Hamid Bashir
Micro Bio Test
105 Carpenter Drive
Sterling, VA 20164

The inspection audited two protocols: Study EM-05-012760 (pivotal) and Study EM-05-13509 (persistence of efficacy). A prior FDA inspection of Dr. Bashir at Micro Bio Test was conducted April 19 – 27, 2009 and was classified NAI.

For Study EM-05-13509, 35 subjects were screened, 27 subjects enrolled, and 25 subjects completed the study. The field investigator reviewed subject files

for 27 subjects. There was no evidence of under-reporting of adverse events and the baseline, 48 hour, and 72 hour data were verifiable.

For Study EM-05-12760, 511 subjects were screened, 489 subjects treated, and 426 subjects completed the study. The field investigator audited 47 subject files. Data audits were done by comparing source data in the subjects' files with the data listings provided with the assignment. Items reviewed included subject demographics, eligibility criteria, protocol deviations, adverse events, physical assessments, and efficacy assessments. Other items audited included test article administration and accountability, custody and retention of records, and monitoring.

Several questions were addressed during the inspection. The test product for study EM-05-12760 and active controls all met the 70% responder rate in the groin area. When asked why he thought the site had a high responder rate compared to the site in Bozeman, Montana, Dr. Bashir stated that study staff were provided with a step by step training on all study-related techniques such as the cup scrub methods, collection of microbial samples, mode of application of test products, timing, and plating.

When asked why the study had fewer screen failures (20-24% fewer) compared to the other site, Dr. Bashir indicated that potential reasons might be the amount of compensation ($500) for adherence to the study protocol, whereas other clinical sites may offer only $50. At his site, if a subject did not adhere to the protocol, he/she would lose $200. Dr. Bashir also attributed the lower number of screen failures to population diversity and greater humidity in the Washington D.C. metropolitan region. Higher humidity and greater population diversity could contribute to much greater bacterial counts of affected regions leading to more subjects becoming eligible to participate. In contrast, Montana or other sites might enroll only Caucasians and have a drier climate.

During the record review of both studies, the field investigator noted employee participation. Dr. Bashir stated that there were no coercions of employees to participate. There did not appear to be any employees that participated more than one time. Also, Study EM-05-13509 occurred in 2015, well beyond the thirty day participation restriction from participation in other studies.

Skin irritation scores (erythema, edema and rash) as provided in the data listings were compared to source data and there were no discrepancies. Skin irritation scores were documented using the Skin Irritation Rating Scale, and it was not noted if the adverse events as documented in the source records used the subjects own language which might have led to a different coding or severity of adverse event.

Monitoring for the study was done by representatives from the Sponsor. Monthly visits were conducted for Study EM-05-012760 between October 8, 2013 and June 24, 2014; for Study EM-05-13509, monitoring occurred between April 14 – 23, 2015.

Protocol deviations were noted for plating times beyond the thirty minutes after collection at various time points. For example, for Subject (b) (6) ten minute contact times for left and right groin and 6 hour contact time for right groin were plated beyond 30 minutes after collection by approximately 1 to 5 minutes. For Subject (b) (6) baseline left and right for both abdomen and groin regions were plated beyond 30 minutes after collection; and for Subject (b) (6) the 10 minute contact sample from the right groin was collected at 11 minutes which was a 30 second delay. There were a total of 10 subjects who had plating times beyond the 30 minutes. In the opinion of the clinical investigator, the delay did not have any negative impact on the study.

For Study EM-05-012760, the primary efficacy data as shown in the data listings was expressed in logarithmic values. The data at the site was expressed in colony forming units (CFU) and Dr. Bashir stated that 3M Healthcare calculated these logarithmic values. The field investigator compared the raw data on the case report form, expressed as colony forming units (CFU) with source data for the abdomen and groin regions for the 47 subjects, and he found no discrepancies.

For Study EM-05-013509, raw data was expressed as CFU in both abdomen and groin regions. Dr. Bashir provided the field investigator with the formula for log conversion of the CFU and gave him a logarithm calculator function to do the calculation. When he calculated the baseline, 48 hour and 72 hour logarithm values for 25 subjects, he did not find any inconsistencies between the sponsor's data listings and raw data at the site.

The field investigator interviewed Dr. Bashir about the technique used, and observed staff apply treatment and collect samples for an un-related study. The field investigator collected the Standard Operating Procedures (SOPs) for the Preoperative Skin Preparation technique, for the Ten-fold Serial Dilutions, and for Counting and Calculating the CFU. Dr. Bashir explained the scrubbing technique used during the EM-05-12760 study.

<u>Description of Technique:</u> *The field investigator observed staff apply treatment and collect samples for another un-related study. For treatment and sample collection, two technicians stood opposite each other on either side of the abdomen or groin region of the patient. Male technicians attended to male subjects while female technicians attended to female subjects in adjacent stalls. Before sampling the patient had templates marked on the abdominal and inguinal regions. The templates were divided into four regions as diagramed on Page 4 of the Study EM-0512760 informed consent document. A stainless steel, interior diameter 3.8 cm cylinder (cup scrub) was pressed against the patient's flesh and a predetermined quantity of solutions was dispensed with a pipette. Dr. Bashir stated that during the EM-0512760 study, 1 ml of the film making solution triacetin was pipetted in the cup scrub. Each technician had a stopwatch to observe correct timing. The scrub application time with isopropyl alcohol at the abdomen was 30 seconds and two minutes at the groin region with a rubber*

policeman. According to Dr. Bashir, for the baseline sample, scrubbing is in a basket-weave like motion. The first two minute scrub, 2 ml solution is scrubbed for one minute, 1 ml triacetin is pipetted in the scrub cup, followed by an additional 3 ml solution and scrubbing for one minute. A drying time of three minutes follows. Post prep sampling is in a circular motion for 30 seconds within the scrub cup. Post prep samples were collected at 30 seconds, 10 minutes, and 6 hour intervals.

Samples were collected with a transfer pipette into pre-labeled vials. The vials were handed by a facilitator in the patient area to an employee in the plating room. One ml sample was plated for each of two separate plates. Ten-fold dilutions are done at -5 levels for groin and -3 levels for abdominal samples. The plates are labeled with subject number, left or/right, abdomen or/groin, baseline or/6 hr. Plates are incubated 72 hours at 30°C ±2°C. After 72 hours, in another room, 3M Healthcare staff performed the plate counting.

Source records described the subjects' exposure to the study articles and protocol required procedures as outlined by the protocol.

No FDA 483 was issued. In general, the data appear acceptable in support of the respective indication

2. **Daryl S. Paulson, Ph.D.**
   BioScience Laboratories
   1755 S. 19th Avenue
   Bozeman, MT 59718

This inspection audited efficacy study EM-05-13260 under NDA 208288. A total of 1035 subjects were screened and 632 subjects treated with test products at this site. The field investigator audited 207 subject files. Data audits included comparison of source documentation with data listings provided with the assignment. Reviewed items included eligibility criteria, randomization, test article accountability and disposition records, primary efficacy endpoints for bacterial counts, and adverse events.

The field investigator interviewed several staff technicians who had been involved in the product application and microbial sample collection for the study. A day crew performed the baseline and ten-minute sample activities whereas an evening crew performed the 6-hour sample activities. A set of the sterilized stainless steel cup and glass rod called a policeman was produced. The Technicians described in detail the process of dispensing the Sterile Sampling Solution into the cup for scrubbing followed by a description of product application with timing measurements of 30 seconds for the abdomen and two minutes for the groin region.

A study coordinator explained that the microbiology laboratory methods used at the site were the same as described in the protocol. During review of the 207

study subject files, the field investigator did not observe any deficiencies with the test procedures for the baseline screening, 10-minute and 6-hour sampling procedures. Three of the 207 study subject files reviewed had plating times outside the 30-minutes as required by the protocol. These protocol deviations were included in the data listings, and not likely to impact the integrity of the data.

The study coordinator stated that no subjects were repeatedly used. No employees were used as study subjects, and although not an exclusion criteria, she was unsure if relatives of employees had been involved in the study. A total of 1035 subjects signed the Informed Consent Document, 831 subjects passed the initial screening, and 631 subjects completed the study. For the 1035 subjects screened, each prospective subject went through a washout period according to the protocol and subjects were not randomized until they fulfilled all inclusion and exclusion criteria, as per the protocol.

The field investigator reviewed the equipment preventive maintenance logs for the three refrigerators and five incubators used during the study. No deficiencies were noted. Training records for study personnel who performed the bacterial enumeration during the study were reviewed. Personnel were adequately qualified and trained to perform their assigned tasks.

All records were organized and complete. Review of records revealed that there was adequate documentation to assure that all study subjects did exist and were alive and available for the duration of their participation in the study. Source records described the subjects' exposure to the study articles and protocol required procedures as outlined by the protocol.

During review of the 207 study subject files, the field investigator did not observe any deficiencies with test procedures. The 30-minute plating times was documented on CRF Page 14.

The field investigator reviewed the Abdomen and Groin Treatment Raw Data form (CRF pages 15 and 16) and found no discrepancies to the data listings. She reviewed the Skin Irritation & Treatment Record (CRF pages 8 and 11 for the abdomen and pages 9 and 12 for the groin) and found no discrepancies.

In comparing source data with the data listings, the field investigator reported that with the exception of reported protocol deviations, all subjects met eligibility criteria. Protocol specified physical assessments were performed and adequately documented. All adverse events were documented and reported. Inter-current illnesses were documented accurately. Drop-outs and discontinuations were well-documented and reported. Review of correspondence filed revealed that the principal investigators and sub-investigators had frequent contact with the sponsor-monitor. No discrepancies were observed with respect to the data listings or information reported to the

sponsor. Test article accountability and disposition records were well maintained

No significant deficiencies were observed and no FDA 483 was issued. The study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

3. Michael Caswell, Ph.D.
Consumer Product Testing Company, Inc.
70 New Dutch Lane
Fairfield, NJ 07004

This inspection audited Study EM-05-12853 conducted under NDA 208288. A prior FDA inspection of Consumer Product Testing Company was conducted between 5/15/2014 and 5/23/2014 and was classified NAI. Study EM-05-12853 was a single-center, positive and negative-controlled safety trial. The primary objective was to determine by repetitive epidermal contact the primary or cumulative irritation potential of the test product compared to the positive control. The primary efficacy endpoint measured the cumulative irritation total (CIT) score, primarily erythema on selected areas on the subject's back applied five times weekly for three weeks for a total of 15 applications. The subject's responses were documented on a form titled "21 Day Cumulative Patch Test Form with Challenge."

The field investigator selected 30 subject files and compared the source documentation with data listings provided with the assignment. The field investigator reviewed the subject's record for Adverse Events (AEs) and Serious Adverse Events (SAEs) and compared responses with the data listings. The field investigator reviewed the listing of Discontinued Subjects with reasons for discontinuing, and reported Protocol Deviations, and compared source records with the data listings. No discrepancies were observed.

Additional areas covered during the inspection were: Standard Operating Procedures, Selection and Training of Clinical Personnel, Monitoring Procedures and Activities, Review of Subject Records, Quality Assurance, Data Collection and Handling, and Drug Accountability records.

No data errors or discrepancies were noted when corroborating source documentation with data listings. There was no under-reporting of AEs or SAEs. No discrepancies were observed during audit of discontinued subjects and protocol deviations. No FDA-483, Inspectional Observations, was issued at the close of this inspection. The data from the site appear acceptable in support of the respective indication

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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/s/

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Signing for Susan D. Thompson, M.D., Team Leader and Kassa Ayalew, M.D., M.P.H., Branch Chief