# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208288Orig1s000

# SUMMARY REVIEW

# Cross-Discipline Team Leader Review

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|---|---|
| **Date** | August 8, 2018 |
| **From** | Francis E. Becker, M.D., F.A.C.P |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA # and Supplement#** | 208288 |
| **Applicant** | 3M Health Care |
| **Date of Submission** | February 9, 2018 |
| **PDUFA Goal Date** | August 9, 2018 |
| **Proprietary Name** | SoluPrep Film-Forming Sterile Solution |
| **Established or Proper Name** | 2% w/v chlorhexidine gluconate and 70% isopropyl alcohol |
| **Dosage Form(s)** | Solution |
| **Applicant Proposed Indication(s)/Population(s)** | Patient Preoperative Skin Preparation (adults and pediatric patients ≥ 2 months of age)<br>• For preparation of the skin prior to surgery<br>• Helps reduce bacteria that potentially can cause skin infection |
| **Applicant Proposed Dosing Regimen(s)** | 10.5 mL applicator (Clear/Tint) for head, neck, and small prep areas<br>26 mL applicator (Tint) for large prep areas below the neck |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | Patient Preoperative Skin Preparation (adults and pediatric patients ≥ 2 months of age) |
| **Recommended Dosing Regimen(s)** (if applicable) | 10.5 mL applicator (Clear/Tint) for head, neck, and small prep areas<br>26 mL applicator (Tint) for large prep areas below the neck |

# 1. Introduction

This is an NDA resubmission by 3M Health Care (3M; the Sponsor) for SoluPrep Film-Forming Sterile Patient Preoperative Skin Preparation (SoluPrep surgical solution) to address the comments listed in the FDA Complete Response (CR) Letter to the Sponsor dated 1 September 2017. This CDTL Review is intended to review and assess the Sponsor's currently submitted Complete Response and will not address issues which were reviewed and satisfactorally resolved in the previous review cycles.

SoluPrep surgical solution is a sterile, antimicrobial topical solution consisting of two well known and established active ingredients, chlorhexidine gluconate (2% w/v CHG) and isopropyl alcohol (70% v/v IPA), together with a film-coating polymer. The film-forming attribute of the solution is due to the inclusion of 3M's proprietary acrylate copolymer as an inactive ingredient. The acrylate copolymer is the same polymer used in 3M's currently marketed DuraPrep surgical solution, except (b) (4) . The Sponsor reports that the copolymer, when formulated with CHG and IPA/water, remains dissolved until it is applied on the skin and produces a water-insoluble film. The potential benefits of the polymer are to improve the resistance to removal during the surgical procedure and to improve the adhesion of adhesive-backed incise drapes.

The Sponsor has developed both a colorless and tinted solution in applicator sizes of 10.5 ml (colorless and tinted) and 26 ml (tinted) for different types of surgical procedures. The bright green tint is intended to provide improved visualization of the surgical area compared to currently available products. In addition, (b) (4) % HEDTA (b) (4) was added (b) (4) Thus, if approved, this product would be the first FDA-approved sterile drug prep solution on the market available for use by healthcare professionals.

# 2. Background

For a complete regulatory history of this drug product, the reader is referred to my previous CDTL Reviews.[1] Briefly, the initial NDA was submitted as a 505(b)(2) on 6 July 2015 and included two pivotal clinical simulation studies to support efficacy of the product. Multiple deficiencies (Clinical, Clinical Pharmacology, Product Quality, Microbiology, and Nonclinical) were identified which

[1]NDA 208288 Soluprep CDTL Review, 26 April 2016, and NDA 208288 SD-45 CDTL Review, 31 August 2017

precluded approval, and a Complete Response (CR) Letter[2] (6 May 2016) was issued to the Sponsor. On 3 March 2017, the NDA was resubmitted to address the CR issues from the 6 May 2016 CR Letter. Many of the CR issues were adequately addressed in the resubmission. However, FDA issued a second Complete Response Letter[3] on 1 September 2017. In the CR letter, remaining nonclinical CR issues were identified. The CR letter stated:

> *The proposed specifications of NMT (b) (4)% for the impurity, (b) (4) and NMT (b) (4)% for the impurity (b) (4) are above the qualification threshold per the ICH guidance for industry* ***Q3B(R2) Drug Product Impurities****. The dermal rabbit study (#16-014) submitted on March 3, 2017, does not include a sufficient tissue battery to assess systemic toxicity.*
>
> *We also note that the doses administered in your rabbit dermal study do not appear to support your proposed impurity specifications for the 26 mL applicator, using the available data. This relies upon your proposed maximal use for the 26 mL applicator, the proposed impurity stability specifications, and conversion of the doses administered to animals to human equivalent doses. As an alternative to human equivalent doses, clinical pharmacokinetic data and animal toxicokinetic data can be used to provide animal-to-human exposure margins. In addition, human pharmacokinetic from an adequate maximal use trial (MUsT) can demonstrate minimal systemic absorption of the impurities of concern. Absent these data, you have not provided adequate qualification data to support your proposed impurity specifications.*
>
> *To resolve this deficiency, provide an adequate qualification study in a single animal species (e.g., a single extended dose study) or otherwise adequately address the systemic exposure to (b) (4) and the impurity (b) (4). As discussed during a teleconference on August 22, 2017, data from a Franz Cell assay does not supplant clinical pharmacokinetic data for informing the animal-to-human exposure margin, or demonstrating minimal absorption of the impurities of concern. In such cases the in vivo assessment of exposure (through a MUsT) is considered the definitive demonstration. Alternatively, you can control the level of impurities to that of a relevant approved product using the total daily exposure resulting from four 26 mL applicators per day. This relies upon your proposed use for the 26 mL applicator, which results in higher estimated patient exposures than the anticipated use of the 10 mL applicator. If you choose this pathway, provide updated stability specifications consistent with your justification.*

[2] NDA 208288 CR Letter, 6 May 2016
[3] NDA 208288 CR2, 1 September 2017

In summary, the Complete Response (CR) of 1 September 2017 was based on deficiencies in nonclinical safety assessment for two CHG impurities, (b) (4) as the proposed specifications of the two impurities were above the qualification threshold per ICH guidance. The current submission is intended to address this issue, which is the only remaining CR issue. Based on FDA recommendation, the Sponsor has conducted a human maximal use trial (MUsT) to assess systemic exposure of (b) (4) under maximal use conditions. In this resubmission, the results of the MUsT are included. In addition, the Sponsor submitted an amended nonclinical study report (Repeat Dose Dermal Toxicity in Rabbits Study) to include additional histopathological data. A clinical safety update was also submitted.

## 3. Product Quality

Product Quality Assessment was completed by the Quality Review Team (see **Table I** below) and is detailed in the Quality Assessment Summary Review of 3 July 2018.[4] In his Sumary Review, Swapan De, PhD, Application Technical Lead, concluded that, "regarding Chemistry Manufacturing and Controls, the application may be approved." The drug product was granted a shelf life of 24 months under controlled room temperature storage conditions.

[4] Quality Assessment, NDA 208288 Review #3; 3 July 2018.

**Table I: Quality Review Team**

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance[1] | Elise Luong, Ph.D. | ONDP/DNDP-II/ Branch VI |
| Drug Product | Elise Luong, Ph.D. | ONDP/DNDP-II/ Branch VI |
| Process[1] | Erin Kim, Ph.D. | OPF/DPAII/BranchVI |
| Microbiology[1] | Maria Cruz-Fisher, Ph.D.<br>Erika Pfeiler, Ph.D. | OPF/DPAII/BranchVI |
| Facility | Xiaohui (Sherry) Shen, Ph.D. | OPF/DIA/B3 |
| Biopharmaceutics | N/A | |
| Regulatory Business Process Manager | Teshara Bouie | OPRO/DRBPMI/RBPMBI |
| Application Technical Lead | Swapan K. De, Ph.D. | ONDP/DNDP-II/ Branch VI |
| Laboratory (OTR) | NA | NA |
| ORA Lead | Paul Perdue | ORA/OMPTO/DMPTPO/MDTP |
| Environmental Assessment (EA) [1] | Elise Luong, Ph.D. | ONDP/DNDP-II/ Branch VI |

ONDP=Office of New Drug Products; OPF=Office of Process and Facilities; DPA=Division of Pharmaceutical Analysis; OPRO=Office of Program and Regulatory Operations; DRBPMI=Division of Regulatory and Process Management; RBPMBI=Regulatory and Business Process Management Branch; ORA=Office of Regulatory Affairs; OMPTO=Office of Medical Products and Tobacco Operations; DMPTPO=Division of Medical Products and Tobacco Program Operations

Electronically copied and reproduced from Dr. De's review.

Regarding specification of impurities, the CR letter of 9 September 2017 stated, "We acknowledge that you have accepted the Agency's recommendation for the drug product impurity levels and updated specifications (dated 21 August, 2017). Since the qualification of impurities is still inadequate, updated specifications for the drug product will remain tentative specifications." Dr. De noted that the since the Sponsor accepted FDA recommendations for drug product impurities and tightened the limit for (b) (4) to not more than (NMT) (b) (4)%, (b) (4) to NMT (b) (4)%, and Total Impurities to (b) (4)% at the end of the previous review cycle, no new CMC information was submitted in this third review cycle. Dr. De noted that Nonclinical review (see **Section 4** below) confirmed that the proposed impurity limit of (b) (4) (NMT (b) (4)%) and (b) (4) NMT (b) (4)%) are acceptable based on MuST study performed

by the Sponsor (see **Section 5** below). Dr. De wrote, "Thus, regarding CMC, drug product specification is no longer tentative and it is the final regulatory specification.

Facility review with "acceptable cGMP recommendation" was completed on 7 June, 2018.

## 4. Nonclinical Pharmacology/Toxicology

As described in **Section 2** above, the primary deficiency is related to proposed drug product impurity specifications for two impurities, (b) (4) that exceed the qualification threshold (<1%) proscribed under ICH Q3B(R2). (b) (4) . In the second CR letter, the Sponsor was advised that part of the safety qualification data proscribed under ICH Q3B(R2) submitted in the first resubmission, namely, the repeat-dose dermal toxicity study in rabbits (Study 16-014) did not include a sufficient tissue battery to assess systemic toxicity. Therefore, in response, the current resubmission includes additional data from new microscopic histopathological evaluations of organ tissues that were collectred and preserved during conduct of the original study but not examined microscopically.

The amended study (16-014) report was reviewed by the Nonclinical Pharmacology/Toxicology team (D. Charles Thompson, RPh, PhD, DABT; and Jane J. Sohn, PhD.). Dr. Sohn and Dr. Thompson concluded that the application is approvable from a nonclinical perspective. For details of Nonclinical assessment, please see the Nonclinical Review[5]. In their review, Dr. Thompson and Dr. Sohn wrote that the new data in the amended study report "do not identify any new and/or increased safety concerns with respect to the elevated impurity levels of the aged test article employed." However, the Nonclinical Team also noted that "provision of the new organ tissue analyses alone does not overcome the other deficiency of the original dermal rabbit study, which is an inadequate dosing regimen to support previous estimates of human systemic exposure to the two impurities of concern." Specifically, the adequacy of doses employed in the rabbit study was not addressed by the additional tissue evaluation.

The Sponsor elected to address the identified deficiencies in the rabbit study dosing regiment by submitting data from a clinical pharmacokinetic study (MUsT). As discussed in **Section 5** below, Clinical Pharmacology has determined this MUsT to be adequate and to demonstrate no quantifiable systemic (plasma) exposure to the two impurities of concern, based on the Sponsor's stated lower limit of quantitation (LLOQ). Dr. Thompson and Dr. Sohn wrote that the "LLOQ for this application is considered sufficient to

[5] Pharmacology/Toxicology NDA/BLA Review and Evaluation; 29 June, 2018.

address remaining nonclinical safety concerns." Thus, the Nonclinical Team found the application to be approvable, "relying on the Clinical Pharmacology assessment that the MUsT study was adequately conducted to quantify and demonstrate clinically insignificant systemic (plasma) exposure of the two impurities of concern."

# 5. Clinical Pharmacology

Clinical Pharmacology review was conducted by Sojeong Yi, PhD, Office of Clinical Pharmacology, Division of Clinical Pharmacology III. Dr Yi reviewed the results of the maximal use trial (MUsT) and concluded that, "From a Clinical Pharmacology standpoint, NDA 208288 is acceptable provided the Applicant adequately addresses the labeling comments." Dr. Yi's labeling comments and recommendations are described in **Table II** below (electronically copied and reproduced from Dr. Yi's review).

For the 10.5-mL and 26-mL applicator, the maximum treatment areas are 178.8 $in^2$ (1153.5 $cm^2$) and 387.5 $in^2$ (=2500$cm^2$). Per the proposed label, the 10.5-mL product is intended to be applied to the head and neck or to small preparation areas, and the 26-mL product is intended for large preparation areas below the neck. The Sponsor has stated in previous submissions that up to four 26-mL SoluPrep products may potentially be used in a single major surgery, such as a cardiovascular procedure, which is therefore considered to be a maximal use. Thus, FDA agrees that a reasonable estimation of maximum use product exposure is 10,000 $cm^2$ of skin area (2500 $cm^2$ per 26-mL applicator X 4) which is approximately 58% of the average total body surface area (BSA) of adults.

For details of the MUsT study design, please see Dr. Yi's review.[6] Briefly, in Study EM-05-014226 (the MUsT study), 24 healthy male and female adults received a single application of four 26-mL applicators of SoluPrep to 10,000 $cm^2$ of the subject's intact skin in the chest/abdomen, upper and lower back, and front and back legs. Each 26-mL applicator contained at least (b) (4) mg (b) (4) and at least (b) (4) mg (b) (4). Subjects were advised to refrain from showering and vigorous physical activity for 48 hours after the application such that the applied "film forming material" containing CHG, (b) (4) remained intact on the skin surface. The mean (range) actual amount of SoluPrep solution applied per subjects was 46.0 g (Range: 38.1 g to 54.3 g). This was a single treatment and blood samples were collected at 0, 2, 4, 8, 12, 24, and 48 hours after the application.

As described by Dr. Yi, the pharmacokinetic results indicated that all of the resulting plasma concentrations of CHG and CHG-related impurities, (b) (4) were below the lower limit of quantitation (LLOQ), i.e., < 1 ng/mL. Dr. Yi concluded that the

[6] Office of Clinical Pharmacology Review; 26 June, 2018.

results suggest that there were no quantifiable systemic concentrations of CHG and the two impurities, (b) (4) under the study's maximal use conditions.

Dr. Yi also noted that the plasma concentrations of isopropyl alcohol (IPA) were not measured in this study. However, Dr. Yi concluded that not measuring the systemic concentrations of IPA in this MUsT "does not preclude the approval as discussed in the previous resubmission." Dr Yi continued, "the information regarding the systemic absorption of isopropyl alcohol will be based on the literature which was submitted in the previous resubmission whereas the lack of quantifiable systemic absorption of CHG can be indicated using the data from the MUsT." The reader is referred to Dr. Yi's Clinical Pharmacology Review[7] from the previous review cycle in which the literature regarding dermal IPA absorption submitted by the Sponsor was reviewed. It was concluded that the IPA blood level after a single use of SoluPrep was expected to be at low enough level to be acceptable.

[7] Office of Clinical Pharmacology Review; August 24, 2017

**Table II: Office of Clinical Pharmacology Labeling Recommendations**
**(underlined text indicates recommended insertion; strike through text indicates recommended deletion)**

| Proposed | Recommended |
|---|---|
| **12 Clinical Pharmacology** | **12 Clinical Pharmacology** |
| (b) (4) | (b) (4) |
| | The systemic absorption of chlorhexidine after topical application of SoluPrep 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 SoluPrep applicators to approximately 1550 $in^2$ (10,000 $cm^2$) surface area |

**Table II (continued): Office of Clinical Pharmacology Labeling Recommendations**
**(underlined text indicates recommended insertion; strike through text indicates recommended deletion)**

| | |
|---|---|
| | of intact skin.<br><br>The systemic absorption of isopropyl alcohol after topical application of SoluPrep 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 IPA ranged from 0.83 to 12.25 mg/L at 1 hour after application. |

## 6. Safety

Clinical safety review was conducted by Teresa Podruchny, M.D., Medical Officer, DNDP. As noted above, the CR letter of 1 September 2017 is based solely on nonclinical deficiencies. However, a safety update was included in this resubmission. The Sponsor reports that six new trials have been conducted since the NDA resubmission of 3 March 2017. The six trials are summarized in **Table III** below. (b) (4)

one (Study EM-05-014226) is submitted as a maximal use study (MUsT; see also **Section 5** above), two are related to visibility, and one is a saline challenge. (b) (4)

## Table III: Clinical Trials Conducted Since NDA Resubmission of 3 March 2017

| Study EM-05- | Test Location | IND Y/N | Type of Study | N = | Exposure Time | Products Tested | Skin Irritation | Adverse Events (AEs) | Drop Outs |
|---|---|---|---|---|---|---|---|---|---|
| 014226 | (b) (4) (USA) | Y | Phase 1: Human Pharmacokinetic (PK) Study | 24 | 48 hours | 3M CHG/IPA Prep tint 26mL | Skin Irritation (erythema, edema, rash, dryness) was assessed prior to product application and again at 2 hours, 4 hours, 8 hours, 14 hours, 24 hours and 48 hours post-application. The preps were well tolerated by the subjects with no rash, edema or dryness observed post-treatment. Mild erythema was observed for one subject on the chest/abdomen treatment site at 4-hour, 8-hour and 12-hour post-treatment. | n = 4 (rhinitis, upper respiratory infection, dental abscess, itching) None of the 4 AEs were SAE. For 1 subject, the AE (itching) was considered by the PI to be related to study product. It was deemed mild in intensity. Overall, all AEs were considered mild or moderate in severity, and were followed to resolution. | 0 |
| 013603 | MBT (USA) | Y | Pilot Evaluation of Residual CHG on Prepped Skin Following a Repetitive Saline Soak/Wipe Challenge | 21 | 15-30 min | 3M CHG/IPA Prep colorless 10.5 mL ChloraPrep clear 10.5 mL | Skin Irritation (erythema, edema, rash, dryness) was assessed prior to product application and again at 10 minutes post-application. No erythema, edema, rash or dryness was reported. | n = 0 No AEs were reported during this study. | 0 |
| 014116 | MBT (USA) | Y | Visibility on Dark Skin Tones | 9 | 2 hours | 3M CHG/IPA Prep tint 10.5 mL ChloraPrep tint 10.5 mL | Skin Irritation (erythema, edema, rash, dryness) was assessed 30 minutes post-removal of prep from test sites. No erythema, edema, rash or dryness observed. | n = 0 No AEs were reported during this study. | 0 |
| 014182 | MBT (USA) | Y | Visibility on Light and Medium Skin Tones | 12 | 2 hours | 3M CHG/IPA Prep tint 10.5 & 26 mL ChloraPrep tint 10.5 & 26 mL | Skin Irritation (erythema, edema, rash, dryness) was assessed 30 minutes post-removal of prep from test sites. No erythema, edema, rash or dryness observed. | n = 0 No AEs were reported during this study. | 0 |
| 012926 | (b) (4) (Romania) | N | (b) (4) Evaluation of Microbial Population Reductions Within a Defined Product Coverage Area | 28 | 16 min | 3M CHG/IPA Prep tint 26 mL | Skin Irritation (erythema, edema, rash, dryness) was assessed immediately after removal of the drape from prepped test sites. No erythema, edema, rash or dryness was reported. | n = 0 No AEs were reported during this study. | 0 |
| 013953 | (b) (4) (Romania) | N | (b) (4) 96-hour Antimicrobial Persistence Following a Repetitive Saline Soak/Wipe Challenge | 69 | 92-100 hours | 3M CHG/IPA Prep colorless 10.5 mL ChloraPrep clear 10.5 mL | Skin Irritation (erythema, edema, rash, dryness) was assessed prior to product application and again at 10 minutes, 48 hours, 72 hours and 96 hours post-application. No erythema, edema, rash or dryness was reported. | n = 0 No AEs were reported during this study. | 0 |

**Source: Safety Update Report – Feb 2018 pdf in section 5.3.5.3**
Electronically copied and reproduced from Dr. Podruchny's review.

In these six studies, a total of 163 subjects were exposed to the IND product for 15 minutes and up to 100 hours, depending on study design. The Sponsor indicates that there have been no significant changes or findings in the safety profile since the resubmission of 3 March 2017.

There were no deaths in the six trials and no reported discontinuations secondary to an adverse event (AE). The Sponsor reported a total of four adverse events (rhinitis, upper respiratory infection, dental abscess, and itching). All four AEs occurred in the maximal use study, were reported as mild to moderate, and were followed until resolution. The investigator considered the event of itching, which resolved without treatment, as related to study product. As Dr. Podruchny noted in her review, this event does seem potentially related and is not unexpected. Dr. Podruchny concluded that these event do not alter the safety profile of the product, and I agree.

No postmarketing data was provided, because the investigational formulation submitted in the NDA is a first drug application for market registration approval in any country in the world. Therefore, the Sponsor reports that there are "no new safety data in the literature or from any post-marketing data of similar products that provide any new learnings that would affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling submitted in NDA 208-288."[8]

# 7. Labeling

*Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Review*

Proprietary Name reassessment was conducted by the DMEPA team: Grace P. Jones, PharmD, BCPS, Reviewer; Chi-Ming (Alice) Tu, PharmD, BCPS, DMEPA Team Leader; Danielle Harris, PharmD, BCPS, DMEPA Acting Deputy Director; and Todd Bridges, RPH, DMEPA Division Director. The proposed proprietary name, SoluPrep, was found conditionally acceptable under IND 076549 on March 3, 2015 and under NDA 208288 on October 9, 2015 and on May 19, 2017. For the current submission, DMEPA reported that their re-assessment "did not identify any names that represent a potential source of drug name confusion." [9] Therefore, DMEPA concluded that the proposed proprietary name is acceptable.

[8] NDA 208288 Section 5.3.5 Safety Update Report February 2018, page 6.
[9] Proprietary Name Memorandum, DMEPA; 3 April 2018, page 4

*Drug Facts Labeling and Target Product Information*

At the time of this writing, internal labeling discussions are ongoing. Clinical Pharmacology recommedations are described in **Table II** above. The Sponsor's proposed Target Product Information (TPI) contains appropriate Contriaindications (Do not use: on patients with known allergies to CHG or any other ingredient in this product; for lumbar puncture or in contact with meninges; on open skin wounds or as a general skin cleanser) and also contains appropriate Warnings and Precautions regarding external use only and flammability. In addition, TPI includes the statement that when using this product, "Keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. The TPI also states that "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 product." This is appropriate.

An additional issue raised in the internal meetings by Dr. Podruchny concerns use in pediatric patients. The proposed product labeling includes language to use with care in premature infants or infants under 2 months of age because these products may cause irritation and chemical burns in this group. This is consistent with labeling of other similar products currently in use. However, as discussed in the Dr. Produchny's second cycle Clinical Review[10] and my second cycle CDTL review[11], some recent literature indicates that chlorhexidine gluconate (CHG) is absorbed into the bloodstream of some preterm infants.[12] [13] [14] [15] [16] The clinical significance of this absorption is unknown. Therefore, Dr. Podruchny has recommended that language to that effect be included in Target Product Information with references to the relevant publications. It is known that, histologically, infant skin is similar to adult skin by about 6 months of age. Younger and premature infants have a very thin stratum corneum, which is the major rate-limiting barrier to molecular diffusion through the epidermis. However, there are few alternatives to CHG/IPA containing products. Providone-iodine (PI) containing products are commonly used but should be avoided in infants because of the known risk of transient hypothyroidism, which may affect the developing brain and potentially result in diminished intellectual capacity. CHG/IPA containing products likely

[10] Clinical Review; NDA 208288 SD-45; 4 August 2017

[11] Cross Discipline Team Leader Review: NDA 208288 SD-45; 31 August 2017

[12] Blood Concentrations of Chlorhexidine in Hospitalized Children Undergoing Daily Chlorhexidine Bathing", Infection Control & Hospital Epidemiology, v32, issue 4, 2011, 395-39

[13] Cowen J et al 1979, Absorption of chlorhexidine from the intact skin of newborn infants, Archive of Disease in Childhood, 54, 379-383

[14] Aggett PJ et al 1981 Percutaneous absorption of chlorhexidine in neonatal cord care. Archives of Diseases in Childhood, 56, 878-891.

[15] Chapman et al Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm infants Journal of Perinatology (2013) 33, 768-771

[16] Review article, Chapman, AK, Aucott, SW, Milstone, AM, Safety of Chlorhexidine gluconate for skin antisepsis in the preterm infant. Journal of Perinatology (2012) 32, 4-9

remain the best option for infants less than 2 months of age who require surgery. Nevertheless, I agree that it is reasonable to provide information on what is known about CHG absorption in premature infants in the Targeted Product Information. There are reports that some hosptials are using CHG off-label in premature infants (for example, CHG bathing in intensive care settings to decrease risk of infection), so information regarding CHG absorption may be useful to these institutions in assessing risk-benefit.

## 8. Conclusions and Recommendations

I recommend approval of SoluPrep Film-Forming Sterile Solution (2% w/v chlorhexidine gluconate and 70% isopropyl alcohol) for patient preoperative skin preparation (adults and pediatric patients ≥ 2 months of age): 10.5 mL applicator (Clear/Tint) for head, neck, and small prep areas; and 26 mL applicator (Tint) for large prep areas below the neck. My recommendation for approval is contingent upon agreement with the Sponsor on appropriate product labeling.

The Sponsor has adequately addressed all Complete Response issues. In the current submission, the Sponsor satisfactorally addressed concerns regarding the level of two impurities (b) (4) by providing additional histopathologic data from the Dermal Rabbit Study (16-014) and by completion of a MUsT study. In the MUsT study, pharmacokinetic assessments demonstrated that both (b) (4) were below the lower limit of quantitation (LLOQ), i.e., < 1 ng/mL. Clinical Pharmacology, Office of New Drug Products (CMC), and Nonclinical Pharmacology/Toxicology all agreed that the CR issues have been adequately addressed.

From Clinical standpoint, the Safety Update provided by the Sponsor in this submission revealed no new or unexpected findings that would change the known safety profile of this product. Chlorhexidine Gluconate (CHG)/Isopropyl Alcohol (IPA) products are known skin irritants, and skin irritation (erythema, burning, itching, dryness) was noted in the clinical trials, although the incidence was low (as described in my first cycle CDTL Review[17]). Overall, based on currently available data, risks appear to be limited to skin irritation, with rare reports of hypersensitivity to chlorhexidine reported in the literature. Therefore, the safety profile of this product is favorable for approval.

Although there are numerous other products available on the market for preoperative skin prep, many of which have the same active ingredients as this product, SoluPrep Film-Forming Solution, if approved, will be the first FDA-approved sterile drug prep solution on the market for use by healthcare professionals. However, the clinical implications of this sterility, that is, whether or not this would

[17] Cross Discipline Team Leader Review; 26 April 2016.

result in clinically significant decreases in post-op infection rates, has yet to be determined. The addition of the acrylate co-polymer has the potential benefits of improving resistance to removal during the surgical procedure and of improving adhesion of the adhesive-backed incise drapes. A tint provides improved visualization of the prepped surgical area. In conclusion, the risk-benefit assessment is favorable for approval of this product.

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/s/

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FRANCIS E BECKER
08/08/2018

**Summary Review for Regulatory Action**

| | |
|---|---|
| **Date** | August 8, 2018 |
| **From** | Theresa M. Michele, MD<br>Director, Division of Nonprescription Drug Products |
| Subject | Division Director Summary Review |
| **NDA/BLA #** | 208288 |
| **Applicant Name** | 3M Health Care Business |
| **Date of Submission** | February 9, 2018 |
| **PDUFA Goal Date** | August 9, 2018 |
| **Proprietary Name / Established (USAN) Name** | SoluPrep™ Film-Forming Sterile Solution / 2%w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol |
| **Dosage Forms / Route of Administration / Strength** | Surgical solution |
| **Proposed Indication(s)** | Patient Preoperative Skin Preparation (adults and pediatric patients ≥ 2 months of age)<br>• For preparation of the skin prior to surgery<br>• Helps reduce bacteria that potentially can cause skin infection |
| **Regulatory Action** | Approval |

This is the third cycle for this 505(b)(2) new drug application seeking approval for direct to OTC combination product of chlorhexidine gluconate 2% and isopropyl alcohol 70% solution (CHG/IPA; proposed trade name SoluPrep™) as a patient preoperative skin preparation for preparation of the skin prior to surgery and to help reduce bacteria that potentially can cause skin infection. This indication is well-established in the OTC space for both NDA and monograph products, and the language is consistent with other approved OTC patient preoperative skin preparation products.

The product contains a film-forming acrylate copolymer which the sponsor states stays dissolved until it is applied on the skin to produce a water-insoluble film. Unlike currently approved CHG/IPA products, the 3M product is provided as a sterile solution in a sterile applicator. Use of a sterile product may potentially provide reduced risk to surgical patients from nosocomially transmitted infections from contaminated antiseptics. The NDA includes 3 different presentations of the product, a colorless solution in a 10.5 mL applicator, a green-tinted solution in a 10.5 mL applicator, and a green-tinted solution in a 26 mL applicator.

In the first cycle, FDA issued a Complete Response determination on May 6, 2017, due to the following deficiencies:

- Clinical: failure to demonstrate replicative efficacy in the groin region and inadequate financial disclosure

- Clinical pharmacology: inadequate data to demonstrate absorption
- Nonclinical: failure to provide qualification data for two impurities
- Product quality: unacceptable limits for impurities, with inadequate justification for expiry dating
- Microbiology: a number of deficiencies related to container closure integrity testing and validation to ensure sterility

In the second cycle, FDA issued a complete response determination on September 1, 2017, for failure to adequately qualify impurities. The other deficiencies from the first cycle were resolved. See my two previous reviews of this application and the CDTL reviews for further details on the regulatory history.

In this cycle, the sponsor submitted the results from a new maximal use PK trial (MUsT) in 24 healthy adult subjects and an amended nonclinical study report containing additional histopathology results for the previously submitted rabbit study intended to qualify impurities. The MUsT demonstrated that all plasma concentrations for CHG and the two CHG-related impurities, (b) (4) were below the lower limit of quantitation (< 1 ng/mL). These results, together with the nonclinical data, are sufficient to resolve the remaining deficiency. At this time, all remaining labeling issues have been resolved. Please see the excellent Cross Discipline Team Leader review by Dr. Francis Becker for complete details.

Based on the new data submitted showing that CHG and the related impurities are not absorbed under maximal use conditions as described in the product label (single use with a maximum of four 26 mL applicators on intact skin) and the toxicology data, the deficiencies identified for this application have been resolved. The overall risk-benefit assessment supports OTC approval of SoluPrep™ Film-Forming Sterile Surgical Solution (2% w/v CHG and 70% v/v IPA) as a patient preoperative skin preparation for the Uses "for preparation of the skin prior to surgery and helps reduce bacteria that potentially can cause skin infection." Approval of this product is notable because it is the first sterile patient preoperative antiseptic approved in the United States.

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THERESA M MICHELE
08/08/2018