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*APPLICATION NUMBER:*

**208288Orig1s000**

**CLINICAL REVIEW(S)**

**Summary Review for Regulatory Action**

<b>Date</b>	September 1, 2017
<b>From</b>	Theresa M. Michele, MD Director, Division of Nonprescription Drug Products
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	208288
<b>Applicant Name</b>	3M Health Care Business
<b>Date of Submission</b>	March 3, 2017
<b>PDUFA Goal Date</b>	September 3, 2017
<b>Proprietary Name / Established (USAN) Name</b>	SoluPrep™ Film-Forming Sterile Solution / 2%w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
<b>Dosage Forms / Route of Administration / Strength</b>	Surgical solution
<b>Proposed Indication(s)</b>	Patient Preoperative Skin Preparation (adults and pediatric patients ≥ 2 months of age) • For preparation of the skin prior to surgery • Helps reduce bacteria that potentially can cause skin infection
<b>Recommended Regulatory Action</b>	Complete response

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review--DNDP	Teresa Podruchny/Francis Becker
Statistical Review	Joo-Yeon Lee/Rima Izem
Pharmacology Toxicology Review	Charlie Thompson/Jane Sohn
CMC Review/OBP Review	Elise Luong/Maria Cruz-Fisher/Erika Pfeiler/ Swapn De
Clinical Microbiology Review	Michelle Jackson
Clinical Pharmacology Review	Sojeong Yi/Dennis Bashaw
CDTL Review	Francis Becker
OSE/DMEPA	Grace Jones/Chi-Ming Tu
RPM DNDP	Lara Akinsanya

CDTL=Cross-Discipline Team Leader  
DMEPA=Division of Medication Error Prevention and Analysis  
DNDP=Division of Nonprescription Drug Products  
IDS=Interdisciplinary Scientist  
OND=Office of New Drugs  
RPM=Regulatory Project Manager  
OBP=Office of Biotechnology Products

## 1 INTRODUCTION

This is the second 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 currently approved, the 3M product is provided as a sterile solution in a sterile applicator. 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

This review will focus only on issues related to the complete response.

## 2 REGULATORY HISTORY

After the complete response, FDA held a Type A meeting with 3M on July 15, 2016. Discussion was held regarding the recommendation to conduct an additional clinical simulation study at the groin site, data necessary to resolve the clinical pharmacology deficiency, and the sponsor's efforts to address the financial disclosure deficiency. The sponsor asserted that based on the totality of the data, the data were sufficient to demonstrate efficacy. 3M also discussed potential reasons for divergent results between the two laboratories performing the clinical simulation studies, including the lower body mass index resulting in differences in skin folds and different microbiomes between the two geographic regions (Virginia versus Montana). The Division provided significant advice on potential pathways to resolve deficiencies but did not agree with the sponsor's assertion that further clinical simulation studies were unnecessary.

On August 12, 2016, 3M requested formal dispute resolution to appeal the Division's determination that the clinical simulation studies were insufficient for approval due to failure to provide replicative evidence of efficacy at the groin site and the recommendation to conduct a repeat study. Dr. Charles Ganley, ODEIV granted this appeal on the basis of a

number of factors, which when taken together, were deemed sufficient to support the efficacy of the proposed product. These factors included: (1) similar results were obtained to that of an approved product containing the same active ingredients, (2) in vitro testing using a time-kill approach demonstrated efficacy, (3) replicative efficacy was demonstrated in one study using two different presentations of the test product (10.5 mL and 26 mL), (4) the study that did not meet the pre-specified response rate at the groin site did meet criteria at the abdominal region, (5) there are only two laboratories in the U.S. that conduct these types of clinical simulation studies and the results are known to be variable between the labs which may reflect different populations enrolled, and (6) the results of a pilot study in Romania showed a mean log reduction in bacteria by greater than 3 log for all study arms, although the study was underpowered to meet the response criteria. Dr. Ganley goes on to note that these conclusions are not generalizable to other products, particularly those containing new active ingredients with more limited data elsewhere to support effectiveness.

At the sponsor's request, the Division held a discipline specific in review meeting on June 12, 2017, to discuss the toxicology information requests. The sponsor asserted that FDA failed to raise concerns regarding the protocol for the rabbit toxicology study conducted to qualify impurities; however, this protocol was never submitted to FDA by the sponsor. FDA provided advice to the sponsor regarding additional data needed to evaluate the submitted toxicology study and noted that additional toxicology data of the requested type would likely constitute a major amendment. Following this teleconference, the product quality and nonclinical teams issued a discipline review letter on August 11, 2017, outlining outstanding deficiencies in the application. Two subsequent teleconferences were held with the sponsor on August 17 and August 23, 2017, to discuss pathways for resolution of these deficiencies.

### 3 CHEMISTRY, MANUFACTURING, AND CONTROLS

In the first cycle, 3M originally proposed an expiration date of 24 months, with impurity limits of (b) (4) % total impurities and (b) (4) % individual impurities. However, data demonstrate increasing amounts of degradants over time, with two impurities (b) (4) exceeding 1.0% at (b) (4) months, respectively. The 1.0% level is based on the ICH Q3B(R2)<sup>1</sup>, which sets limits for impurity specifications above which toxicology qualification is required. The sponsor subsequently proposed alternative analyses of impurities and a shelf life of (b) (4) months; however, these approaches failed to limit the impurities below the 1.0% level considered acceptable by ICH standards. A further decrease in shelf life to below (b) (4) months would not be acceptable from a clinical standpoint, because these products are stored in various hospital environments in which checking for expiration dates very frequently would likely pose an undue burden on the health care system and put patients at risk of use of expired product with untested impurities.

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<sup>1</sup> ICH Harmonized Tripartite Guideline: Impurities in New Drug Products Q3B(R2), Step 4 version dated 2 June 2006. Downloaded at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q3B\\_R2/Step4/Q3B\\_R2\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2_Guideline.pdf)

In this cycle, the sponsor submitted qualification data for these two impurities; however, the proposed specifications for these two impurities as well as the total impurities remained unacceptably high. Based on levels of impurities in the product real time stability data, the quality team recommended lowering the specifications, as follows: (b) (4)

(b) (4) The sponsor accepted this recommendation. The quality team concluded that the application is potentially approvable, provided the specified levels are qualified. Control of overall impurities is especially important for an antiseptic product in which a lower concentration of the active ingredient (due to active ingredient degradation to form impurities) could result in decreased efficacy, leading to a higher incidence of surgical wound infections.

(b) (4)  
(b) (4) The manufacturing quality microbiology review in the first cycle concluded that sterility of the finished product could not be assured due to a number of deficiencies. These included lack of validation data for the container closure integrity test, inadequate (b) (4) monitoring during production, inadequate requalification schedule for (b) (4) inadequate validation of the bioburden testing method, inadequate testing of the (b) (4), and inadequate specifications for sterility testing the drug product applicator among other issues. Based on information submitted in the complete response, this deficiency was resolved.

I concur with the conclusions of the manufacturing quality review team that the deficiencies are satisfactorily resolved, although final specifications and expiry cannot be set until impurities are satisfactorily qualified.

#### 4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In the first cycle, the pharmacology/toxicology reviewer recommended qualification of two impurities, (b) (4) that exceed the qualification threshold of 1.0% during the initially proposed shelf life of 24 months. To address this deficiency, the sponsor submitted a dermal toxicity study in rabbits. The toxicology review team identified a number of concerns with this study, including a limited number of tissues with histopathological evaluation, 3 day recovery period prior to sacrifice, lack of toxicokinetics, and inadequate dosing resulting in failure to establish adequate exposure margins. The most critical of these deficiencies are the limited histopathology data and the failure to establish adequate exposure margins.

To determine exposure margins, the nonclinical team converted the doses administered to rabbits to Human Equivalent Doses (HEDs) to allow comparison to the amount proposed for clinical use. Because the sponsor does not have animal toxicokinetic data or human pharmacokinetic data that would allow actual exposure calculations to be made, both impurities were presumed to be 100% bioavailable after dermal exposure. These calculations were based on the maximum doses expected in clinical use, which the sponsor states are 2 of the 10.5 mL applicators (labeled for head/neck and small areas) and 4 of the 26 mL applicators (labeled for larger body areas). Four 26 mL applicators cover approximately 58% of the total body surface area of an adult. The clinical team reviewed and concurred with the sponsor's proposed maximum dosing.

These concerns were raised with the sponsor in an information request on June 7, 2017, requesting a full battery of tissues from the rabbit dermal toxicity study to address systemic toxicity. The team also discussed these issues with the sponsor in a teleconference on June 12, 2017.

3M submitted an amendment on July 31, 2017 (34 days prior to the action date), which included additional histopathology data as well as in vitro absorption data using a Franz cell system. FDA informed the sponsor that being so close to the action date, this submission would constitute a major amendment. After receiving the discipline review letter and two subsequent teleconferences with the Division, 3M requested to withdraw the supplement rather than have it be reviewed as a major amendment.

Issues that remain are as follows:

- The rabbit toxicity study does not contain histopathology data from a sufficient number of tissues to make an adequate assessment for qualification. It is possible that the amendment the sponsor chose to withdraw contains adequate data, but review is required to determine this.
- The rabbit toxicity study does not provide adequate exposure margins for qualification. Lowering the impurity specifications as FDA proposed would allow for a calculated exposure margin of  $> 1$  for the 10.5 mL applicator; however, the 26 mL applicator would still have a calculated exposure margin of substantially less than one. Using these specifications, the toxicology team concluded that the exposure margin is potentially adequate for the 10.5 mL applicator if the inadequate tissue battery issue is resolved, but would not be adequate for the 26 mL applicator.

To address the second deficiency, the sponsor has several different potential pathways forward.

- Conduct a human dermal PK study under conditions of maximal use using aged material (which would contain higher impurities) to determine systemic absorption. A toxicokinetic study could also be conducted to determine absorption in rabbits. Using the human PK data (and the animal TK data, if available), an actual exposure margin could be calculated, which presumably would be greater than that calculated using the conservative estimate of 100% absorption used to calculate a HED. This would be the ideal approach because it would also provide better data to address the less than complete clinical pharmacology data available from the literature. It could also benefit the sponsor if they choose to rely upon this application for future indications that are not limited to single use. The sponsor's approach of using in vitro data (Franz cell assay) to address absorption does not provide an adequate surrogate for human data.
- Conduct another animal qualification study in which drug is applied in an amount sufficient to provide an adequate exposure margin for each applicator. The study would need to include sufficient histopathology to evaluate systemic toxicity and not include a lengthy recovery period prior to evaluation.
- Control the level of impurities in the product to that of a relevant approved product or to a level below the qualification threshold in the ICH guidance for industry *Q3B(R2) Drug Product Impurities*.

Given the sponsor's withdrawal of the amendment containing additional histopathology data, I concur with the recommendation of the toxicology team for a complete response. If this amendment had been reviewed and fully addressed the histopathology issue, it may have been possible to approve the 10.5 mL applicator. However, inadequate exposure margins exist for the 26 mL applicator. While noting that no review decisions had yet been made for this application, this possibility was discussed with the sponsor in the teleconferences held on August 17 and 21, 2017.

From a clinical perspective, adequate qualification of impurities is important for this product. If approved, Soluprep would be the first sterile pre-operative antiseptic product approved in the U.S., so it likely would be very widely used. However, (b) (4) impurities that have an unknown safety profile, the benefits of a sterile product may not outweigh the risks.

## 5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The sponsor proposes to rely on the literature to provide evidence regarding systemic absorption of this product. In the first cycle, the sponsor submitted some data regarding CHG, but little evidence for IPA or the combination of CHG/IPA. To resolve this deficiency, FDA recommended that the sponsor cite adequate literature for IPA and CHG/IPA to demonstrate absorption after use as a surgical skin preparation with a similar level of skin coverage to that proposed for the largest size product (26 mL), rely on FDA's findings of safety for a listed drug product, or conduct a maximum use pharmacokinetic trial (MUST).

To address this deficiency, 3M submitted additional literature references, a cross-reference to rely on DuraPrep Surgical Solution [Iodine Povacrylex (0.7% Available Iodine) and IPA (74% w/w)] under NDA 21-586, and results from in vitro skin permeation tests for CHG using Soluprep and Chloraprep.

The clinical pharmacology team found that the literature submitted suggest that the systemic exposure to CHG and IPA is expected to be low in adults. However, literature submitted is inadequate to fully characterize the absorption of the product at the intended usage level, because the products used in the literature primarily contained either CHG or IPA not both, had lower strengths of the active ingredient(s), or were applied to a smaller skin area. The cross reference to Duraprep is not helpful because no data evaluating the absorption of IPA was included in this application and the product contains iodine rather than CHG. Further, the clinical pharmacology team concluded that the in vitro data cannot replace a MUST.

The clinical pharmacology team also took into account the known absorption and metabolism properties of CHG and IPA. As noted in the previous review cycle, CHG is recognized to be minimally absorbed in adults after dermal application, although absorption does occur in neonates and premature infants. IPA is metabolized to acetone and CO<sub>2</sub> and excreted via expired air. Toxicity is well known, primarily from intentional oral consumption to achieve intoxication, with CNS and respiratory depression, shock, and circulatory collapse occurring in severe poisoning. While IPA is known to have some level of absorption after dermal administration in humans, the clinical effects in humans would

likely occur at levels that are expected to be substantially below the levels that are expected to be achieved with a single dermal administration.

Taking all of these factors under consideration, the clinical pharmacology team concluded that for this particular product for the proposed single use indication, data are sufficient to recommend approval. Important considerations are: (1) the product is unlikely to be used more than a few times over the course of a lifetime, (2) CHG is known to have minimal absorption in adults, (3) IPA has a known toxicity profile in humans that occurs at much higher levels than are expected to be achieved with a single dermal administration, and (4) IPA is readily eliminated via exhaled air and urine.

I concur with these conclusions, which resolves the clinical pharmacology deficiency for this application. It is important to note that this conclusion cannot be easily generalized to other products or to other indications for this product, particularly if use were more frequent than “once in a lifetime”, the toxicity profile in humans were less well-known (as with a new ingredient), or for a different population/condition of use (e.g. neonates or use in an open wound).

## 6 CLINICAL AND STATISTICAL EFFICACY

The clinical efficacy deficiency was resolved in appeal at the ODEIV level. Of note, the efficacy criteria used for the clinical simulation studies in this application were based on the proposed rule for health care antiseptics regulated under the OTC Drug Review, issued in May 2015. While this rule does not directly apply to nonprescription antiseptics regulated under the NDA process, as a matter of policy, the Division attempts to use similar efficacy criteria for both NDA and monograph products unless there is a scientific or clinical reason to do otherwise. Based on comments submitted on the 2015 Health Care Antiseptic proposed rule and FDA’s further evaluation of additional data, FDA is updating the statistical analysis related to log reduction criteria for classifying health care antiseptic active ingredients as Generally Recognized as Effective.

The revised statistical analysis criteria are laid out in a series of deferral letters for active ingredients for which additional time was granted to complete necessary studies for FDA to complete an evaluation of whether the ingredient is Generally Recognized as Safe and Effective (GRASE).

The following excerpt outlining these criteria is taken from the deferral letter for IPA issued on January 19, 2017.<sup>2</sup>

*The updated analysis applies the use of non-inferiority of test product to active control by a margin of 0.5 and superiority of test product to negative control by an indication-specific margin. Rather than using only a change from baseline, each criterion uses the average treatment effect, an estimated difference of the effect of two treatments correcting for baseline count. That is, the average treatment effect is estimated from a linear regression of post-treatment bacterial count (log<sub>10</sub> scale) correcting for baseline or pre-treatment measurement (log<sub>10</sub> scale).*

*Superiority to negative control by a specific margin is needed because our evaluation suggests that application of a negative control, whether vehicle or saline, may exhibit some minimal antimicrobial*

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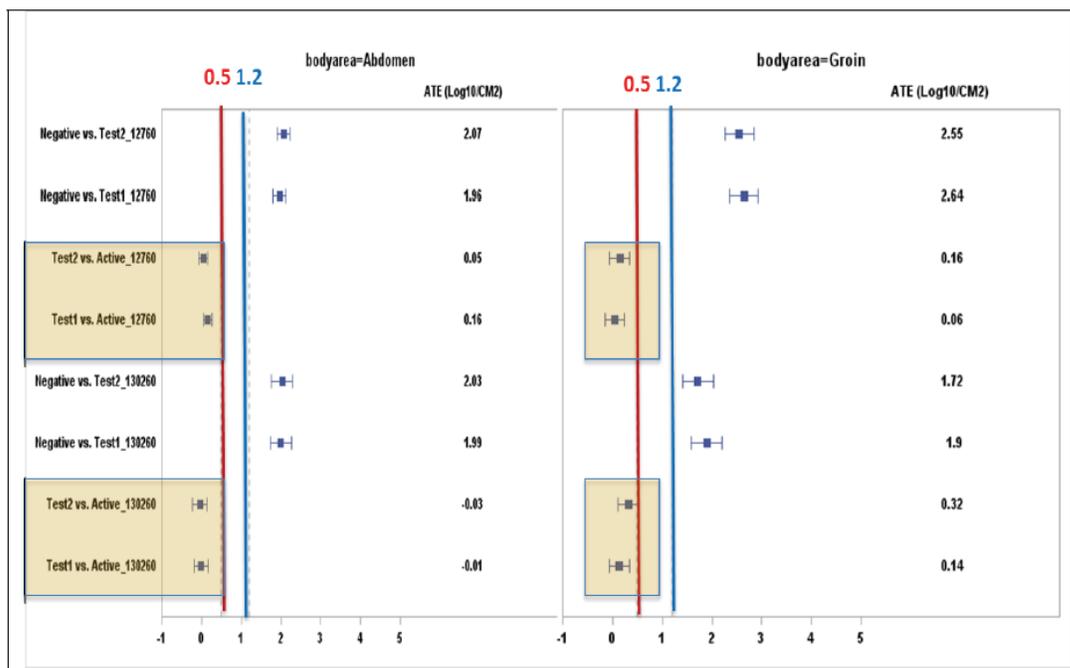
<sup>2</sup> Docket number FDA-2015-N-2001, Deferral Letter for Isopropyl Alcohol available at <https://www.regulations.gov/document?D=FDA-2015-N-0101-1325>

*properties. Thus, using superiority to negative control by the margins listed below will help ensure that we can appropriately assess the effectiveness of the antimicrobial products.*

- *Ensure that the test product is non-inferior to an FDA-approved NDA active control with a 0.5 margin. That is, we expect the upper bound of the 95 percent confidence interval of the average treatment effect of test product versus active control to be less than 0.5. An active control is not intended to validate the study conduct or to show superiority of the test drug product but to show that the test drug product is not inferior (i.e., assurance that the test drug product is not any less effective than the control). We expect non-inferiority to active control to be met at the following area and times for each indication:*
  - *Patient preoperative skin preparation*
    - *per square centimeter on abdominal site within 30 seconds after drying, or within 10 minutes after drying*
    - *per square centimeter on groin site within 30 seconds after drying, or within 10 minutes after drying*
- *Ensure that the test product is superior to the vehicle control by an indication-specific margin. That is, we expect the lower bound of the 95 percent confidence interval of the average treatment effect of the test product versus the vehicle product to be greater than the indication-specific margin. In cases where the vehicle cannot be used as a negative control, non-antimicrobial soap or saline solution could be used. We expect the following indication-specific superiority margins to be met for isopropyl alcohol:*
  - *Superiority margin of  $1.2 \log_{10}$  for patient preoperative skin preparation*
    - *per square centimeter on abdominal site within 30 seconds after drying, or within 10 minutes after drying*
    - *per square centimeter on groin site within 30 seconds after drying, or within 10 minutes after drying*

In order to address labeling for this application, the statistical team reanalyzed the data from the two pivotal studies using the new criteria. Based on this analysis, Soluprep is shown to be effective in both body areas in both studies. See Figure 1, taken from the statistical review.

Figure 1: The average treatment effect of SoluPrep to Active Control (ChloraPrep) and Negative Control (saline) from two pivotal studies (EM-05-012760 and EM-05-013260).



Footnote: Test1 and Test 2 in the study 130260 are SoluPrep 10.5 ml clear with and without HEDTA (Hydroxyethyl Ethylenediaminetriacetic Acid). Test1 and Test2 in the study 12760 are SoluPrep tinted 10.5ml and 26 ml, respectively. Active and Negative refer to active control (ChloraPrep) and negative control (saline).

## 7 OTHER RELEVANT REGULATORY ISSUES

### Financial Disclosure

In the first cycle, the clinical review identified a number of deficiencies in the financial disclosure information. Specifically, information on the subinvestigators was not reported for the two pivotal studies as well as the discontinued pivotal study, the persistence of efficacy study, the three safety challenge studies, and one of the two coverage/drying time studies. To address this deficiency, the sponsor retrospectively collected this information from all but one of the subinvestigators for the pivotal studies. Removing data from this subinvestigator did not influence the results of the study. Of note, several of the subinvestigators were employees of the contract laboratories conducting the studies. While this approach is suboptimal, the clinical team concluded that the sponsor did exercise due diligence in providing as much data as possible, and the likelihood of study bias is low. I concur with their conclusion that the deficiency is sufficiently addressed.

## **8 DECISION/ACTION/BENEFIT RISK ASSESSMENT**

### **8.1 Regulatory action**

3M has not submitted adequate data to support approval of CHG/IPA for OTC use as a patient preoperative skin preparation antiseptic due to lack of adequate impurity qualification. As such, the action for this application will be a Complete Response.

### **8.2 Risk Benefit Assessment**

The overall risk-benefit assessment does not support 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.” While 3M has resolved deficiencies in the areas of CMC (drug product and microbiology), clinical pharmacology, clinical efficacy, and financial disclosure, the sponsor has failed to adequately qualify impurities. The product demonstrates an increase in impurities over time above the level acceptable by ICH guidelines. These impurities have not been qualified with an adequate toxicology assessment. Specifically, the rabbit toxicity study submitted does not contain histopathology data from a sufficient number of tissues to make an adequate assessment for qualification, and the study does not provide sufficient exposure margins for qualification, particularly for the 26 mL applicator.

Pre-operative skin preps are used by a wide segment of the U.S. population across all age groups. Although there are labeled warnings for use of CHG products in infants under the age of 2 months due to the potential for absorption and skin reactions, CHG products are known to be used off label for these indications due to limited other safe options. As such, adequate qualification of impurities is important for this product. If approved, Soluprep would be the first sterile pre-operative antiseptic product approved in the U.S.; therefore, it likely would be very widely used. However, [REDACTED] (b) (4) [REDACTED] impurities that have an unknown safety profile, the benefits of a sterile product may not outweigh the risks. In addition, a variety of other products containing the same ingredients are already available on the market, so there is no unmet medical need that could be used to outweigh this safety concern.

### **8.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

None.

### **8.4 Recommendation for other Postmarketing Requirements and Commitments**

None.

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/s/  
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THERESA M MICHELE  
09/01/2017

## Cross-Discipline Team Leader Review

<b>Date</b>	August 31, 2017
<b>From</b>	Francis E. Becker, M.D., F.A.C.P
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 208288
<b>Supplement#</b>	SD-45
<b>Applicant</b>	3M Healthcare Business
<b>Date of Submission</b>	3 March 2017
<b>PDUFA Goal Date</b>	3 September 2017
<b>Proprietary Name / Non-Proprietary Name</b>	SoluPrep Film-Forming Solution / 2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
<b>Dosage form(s) / Strength(s)</b>	Solution
<b>Applicant Proposed Indication(s)/Population(s)</b>	Patient Preoperative Skin Preparation <ul style="list-style-type: none"> <li>• For preparation of the skin prior to surgery</li> <li>• Helps reduce bacteria that potentially can cause skin infection</li> </ul>
<b>Recommendation on Regulatory Action</b>	Complete Response
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Adults and pediatric patients $\geq$ 2 months of age

### I. Introduction

The following is a review of the Sponsor's resubmission of a 505(b)(2) New Drug Application (NDA) following FDA Complete Response (CR) action (CR letter; 6 May, 2016). The proposed product is a combination product containing chlorhexidine gluconate (CHG) 2% and isopropyl alcohol (IPA) 70% solution (proposed trade name SoluPrep). The proposed indication is for use as a preoperative skin preparation for preparation of the skin prior to surgery and to help reduce bacteria that can potentially cause skin infection.

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. (b) (4)  
 (b) (4) unlike currently approved CHG/IPA products, the Sponsor's product is provided as a sterile solution in a sterile applicator. 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 addition, (b) (4) % HEDTA (b) (4) was added (b) (4)

## II. Background

In the initial NDA, the Sponsor submitted two pivotal clinical simulation studies (Studies EM-05-012760 and EM-05-013260) to support the efficacy of the product. In these studies, the reduction in bacteria on abdominal and inguinal regions (based on log reductions) was measured after application of test product, active control and negative control and is compared to baseline measures of bacteria. The Sponsor initially proposed (b) (4) however, during the first review cycle, 3M requested to modify this to reliance on literature only.

This review will focus on issues related to the Complete Response. The reader is referred to the first cycle reviews, including my CDTL Review (26 April 2016) for complete regulatory history and complete reviews of the original NDA.

### Complete Response Letter

The CR letter identified several CR issues which are described as follows:

1. The Sponsor “failed to demonstrate replicative efficacy in two pivotal clinical simulation studies, based on the previously agreed upon primary endpoints and statistical analyses. Study EM-05-012760 passed on all primary efficacy analyses; however, Study EM-05-013260 did not pass the  $\geq 70\%$  responder rate primary endpoint for the inguinal site. Thus, replicative efficacy was demonstrated for the abdominal site, but replicative efficacy was not demonstrated for the inguinal site.” The Sponsor was advised to “conduct a repeat study of the inguinal region with adequate controls that meets the prespecified primary endpoint.”
2. The financial disclosure information was not sufficient. Specifically, “eleven of 20 subinvestigators listed on the revised 1572 for pivotal study EM-05-012760 are missing disclosure information. Also, one of the five subinvestigators is missing financial disclosure information for study EM-05-013260.”
3. The Sponsor proposed to rely on literature to support the pharmacokinetics and absorption profile of CHG/IPA in humans. However, FDA determined that the literature submitted was inadequate for evaluation of human pharmacokinetic (PK) data for IPA and for the combination of CHG/IPA. FDA advised that the Sponsor “may rely on adequate literature for IPA and CHG/IPA to demonstrate absorption after use as a surgical skin preparation with a similar level of skin coverage to that proposed for the largest size product (26 mL), rely upon FDA’s findings of safety for a listed drug(s), or conduct a maximal use pharmacokinetic study with the final, to-be-marketed formulation of your product.”
4. The Sponsor “failed to provide qualification data for two impurities, (b) (4) which exceed the allowed impurity threshold per ICH Q3B (R2) guidance (i.e.,  $<1\%$ ).” Furthermore, based on the Sponsor’s quantitative stability data, (b) (4) will reach 1.0% at (b) (4) months, and (b) (4) will exceed 1.0% at (b) (4) months. These degradants continue to rise and accumulate in the drug product throughout the shelf-life. Even though you have proposed interim specifications for an interim shelf-life of (b) (4) months, impurity (b) (4) still exceeds the ICH limit of  $<1.0\%$ . Therefore, at this

time, no expiration date can be granted for this drug product.” The Sponsor was advised to conduct qualification studies for (b) (4)

5. Several Microbiology issues were identified, including issues regarding container closure integrity (CCIT), bioburden testing, and issues regarding the requalification schedule for (b) (4)

### **Type A Meeting**

A face-to-face Post-action Type A meeting was held with the Sponsor on 15 July 2016. The discussion centered around two issues. First, the Sponsor provided its argument as to why it believes that, based on the totality of the data, the results of the pivotal trials support NDA approval and, therefore, a repeat study of the inguinal region is not required. FDA re-iterated its disagreement. Second, the Sponsor inquired as to whether or not FDA would accept reference to (b) (4) as the listed drug. The Sponsor stated that no other NDA sponsor in the product category had previously conducted any PK absorption studies in final marketed formulations and that all approved products in this category have been approved based on the same historical literature. FDA responded that reliance on (b) (4) is likely to be inadequate (b) (4)

FDA indicated that the SoluPrep NDA contains sufficient data to support the safety profile of CHG. However, FDA noted that 3M will need to establish a bridge to the relied upon published literature and explain why the literature is adequate to support that the combination of IPA and CHG does not significantly change the absorption of either active ingredient. 3M stated that in its resubmission, it will cross reference its own DuraPrep NDA for findings of safety for IPA, make a scientific bridge to support the safety of CHG, and provide information to support that both active ingredients do not have increased absorption in the presence of each other. 3M stated that it will rely on both the previously submitted literature in the NDA and literature included in its meeting package.

### **Dispute Resolution**

The Sponsor submitted a Formal Dispute Resolution Request (FDRR) on 11 August 2016. Specifically, 3M disputed the portion of the clinical deficiency that pertains to the results of the inguinal region clinical simulation study (Study EM-05-013260) which did not achieve the threshold for primary analysis. The Sponsor did not dispute the results of the study but the interpretation of the totality of the results and DNDP’s recommendation that 3M conduct another clinical simulation study on the inguinal region. The FDRR was reviewed and evaluated by Charles J. Ganley, M.D., Director of Office of Drug Evaluation IV. Dr. Ganley concluded, “There is sufficient information to support the efficacy of the 3M products and an additional study of the inguinal region in a clinical simulation study is not necessary.” Dr. Ganley based his decision on “a multitude of factors” which is described in detail in his review<sup>1</sup>. Dr. Ganley wrote, “When all of these factors are taken together, I believe there is sufficient information to support the efficacy of the proposed 3M product because of its similarity to the efficacy of an approved product, ChloroPrep.”

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<sup>1</sup> ODE Director Memo; 14 October 2016

### III. Product Quality

The Quality Review Team for this application is listed in the **Table 1** below. In this section, the relevant CMC issues related to the CR will be discussed. For details of each review, the reader is referred to the Combined OPQ Review<sup>2</sup>.

**Table 1: Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Erin Kim, Ph.D.	OPF/DPAIL/BranchVI
Microbiology	Maria Cruz-Fisher, Ph.D. Erika Pfeiler, Ph.D.	OPF/DPAIL/BranchVI
Facility	Xiaohui (Sherry) Shen, Ph.D.	OPF/DIA/B3
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Thao, Vu	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)	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

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#### Summary Review

In his summary review<sup>3</sup> dated 10 August 2017, Swapan De, Ph.D., Application Technical Lead, concluded that, “Regarding quality aspects of the resubmitted application the drug substance, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application.” However, he also noted that, “The drug product has not been granted a shelf life due to pending resolution of specifications for specified impurities in the drug product.” Therefore, “The application is approvable pending resolution of the impurities specifications of the drug product,” and “Based on finalized drug product specification, shelf life of the product needs to be assigned.”

As briefly mentioned in **Section II** above, several microbiology issues were identified in the CR letter. Specifically, there were 10 issues related to sterility assurance of the product. As stated by Dr. De, the Microbiology Review (Maria Cruz-Fisher, Ph.D and Erika Pfeiler, Ph.D; 14 June 2017) indicates that all outstanding issues related to sterility are resolved.

Regarding quality, as noted in **Section II**, the CR letter included additional concerns on two impurities (b)(4) in the drug product which exceeded the ICH Q3B (R2) limits (i.e., <1.0%) and increased during stability studies. Dr. De wrote, “As a result, no reasonable expiration date could be granted for the drug product. Nonclinical review required the applicant to conduct qualification studies for (b)(4).” He continued, “The

<sup>2</sup>Combined OPQ review NDA 208288; 10 August 2017

<sup>3</sup> Combined OPQ review NDA 208288

non-clinical team determined that the qualification studies for these impurities is not adequate based on non-clinical review dated 24 July 2017. Thus, CMC drug product impurity specifications could not be finalized.”

**Drug Product Review**

Dr. Elise Luong completed the Drug Product Review. In the first cycle, as described in **Section II**, the proposed product was not approved from CMC standpoint because of excessive levels of impurities/degradants observed in the stability batches, and no shelf-life was granted. The nonclinical pharmacology/toxicology team requested that the Sponsor conduct qualification studies on impurities that exceed the ICH limit of 1.0%. Therefore, CMC could not grant a viable expiry for the drug product during the first review cycle.

The Sponsor’s Complete Response indicated that qualification studies have been completed for both degradation products/impurities of concern (b) (4) per ICH Q3B (R2) guidance *Impurities in New Drug Products* and as agreed to in a teleconference with FDA on 12 January 2016. Specification settings are based on 13 clinical and registration lots manufactured under conditions representative of the intended commercial manufacturing process. Of these lots, 6 were produced earlier in the development process, at a time when the addition of trace quantity of HEDTA had not yet been introduced. The remaining lots contained HEDTA and trending for all stability parameters was unchanged by the addition of HEDTA. The new impurities specifications are shown in **Table 2** below:

**Table 2: Finished Product Impurities Specifications**

<b>Parameter</b>	<b>Specification</b>
Total Impurities Content (%w/w)	(b) (4)
Individual Impurity: (b) (4) Content (%w/w)	(b) (4)
Individual Impurity: Content (%w/w)	

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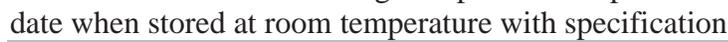
Testing completed on (b) (4) showed no genotoxic effects. In addition, local tolerance testing showed no differences between fresh and aged formulations. The Sponsor reported that the impurities present in the proposed drug product show no clinically relevant adverse effects. Dr. Luong concluded that impurities (b) (4) “are considered qualified per the testing outlined in ICH Q3B(R2).”

The stability results as compared to the specifications from **Table 2** above are as follows:

**Table 3: Comparison of Specifications Based on Qualified Levels and Stability Results**

(b) (4)



In conclusion, Dr. Luong wrote, “The accelerated and long term stability conducted on 3M 2% CHG 70% IPA Film-Forming Preoperative Preparation support a 24-month product expiration date when stored at room temperature with specifications for total impurity of NMT <sup>(b) (4)</sup> ” Note that at higher temperatures and higher relative humidity (RH), the specifications do not support the 24-month expiration date. This is illustrated in the Figures below, with each line representing one of the 13 clinical and registration lots tested (electronically copied from Dr. Luong’s Review; Combined OPQ Reviews, pages 32-34).

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### **Discipline Review Letter**

Based on the CMC review above, a Discipline Review (DR) letter was sent to the Sponsor on 11 August 2017 with the following quality comment:

*“The proposed drug product specifications for individual impurity (b) (4) of NMT (b) (4)%, (b) (4) of NMT (b) (4), and Total Impurities of NMT (b) (4)% have not been adequately justified. Refer to Nonclinical comments. However, based on levels of impurities in the product real time stability data, 3M may tighten limits for (b) (4) to NMT (b) (4), (b) (4) to NMT (b) (4), and Total Impurities to NMT (b) (4)%. These limits would support a shelf-life of 2 years pending final non-clinical evaluation.”*

## **Sponsor's Response to DR Letter**

On 15 August 2017, 3M communicated via email that it accepts the Agency's tightened individual and total impurity limits and will change the drug product specifications for (b) (4) to NMT (b) (4)%, (b) (4) to NMT (b) (4)% and Total Impurities to NMT (b) (4)% to support a shelf-life of two years.

## **CMC Addendum Review and Final Conclusions**

In a follow-up Addendum Review<sup>4</sup> on 23 August 2017, Dr. De acknowledged the Sponsor's response to the DR Letter and concluded that, "regarding quality aspect of the drug product, all CMC issues are resolved." However, he also noted that the qualification of individual impurities (b) (4) remains inadequate. Therefore, "specifications of the drug product...with regards to the impurities of the drug product remain as tentative specifications."

*CDTL Comment: I agree with Dr. De's conclusion. CMC issues appear to be resolved. The impurity concerns were evaluated by the Nonclinical Pharmacology/Toxicology Team and are discussed below.*

## **IV. Nonclinical Pharmacology/Toxicology**

Nonclinical review<sup>5</sup> was conducted by D. Charles Thompson, RPh, PhD, DABT. The nonclinical data contained in the current submission were generated solely for the purposes of qualifying the safety of the two degradant impurities, (b) (4). In his review, Dr. Thompson wrote, "In vitro data on bacterial mutagenicity and mammalian cell chromosome aberration potential were submitted on each impurity individually and were considered sufficient and adequate, confirming negative genotoxic activity potential. In vivo data addressing the skin irritation and skin sensitization potential of fresh versus aged finished DP [Drug Product] solution in rabbits and mice, respectively, also confirmed a lack of clinically relevant toxicity. However, a pivotal dermal general toxicity study of the same fresh versus aged DP solution in rabbits is considered inadequate by design and conduct and the data cannot be relied upon to qualify the safety of the two DP degradant impurities at currently proposed product specifications and clinical use exposure scenarios."

Dr. Thompson noted that (b) (4) resulted in drug product instability. He wrote, "That instability was a primary reason for DP degradant impurity specifications that exceeded the qualification threshold ( $\leq 1\%$ ) proscribed under ICH-Q3B(R2) and was a key deficiency of NDA 208288 identified by FDA in the resulting CR action."

The Sponsor provided data from a pivotal, general dermal toxicity study conducted in rabbits that evaluated the effects of fresh versus aged (b) (4) DP solution formulations. Dr. Thompson reported that the Sponsor's pivotal dermal study "did not assess systemic absorption

<sup>4</sup> Executive Summary Review #2 Addendum; 23 August 2017

<sup>5</sup> NonClinRev1-NDA208288; 24 July 2017

of impurities by animals, nor were clinical exposure data available. In the absence of such data, it is assumed that the impurities are 100% bioavailable after dermal exposure.” Therefore, Dr. Thompson calculated that the systemic doses to a rabbit would equate to human equivalent doses (HED) of (b) (4) mg/kg, respectively, if normalized based on body surface area (BSA). These dose rates correspond, in turn, to total administered doses of each impurity of (b) (4), respectively, in a reference 60-kg human.

According to the Sponsor’s proposed professional product labeling, each 26-mL DP applicator will cover a maximum area of approximately 19.5 in x 19.5 in, or 380.25 in<sup>2</sup>, which is approximately equivalent to 2453 cm<sup>2</sup>. It is noteworthy that, in the Sponsor’s current submission (Pharmacokinetic Written Summary, 2.6.4.1.1. Absorption, pg. 11), it is stated that “In a single major surgery, such as a cardiovascular procedure, standard of care dictates that up to four 26-mL product applicators may be used which represents a maximal use circumstance.” Based on this information, Dr. Thompson calculated the following animal-to-human exposure margins (see Dr. Thompson’s review for details of his calculation methods):

**Table 4: Animal vs. Human Exposure Comparison (at current proposed specifications)**

	Rabbits		Humans		Animal:Human Ratio	
	Impurity 1	Impurity 2	Impurity 1	Impurity 2	Impurity 1	Impurity 2
Surface Area (mg/cm <sup>2</sup> )	(b) (4)					
Systemic Dose (mg/kg) <sup>a</sup>						

<sup>a</sup>Assuming 100% bioavailability; animal doses converted to HED based on BSA

<sup>b</sup>Based on MDD of 2 x 26-mL applicators

<sup>c</sup>Based on MDD of 3 x 26-mL applicators

<sup>d</sup>Based on MDD of 4 x 26-mL applicators

(Electronically copied and reproduced from Dr. Thompson’s review)

Dr, Thompson expressed significant concerns with other aspects of the design and conduct of this study. He wrote, “The animals were allowed to recover for a full 3-day non-dosing period between removal of the final drug patch application and terminal necropsy, which is not optimal. Further, the Sponsor performed microscopic examination on an inadequate number of organ tissues in their histopathology evaluations, though they do indicate that an adequate battery of tissues was collected and preserved. In subsequent communications<sup>6</sup>, the Sponsor has committed to submitting an amended study report containing results of microscopic observations on a full battery of organ tissues. Finally, no toxicokinetic analyses were performed as part of the study, so there are no data to address whether the impurities were systemically absorbed and, if so, to what extent.” Dr. Thompson concluded that “These deficiencies—individually and in total—represent significant design flaws in a study that is intended to provide a full and complete assessment of the potential for these impurities to induce local and/or systemic toxicity,” and “the data provided are inadequate to establish the safety under proposed clinical use conditions of the two DP impurities.”

<sup>6</sup> NDA 208288 Information Request; 7 June 2017

Furthermore, Dr. Thompson wrote, “Absent a Clinical Review Team finding that the benefit-risk assessment regarding the potential clinical utility of such a sterile drug product outweighs any potential safety risk due to the impurities, it is, thus, recommended that the dermal general toxicity study be repeated. In such case, it is recommended that a final study protocol be submitted for comment prior to study initiation. Alternatively, consideration was given to the possibility that the Sponsor might agree to lower the proposed DP impurity specifications and how this might affect approvability from a nonclinical safety perspective. Such consideration is captured quantitatively in summary table [Table 5] below, which reflect the underlying assumptions shown below. It will be a Clinical Review Team decision as to the appropriateness of discussing such product use and quality alternatives with the Sponsor.”

**Table 5: Maximal Supported Specifications**

Anticipated Clinical Use		Maximal Supported Specification (%, NMT ???)	
Appl. No. & Size (CHG dose, mg)	Recommended Coverage Area (cm <sup>2</sup> )*	Impurity 1	Impurity 2 (b) (4)
1 x 26-mL (520)	2453		
2 x 26-mL (1040)	4906		
3 x 26-mL (1560)	7359		
4 x 26-mL (2080)	9812		
1 x 10.5-mL (210)	1090		
2 x 10.5-mL (420)	2180		
3 x 10.5-mL (630)	3270		
4 x 10.5-mL (840)	4360		
5 x 10.5-mL (1050)	5450		

(Electronically copied and reproduced from Dr. Thompson’s review)

**Information Request and Sponsor’s Submission of Amended Rabbit Dermal Toxicity Final Study Report**

The Information Request of 7 June 2017 requested that the Sponsor submit data on a full battery of tissues from the rabbit dermal toxicity study to address systemic toxicity. This was further discussed with the Sponsor via teleconference<sup>7</sup> on 12 June 2017, at which time the Sponsor committed to providing the data. FDA informed the Sponsor at that time that it would be determined at a later date how the submission would affect the timing of review and whether or not the submission would be a major amendment. Subsequently, the Sponsor submitted the amended rabbit dermal toxicity final study report on 31 July 2017.

**Discipline Review (DR) Letter**

Nonclinical comments were conveyed to the Sponsor in the DR Letter dated 11 August 2017 (see also **Section III** above). The comments included the following:

<sup>7</sup> NDA 208288\_tcon\_MM\_6-12-17

1. *Using your proposed specifications of NMT [REDACTED] (b) (4) of the impurity at [REDACTED] (b) (4), there is no safety margin using the systemic dose in rabbits as compared to anticipated human clinical exposures. In the absence of nonclinical or clinical toxicokinetic or pharmacokinetic data, 100% bioavailability was assumed for the two DP degradant impurities.*
2. *Your histopathology evaluation in the original submitted rabbit dermal toxicity study report included microscopic examination of an inadequate number of organ tissues. We hereby acknowledge your submission in response to our prior information request of an amended final study report for the rabbit dermal toxicity study that may address this deficiency. Review of these additional data may trigger the submission to be considered a major amendment.*

### **Sponsor's Response to DR Letter**

In response to the DR Letter, 3M requested follow-up teleconferences with FDA for further clarification.

#### **Teleconference (17 August 2017):**

At the teleconference of 17 August 2017, FDA acknowledged that 3M had submitted additional data in a final nonclinical study report on 31 July 2017 to address the inadequate tissue battery. FDA also stated its determination that review of these data would trigger a major amendment, which would extend the goal date by 3 months. Furthermore, FDA stated that if the data are adequate, then a sufficient exposure margin may be determined for the 10.5 mL applicator. However, FDA does not anticipate that the new data will provide a sufficient safety margin for the proposed use of the 26 mL applicator.

During the teleconference, 3M proposed that submitted data from a Franz cell assay illustrated that the systemic exposure to impurity [REDACTED] (b) (4) were lower than that of the active ingredient (chlorhexidine gluconate). Therefore, 3M hypothesized that no additional data are needed to qualify either impurity. FDA stated that data from the Franz cell assay may be useful for formulation development, but does not supplant the need for clinical pharmacokinetic data regarding dermal absorption in vivo. This is consistent with FDA policy with the use of other in vitro methods where a linkage between in vitro and in vivo methods has been demonstrated and accepted by the FDA, prior to the use of in vitro methods alone in a regulatory manner.

FDA also suggested that there are several pathways available to the sponsor regarding the 26 mL applicator. First, clinical pharmacokinetic data from an adequate maximum use trial (MUsT) can illustrate if, indeed, there is minimal systemic absorption of the two impurities of concern. If there is more than minimal systemic absorption, 3M may be able to provide a safety margin by comparing systemic exposure in humans to systemic exposures in animals. Finally, a new animal qualification study with higher doses of the impurities may provide support for the proposed 26 mL applicator; the previously cited human equivalent dose (HED) conversion factors can be used in the absence of human pharmacokinetic data.

### Teleconference (18 August 2017):

At a second teleconference on 18 August 2017, the Sponsor asked if it were to withdraw the 26 mL applicator from the NDA, would it be likely that FDA would approve the NDA for the 10.5 mL applicator. FDA responded that without reviewing the updated histopathology data submitted on July 31, 2017, it does not appear that the original nonclinical data support the impurity specifications for either the proposed 10.5 or 26 mL applicators. FDA noted that a sufficient safety margin may be determined for the 10.5 mL applicator, if the data submitted on July 31, 2017 is adequate. It does not appear the recently submitted data will provide a sufficient safety margin for the impurity specifications proposed for the 26 mL applicator.

### **Sponsor's Decision to Withdraw Amended Rabbit Dermal Toxicity Final Study Report**

On 22 August 2017, the Sponsor informed FDA of its decision to withdraw the histopathology data submitted on 31 July 2017 from the NDA. Consequently, there is no major amendment and the PDUFA time line will not be extended.

### **Nonclinical Pharmacology/Toxicology Review Addendum and Final Conclusion**

In response to the above communications, Jane Sohn, Ph.D, Nonclinical Team Leader, DNDP, provided a Review Addendum<sup>8</sup> on 23 August 2017. In her review, she noted that the Sponsor's commitment to decrease the specifications for impurities (b) (4) do not fully address the two nonclinical issues in the DR letter.

The first nonclinical issue was regarding inadequate dosing in the dermal rabbit study (Study #16-014). Dr. Sohn noted that the decreased specifications could address the inadequate dosing to *potentially* provide an adequate exposure margin (rabbit: human) >1 for the impurities in the 10.5 mL applicator. However, the decreased specifications do not address the impurity specifications for the 26 mL applicator, which results in a higher dose of impurities than the 10.5 mL applicator.

The second nonclinical issue in the DR Letter was regarding the inadequate characterization of systemic toxicity in the dermal rabbit study. Dr. Sohn reported that, relying on the data submitted to the new NDA on March 3, 2017, Pharm/Tox is precluded from determining a systemic exposure margin for impurity (b) (4) because of the inadequate tissue battery evaluated in the dermal rabbit study. This issue applies to both the 10.5 mL and 26 mL applicator. As noted above, the Sponsor submitted data on July 31, 2017 to address the inadequacy of the tissue battery, but the data was withdrawn on August 22, 2017 after 3M received the Discipline Review Letter. As a result of the data withdrawal, Pharm/Tox cannot adequately assess the systemic toxicity of impurity (b) (4)

Therefore, Dr. Sohn concluded that, "A complete response is recommended due to inadequate qualification of impurities. The impurity (b) (4) and the impurity (b) (4)

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<sup>8</sup> NDA 208288\_170822; 23 August 2017

(b) (4) are above the qualification threshold in the ICH guidance for industry Q3B(R2) *Drug Product Impurities*.”

In addition, she wrote, “As stated previously in the review dated July 24, 2017, absent the Clinical Review Team finding that the benefit-risk assessment of the proposed sterile product outweighs any potential safety risk due to the impurities, it is recommended that additional impurity qualification data is needed.”

Dr. Sohn continued, “The Applicant may respond with an adequate qualification study in a single animal species (e.g., a single extended dose study), or otherwise address the systemic exposure to (b) (4) and impurity (b) (4). Alternatively, the Applicant can control the level of impurities to that of a relevant approved product.”

*CDTL Comment: I agree with the conclusions of Dr. Sohn that the two impurities (b) (4) are above the qualification threshold and therefore a complete response is warranted. As Dr. Sohn noted, Pharm/Tox is precluded from determining a systemic exposure margin for impurity (b) (4) because of the inadequate tissue battery evaluated in the dermal rabbit study. This issue applies to both the 10.5 mL and 26 mL applicator. The Sponsor submitted data (Amended Rabbit Dermal Toxicity Final Study Report) on July 31, 2017 to address the inadequacy of the tissue battery; however, the data was withdrawn on August 22, 2017 after 3M received the Discipline Review Letter. As a result of the data withdrawal, Pharm/Tox cannot adequately assess the systemic toxicity of impurity (b) (4). The Sponsor was informed that review of the Amended Final Study Report, which was submitted late in the review cycle (31 July 2017), would be considered a Major Amendment which would extend the review clock by 3 months. Without a thorough review of the Amended Final Study Report, it is unknown whether the histopathology data is adequate to assess the systemic toxicity of impurity (b) (4) and potentially provide an adequate exposure margin for the 10.5 mL applicator (but not the 26 ml applicator).*

*As stated by Dr. Sohn, in order to address this deficiency, the Sponsor will need to either: 1) provide an adequate qualification study in a single animal species (e.g., a single extended dose study), or otherwise address the systemic exposure to (b) (4) or 2) control the level of impurities to that of a relevant approved product.*

*Dr. Sohn and Dr. Thompson also commented that the recommendation for additional impurity qualification data is made “absent the Clinical Review Team finding that the benefit-risk assessment of the proposed sterile product outweighs any potential safety risk due to the impurities.” From clinical standpoint, I do not consider the benefit-risk assessment for this product to be adequate in the absence of a thorough assessment of the systemic toxicity of the two impurities in question. Until this is adequately addressed, it is not possible to accurately assess risk-benefit. Furthermore, as I noted in my first cycle CDTL Review, there are numerous other products available on the market for patient preoperative skin prep, many of which have the same active ingredients as this product, which precludes an urgent need for this product. In addition, although if approved, this would be the first FDA-approved sterile product, the clinical*

implications of this sterility (i.e. effect on postoperative infection rates) is unclear, and, in any case, (b) (4) further complicating assessment of risk-benefit.

## V. Clinical Pharmacology

The Clinical Pharmacology Review<sup>9</sup> was conducted by Sojeong Yi, Ph.D., and Dennis Bashaw, PharmD, Division of Clinical Pharmacology 3, Office of Clinical Pharmacology (OCP). OCP concluded that, “from a clinical pharmacology standpoint the information provided was acceptable to support the approval of the combination of CHG 2% (w/v) and IPA 70% (v/v) (as formulated in this NDA) as a film-forming solution for use as a preoperative skin preparation.”

SoluPrep is designed for single-use topical application to the intact skin prior to a surgical procedure. For the 26-ml and 10.5 ml applicator, the maximum treatment areas are 178.8 in<sup>2</sup> (1153.5 cm<sup>2</sup>) and 387.5 in<sup>2</sup> (2500 cm<sup>2</sup>), respectively. Per the proposed label, the smaller product (10.5 ml) is to be applied to head, neck or small areas and the larger product (26 ml) is for large preparation area below the head and neck. On dry surgical sites (e.g., abdomen or arm), the product should be applied for 30 seconds while it is to be used for 2 minutes on moist surgical sites (e.g., inguinal fold). The proposed label directs the user to wait until the solution is completely dry (minimum of 3 minutes on the hairless skin and up to 1 hour in hair) before draping the surgical site or starting the surgical site or starting the procedure. The Sponsor stated that up to four 26-ml Soluprep products may potentially be used in a single major surgery, such as a cardiovascular procedure, which represents a maximal use.<sup>10</sup> OCP calculated that four 26-ml products (a total of 104 ml solution) would be maximally applied to 10,000 cm<sup>2</sup> of skin area which is approximately 58% of 1.73 in<sup>2</sup>, the average body surface area in adults.

OCP noted that, in the original NDA review, the literature demonstrating the dermal absorption of CHG was deemed acceptable whereas those for IPA and the CHG/IPA combination were inadequate. Thus, in this resubmission, the Sponsor intended to address the dermal absorption of IPA and the combination of CHG/IPA. Therefore, in the current submission, the Sponsor submitted the following:

- A literature review with regard to the human pharmacokinetic data evaluating CHG and IPA as a preoperative skin preparation and for the combination CHG/IPA
- A proposal to establish clinical pharmacology safety for IPA of SoluPrep based on the cross-reference to safety and effectiveness data of DuraPrep Surgical Solution [Iodine Povacrylex (0.7% Available Iodine) and IPA (74% w/w)] under NDA 21-586
- Results from an in vitro skin permeation test for CHG using SoluPrep compared to that of ChlorPrep

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<sup>9</sup> NDA 208288\_SoluPrep\_Resub\_Clin Pharm Review\_ver2e; 24 August 2017

<sup>10</sup> Section 2.6.4 Pharmacokinetics Written Summary, Page 11

## Literature Review

Based on the literature submitted, CHG generally shows minimal absorption following topical administration except when it is applied to neonates and preterm infants. IPA is slightly absorbed after topical administration while it depends on the frequency of application, surface area involvement, and other factors. Therefore, OCP concluded that the expected IPA blood level after a single use of SoluPrep “is far lower than 500 mg/L that is known to be associated with a mild adverse effect of IPA.” The highest blood level of IPA across the publications provided was 12.25 mg/L which is far below than 500 mg/L associated with adverse events. OCP also noted that IPA is readily eliminated via exhaled air and urine following metabolism once it is absorbed through the skin.

OCP also pointed out that while the literature submitted suggested that the systemic exposure to CHG and IPA used as active ingredients in topical antiseptic products is expected to be low, none of the literature submitted had evaluated in vivo bioavailability of the two active ingredients with the CHG 2%/IPA 70% combination product proposed by the Sponsor at the intended usage level (i.e., a single application of up to four 26-ml products to 10,000cm<sup>2</sup>). OCP wrote, “In fact, the products used in the literature primarily contained either CHG or IPA not both, had lower strengths of either one of the two active ingredients than the proposed CHG 2%/IPA 70% combination, or were applied to smaller skin areas than the expected maximal application area for the proposed product. Subsequently, the literature provided was not sufficient to demonstrate the dermal absorption of either IPA or the CHG/IPA combination under a maximal usage condition for a preoperative skin preparation (i.e., a single application of four 26-mL products).”

Despite these limitations to the available literature, OCP concluded, “the single-use application of the combination of CHG 2% (w/v) and IPA 70% (v/v) as formulated in this NDA as a film-forming solution is justifiable from a clinical pharmacological perspective, because it is unlikely to cause a significant systemic exposure to either CHG or IPA given that this type of single-use product will be used only a few times in one’s lifetime aside from an exceptional case such as a massive traumatic situation that requires multiple surgeries in a short period or in the case of patients with a cerebral shunt which may need multiple revisions throughout their life (albeit at significant intervals).” Importantly, OCP also noted that “this determination is not applicable to other products where chronic use and multiple administrations over a day are expected (e.g., a hand rub or a hand wash) or where prior information of human exposure is lacking as in the case of a new ingredient.”

## Cross-reference to DuraPrep

The Sponsor also proposed to establish the clinical pharmacology safety of IPA for SoluPrep by cross-referencing information of safety and effectiveness from NDA 21586 for DuraPrep Surgical Solution [Iodine Povacrylex (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w)]. However, OCP noted that this cross-reference “is deemed inapplicable because DuraPrep differs from SoluPrep in terms of active ingredients, formulation, and application regimen,” as shown in **Table 6** below. OCP pointed out that the safety and effectiveness data of IPA in DuraPrep is confounded by iodine so it cannot be used to establish the clinical pharmacology

safety of SoluPrep. Furthermore, DuraPrep is applied with a lower dose of IPA per cm<sup>2</sup> than SoluPrep (5.701 mg/cm<sup>2</sup> vs. 5.840 mg/cm<sup>2</sup>).”

**Table 6: Comparison of Exposure to IPA between SoluPrep and DuraPrep**

	SoluPrep (NDA 208288)	DuraPrep (NDA 21586)
Active ingredients	CHG 2%/IPA 70%	Iodine 0.7%/IPA 74%
Strength of IPA	70% (v/v)= 64.1% (w/w)	74% (w/w)
Amount of IPA in a single product (g)	14.60 g in 26 mL	16.55 g in 26 mL
Maximum skin coverage (cm <sup>2</sup> )	19.5*19.5 inch <sup>2</sup> = 380.25 inch <sup>2</sup> = 2500 cm <sup>2</sup>	15*30 inch <sup>2</sup> = 450 inch <sup>2</sup> = 2903 cm <sup>2</sup>
Applied dose per cm <sup>2</sup> (mg/cm <sup>2</sup> )	<u>5.840 mg/cm<sup>2</sup></u>	<u>5.701 mg/cm<sup>2</sup></u>

Electronically copied and reproduced from OCP review.

### **In Vitro Skin Permeation Test**

OCP concluded that the in vitro skin permeation (Franz Cell) test for CHG that the Sponsor conducted using SoluPrep “cannot be considered representative of in vivo dermal absorption data unless there is in vivo data generated from a maximal usage trial with which to anchor the in vitro methodology.” While in vitro permeation data may be useful to supplement in vivo absorption data generated via maximal usage trial, it cannot supplant in vivo absorption data. This was discussed with the Sponsor at the teleconference on 17 August 2017 (See **Section IV** above).

### **Overall OCP Conclusion**

In summary, OCP concluded that based on the literature provided, assuming no other factors increasing dermal absorption of IPA, the relative proportion of IPA absorbed is expected to be very low, approximately 0.4%-1.1% of the applied dose. OCP acknowledged that SoluPrep’s potential dermal absorption for IPA after use as a preoperative skin preparation could not be fully addressed with the literature submitted because none of the literature covered the maximal usage condition of SoluPrep, i.e., single application of four 26-mL products to 10,000 cm<sup>2</sup> area. Moreover, the potential impact of 2% CHG on dermal absorption of IPA has not been addressed.

Even so, OCP concluded that “from a clinical pharmacology perspective, considering both the typical usage pattern of preoperative skin preparation (i.e., single-use application) and the known pharmacokinetic information of IPA (e.g., readily eliminated from the bloodstream through metabolism into acetone and CO<sub>2</sub> followed by excretion via urine and air), the submitted data is acceptable to justify the usage of SoluPrep as a preoperative skin preparation; in other words, it is not likely to cause significant systemic exposure that may arise [in] safety concern, e.g., > 500 mg/L. This determination is not warranted for other IPA-containing products where chronic uses are expected, however.”

*CDTL Comment: I agree with OCP conclusions. Although the dermal absorption of CHG and IPA after applying CHG 2%/IPA 70% combination as a preoperative skin preparation has not been adequately addressed in this NDA, it is likely that, from a clinical standpoint, the risk is acceptable for the CHG/IPA combination in this product, which FDA considers to be a single use product. For IPA, OCP noted that the highest blood level of IPA across the publications provided was 12.25 mg/L which is far below than 500 mg/L that may cause mild CNS depression. Therefore, from a clinical pharmacology perspective, considering the typical usage pattern of SoluPrep as a preoperative skin preparation (i.e., single-use application to a limited skin area), it is not likely to cause significant systemic exposure that may cause an adverse effect, e.g., > 500 mg/L. This is reassuring, although the potential impact on dermal absorption of IPA has not been fully addressed for final film-forming formulation combined with CHG 2% and a maximal usage condition. It is noteworthy that there are many CHG/IPA containing antiseptic products already available. See also my CDTL comments in **Section VI Clinical Review**.*

## **VI. Clinical Review**

The clinical review<sup>11</sup> was completed by Teresa Podruchny, M.D., Medical Officer, Division of Nonprescription Drug Products. Dr. Podruchny's review addressed the clinical approvability issue related to Financial Disclosure. In addition, Dr. Podruchny reviewed the Sponsor's Safety Update which was submitted as requested in the CR letter, and the Sponsor's responses to additional (not CR) clinical comments provided in the CR letter. Lastly, Dr. Podruchny discussed pediatric development. Regarding the remaining CR issue of financial disclosure, Dr. Podruchny concluded that the application is "approvable (acceptable)."

### **Financial Disclosure**

Dr. Podruchny concluded that financial disclosure was "not optimal, but probably acceptable." In the Sponsor's Complete Response, the Sponsor reported getting post-trial financial disclosure on all subinvestigators (SIs) except one, and the Sponsor described its due diligence in its unsuccessful attempt to contact the remaining subinvestigator. In addition, some of the SIs may have been employees of the companies conducting the studies (Microbiotest and Bioscience).

The Sponsor opined that although financial disclosure was not obtained from the subinvestigators prior to study initiation, data integrity was not compromised. The Sponsor quoted part 54 of 12 CFR and argued, essentially, that the listed subinvestigators were not subinvestigators because they had ancillary responsibilities and tasks and that their tasks were performed under the direction and guidance of the Principle Investigator (PI). The ancillary tasks were listed by the sponsor as including:

- Subject recruitment and consent
- Skin assessment, product application and sample collection
- Diluting and plating samples
- Bacterial enumeration

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<sup>11</sup> Clinical\_CR response\_f2\_NDA 208288; 11 August 2017

- Data entry into electronic data capture (eDC) system

The Sponsor reported that the totality of all completed tasks resulted in the outcome for each subject but that all tasks completed for a subject were not performed by a single investigator and that every subject interacted with several investigators during their study participation. The Sponsor also argued that the potential for bias was minimized by including randomization and blinding in the study design. Study products were assigned to test sites based on a computer-generated randomization schedule. Study staff involved in the bacterial enumeration was not involved in the study product application or the collection of samples.

The subinvestigator (SI) for whom financial disclosure was not obtained, participated in Study EM-05-12760 from 12 February 2014 to 4 April 2014. This subinvestigator was involved in collecting samples and diluting and plating for six subjects. The Sponsor reported that it removed these six subjects from its data analysis and stated that the efficacy results remained unchanged.

Dr. Podruchny noted that, from an efficacy standpoint, the Clinical Study Reports for the pivotal efficacy studies EM-05-12760 and EM-013260 state that “The study staff performing the bacterial enumeration and the statistician performing the analyses were blinded to the study products,” which should act to reduce bias. Additionally, both pivotal studies and two other studies (persistence of efficacy study 013509 and a safety challenge study 12853) were inspected by FDA and no regulatory violations were found. However, she also noted that an analysis of all SIs without pretrial disclosure and the possible impact on safety was not submitted, and “it is unclear that obtaining financial disclosure before or after the trial changes the value of the disclosure in terms of impact on bias assessment.” In her review, she wrote, “If this financial disclosure had been before trial initiation, it would not be a problem. In terms of bias, whether the obtainment of financial disclosure pre or post-trial significantly alters bias assessment is unclear to me. Some of the SIs may have been employees of the labs (MBT or BSL). It appears that some of the SI tasks could be used to alter efficacy study results (recruitment, bacterial enumeration, data entry).”

Dr. Podruchny recommended that, in order to reduce bias in future studies of antiseptics, DNDP:

*“A) require that Sponsor’s add placebo products to trials intended to support labeling. If Sponsors feel this cannot be accomplished, they should provide a rationale for FDA review. A placebo could provide some level of blinding, which might reduce bias. For example, from a safety perspective, assessment of skin reactions appears somewhat subjective.*

*B) encourage that trials intended to be used to support labeling of preoperative scrub be performed in an independent facility. Several trials were conducted at 3M on 3M employees by 3M employees. This situation does not mean the data are not legitimate but on-face it has an appearance of conflict, especially if there is an absence of blinding. Also, the use of in-company subjects provides an environment for re-use of subjects and may underestimate in labeling reactions that will occur with exposure to naïve populations.”*

*CDTL Comment: I agree with Dr. Podruchny's conclusion that the financial disclosure information provided was not optimal, but acceptable. The Sponsor has exercised due diligence in providing as much information as possible in response to the CR. Based on this additional information, it is reasonable to conclude that the likelihood of study bias is low. It is also assuring that the active ingredients, CHG and IPA, have a well-known safety profile, such that any potential bias is unlikely to mask a serious safety signal. Regarding Dr. Podruchny's recommendations for future antiseptic studies, these recommendations may be considered and discussed within DNDP as additional antiseptic applications are evaluated.*

## **Safety Update**

Dr. Podruchny concluded that “Nothing new is reported that changes previous review conclusions. Post-marketing data for Avagard does not appear to be updated. However, Avagard contains a different alcohol and a lower concentration of CHG with limited comparability to the NDA product in my opinion.”

Six new clinical trials were conducted after the filing of the NDA on 6 July 2015, as shown in **Table 7** below. The Sponsor reported these trials were not intended to incorporate into the NDA because they were not designed as “full safety or efficacy studies.” (p 1/5 Safety Update Report, 3-3-17 submission). According to the Sponsor, there were no deaths in the history of development and no serious adverse event in any study. There were two subjects with adverse events and one of these did not complete the study due to the adverse event.

Four of the six studies evaluated drape adhesion (Studies 013565, 013689, 013699, and 013721) and were performed at 3M at the in-house clinical facility. Two studies (Studies 013655 and 013718) were for visibility on dark skin tones and product characteristics respectively and were conducted at Microbiotest (MBT). Exposure time for study 013721 was up to 4 hours and was 2 or 3 hours for study 013655. The six trials exposed 9 to 36 subjects each, although Dr. Podruchny pointed out that the number of unique subjects is not clear, as 3M is using its employees in the studies and therefore may have allowed for subjects to participate in more than one study.

Two subjects reported itchy skin and mild skin irritation on the treatment sites which were both recorded as adverse events.

- Subject (b) (6) in study 013689 experienced dry and itching skin on both knees, medially, seven days post treatment. The event is recorded as resolved.
- Subject (b) (6) in study 013721 experienced the events of itchy skin and mild erythema returned two hours after applications of products to the back (comparator on one side and NDA/IND product on the other) and did not complete the 4-hour treatment phase of the study. The Adverse Event Record captured the event as “moderate” severity (defined as signs, symptoms are sufficient to restrict but not prevent subject’s daily activity) and that the subject declined further evaluation at 3M’s clinic.

**Table 7: Clinical Trials Performed Post-NDA Submission**

<b>Trial #</b>	<b>Study</b>	<b>N, duration</b>	<b>Safety</b>
EM-05-013565	Drape Lift of NDA product versus Other Preps Using a Simulated Knee Surgery Model with Ioban Incise Drape	18 3M 15-30 min	No AEs, no rash, no edema, no dryness, no erythema  The sponsor reports evidence that drapes may lift more on the NDA product prep than on DuraPrep
EM-05-013699	Drape Lift of Ioban™ Incise Drape over NDA product versus Chloraprep® simulated knee	30 3M 15-30 min	no AEs reported, no skin irritation (no erythema, no rash, no edema, no dryness) Removal force “slightly lower” for ioban drapes on skin prepped with NDA product compared to skin prepped with Chloraprep (p=0.057)
EM-05-013689	Drape Lift of Ioban™ and two 3M™ CHG Antimicrobial Incise Drapes over NDA product versus Chloraprep® Simulated Knee	36 3M 15-30 min	One week after participation, subject 27- mild skin irritation (dry and itch) on medial test sites both knees, recorded resolved. On treatment day, no erythema, rash, edema, or dryness observed on any of the subjects.
EM-05-013721	Evaluation of skin irritation with Ioban™ on volunteers’ backs under dry conditions NDA product versus Chloraprep	12 3M 4 hours	One subject (10) reported itching under the drape samples, mild erythema was noted on the test sites. Drape samples and prep products removed after about 2 hours. The event was recorded as resolved. The Adverse Event Record* captured the event as “moderate” severity (defined as signs, symptoms are sufficient to restrict but not prevent subject’s daily activity) and that the subject declined further evaluation at 3M’s clinic.  No rash, edema, or dryness is reported CSR reports no death, no SAE, no dc secondary to AE.
EM-05-013718	Evaluation of Product Characteristics of NDA product Test location MBT	12 30-60 min	No AEs No skin irritation

EM-05-013655	Visibility of NDA product on dark skin tones. MBT.	9 males 2 hrs on back	no AEs were reported and no skin irritation was observed for any subject on any treated section
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Electronically copied and reproduced from Dr. Podruchny's review, Appendix I, page 15.

The Sponsor's Safety Update Report concluded 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."

### **Additional Comments from the CR Letter**

In her review, Dr. Podruchny addressed several of the Sponsor's responses to additional (non-approvability) comments provided to the Sponsor in the CR letter. Noteworthy responses are as follows:

1. **Safety-related Labeling:** In the CR letter, it was requested that, "for all safety-related proposed labeling statements that are not directly supported by data from your clinical studies, such as conditions of use, 'Do Not Use,' pediatric use, and hypersensitivity analysis, specify the literature articles that you are relying upon to support each labeling statement. Provide an adequate summary of the relied upon literature. If you intend to rely upon 'non-product specific literature' for such purposes, as stated in your application, you should ensure that the specified literature articles conform to your intent." Dr. Podruchny reported that the Sponsor's response did not provide an overall summary that easily shows which studies rely on branded products, and the Sponsor's summaries of publications do not always identify branded products that were used in the publication.
2. **Pediatric Use:** Regarding pediatric use, review of FDA Meeting Minutes from a Type B pre-NDA meeting (20 January 2015) indicate that the Pediatric Research Equity Act (PREA) was not triggered (i.e., the application was exempt at the time) by this application as it did not meet any of the criteria of new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration. In the current submission, the proposed product labeling includes language to use with care in premature infants and infants less than 2 months of age due to irritation and chemical burns. Dr. Podruchny noted that the Sponsor's literature review included an article by Chapman<sup>12</sup> which reported that chlorhexidine gluconate (CHG) is absorbed into the bloodstream of some preterm infants after a single exposure to CHG with higher concentrations 2-3 days post exposure. This Chapman publication references three other published studies documenting CHG absorption in preterm infants < 32 weeks gestation

<sup>12</sup> Chapman et al, Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonate. Journal of Perinatology (2013) 33, 768-771. Doi 10.1038/jp.2013.61

post topical exposure. In addition, a publication by Garland<sup>13</sup> concluded that chlorhexidine gluconate was absorbed cutaneously after antiseptics of skin with 2% CHG in neonatal intensive care, critically ill neonates weighing  $\geq 1500$  g, age 7 days or older but less than 2 months. Dr. Podruchny recommended that DNDP consider whether labeling language should be updated to incorporate these literature findings. She wrote, “It is unknown whether there is associated toxicity with systemic absorption (insufficient information to assess the risks in humans). Also, if the absorption of CHG/IPA combination and of IPA is determined by DNDP to require additional study, this may change labeling.” Dr. Podruchny concluded that “There are sections of labeling without direct trial support and for which in some cases, there appears to be some literature support that names branded products. Whether these sections can be supported as class labeling is deferred to the Division.”

3. **Adverse Event Datasets:** The CR letter requested that the sponsor “Submit datasets that correspond to Listings 16.2.8.1 and 16.2.8.2 in the study report for Study EM-05-013260 such that a comparison of adverse events with and without HEDTA could be verified.” The Sponsor did not comply with this request and noted that an adverse event required a score of 3 (severe) in any category (erythema, edema, rash, or dryness). Therefore, there were no adverse events to report. This is not an approvability issue; therefore, Dr. Podruchny recommended that, for completeness in the next cycle, the datasets showing all raw scores be requested regardless of whether it was an adverse event or not.

*CDTL Comment: Although the safety data provided are not ideal, the data are satisfactory to support approval of the Sponsor’s application from clinical standpoint, particularly for a single-use preoperative antiseptic product. The fact that there are numerous other antiseptic products in use containing CHG and IPA are reassuring that the safety profile is well-characterized and that the likelihood of unanticipated adverse events is low.*

*An important consideration is pediatric use. As Dr. Podruchny noted, some literature indicates that chlorhexidine gluconate (CHG) is absorbed into the bloodstream of some preterm infants. The clinical significance of this absorption is unknown. The proposed product labeling includes language to use with care in premature infants and infants less than 2 months of age due to irritation and chemical burns, which is consistent with labeling from some of the other similar products currently in use. 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 remain the best option for infants less than 2 months of age who require surgery.*

*In its Clin Pharm Review (discussed in **Section V** above), OCP made the following labeling recommendations for SoluPrep. In the future, if all CR issues are addressed such that SoluPrep*

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<sup>13</sup> Garland et al, Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antiseptics for central venous catheter placement in neonate. Journal of Perinatology (2009) 29, 808-813

is approved for OTC use, the following proposed labeling may be considered to better inform clinicians who are making decisions about the use of SoluPrep in infants:

**Table 8: OCP Proposed Labeling**

Proposed	Recommended
<p><b>12 Clinical Pharmacology</b> (b) (6)</p>	<p><b>12 Clinical Pharmacology</b> (b) (6)</p>
	<p><u>Isopropyl alcohol is slightly absorbed</u></p>
	<p><u>approximately 1% of the amount applied to the intact skin. In a published study, a 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.</u></p>

## VII. Biostatistics Review

A Statistical Memorandum<sup>14</sup> was completed by Joo-Yeon Lee, Ph.D. and Rima Izem, Ph.D, Division of Biometrics VII, Office of Biostatistics. As noted above (**Section II**), one of the reasons for the CR was that the Sponsor failed to show effectiveness of SoluPrep in the groin area in one of two clinical simulation studies. Therefore, the CR letter required the Sponsor to conduct another clinical simulation study at the groin area. The Sponsor requested a formal dispute resolution arguing that there was no need to conduct a new clinical simulation study. The sponsor’s request was granted by the Agency. As a result, there is no new clinical simulation study for review in this resubmission. However, the Biostatistics Review focused on the

<sup>14</sup> DB7 review\_final; 24 August 2017

Sponsor's label statement in Section 14 Clinical Studies. The Biostatistics Team provided recommendations on labeling based on preplanned analyses and new analyses of the data in the original submission. The new analyses follow effectiveness criteria outlined in the upcoming 2018 Final Rule for healthcare professional topical antiseptics. Dr. Lee and Dr. Izem proposed to include results of both analyses of responder and average treatment effect in labeling.

For a detailed statistical analysis and detailed labeling recommendations, please see the Biostatistics Review. Briefly, the effectiveness criteria in the 2015 Tentative Final Monograph (TFM) are based on responder rate in each treatment arm, where the responder rate is the proportion of those subjects with a change from baseline bacterial count exceeding a specific threshold;  $2 \log_{10}/\text{cm}^2$  for abdomen at 30 seconds;  $3 \log_{10}/\text{cm}^2$  for groin at 30 seconds. Then, a test product is considered effective only if the responder rate significantly exceeds 70%. The new effectiveness criteria in 2018 Final Rule is based on average treatment effect (ATE), which is estimated by linear regression of bacterial count at 10 mins (or 30 seconds) in  $\log_{10}$  scale on the effect of treatment arm and bacterial count at baseline in  $\log_{10}$  scale. There are two criteria required to show effectiveness of test product: non-inferiority to active control and superiority to negative control.

The Biostatistics Team re-analyzed the data submitted in the original submission and applied the new criteria. Dr. Lee and Dr. Izem concluded that SoluPrep is shown to be effective at both body areas in both pivotal studies by the new criteria.

*CDTL Comment: Overall, I agree with the proposed labeling changes. However, this will require further internal discussion in the future in the event that the NDA is approved.*

## VIII. Conclusions and Recommendations

I recommend a Complete Response action for this application. I agree with the conclusions of the Nonclinical Team that the two impurities (b) (6) are above the qualification threshold and therefore a Complete Response is warranted. As Dr. Sohn noted, Pharm/Tox is precluded from determining a systemic exposure margin for impurity (b) (6) or the impurity (b) (6) because of the inadequate tissue battery evaluated in the dermal rabbit study. This issue applies to both the 10.5 mL and 26 mL applicator. The Sponsor submitted data (Amended Rabbit Dermal Toxicity Final Study Report) on July 31, 2017 to address the inadequacy of the tissue battery; however, the data was withdrawn on August 22, 2017 after 3M received the Discipline Review Letter. As a result of the data withdrawal, Pharm/Tox cannot adequately assess the systemic toxicity of impurity (b) (6) and the impurity (b) (6). Without a thorough review of the Amended Final Study Report, it is unknown whether the histopathology data is adequate to assess the systemic toxicity of impurity (b) (6) and the impurity (b) (6) and potentially provide an adequate exposure margin for the 10.5 mL applicator (but not the 26 ml applicator).

From clinical standpoint, I do not consider the benefit-risk assessment for this product to be adequate in the absence of a thorough assessment of the systemic toxicity of the two impurities in question. Until this is adequately addressed, it is not possible to accurately assess risk-benefit.

As stated by Dr. Sohn, in order to address this deficiency, the Sponsor will need to either: 1) provide an adequate qualification study in a single animal species (e.g., a single extended dose study), or otherwise address the systemic exposure to (b) (6); **or** 2) control the level of impurities to that of a relevant approved product.

Other First Cycle Complete Response issues appear to be resolved:

1. Regarding quality aspect of the drug product, CMC issues are resolved. However, given that the qualification of individual impurities (b) (6) remains inadequate, specifications of the drug product with regards to the impurities of the drug product remain as tentative specifications.
2. From a clinical pharmacology perspective, considering both the typical usage pattern of preoperative skin preparation (i.e., single-use application) and the known pharmacokinetic information of IPA, the submitted data is acceptable to justify the usage of SoluPrep as a preoperative skin preparation. However, it is important to note that this determination is not warranted for other IPA-containing products where chronic uses are expected.
3. From clinical standpoint, the financial disclosure information provided was not optimal, but acceptable. The Sponsor has exercised due diligence in providing as much information as possible in response to the CR. Based on this additional information, it is reasonable to conclude that the likelihood of study bias is low. It is also reassuring that the active ingredients, CHG and IPA, have a well-known safety profile, such that any potential bias is unlikely to mask a serious safety signal.
4. Although the safety data provided by the Sponsor are not ideal, the data are satisfactory to support approval of the Sponsor's application from clinical standpoint, particularly for a single-use preoperative antiseptic product. The issue of pediatric use remains a concern. However, if this NDA is approved in the future after remaining CR issues are addressed, the concern may be mitigated in labeling (as recommended by OCP; see **Table 8** above), and it is important to note that there are few alternatives to CHG/IPA containing products for pediatric patients. 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.
5. Regarding the efficacy issue (failure to demonstrate replicative efficacy in two pivotal clinical simulation studies, based on the previously agreed upon primary endpoints and statistical analyses), this has previously resolved in Dispute Resolution. In addition, Biostatistics has provided data to demonstrate that based on revised statistical criteria (2018 Final Rule), SoluPrep is shown to be effective at both body areas in both pivotal studies. If SoluPrep is approved in the future, consideration can be given to incorporating the new statistical analyses into Targeted Product Labeling.

Given my recommendation for Complete Response, further labeling discussion will be deferred until CR issues are adequately resolved.

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FRANCIS E BECKER  
08/31/2017

### CLINICAL REVIEW

<b>Application Type</b>	NDA Resubmission after CR
<b>Application Number(s)</b>	208288
<b>Priority or Standard</b>	S
<b>Submit Date(s)</b>	3-3-17
<b>Received Date(s)</b>	
<b>PDUFA Goal Date</b>	9/1/17 goal date, date 9/3/17
<b>Division/Office</b>	DNDP/ODE IV
<b>Reviewer Name(s)</b>	Teresa A. Podruchny
<b>Review Completion Date</b>	8-4-17
<b>Established Name</b>	2% w/v chlorhexidine gluconate and 70% isopropyl alcohol
<b>(Proposed) Trade Name</b>	SoluPrep™
<b>Applicant</b>	3M Health Care Business
<b>Formulation(s)</b>	Solution
<b>Dosing Regimen</b>	Single-use
<b>Applicant Proposed Indication(s)/Population(s)</b>	Pre-operative skin preparation
<b>Recommendation on Regulatory Action</b>	The following recommendation is limited in scope to the remaining CR clinical issue of financial disclosure- approvable (acceptable)
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Adult and pediatric patients ≥ 2 months of age

Submissions used in this review:

- 1) SDN 45 3-3-17 NDA resubmission, module section 1.11.4 3M Response to Complete Response Letter dated 5-06-16, Summary of Clinical Safety, module 2.7.4 pages 1-26 were not reviewed as these pages appear to describe studies reported in the initial NDA submission and did not have information from the six new studies. Other pages used as needed.
- 2) SDN 34 8-5-16 Financial Disclosure
- 3) SDN 46 3-28-17 Response to Information Request, Clinical Study Reports
- 4) SDN 48 5-24-17 two page response to clinical Information Request
- 5) SDN 1 7-6-15 Financial disclosure information
- 6) SDN 55 7-19-17 Response to Information Request regarding financial disclosure

## Summary

This NDA received a Complete Response (CR) on 5-6-16. Two of the approvability issues were clinical. Of these, one was related to efficacy and one to financial disclosure. The Company requested a Formal Dispute Resolution of the efficacy issue. The Office Director completed his decisional memo on 10-14-16, overruling the efficacy approvability issue. The remaining clinical approvability issue is related to Financial Disclosure. Additionally, there were other clinical comments made in the CR letter that were not approvability level and the CR letter requests a Safety Update. Finally, pediatric development is discussed. Though it is not part of the CR, it is a clinical topic that may require comment.

Overall review conclusions and recommendations are made in this section with the CR approvability issue summarized also in this section. Financial Disclosure, the Safety Update, and the response to additional Clinical Comments are reviewed in detail in the sections following this summary section.

### Financial disclosure:

Financial disclosure is required of clinical investigators of “covered studies”<sup>1</sup>. Financial disclosure information in the original NDA submission was insufficient. Information post the CR letter indicates the following,

- 1) There is a discrepancy in the studies the sponsor identified as covered studies between the initial NDA submission (11 studies) and the August, 2016 response (6 studies). The Sponsor was queried about this and reported the identification of some studies as covered was erroneous. The Sponsor considers there are six covered studies. From a practical point of view, all of the eleven studies identified in the first NDA are included as support in the Sponsor’s proposed annotated Target Product Information (TPI). In my opinion, studies used in support of labeling should meet certain thresholds.
- 2) Financial disclosure (Form FDA 3454) was obtained from each investigator, apparently this means for four principle investigators (SDN 55)<sup>2</sup>, of a covered safety or efficacy study prior to study initiation and after study completion. There is also an Investigator who is a company

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<sup>1</sup> 21 CFR 54.2 defines a covered clinical study. Essential elements of the definition are that the study is in humans, is submitted in a marketing application or reclassification petition and is relied on to establish that the product is effective (including equivalency to an effective product), or in which a single investigator makes a significant contribution to safety demonstration.

<sup>2</sup> SDN 55 7-19-17, Module 1.3.4

employee (of 3M). This person has a Form FDA 3455 for three studies; studies 12985, 12794, and 12680.

- 3) Disclosure was obtained for subinvestigators (SI) prior to the start of studies and after completion for covered safety studies.
- 4) Disclosure was not obtained before trial initiation from the SIs for covered efficacy studies; it was obtained after study completion, except for one SI (EF), for whom no financial disclosure was obtained.
- 5) The Sponsor's due diligence efforts to acquire the disclosure from the one SI (EF) were made subsequent to the CR letter. EF is no longer an employee of the lab per the Sponsor. The sponsor identified six subjects from study 12760 as involved with the EF, removed the data, and reports the efficacy conclusions were unchanged.
- 6) No analysis, datasets, or discussion was performed in terms of the other SIs for whom financial disclosure was not obtained until post-trial.
- 7) Sponsor's argument is that although financial disclosure was not obtained from SIs prior to study initiation, data integrity was not compromised because the SIs performed ancillary tasks under the guidance of a PI, that the "totality of all completed tasks resulted in the outcome data for each treated subject, while not all tasks completed for a subject were performed by a single sub investigator", and that every subject interacted with several subinvestigators.

From an efficacy perspective, the Clinical Study Reports for the pivotal efficacy studies EM-05-012760 and EM-013260 state that "The study staff performing the bacterial enumeration and the statistician performing the analyses were blinded to the study products."<sup>3</sup> This should act to reduce bias. Also, pivotal efficacy studies EM-05-12760 and EM-05-13260 both were single center studies<sup>4</sup>. Both studies were audited and no regulatory violations were found at inspected sites (Dr. Bashir for EM-05-12760 and Dr. Paulson for EM-05-13260)<sup>5</sup>. Additionally, Dr. Bashir was inspected for study 013509 (persistence of efficacy) and Dr. Caswell for study 12853 (a safety challenge study). All inspections resulted in final classifications of no deviation from regulations.<sup>5</sup> The Office Director's Dispute Resolution Memo (C. Ganley, 10-14-16) discusses that the effectiveness of the combination product of CHG/IPA is well established in the literature and also indicates his decision was made within the context of awareness of the issues of subinvestigators as known at that time.<sup>6</sup>

Financial disclosure was not optimal, but probably acceptable. The Sponsor reports getting post trial financial disclosure on all subinvestigators except one. If this financial disclosure had been before trial initiation, it would not be a problem. In terms of bias, whether the obtainment of financial disclosure pre or post trial significantly alters bias assessment is unclear to me.

Some of the SI's may have been employees of the labs (MBT or BSL). It appears that some of the SI tasks could be used to alter efficacy study results (recruitment, bacterial enumeration, data entry). In order to reduce bias in future studies of antiseptics, I recommend DNDP consider,

- A) require that Sponsor's add placebo products to trials intended to support labeling. If Sponsor's feel this cannot be accomplished, they should provide a rationale for FDA review. A

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<sup>3</sup> Final CSR EM-05-012760, p.19 bottom right hand page number, Final CSR EM-05-013260, p. 22 bottom right hand page number, CSRs found in the submission dated 7-6-15, module 5.3.5.1 012760, 5.3.5.1 013260

<sup>4</sup> Same as footnote 3 above

<sup>5</sup> Clinical Inspection Summary, NDA 208288, signed 6-23-16, S Gershon and J. Pohlman

<sup>6</sup> Office Director Memo-Dispute Resolution, NDA 208288, C. Ganley, 10-14-16, DARRTS reference ID 3999368

placebo could provide some level of blinding, which might reduce bias. For example, from a safety perspective, assessment of skin reactions appears somewhat subjective.

B) encourage that trials intended to be used to support labeling of preoperative scrub be performed in an independent facility. Several trials were conducted at 3M on 3M employees by 3M employees. This situation does not mean the data are not legitimate but on-face it has an appearance of conflict, especially if there is an absence of blinding. Also, the use of in-company subjects provides an environment for re-use of subjects and may underestimate in labeling reactions that will occur with exposure to naïve populations.

**Safety Update:** Nothing new is reported that changes previous review conclusions. Post-marketing data for Avagard does not appear to be updated. However, Avagard contains a different alcohol and a lower concentration of CHG with limited comparability to the NDA product in my opinion.

**Additional Clinical Comments:** The Sponsor may be supporting parts of labeling with literature that includes literature on ChlorPrep or other FDA approved antiseptics.

With respect to Additional Clinical Comment #1, proposed product labeling (TPI) includes language to use with care in premature infants and infants less than 2 months of age due to irritation and chemical burns in section 8, "Use in Specific Populations". Literature by Chapman<sup>7</sup> reported that chlorhexidine gluconate (CHG) is absorbed into the bloodstream of some preterm infants after a single exposure to CHG with higher concentrations 2-3 days post exposure. This Chapman publication references three other published studies documenting CHG absorption in preterm infants < 32 weeks gestation post topical exposure. A publication by Garland<sup>8</sup> concluded that chlorhexidine gluconate was absorbed cutaneously after antiseptics of skin with 2%CHG in neonatal intensive care, critically ill neonates weighing ≥ 1500 g, age 7 days or older but less than 2 months. Additionally, recently DNDP placed a study on hold due to systemic exposure in infants less than 2 months old (b) (4). It is unknown whether there is associated toxicity with systemic absorption (insufficient information to assess the risks in humans).

I recommend DNDP consider whether labeling language should be updated to incorporate the literature findings described above. Also, if the absorption of CHG/IPA combination and of IPA is determined by DNDP to require additional study, this may change labeling. It is noted that a Preventions Swabsticks are 3.15% CHG/70% IPA though the coverage area of the swabsticks may be too little when compared to this NDA product.

There are sections of labeling without direct trial support and for which in some cases, there appears to be some literature support that names branded products. Whether these sections can be supported as class labeling is deferred to the Division.

With respect to Comment #4, we requested datasets for certain listings such that a comparison of adverse events could be verified specifically for the NDA product that contains HEDTA and the NDA product that did not. The sponsor did not send any noting that an AE required a score of 3 (severe) in

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<sup>7</sup> Chapman et al, Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antiseptics prior to catheter insertion in preterm neonate. Journal of Perinatology (2013) 33, 768-771. Doi 10.1038/jp.2013.61

<sup>8</sup> Garland et al, Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antiseptics for central venous catheter placement in neonate. Journal of Perinatology (2009) 29, 808-813

any category (erythema, edema, rash, or dryness). DNDP could request datasets showing all the raw scores for skin irritation regardless of whether it met AE criterion of a score of 3. As this was not considered an approvability issue, I did not request datasets as an Information Request.

Pediatric: FDA meeting minutes from a Type B pre-NDA meeting held on January 20, 2015<sup>9</sup> indicate that the Pediatric Research Equity Act (PREA) was not triggered (i.e. the application was exempt at that time) by this application as it did not meet any of the criteria of new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration.

## 2. Detailed Review:

### 2.1 Financial Disclosure:

The exact wording of the Complete Response letter is copied from the CR letter with italicized font added

*“The financial disclosure information provided in the NDA is not sufficient. Eleven of the 20 subinvestigators listed on the revised 1572 for pivotal study EM-05-012760 are missing disclosure information. Also, one of the five subinvestigators is missing financial disclosure information for study EM-05-013260. The guidance for industry (E6) Good Clinical Practice Guidance: Consolidated Guidance, section 8.2, (<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf>) indicates that this information should be documented before the trial starts formally. Financial arrangements between investigators and the sponsor can introduce bias in trial data that may be difficult to evaluate. In addition to the potential impact on efficacy outcome data, this is an issue of study conduct.*

*Describe your efforts to obtain financial disclosure both before and after the trial. Discuss the potential impact lack of financial disclosure may have on data integrity, especially efficacy data in the pivotal trials. Provide specific information regarding the role of each subinvestigator in the trials and whether that role had any involvement in determination or documentation of outcome data. In order to evaluate the possible impact on efficacy outcomes, identify how many subjects each subinvestigator had a role with during the trial. To the extent feasible for a single center trial, submit analyses dropping the subjects of all subinvestigators without financial disclosure per pivotal trial. Provide datasets for each pivotal trial that allow independent verification of the sensitivity analyses, (i.e. the subinvestigator is named for each subject by “usubjid” in efficacy datasets for each study). As a subinvestigator may have participated in more than one trial, for each trial in the NDA indicate whether there is missing subinvestigators in the respective trial. For any additional clinical trials you conduct for this NDA, ensure that you collect financial disclosure information prior to start of the trial. You may also provide additional strategies you believe may evaluate this issue.”*

- 1) Describe your efforts to obtain financial disclosure both before and after the trial.

The sponsor submitted a 10-page response on 8-5-16. Per the Sponsor’s 8-5-16 submission, financial disclosure was obtained from each investigator<sup>10</sup> (Investigator defined as FDA Form 1572 box 1)

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<sup>9</sup> Minutes, p.14/17, signature date 2-22-15

<sup>10</sup> Footnoted in the 8-5-16 response as “Form FDA 1572, box 1 (Names and address of Investigator)”

conducting a covered efficacy or safety study prior to study initiation and after study completion. Also per the Sponsor, financial disclosure was obtained from the subinvestigators<sup>11</sup> prior to study initiation and after study completion for covered safety studies. For covered efficacy studies, the Sponsor reports that financial disclosure was obtained from all except one subinvestigator (Elliott Frye) after study completion. The Sponsor did not address the other requests to identify subjects per SI apparently since they report obtaining financial disclosure after the trial for all except one SI.

The Sponsor includes an attachment to show due diligence in obtaining the financial disclosure for Elliott Frye (EF). EF no longer works at MicroBioTest. Attempts include 3 phone calls to his cell phone starting May 25, 2016 and ending June 15, 2016 resulting in voicemails left asking for a return call and in one voicemail message, the company offered an email address. The dates of the attempts to reach EF were subsequent to the CR letter dated 5-6-16. The Company identified a possible Facebook page for him in June 2016 and posted a message. The Company had received no responses to these inquiries.

There was a discrepancy in the studies the Sponsor identified as covered studies<sup>12</sup> in the initial NDA and those considered covered in the August 2016 submission. The Sponsor was queried. Their response of 7-19-17 notes that they consider the covered studies as per the August 2016 submission. The cover letter for the response reports “erroneously” identifying as covered studies the discontinued pivotal study, two coverage studies (012985 and 013337), and two drape adhesion studies (012680 and 012794). The cover letter reports that “For these 5 studies, no efficacy or major safety information was collected” and that it was determined they should not have been included as covered studies. The determination of which studies are “covered” study is a regulatory call. From a practical point of view, all of the eleven studies are used to support language in the TPI.

The table below shows the covered studies as identified by the Sponsor. Yellow highlight was added to show studies common to submissions.

STUDY/PI	INITIAL NDA COVERED STUDIES	AUGUST 2016 & SDN 55	Form 3454 or 3455 PI*
EM-05-012760-pivotal efficacy-/Bashir	YES	YES	YES
EM-05-013260-pivotal efficacy/McCormack & Miller	YES	YES	YES
EM-05-012759-pivotal efficacy/McCormack	YES	NO	
EM-05-013509-persistence of efficacy/Bashir	YES	YES	YES
EM-05-012853- safety challenge study-21 day patch test with challenge/ Caswell	YES	YES	YES

<sup>11</sup> Footnoted in the 8-5-15 response as “Form FDA 1572, box 6 (Names of subinvestigators)

<sup>12</sup> The CFR: 21 CFR 54.2 defines a covered clinical study. The essential elements of the definition are that --the study is in humans

--is submitted in a marketing application or reclassification petition and is relied on to establish that the product is effective (including equivalency to an effective product) or

-- in which a single investigator makes a significant contribution to safety demonstration.

The referenced regulation notes that in general phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless critical to efficacy), large open safety studies conducted at multiple sites, treatment protocols, and parallel track studies are not included. The referenced regulation defines a clinical investigator as a listed or identified investigator or subinvestigator directly involved in the treatment or evaluation of research subjects and includes spouse and each dependent child of the investigator.

EM-05-012952-safety challenge study-phototoxicity/ Caswell	YES	YES	YES
EM-05-013062-safety challenge study- photoallergy potential/Caswell	YES	YES	YES
(b) (6)			
EM-05-013337-coverage and dry time/ Bashir	YES	NO	
(b) (6)			
(b) (6) For			

subinvestigators, the Sponsor reports before and after for covered safety studies, after for covered efficacy except and could not get 1 subinvestigator.

- 2) *Discuss the potential impact lack of financial disclosure may have on data integrity, especially efficacy data in the pivotal trials. Provide specific information regarding the role of each subinvestigator in the trials and whether that role had any involvement in determination or documentation of outcome data. In order to evaluate the possible impact on efficacy outcomes, identify how many subjects each subinvestigator had a role with during the trial. To the extent feasible for a single center trial, submit analyses dropping the subjects of all subinvestigators without financial disclosure per pivotal trial. Provide datasets for each pivotal trial that allow independent verification of the sensitivity analyses, (i.e. the subinvestigator is named for each subject by "usubjid" in efficacy datasets for each study). As a subinvestigator may have participated in more than one trial, for each trial in the NDA indicate whether there is missing subinvestigators in the respective trial.*

Sponsor:

The Sponsor's opines that although financial disclosure was not obtained from the subinvestigators prior to study initiation, data integrity was not compromised. The Sponsor quotes part 54 of 12 CFR and argues, essentially, that the listed subinvestigators were not subinvestigators because they had ancillary responsibilities and tasks and that their tasks were performed under the direction and guidance of the PI. The ancillary tasks were listed by the sponsor as including,

- Subject recruitment and consent
- Skin assessment, product application and sample collection
- Diluting and plating samples
- Bacterial enumeration
- Data entry into electronic data capture (eDC) system

The Sponsor reports that the totality of all completed tasks resulted in the outcome for each subject but that all tasks completed for a subject were not performed by a single investigator and that every subject interacted with several investigators during their study participation. The Sponsor also argues that the potential for bias was minimized by including randomization and blinding in the design. Study products were assigned to test sites based on a computer-generated randomization schedule. Study staff involved in the bacterial enumeration was not involved in the study product application or the collection of samples. Also, per the Sponsor, copied from the August 2016 submission and pasted below,

In addition, the potential for bias in each study was minimized by including randomization and blinding in the design. Study products were applied to assigned test sites according to a computer-generated randomization schedule. The PI was responsible for ensuring that the study randomization schedule was followed. And, although the study products could not be blinded from the study staff during product application and sample collection due to obvious differences in applicator design and other physical characteristics, the study staff performing the bacterial enumeration was not involved in the study product application or the collection of samples. Consequently, the study staff performing the bacterial enumeration were blinded to the study products.

Reviewer:

The CFR defines a clinical investigator<sup>13</sup> as “*Clinical investigator* means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.” Recruitment, bacterial enumeration and data entry are listed as tasks. These potentially could allow someone to alter results or for bias to influence results. The Sponsor’s also reports that all tasks completed for a subject were not performed by a single investigator and that every subject interacted with several investigators. Whether it would matter that financial disclosure was performed after the trial compared to before the trial is unclear.

One investigator [REDACTED] (b) (6) who was involved in multiple studies in some capacity<sup>14</sup> was not involved with the safety challenge studies based on information in the study reports. The safety studies provide critical safety information to support the NDA. Also, reportedly, there was not delayed acquisition of financial disclosure for subinvestigators in covered safety studies (when using the six studies more recently identified as covered.)

Also, please refer to the Summary section earlier in this review.

- 3) *To the extent feasible for a single center trial, submit analyses dropping the subjects of all subinvestigators without financial disclosure per pivotal trial. Provide datasets for each pivotal trial that allow independent verification of the sensitivity analyses, (i.e. the subinvestigator is named for each subject by “usubjid” in efficacy datasets for each study). As a subinvestigator may have participated in more than one trial, for each trial in the NDA indicate whether there is missing subinvestigators in the respective trial.*

Sponsor:

As noted, the Sponsor reports that other subinvestigators provided post-study financial disclosure except for Elliott Frye. Elliott Frye, the subinvestigator without any financial disclosure, participated in the study EM-05-12760 from 2-12-14 to 4-4-14. The sponsor reports involvement of this subinvestigator

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<sup>13</sup> 21 CFR 54.2 (d)

<sup>14</sup> [REDACTED]

Teresa A. Podruchny, M.D.

with six subjects in the capacity of collecting samples and diluting and plating. The sponsor removed from the analysis the “datasets” from these 6 subjects and states the efficacy results remain unchanged.

No analysis (es) dropping other involved subinvestigators was performed.

Reviewer: An analysis of all SIs without pretrial disclosure and the possible impact on safety was not submitted. It is unclear that obtaining financial disclosure before or after the trial changes the value of the disclosure in terms of impact on bias assessment.

- 4) *As a subinvestigator may have participated in more than one trial, for each trial in the NDA indicate whether there is missing subinvestigators in the respective trial.*

Sponsor:

Elliott Frye participated in one trial. Several participated in more than one trial.

Reviewer: The table below is duplicated from the Sponsor’s material.

**Subinvestigators for Covered Efficacy and Safety Studies**

Subinvestigator listed on Statement of Investigator (FORM FDA 1572, line 6)					
Covered Efficacy Studies			Covered Safety Studies		
Pivotal EM-05-012760	72-hr Persistence EM-05-013509	Pivotal EM-05-013260	HRIPT EM-05-012853	Phototoxicity EM-05-012952	Photoallergenicity EM-05-013062
Angela Hollingsworth	Angela Hollingsworth				
Kathryn Dormstetter	Kathryn Dormstetter				
Shirshendu Saha	Shirshendu Saha				
Sean M. Stuekerjuergen	Sean M. Stuekerjuergen				
Travis Farley	Travis Farley				
Candace Robinson	Candace Robinson				
Tatiana Ballreich	Tatiana Ballreich				
Kelsey Roach	Kelsey Roach				
Alia Abdelhadi	Alia Abdelhadi				
Jahangir Syed	Jahangir Syed				
Arif A. Rao	Arif A. Rao				
Emily Winokurzew					
Brian Sato					
John Cordero					
Kelly So					
Marco Montero					
Laurie Williams					
Shazia Hamid					
Laura Rowson					
Gardner Villagomez					
Jacquelyn Doroski					
Elliott Frye					
	Hilary Kurland				
	Lenny Godinbo				
		Chelsey Allison			
		Samuel Kupersmith			
		Patricia A. Mays Suko			
		Christopher Beausoleil			
		Chelsey Allison			
			Joy Frank		
			Doreen Hackett		
			Longina Burdzy		
			Richard Eisenberg	Richard Eisenberg	Richard Eisenberg
				Michael Lutz	Michael Lutz
				Alexa Martinez	Alexa Martinez

- 5) *For any additional clinical trials you conduct for this NDA, ensure that you collect financial disclosure information prior to start of the trial. You may also provide additional strategies you believe may evaluate this issue.*

Sponsor:

3M stated confirmation that financial disclosure will be obtained for all participating clinical investigators (PI and subinvestigators) will be collected prior to start of the trial and 1-year after study completion. There is an error in the Sponsor's column for the study EM-05-013260. Chelsey Allison is on the list twice and Robinson is not on the list. Robinson was listed and had 3454 (per my previous review of financial disclosure data).

## 2.2 Safety Update

FDA comments are as from the CR letter and are bolded.

### 1. Describe in detail any significant changes or findings in the safety profile.

The Sponsor 's Safety Update Report<sup>15</sup> reports "no new safety information of any kind that would affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling has been learned after NDA 208-288 was submitted on July 6, 2015." Six new clinical trials were conducted after the filing of the NDA on 7-6-15. The Sponsor reports these were not intended to incorporate into the NDA because they were not designed as "full safety or efficacy studies." (p 1/5 Safety Update Report, 3-3-17 submission). The Sponsor reports there were no deaths in the history of development and no serious adverse event in any study. There were two subjects with adverse events and one of these did not complete the study due to the adverse event (subject 10, per Safety Update Report, p.1/5).

Four of the six studies evaluated drape adhesion (013565, 013689, 013699, 013721 and were performed at 3M at the in-house clinical facility. Two studies (013655 and 013718) were for visibility on dark skin tones and product characteristics respectively and were conducted at MBT. Exposure time for study 013721 was up to 4 hours and was 2 or 3 hours for study 013655. The six trials exposed 9-36 subjects each (though not sure how many unique subjects, as 3M using employees may have allowed for subjects who have participated in more than one study. The six studies are presented in tabular summary in the appendix for the interested reader.

Two subjects reported itchy skin and mild skin irritation on the treatment sites which were both recorded as adverse events.

- Subject (b) (6) in study 013689 experienced dry and itching skin on both knees, medially, seven days post treatment. The event is recorded as resolved.
- Subject (b) (6) in study 013721 experienced the events of itchy skin and mild erythema returned two hours after applications of products to the back (comparator on one side and NDA/IND product on the other) and did not complete the 4-hour treatment phase of the study. The Adverse Event Record captured the event as "moderate" severity (defined as signs, symptoms are sufficient to restrict but not prevent subject's daily activity) and that the subject declined further evaluation at 3M's clinic.

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<sup>15</sup> SDN 45, 3-3-17, Module 5.3.6

Avagard postmarketing is discussed in the Clinical Summary of Safety, but the information appears not to be updated since the initial NDA submission. There is no updated Avagard information in the Safety Update Report of the 3-3-17 submission. The Sponsor's Safety Update Report notes 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." Avagard is contains a different alcohol, is 1% CHG, and is a hand antiseptic. In my opinion, the post-marketing data for Avagard essentially is non-contributory for this product terms of the safety profile.

2. **When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:**
  - **Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.**

Sponsor reports new data in a summary tables; one table for clinical and one for nonclinical. I reviewed the clinical table and discussed it above under #1.

**Present tabulations of the new safety data combined with the original NDA data.**

The six new studies are discussed above and summarized in a table in the appendix of this review.

**Include tables that compare frequencies of adverse events in the original NDA with The retabulated frequencies described in the bullet above.**

Not performed. Per the Sponsor, January 20, 2015 meeting with the Agency, it was agreed this was not necessary. Based on the information provided by the Sponsor for the six trials since the initial NDA, this is not necessary.

**For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.**

Not applicable. There are no other proposed indications.

3. **Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.**

Not performed. Not necessary.

4. **Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.**

There were no deaths and no serious adverse events reported by the Sponsor in the six new studies.

5. **Describe any information that suggests a substantial change in the incidence of common, but**

**less serious, adverse events between the new data and the original NDA data.**

Sponsor reports there is nothing new which suggests a “substantial change in the incidence of common but less serious, adverse events between the new data and the original NDA data.”<sup>16</sup>

**6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).**

Discussed above with #1.

**7. Provide a summary of worldwide experience on of this drug. Include an updated estimate of use for drug marketed in other countries.**

Per the Sponsor, the NDA product is not marketed in any country to date with U.S. approval to be the first.

**8. Provide English translations of current approved foreign labeling not previously submitted.**

Not applicable.

### **2.3 Additional Clinical comments from the CR letter:**

1. For all safety-related proposed labeling statements that are not directly supported by data from your conducted clinical studies, such as conditions of use, “Do Not Use”, pediatric use, and hypersensitivity/anaphylaxis, specify the literature articles that you are relying upon to support each labeling statement. Provide an adequate summary of the relied upon literature. If you intend to rely upon “non-product specific literature” for such purposes, as stated in your application, you should ensure that the specified literature articles conform to your intent. Note that reliance on published literature describing a listed drug(s) is considered to be reliance on FDA’s findings of safety and/or effectiveness for the listed(s).

Sponsor: The sponsor indicating providing a summary of the literature for safety-related proposed labeling listed in Contraindications, Warnings and Precautions, and Use in Specific Populations in the TPI.

- Module 2.7.4.5.9 was referenced for Safety in Special Groups and Situations/Contraindications, Warnings and Precautions
- Module 2.7.4.5.1.1 was referenced for Intrinsic Factors/Vulnerable Pediatric Populations
- Module 1.9.1 was referenced for Pediatric Administrative Information/Pediatric Study Waiver

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<sup>16</sup> 3M Response to Complete Response Letter dated 5-6-16 pdf submitted 3-3-17, p.34/39.

- Flammability and “keep out of eyes, ears, and mouth” statements were aligned with the DuraPrep Drug Facts Label. (DuraPrep is Iodine Povacrylex 0.7% iodine and Isopropyl Alcohol 74% w/w preoperative skin preparation.)

Reviewer: Module 2.7.4.5.9 is 75 pages.

The Sponsor did not provide an overall summary that easily shows which studies rely on branded products such as Chloraprep, though in some texts, it is noted that at least some of the publications are. For example, a study by Garland et al of absorption of chlorhexidine after skin antisepsis in some critically ill infants notes the antisepsis was ChloraPrep. The Sponsor’s summaries of publications do not always identify branded products that were used in the publication. For example the publication referenced as #45 names Hydrex as the product (0.5% chlorhexidine and 70% IPA). This is not noted in the Sponsor’s presentation on page 34 of 75. AquHex is named in another publication (reference 39 of the Clinical Summary, p.34/75).

Other parts of the document, relative to the pediatric population in the Summary of Clinical Safety, (for example, pages 30) seem identical to those in the previous summary of clinical safety.

With respect to pediatric use, the Sponsor also submits discussion of skin barrier function and development. The pediatric use language may be considered as class labeling and may require no additional support. As well, other label language such as “do not use on open skin wounds or as a general skin cleanser” and warnings about ototoxicity, ocular toxicity, and oral toxicity also may be considered as part of class labeling for CHG products. This is deferred to DNDP.

Hypersensitivity- Hypersensitivity with CHG is known to DNDP.

Not to use in lumbar puncture-discussion by the Sponsor is based on animal data.

Whether these sections of labeling can be considered as class labeling is deferred to DNDP.

## **2. Discuss the drape adhesion study designs as related to real-world use.**

Sponsor: The purpose of the unchallenged condition was to simulate the incise drape adhesion outside of the immediate area. The intent of the saline-challenged test condition is to simulate fluids present at the incision site during surgery.

The drape lift studies 13565, 13689, and 13699 used a simulated knee model and simulated some conditions of surgery such as irrigation and movement. Study 13721 used a dry challenge model to evaluate skin irritation of the draped area after 4 hours.

Reviewer: Studies 13565, 13689, 13699, and 13721 were not submitted with the initial NDA and the Sponsor reports in the Safety Update Report that these studies were not designed to as full safety or efficacy studies.

## **3. Describe efforts to minimize or address bias in the small, open-label studies conducted by employees and used to support labeling (e.g. coverage and dry time studies).**

Sponsor: Reports using SOPs like GCP, and used trained 3M employees (n=2) and notes that dry time was confirmed with quantitative analytic vapor dissipation analysis and the quantitative report was

completed by an independent testing company. A 3M employee was the technical contact and is stated to have reported through an independent structure from the PI (“i.e., different 3M Division).

**4. Submit datasets that correspond to Listings 16.2.8.1 and 16.2.8.2 in the study report for study EM-05-013260 such that a comparison of adverse events with and without HEDTA could be verified.**

The sponsor did not send any noting that an AE required a score of 3 (severe) in any category (erythema, edema, rash, or dryness).

In the next cycle, for completion though this was not determined to be an approvability issue for the CR, we could request the datasets showing all the raw scores per product regardless of whether it was an AE or not.

**5. The protocol for study EM-05-012680 submitted to the NDA on March 15, 2016 in amendment 23 does not appear to contain changes in dwell time noted on page 51/90 (adobe page number). Specify which pages of the protocol submitted in amendment 23 contain these changes.**

Sponsor: The protocol itself was not revised. Instead a 4-page protocol amendment was required to be kept on top of the final implemented protocol. The Sponsor says the 4 page amendment was IRB-approved before implementation.

Reviewer: It might have made it more difficult for protocol reader to easily see changes made. Track change version would have been optimal.

**6. Provide a dataset showing adverse events for study EM-05-012680 by unique subject id (column variable “usubjid”).** Sponsor reports there were no adverse events.

**APPENDIX:**

Studies reported since the original NDA.

<b>Trial #</b>	<b>Study</b>	<b>N, duration</b>	<b>Safety</b>
EM-05-013565	Drape Lift of NDA product versus Other Preps Using a Simulated Knee Surgery Model with Ioban Incise Drape	18 3M  15-30 min	No AEs, no rash, no edema, no dryness, no erythema  The sponsor reports evidence that drapes may lift more on the NDA product prep than on DuraPrep
EM-05-013699	Drape Lift of Ioban™ Incise Drape over NDA product versus Chloraprep® simulated knee	30 3M 15-30 min	no AEs reported, no skin irritation (no erythema, no rash, no edema, no dryness) Removal force “slightly lower” for Ioban drapes on skin prepped with NDA product compared to skin prepped with Chloraprep (p=0.057)
EM-05-013689	Drape Lift of Ioban™ and two 3M™ CHG Antimicrobial Incise Drapes over NDA product versus Chloraprep® Simulated Knee	36 3M 15-30 min	One week after participation, subject (b) (6)-mild skin irritation (dry and itch) on medial test sites both knees, recorded resolved. On treatment day, no erythema, rash, edema, or dryness observed on any of the subjects.
EM-05-013721	Evaluation of skin irritation with Ioban™ on volunteers’ backs under dry conditions NDA product versus Chloraprep	12 3M 4 hours	One subject (b) (6) reported itching under the drape samples, mild erythema was noted on the test sites. Drape samples and prep products removed after about 2 hours. The event was recorded as resolved. The Adverse Event Record* captured the event as “moderate” severity (defined as signs, symptoms are sufficient to restrict but not prevent subject’s daily activity) and that the subject declined further evaluation at 3M’s clinic.  No rash, edema, or dryness is reported CSR reports no death, no SAE, no dc secondary to AE.
EM-05-013718	Evaluation of Product Characteristics of NDA product Test location MBT	12  30-60 min	No AEs No skin irritation
EM-05-013655	Visibility of NDA product on dark skin tones. MBT.	9 males 2 hrs on back	no AEs were reported and no skin irritation was observed for any subject on any treated section

Unless noted otherwise, table information is from individual study reports found in SDN 46 to the NDA, 3-28-17, module section 5.3.5.4. 3M means employees of 3M. \* information is from Adverse Event Record in submission 3-3-17, module 5.3.6

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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.**  
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/s/  
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TERESA A PODRUCHNY  
08/07/2017

FRANCIS E BECKER  
08/11/2017

I agree with Dr. Podruchny that the remaining CR clinical issue of financial disclosure has been adequately addressed and supports approvability from clinical standpoint only. Regarding issues of labeling revisions, particularly regarding use of the proposed product in infants, this will require further discussions pending other discipline reviews and will be further discussed in my CDTL Review.

**Summary Review for Regulatory Action**

<b>Date</b>	May 4, 2016
<b>From</b>	Theresa M. Michele, MD Director, Division of Nonprescription Drug Products
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	208288
<b>Applicant Name</b>	3M Health Care Business
<b>Date of Submission</b>	July 6, 2015
<b>PDUFA Goal Date</b>	May 6, 2016
<b>Proprietary Name / Established (USAN) Name</b>	SoluPrep™ Film-Forming Sterile Solution / 2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
<b>Dosage Forms / Route of Administration / Strength</b>	Surgical solution
<b>Proposed Indication(s)</b>	Patient Preoperative Skin Preparation (adults and pediatric patients ≥ 2 months of age) • For preparation of the skin prior to surgery • Helps reduce bacteria that potentially can cause skin infection
<b>Recommended Regulatory Action</b>	Complete response

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review--DNDP	Teresa Podruchny/Francis Becker
Medical Officer Review--DDDP	Gary Chiang/David Kettl
Statistical Review	Mushfiqur Rashid/Karen Higgins
Pharmacology Toxicology Review	Wafa Harrouk/Paul Brown
CMC Review/OBP Review	Elise Luong/Erika Englund/Erin Kim/Maria Cruz- Fisher/Vipulchandra Dholakia/Vu Thao/Swapan De
Clinical Microbiology Review	Michelle Jackson
IDS Labeling Review	Michelle Jackson/Betsy Scroggs
CDTL Review	Francis Becker
OSE/DMEPA	Grace Jones/Chi-Ming Tu
DSI	Sharon Gershon/Susan Thompson
RPM DNDP	Celia Peacock

CDTL=Cross-Discipline Team Leader  
DMEPA=Division of Medication Error Prevention and  
DNDP=Division of Nonprescription Drug Products  
IDS=Interdisciplinary Scientist  
OND=Office of New Drugs  
RPM=Regulatory Project Manager

DDMAC=Division of Drug Marketing, Advertising and Communication  
Analysis  
DSI=Division of Scientific Investigations  
OBP=Office of Biotechnology Products  
OSE= Office of Surveillance and Epidemiology

## 1 INTRODUCTION

3M Health Care Business (3M) submitted 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 currently approved, the 3M product is provided as a sterile solution in a sterile applicator. 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.

3M initially proposed to rely on (b) (4) for some aspects of this application; however, during the review cycle, 3M requested to modify this to reliance on literature only.

This review serves as a summary review for the application.

## 2 BACKGROUND

### 2.1 Patient preoperative skin preparations

A variety of patient preoperative skin preparation products are available OTC for use prior to surgery. The patient preoperative skin preparation indication was established under the OTC drug monograph for healthcare antiseptics (21 CFR 310). Most recently, FDA's preliminary findings regarding the ingredients and criteria for safety and effectiveness were established in a tentative final monograph in 2015 (80 FR 25166). Products containing CHG, such as the 3M proposed product, do not fall under the monograph and must be submitted as NDAs. NDA drugs include a variety of CHG/IPA products, as well as those containing CHG/alcohol, CHG alone, and iodine/IPA. Products available under the OTC drug monograph include a number of different ingredients, including alcohol (ethyl alcohol), benzalkonium chloride, benzethonium chloride, iodine, and IPA.

In 2013, FDA issued a drug safety communication (DSC) to alert healthcare professionals that although antiseptic products have inherent antimicrobial activity, OTC patient preoperative and preinjection skin antiseptics that are not manufactured as sterile drug products may become contaminated with bacteria during manufacture or use. The DSC was based on reports linking outbreaks of infection to antiseptic preoperative and pre-injection products contaminated with microorganisms. FDA asked manufacturers of these antiseptic products to revise labeling to indicate whether the product is sterile or non-sterile and ensure that products are packaged in single-use containers, i.e. containers that hold only enough product for one patient application. Currently, there are no approved OTC preoperative or preinjection antiseptic products that are sterile.

## 2.2 Relevant Regulatory History

The proposed CHG/IPA product was developed under IND 76,549 initially submitted in 2006 and placed on clinical hold due to lack of definition of the specific formulation and need for preclinical data. The hold was lifted after a data submission in 2012. FDA provided significant advice throughout the development program, including a variety of responses about proposed protocols and statistical analysis plans, an End of Phase 2 meeting, and a pre-NDA meeting.

In February 2014, there was a Type A meeting to discuss compliance issues at one of the laboratories conducting the Phase 3 clinical trials. FDA emphasized that for the study to be valid, the test product and active control must meet the performance criteria and be superior to the vehicle control. Also in 2014, 3M modified the formulation by the addition of (b) (4) % (hydroxyethyl)ethylenediaminetriacetic acid (HEDTA) (b) (4). 3M agreed to add an arm to one of the pivotal studies to compare the non-HEDTA formulation with the new formulation as a bridging study. In April of 2015, FDA provided written feedback regarding the replacement protocol for the Phase 3 study, noting that it disagreed with 3M's alternative primary analysis, recommending that the primary analysis be the lower bound of 95% confidence interval for responder rate (must meet a threshold of 70%), with the secondary analysis of mean log reduction (must meet a threshold of 2 log<sub>10</sub> reduction on the abdominal site and 3 log<sub>10</sub> reduction at the inguinal site within 30 seconds of use).

In the filing review letter, FDA identified potential review issues noting that one of two pivotal studies did not meet the primary endpoint of greater than or equal to 70% responder rate for the inguinal region (study EM-05-013260) and the analysis excluded subjects with missing data at 10 minutes or 6 hours. There was also extensive correspondence with 3M during this NDA review cycle, with numerous information requests and several teleconferences. Key issues included the need to qualify impurities that developed over time and reached above the qualification threshold, the overall stability of the product, and lack of validation of sterilization procedures. To further communicate these issues to the sponsor, a discipline review letter covering issues related to pharmacology/toxicology, chemistry/manufacturing/controls drug product, and microbiology manufacturing was issued on April 18, 2016.

## 3 CHEMISTRY, MANUFACTURING, AND CONTROLS

The 3M CHG/IPA product contains the drug solution (b) (4)

(b) (4) The entire applicator is packaged in a sealed (b) (4) pouch (b) (4)

Just prior to use, the ampule is broken, either by depressing a lever for the 10.5 mL applicator or by pressing down on the end-cap for the 26 mL applicator, allowing the solution to flow through the sponge for application to the skin. The final formulation includes CHG 2%, IPA 70%, water, actyltributyl citrate (b) (4), 3M acrylate copolymer, tint, and trisodium HEDTA (b) (4)

**Figure 1: SoluPrep™ Applicator System**



Source: NDA 208822 Quality Summary Drug Product 2.3.P

Manufacturing quality reviews were performed for the drug substance, drug product, process, microbiology, facilities inspections, and environmental assessment. Reviews demonstrated that quality aspects of the application were acceptable for the drug substances and facilities inspections. However, both the drug product and microbiology reviewers recommend a complete response for this application due to significant issues with drug product impurities, stability of the drug product, and sterility assurance of the finished product. The acrylate copolymer in this CHG/IPA product was determined to be highly similar to the polymer complex in DuraPrep™ Surgical Solution (NDA 21,586; 3M), hence was not considered to be a novel excipient.

3M originally proposed an expiration date of 24 months, with impurity limits of (b) (4) % total impurities and (b) (4) % individual impurities. However, data demonstrate increasing amounts of degradants over time, with two impurities (b) (4) exceeding 1.0% at (b) (4) months, respectively. The 1.0% level is based on the ICH Q3B(R2)<sup>1</sup>, which sets limits for impurity specifications above which toxicology qualification is required. The sponsor subsequently proposed alternative analyses of impurities and a shelf life of (b) (4) months; however, these approaches failed to limit the impurities below the 1.0% level considered acceptable by ICH standards. A further decrease in shelf life to below (b) (4) months would not be acceptable from a clinical standpoint, because these products are stored in various hospital environments in which checking for expiration dates very frequently would likely pose an undue burden on the health care system and put patients at risk of use of expired product with untested impurities.

(b) (4)  
The manufacturing quality microbiology review concluded that sterility of the finished product could not be assured due to a number of deficiencies. These included lack

<sup>1</sup> ICH Harmonized Tripartite Guideline: Impurities in New Drug Products Q3B(R2), Step 4 version dated 2 June 2006. Downloaded at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q3B\\_R2/Step4/Q3B\\_R2\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2_Guideline.pdf)

of validation data for the container closure integrity test, inadequate (b) (4) monitoring during production, inadequate requalification schedule for the (b) (4), inadequate validation of the bioburden testing method, inadequate testing of the (b) (4) and inadequate specifications for sterility testing the drug product applicator among other issues.

I concur with the conclusions of the manufacturing quality review team and the recommendation for a Complete Response.

#### 4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The nonclinical review of CHG and IPA relied mostly upon literature. The intended use of SoluPrep™ is for an acute indication; therefore, the nonclinical requirements focused on short-term general toxicology, developmental and reproductive toxicology, and genetic toxicology. For CHG, all nonclinical concerns were addressed using references from the literature. For IPA, the sponsor provided published literature to address genetic toxicology, and developmental and reproductive toxicology. During IND development, 3M also submitted a short-term dermal irritation study to support the use of the proposed product. Carcinogenicity testing was not required for the proposed acute indication.

Regarding excipients, 3M conducted and submitted nonclinical data to qualify a copolymer that was initially identified as a potential novel excipient. The data included exploratory studies<sup>2</sup> to qualify the copolymer in a skin irritation study in rabbits, a murine local lymph node assay in mice, and a multiple dose (10 exposures over a 37-day study period) systemic toxicity study using various formulations in rabbits. However, the copolymer was subsequently determined to not be a novel excipient, based on being sufficiently similar to the copolymer in another approved product.

Overall, it was concluded that adequate nonclinical data are available in the literature and submitted studies to support the acute use of the active ingredients as a preoperative skin preparation under this NDA.

Based on the stability data of the product, the pharmacology/toxicology reviewer recommended qualification of two impurities, (b) (4) that exceed the qualification threshold of 1.0% during the initially proposed shelf life of 24 months. No qualification data have been submitted to FDA. 3M's proposal to rely upon genotoxicity testing based on (quantitative structure-activity relationship) QSAR analysis alone is not adequate. QSAR is not a validated replacement for genotoxicity testing. I concur with the conclusion of the toxicology reviewer that the shelf life for this product will have to be supported by the level of impurities and the results of the qualification program for any impurities that exceed the limit. Therefore, there is also a complete response deficiency for pharmacology/toxicology. During the review cycle, 3M proposed to limit the shelf life to (b) (4) months. If the shelf life were to be limited to (b) (4) months, only one impurity, (b) (4) would need to be qualified to resolve the deficiency.

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<sup>2</sup> The following tests were conducted for CHG/IPA: a skin irritation study in rabbits, a murine local lymph node assay in mice and a short term (10 doses over a 37-day study period) dermal toxicity study in rabbits.

## 5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

No new clinical pharmacology data were submitted as part of this application. The sponsor intends to rely on the literature to support the pharmacokinetics and absorption profile of their CHG/IPA product. In general, these data demonstrate that CHG is minimally absorbed in adults after dermal application, although there may be some absorption in neonates and premature infants, particularly if CHG is combined with a penetration enhancer such as alcohol. In contrast, data demonstrate that IPA is absorbed, with approximately 15% of the dermally applied dose of a 70% IPA solution being absorbed in rats.<sup>3</sup> (Reference submitted by the sponsor.) IPA is known to be metabolized to acetone and CO<sub>2</sub> and excreted via expired air. Based on literature review by FDA (not submitted by the sponsor), the highest median blood level in humans after IPA hand rub administration followed by occlusion with surgical gloves was 2.6 mg/L after the third application.<sup>4</sup> These data do not necessarily support use of IPA as a patient preoperative preparation. While the sponsor submitted human data for CHG, the sponsor submitted no literature references evaluating the pharmacokinetics of IPA in humans and no literature references for the combination of CHG/IPA.

In general, for products intended to have primary action on the skin, we require a maximal use pharmacokinetic trial (MUsT) as a safety study to determine absorption under conditions of maximal use for all new dermal formulations. Given the similarities of this formulation to other approved CHG/IPA formulations and the initial discussions with the sponsor in which the intent was to rely on (b) (4) as a 505(b)(2), FDA did not anticipate that a MUsT would be needed nor was a specific clinical pharmacology review performed since new data were not submitted. While the literature data for CHG absorption submitted by the sponsor may be sufficient to justify an acute use as a surgical prep, the data for IPA and the combination of CHG/IPA are not. As such, inadequate clinical pharmacology data were submitted to support use of CHG/IPA as a preoperative skin preparation. To resolve this deficiency, the sponsor would need to cite adequate literature for IPA and CHG/IPA to demonstrate absorption after use as a surgical skin preparation with a similar level of skin coverage to that proposed for the largest size product (26 mL), reference FDA's findings of safety for an approved product, or conduct a MUsT study.

## 6 CLINICAL MICROBIOLOGY

As part of the efficacy assessment of CHG/IPA, 3M submitted two modified time kill studies, with and without organic challenge. In addition, the application included an antimicrobial resistance study and a neutralization validation study. Because CHG is a well-known antimicrobial agent with broad spectrum activity, FDA accepts a modified in vitro testing scheme with a limited number of organisms using a time-kill approach rather than requiring a full battery of organisms and minimum inhibitory concentration (MIC) testing as well. In both studies, CHG/IPA demonstrated greater than a 5 log<sub>10</sub> reduction killing effect in 3 minutes and 5 minutes for all organisms tested both at full strength and

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<sup>3</sup> Boatman, R. J., et al., "Dermal Absorption and Pharmacokinetics of Isopropanol in the Male and Female F-344 Rat," *Drug Metabolism and Disposition*, 26:197-202, 1998.

<sup>4</sup> Below, H., et al., "Dermal and Pulmonary Absorption of Propan-1-ol and Propan-2-ol From Hand Rubs," *American Journal of Infection Control*, 40:250-257, 2012.

half strength without serum and greater than a 5 log<sub>10</sub> reduction at full strength with a serum challenge. The resistance study did not show trends towards increased resistance over time with serial passage through increasing concentrations of the antiseptic, nor was there any evidence of cross resistance to various antibiotics after incubation with sublethal concentrations of the antiseptic. These results are acceptable for approval.

## 7 CLINICAL AND STATISTICAL EFFICACY

3M submitted two pivotal clinical simulation efficacy trials to support their application, EM-05-012760: MicroBioTest Laboratories; and EM-05-01360: BioScience Laboratories. Both studies were randomized within subject, active and placebo controlled, single-center studies in healthy volunteers. Although the design was open label, study staff performing bacterial counts and statistical analyses were blinded to treatment. Subjects meeting inclusion criteria underwent a 3 day run in period during which bathing was prohibited, followed by baseline bacterial sampling from two abdominal and two groin sites. Subjects with baseline counts of  $\geq 3.00 \log_{10}$  per cm<sup>2</sup> bilaterally on the abdominal region and  $\geq 5.00 \log_{10}$  per cm<sup>2</sup> bilaterally on the inguinal region were eligible for entry into the treatment phase for study EM-05-012760; baseline counts were required to be  $\geq 2.5 \log_{10}$  per cm<sup>2</sup> bilaterally on the abdominal region and  $\geq 5.00 \log_{10}$  per cm<sup>2</sup> bilaterally on the inguinal region to enter the treatment phase for study EM-05-013260. On treatment day, subjects had one surgical prep solution placed on each of the 4 sites, followed by bacterial sampling at 10 minutes and 6 hours post-prep. Study EM-05-012760 included 4 arms: 3M CHG/IPA 10.5 mL (tinted), 3M CHG/IPA (tinted) 26 mL, ChloroPrep<sup>®</sup> (tinted) 26 mL, and saline (negative control). Study EM-05-013260 included 4 different arms: 3M CHG/IPA 10.5 mL (colorless), 3M CHG/IPA with HEDTA 10.5mL (colorless); ChloroPrep<sup>®</sup> (colorless) 10.5 mL, and saline (negative control). Choice of arms for the studies was designed to provide replicative efficacy of the various different presentations as well as to provide bridging to the final to-be-marketed formulation containing HEDTA, and are acceptable.

Outcome measures for the studies were based on criteria established in the FDA 1994 Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products (59 FR 31402) for preoperative antiseptics. The primary endpoint for each site (abdomen and groin) was the responder rate at 10 minutes with a secondary endpoint of the absolute reduction in bacterial counts at 10 minutes. Consistent with efficacy criteria established in the monograph and for other NDA products relying upon clinical simulation studies, antimicrobial efficacy is based on an absolute responder rate and absolute reduction in bacterial counts rather than demonstrating a statistically significant improvement over placebo. Having an absolute standard is appropriate given that clinical simulation studies are a surrogate endpoint for a reduction in surgical site infections, although as the microbiology reviewer Dr. Jackson points out, we do not have dose response data clearly linking a particular level of magnitude of bacterial reduction in simulation studies to the level of reduction in surgical site infections. Recent data do, however, demonstrate a reduction in surgical site infections compared to an active control with use of a CHG/IPA

preoperative preparation<sup>5</sup>, all of which were approved based on absolute log reduction criteria.

A predefined “win” was based on achieving a lower bound of the 95% confidence interval of percent responders that was greater than or equal to 70%. On the abdomen, a responder was defined as a subject with a  $2 \log_{10}$  per  $\text{cm}^2$  bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. On the groin, a responder was a subject with a  $3 \log_{10}$  per  $\text{cm}^2$  bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. Of note, the criteria defining a responder under the OTC drug monograph was recently modified in a new proposed rule published in May 2015. The new criteria require testing at 30 seconds after the product is dry rather than 10 minutes after the product is dry, with the absolute log reduction requirements staying the same. This proposed change was based on labeling and anticipated use of the products in which surgical incisions are likely to commence immediately after drying. For the purposes of this NDA, FDA agreed to accept the 10 minute time point given that comments are still being evaluated for the proposed rule.

Results of the studies were disparate and are shown in Table 1. Study EM-05-012760 met the primary end point of 70% responders for both the abdomen and groin sites for both 3M CHG/IPA products tested (10.5 mL tinted and 26 mL tinted). The active control also met the endpoint, while the negative control did not. This study is supportive of efficacy of the products, and results were verified by the FDA statistical reviewer.

In contrast, study EM-05-013260 met the primary endpoint for the abdominal site, but not for the groin site. In the inguinal region, only 32% and 40%, respectively, of subjects receiving the 3M products tested (10.5 mL colorless without HEDTA and 10.5 mL colorless with HEDTA) were considered responders based on the lower bound of the 95% confidence interval. The active control also failed, suggesting that the failure may have been a study-related issue rather than a drug issue. However, even when the upper bound of the confidence interval is considered, responders still are only 46 and 54%, respectively. The study also failed to reach the secondary endpoint of absolute log reduction for the test products in the inguinal region.

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<sup>5</sup> Tuuli MG, Liu J, Stout MJ, et al. A randomized trial comparing skin antiseptic agents at cesarean delivery. *New Engl J Med* 2016; 374:647-55.

**Table 1: Efficacy Results Studies EM-05-012760 and EM-05-13260**

<b>Study EM-05-012760</b>				
<b>Abdominal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep, 26 mL	ChloroPrep <sup>®</sup>	Saline
N	205	201	198	62
Responder, n (%)	167 (81.5)	175 (87.1)	178 (89.9)	0
95% CI for rate	76.1%, 86.8%	82.4%, 91.7%	85.7%, 94.1%	NA
P-value relative to negative control	<0.001	<0.001	<0.001	NA
Mean log reduction (95% CI)	2.66 (2.56, 2.77)	2.74 (2.65, 2.83)	2.79 (2.71, 2.87)	0.64 (0.52, 0.76)
<b>Inguinal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep, 26 mL	ChloroPrep <sup>®</sup>	Saline
N	204	203	200	59
Responder, n (%)	168 (82.4)	162 (79.8)	168 (84.0)	4 (6.8)
95% CI for rate	77.1%, 87.6%	74.3%, 85.3%	78.9%, 89.1%	0.4%, 13.2%
P-value relative to negative control	<0.001	<0.001	<0.001	NA
Mean log reduction (95% CI)	3.98 (3.84, 4.12)	3.89 (3.76, 4.01)	4.03 (3.90, 4.16)	1.34 (1.06, 1.62)
<b>Study EM-05-013260</b>				
<b>Abdominal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep with HEDTA, 10.5 mL	ChloroPrep <sup>®</sup>	Saline
N	196	202	196	59
Responder, n (%)	159 (81.1)	165 (81.7)	163 (83.2)	5 (8.5)
95% CI for rate	75.6%, 86.6%	76.3%, 87.0%	77.9%, 88.4%	NA
P-value relative to negative control	<0.001	<0.001	<0.001	NA
Mean log reduction (95% CI)	2.78 (2.65, 2.91)	2.73 (2.59, 2.89)	2.75 (2.61, 2.89)	0.76 (0.55, 0.97)
<b>Inguinal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep with HEDTA, 10.5 mL	ChloroPrep <sup>®</sup>	Saline
N	208	209	219	61
Responder, n (%)	81 (38.9)	98 (46.9)	116 (53.0)	1 (1.6)
95% CI for rate	<b>32.3%</b> , 45.6%	<b>40.1%</b> , 53.7%	<b>46.4%</b> , 59.6%	NA
P-value relative to negative control	<0.001	<0.001	<0.001	NA
Mean log reduction (95% CI)	2.84 (2.68, 3.00)	2.99 (2.84, 3.14)	3.17 (3.00, 3.33)	1.01 (0.84, 1.18)

Table adapted from Table 18, p. 72, Module 2 of NDA 208,288

CI=confidence interval, calculated based on the normal approximation to the binomial distribution.

The sponsor performed and submitted a post-hoc non-inferiority analysis to Chloraprep<sup>®</sup>, the active control for this study. Given that the study is a clinical simulation study examining a surrogate endpoint rather than a clinical outcome trial and the active comparator also failed, this is not adequate justification for the failed study. While the microbiology reviewer recommended approval based on potential differences in sampling techniques between the two test sites, this fails to explain why only the inguinal site would fail while the abdominal site did not for Study EM-05-13260.

Because the sponsor was attempting to gain approval for 3 different presentations of the test product (10.5 mL in tinted and colorless and 26 mL in tinted), the pivotal studies are not fully replicative and instead rely on a win in each of the arms to demonstrate replication. This is acceptable if all of the arms demonstrate efficacy, which in this case, they did not. The statistical reviewer also noted that the analysis data excluded subjects if no data were available at 10 minutes or 6 hours due to laboratory accidents or site contamination. Such exclusions could introduce bias and impact the interpretability of the findings. In addition, this study used a 10 minute endpoint. While this was agreed upon for this development program and is acceptable as a primary endpoint while the standards are currently in transition, it might be anticipated that the outcome at 30 seconds would be even worse. FDA also evaluated whether changing the threshold for a responder from a 3.0 log<sub>10</sub> reduction to a lower number would have resulted in a different outcome, which it did not, again calling into question whether the drug was in fact efficacious.

In his CDTL review, Dr. Becker concludes that the studies fail to demonstrate replicative efficacy and recommends a Complete Response based on this finding. I concur with this assessment. Since the two different body regions tested (abdomen and inguinal) may be considered independently, to correct the deficiency, a repeat study demonstrating a 70% responder rate for the inguinal region using appropriate positive and negative controls will be required. Of note, this issue was pointed out in the filing letter as a potential review issue.

## 8 SAFETY

For this NDA, 3M conducted three specific dermal safety trials to evaluate cumulative irritation/sensitization, phototoxicity, and photoallergenicity. In addition, safety data are also available from three pivotal clinical simulation efficacy trials, one persistence of efficacy trial, two coverage and drying time studies, two drape adhesion studies, and two pilot studies. Overall, there were 1568 unique subjects exposed to CHG/IPA as part of this development program. Of these, 507 were exposed to the to-be-marketed formulation containing HEDTA. 3M included both the non-HEDTA formulation and the HEDTA-formulation in one of the pivotal efficacy trials to create a bridge between formulations. I concur with Dr. Becker's conclusion that the addition of small amounts of HEDTA is unlikely to have a significant safety impact, and the number of exposures is adequate to inform the safety profile of the proposed product.

The sponsor also proposed to rely on literature to support the safety profile. The clinical reviewer, Dr. Podruchny, did review the submitted literature, which revealed no new safety concerns. The primary concern is related to skin burns in premature infants exposed to CHG, for which class labeling is already in place. For the clinical safety profile of this

specific 3M CHG/IPA product, the literature references are supportive, but not necessary for approval because 3M provided adequate new clinical safety studies conducted using their CHG/IPA product. It is appropriate to rely on the literature for class-labeling related safety issues.

### **8.1 Safety in clinical trials**

There were no deaths or serious adverse events in any of the clinical trials and few non-serious events were reported. Across all studies, all AEs that were considered related to CHG/IPA were skin events of mild to moderate severity, most of which related to skin irritation or burning. As these are expected events with CHG products, they do not raise new safety concerns for the product. Labeling would be expected to reflect the irritation potential.

#### *Dermal safety*

The cumulative irritation/sensitization study was a single-site, open label, randomized study in 234 subjects comparing 3M CHG/IPA (tinted and colorless) to ChloroPrep<sup>®</sup> tinted (active control), 0.4% sodium lauryl sulfate (positive control), and 0.9% saline (negative control). Trial design included a 21 day induction period, followed by a rest phase and rechallenge. As expected, the 3M products demonstrated mild irritation potential consistent with the known profile of CHG, the negative control showed no irritation, and the positive control showed strong potential for irritation. Surprisingly, the ChloroPrep<sup>®</sup> control was similar to placebo, which is atypical. However, given the expected performance of the other controls, the dermatology reviewer concluded that this study was an acceptable demonstration of the irritation potential of the 3M CHG/IPA products. No sensitization potential was observed. Non-serious adverse events were observed in 9 (3.8%) of subjects, of whom 6 discontinued. Overall, these adverse events were either likely unrelated or consistent with the known safety profile of CHG/IPA.

The phototoxicity and photoallergenicity studies compared 3M CHG/IPA (tinted and colorless) to ChloroPrep<sup>®</sup> tinted (active control) and untreated skin (negative control). Both studies were adequately designed; the studies did not demonstrate phototoxicity or photoallergenicity.

### **8.2 Consumer studies**

Given that antiseptic preoperative skin preparations represent a well-established OTC indication and use of class labeling is anticipated, no consumer studies (label comprehension, self-selection, or actual use) were required for this application.

## **9 ADVISORY COMMITTEE MEETING**

An advisory committee meeting was not held for this application as it is not a new class switch and does not raise significant public health issues.

## **10 PEDIATRICS**

Other CHG/IPA products are approved for use in adults and children of all ages, with the following precaution for use in children younger than two months of age, "Use with care in

premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.”

As this application does not include a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration, PREA is not triggered. The product label will need to include precautionary language regarding use in children younger than 2 months.

## **11 OTHER RELEVANT REGULATORY ISSUES**

### **11.1 OSI Audits**

OSI site inspections were conducted at the two laboratories performing efficacy testing as well as the site performing safety testing for the human irritation study. No significant issues were identified during the inspections, and the sites received a classification of No Action Indicated (NAI).

### **11.2 Financial Disclosure**

The clinical review identified a number of deficiencies in the financial disclosure information. Despite significant correspondence with the sponsor, these deficiencies have not been satisfactorily resolved. Specifically, information on the subinvestigators was not reported for the two pivotal studies as well as the discontinued pivotal study, the persistence of efficacy study, the three safety challenge studies, and one of the two coverage/drying time studies. In addition, the principal investigator was a company employee for the two drape adhesion studies and one of the coverage/drying time studies. I concur with the conclusion of the clinical reviewer and the CDTL reviewer that these deficiencies fail to follow Good Clinical Practice guidelines. I also agree that substantial bias was unlikely to be introduced into the coverage and drying time studies; however, pivotal efficacy and safety studies are of greater concern. It is not possible to do a complete assessment of the safety and efficacy results without this information, as such, this is a clinical Complete Response issue.

### **11.3 Environmental Assessment**

A categorical exclusion was granted for this application.

## **12 LABELING**

### **12.1 Proprietary name**

The proposed proprietary name, SoluPrep<sup>™</sup>, was deemed acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). Given the Complete Response action for this application, the proprietary name finding is conditionally acceptable pending another review at the time of approval.

### **12.2 Consumer labeling**

3M submitted labeling for three different presentations: SoluPrep<sup>™</sup> 10.5 mL Brite Green, 10.5 mL Clear, and 26 mL Brite Green. Labeling included immediate container (handle), consumer information leaflet, outer container pouch with Drug Facts, and package insert.

Labeling reviews were completed by DMEPA and DNDP labeling reviewers, who recommended a number of changes to the proposed label for consistency between the different SoluPrep™ presentations and consistency with class labeling, among other issues. However, given the multiple deficiencies in this application precluding approval, labeling negotiations were not held with the sponsor. In the CDTL review, Dr. Becker recommended that the labeling deficiencies also be a Complete Response issue. While I agree with the recommendations of the primary labeling reviewer, it is premature to make a complete label assessment at this time due to various other deficiencies in the application, which may affect labeling. As such, labeling will be deferred for this review cycle.

## **13 DECISION/ACTION/BENEFIT RISK ASSESSMENT**

### ***13.1 Regulatory action***

3M has not submitted adequate data to support approval of CHG/IPA for OTC use as a patient preoperative skin preparation antiseptic. As such, the action for this application will be a Complete Response.

### ***13.2 Risk Benefit Assessment***

The overall risk-benefit assessment does not support 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.” There are significant deficiencies for CMC (drug product and microbiology), toxicology, clinical pharmacology, and clinical efficacy. The product demonstrates limited stability with an increase in impurities over time above the level acceptable by ICH guidelines. These impurities have not been qualified with an adequate toxicology assessment. In addition, the sponsor has proposed this to be a sterile product but did not adequately demonstrate a reasonable assurance of sterility. While the sponsor cites human absorption data in the literature for CHG, these data are insufficient to demonstrate absorption of the proposed product for a preoperative skin prep indication, particularly for IPA and the combination product.

In terms of clinical safety of 3M CHG/IPA, the safety database is adequate for approval, with adverse events primarily related to skin irritation. This is a known effect of CHG products. The effect was as expected in the dermal safety irritation study, suggesting that the proposed formulation does not lead to a product that is substantially more irritating. Dermal safety studies did not demonstrate evidence of sensitization, phototoxicity, or photosensitization.

In terms of efficacy, the pivotal studies failed to replicate efficacy findings for the inguinal region, with one of two studies substantially missing the primary endpoint of a 70% responder rate for the inguinal region, with responders being defined as subject with a 3 log<sub>10</sub> per cm<sup>2</sup> bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. Further complicating this finding was the lack of adequate financial disclosure for the pivotal studies, without which it is not possible to fully assess potential study bias. To resolve these deficiencies, the sponsor will need to conduct a repeat, adequately controlled clinical simulation study meeting efficacy criteria for the inguinal region. In addition, the sponsor will need to submit financial disclosure information for

investigators and subinvestigators for the pivotal trials or provide adequate justification and analysis regarding potential bias introduced in the pivotal trials by lack of such information.

***13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies***

None.

***13.4. Recommendation for other Postmarketing Requirements and Commitments***

None.

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/s/  
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THERESA M MICHELE  
05/06/2016

## CLINICAL REVIEW ADDENDUM

Application Type NDA  
Application Number(s) 208288  
Priority or Standard Standard

Submit Date(s) 7-06-15  
Received Date(s)  
PDUFA Goal Date 5-6-16  
Division / Office CDER/OND/DNDP

Reviewer Name(s) Teresa A. Podruchny  
Addendum Completion Date 4-26-16

NDA 208288 proposes a sterile, surgical pre-operative antiseptic skin solution, SoluPrep™ (2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol). This is an addendum to my 3-22-16 review for NDA 208288 which reviewed safety data as described in the referenced review and to my financial disclosure review dated 4-13-16. This addendum is to address outstanding clinically-related issues (financial disclosure, exposure).

Outstanding issue: Financial Disclosure

The initial NDA financial disclosure information did not include subinvestigator information. Subinvestigator disclosure was requested on 4-4-16 (my review of financial disclosure dated 4-13-16 erroneously reported the request date as 4-6). Emailed responses from the company were received and these are described in my “Clinical Investigator Financial Disclosure Review” dated 4-13-16. The formal response was received on 4-25-16 (Amendment 028 to the NDA, SDN 29). Amendment 028 has not been thoroughly reviewed due to time of receipt relative to the goal date for the NDA. Information in the cover letter and in module section 1.3.4 of Amendment 28 appears similar, and may be identical in terms of the content related to the subinvestigator disclosure, to that submitted in the 4-6 and 4-7-16 emails (and to the attachments provided with the referenced emails). The cover letter of Amendment 028 verifies that eleven subinvestigators at MicroBio Test and one at BioScience Labs are reported as no longer able to be contacted because they are former employees. The sponsor states they cannot “directly double check financial disclosure information” for these subinvestigators. These subinvestigators are not listed on any of the Form 3454s submitted with Amendment 28 (or previously).

Conclusion: The following italicized comment is almost identical to the comment made in the draft Complete Response letter and is recommended as an approvability issue due to the number of reported subinvestigators with missing Form 3454s (11/20 in study 12760 and 1/5 in study 13260) and the possible impact on data as indicated in the proposed comment. Based on subinvestigator information included in an 11-06-15 submission, several of these subinvestigators appear to have been subinvestigators in at least one other study submitted in support of the NDA. The sponsor notes they are unable to double check these subinvestigators. The preponderance of evidence suggests that such disclosure has not been obtained before (as compared to double-checking) and it is not clear whether due diligence occurred.

The sponsor also reports that no additional Form 3454s will be provided for studies 13337 and 12985 because these “studies did not collect any efficacy or major safety information” (cover letter, 4-25-16). These studies are listed as support of information in the Target Product Information (TPI) and the total number of subject in the TPI appears to include these studies.

*Financial disclosure information is not sufficient. Eleven of twenty of the sub investigators listed on the revised 1572 for pivotal study 12760 are missing disclosure information and one in five is missing financial disclosure information in study 13260. Good Clinical Practice Guidance, section 8.2 (<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf>) indicates this information should be documented before the trial starts formally. As you know, financial arrangements between investigators and the sponsor can introduce bias in trial data that may be difficult to evaluate. In addition to the potential impact on efficacy outcome data, this is an issue of study conduct.*

*In order to evaluate the possible impact on efficacy outcomes, identify how many subjects each sub investigator contributed in each of the named studies. Submit analyses dropping the subjects of all sub investigators without financial disclosure per pivotal trial. Provide datasets for each pivotal trial that allow independent verification of the sensitivity analyses, (i.e. the sub investigator is named for each*

subject by usubjid in efficacy datasets for each study). As a sub investigator may have participated in more than one trial, for each trial in the NDA indicate whether there is missing sub investigator information, list the missing sub investigator, and provide a listing of all sub investigators in the respective trial. Also, describe your efforts to obtain financial disclosure. Feel free to discuss and provide other strategies you believe may evaluate this issue and to discuss the potential impact on data integrity, especially efficacy data in the pivotal trials.

Outstanding issue: Unique subject exposures and literature support

Amendment 26 (4-20-16, SDN 27, letter dated 4-18-16) is a response to a request to clarify unique subject exposure to the to-be-marketed formulation. The cover letter contains/is the response. The sponsor defined the “NDA product” in the letter dated 4-18-16 as “the final formulations of the active ingredients, polymer, and other ingredients WITH and WITHOUT a Trace amount of HEDTA added.” This response included a table, reproduced below from Amendment 26. I added a red arrow to the table to point out a study that is not characterized as a covered study and not submitted in the initial NDA (study 13447). With or without this study, there would be over 1500 unique exposures to the NDA product based on the sponsor’s information.

Some of the subjects may not have been naïve and this may underestimate common skin reactions (or even rare ones, though rare reactions may not be captured anyway in a dataset of this size). However, the active ingredients are well known to DNDP.

<b>Subjects exposed to NDA product (with and/or without HEDTA)</b>				
Study Site	3M Study #	# of subjects treated with NDA product	Total # of subjects treated with NDA product	Unique # of subjects exposed to NDA product
<b>3M Health Care In-house Clinical Study Facility</b> →	12680	32 subjects	101 subjects	83 unique subjects
	12794	30 subjects		
	12985	18 subjects		
	13447	21 subjects		
<b>MicroBioTest Laboratories, Inc.</b>	12760	418 subjects	459 subjects	437 unique subjects
	13337	16 subjects		
	13509	25 subjects		
<b>BioScience Laboratories, Inc.</b>	12759	169 subjects	782 subjects	716 unique subjects
	13260	613 subjects		
<b>Consumer Product Testing Company, Inc.</b>	12853	234 subjects	332 subjects	332 unique subjects
	12952	38 subjects		
	13062	60 subjects		
<b>TOTAL</b>			1674 subjects	1568 unique subjects

Source: sponsor, Amendment 26 to the NDA, red arrow from reviewer

The literature support for the NDA has been a subject of considerable discussion, especially with Dr. Becker and with regulatory staff including the Associate Director, Regulatory Affairs (J. Grewal). The 11-06-15 TPI section 4, “Do not use” references four publications for support of the three bullets in this section (one for allergies to the actives, one for lumbar puncture or meningeal contact, and one for open skin wounds or as a general skin cleanser). Two of four of the publications are non-clinical

literature and appear to be submitted to support the lumbar puncture/meningeal contraindication. The other two are intended to support the allergy contraindication and the skin wound/cleanser. These publications are not at the level of scientific rigor as would be expected for a new molecular entity (one is the results of a questionnaire sent to health care workers using hand wash products and one is a case series of patch testing). However, this product is not a new molecular entity.

Literature submitted to support the general safety was included in the application. I made recommendations in my review for the Division to ask the sponsor to resubmit the literature, specifically the pediatric literature and for the clinical literature submitted to support use and "Do not use" that was not supported directly by trial data. I should clarify that this was a recommendation for consideration by the Division. It may be the case that the large history of use with the active ingredients provides reasonable support given that this product is not considered a new molecular entity and that there are about 1500 exposures reported to the NDA product (as defined) in the development program. It should be noted that currently there is a Tracked Safety Issue for hypersensitivity/anaphylaxis with chlorhexidine gluconate products. This may result in changes to labeling of products containing CHG.

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TERESA A PODRUCHNY  
04/26/2016

FRANCIS E BECKER  
04/28/2016

## Cross-Discipline Team Leader Review

<b>Date</b>	April 26, 2016
<b>From</b>	Francis E. Becker, M.D., F.A.C.P
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA</b>	208288
<b>Applicant</b>	3M Health Care
<b>Date of Submission</b>	July 6, 2015
<b>PDUFA Goal Date</b>	May 6, 2016
<b>Proprietary Name / Non-Proprietary Name</b>	SoluPrep Film-Forming Sterile Solution / 2%w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
<b>Dosage form(s) / Strength(s)</b>	Surgical solution
<b>Applicant Proposed Indication(s)/Population(s)</b>	Patient Preoperative Skin Preparation (adults and pediatric patients $\geq$ 2 months of age) <ul style="list-style-type: none"><li>• For preparation of the skin prior to surgery</li><li>• Helps reduce bacteria that potentially can cause skin infection</li></ul>
<b>Recommendation on Regulatory Action</b>	Complete Response
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Not applicable.

### 1. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

I recommend that a Complete Response Action be taken for this application. There are Product Quality, Pharmacology/Toxicology, Regulatory, Clinical, and Labeling issues which have not been adequately addressed. The deficiencies are as follows:

1. Pharmacology/Toxicology: Stability testing detected two impurities which exceed the allowed impurity threshold per FDA guidance and which have not been qualified. The sponsor must conduct qualification studies for the two impurities (b) (4) according to the qualification program as stated in ICH Q3B(R2) Guidance. This is a Complete Response Issue.

2. Product Quality: The proposed limits for the two impurities exceed ICH Q3B (R2) limits of 1.0%. (b) (4) will reach 1.0% at (b) (4) months, and (b) (4) will exceed 1.0% at (b) (4) months. Even though the sponsor's proposed specifications for an interim shelf-life of (b) (4) months, impurity (b) (4) would be (b) (4)% and therefore still exceeds the ICH limit. This is not a negotiable review issue. The impurity level continues to increase over time ((b) (4)% at 2 years). This is a Complete Response issue.
3. Microbiology: Deficiencies or inadequacies were identified in: 1) the container closure integrity test (CCIT) validation data and testing method; 2) the requalification (RO) schedule for the (b) (4); 3) the bioburden testing method; 4) the validation data for the testing of the (b) (4); and 5) several other issues regarding sterility testing. These are Complete Response issues.
4. Carton and Container Labeling: Numerous errors in labeling were identified including failure to utilize class labeling in some cases as well as various other inconsistencies (see **Section 12** below for specifics). These are Complete Response issues.
5. Clinical (Efficacy): The sponsor failed to demonstrate efficacy in two pivotal clinical simulation studies, based on the previously agreed upon statistical analyses and primary endpoints. Study **EM-05-012760** (MicroBiotest) passed on all primary efficacy analyses; however, Study **EM-05-013260** (BioScience Laboratories) did not pass the  $\geq 70\%$  responder rate (primary endpoint). It can be argued that the primary efficacy endpoint is too stringent, because other sponsors have encountered similar difficulties with studies of this type. However, this is conjecture. The sponsor has not met the primary endpoint for the inguinal region in one of the two studies. Therefore, a repeat study of the inguinal region will be required. This is a Complete Response issue.
6. Clinical (Financial Disclosure): The financial disclosure information is inadequate. The sponsor did not exercise due diligence in obtaining the required information, which should have been done prior to starting the studies. Due to missing information, it is unclear whether bias could have been introduced into the development program. It is entirely possible that no significant bias was introduced, but it is impossible to confirm this based on the lack of information. The sponsor must provide the missing information, or provide adequate explanation for the missing information. The sponsor must also submit a list of investigators for whom information is not known for each trial, so that sensitivity analyses can be done. This is a Complete Response issue.
7. Clinical (Safety): The sponsor did not provide adequate summaries of the medical literature, and the sponsor failed to separate the product specific literature from the literature which is not product specific. In addition, a question has been raised as to whether or not the safety data from the submitted studies is adequate for evaluation. If it is not, then the literature must be relied upon. In this instance, numerous products contain the active ingredients, and the safety profile of chlorhexidine gluconate (CHG) and isopropyl alcohol (IPA) are well known. In addition, no new safety signals were identified in the clinical studies. Therefore, I conclude that safety data from the studies is adequate. CHG and IPA products are known skin irritants and should be labeled as such. Proposed labeling would appropriately provide warnings about use in neonates and infants less than 2 months of age. Furthermore, FDA agrees that the addition of the acrylate copolymer and the addition of HEDTA as inactive ingredients are unlikely to adversely affect safety. However, the sponsor should provide adequate summaries of the medical literature and identify the product specific literature from the literature that is not product specific. This is not a Complete Response issue.

Until the above issues are adequately addressed, it is not possible to accurately assess risk-benefit of this product. It is noteworthy that there are numerous other products available on the market for patient preoperative skin prep, many of which have the same active ingredients as this product. If the above issues can be adequately addressed, SoluPrep Film-Forming Solution, if approved, would be the first FDA-approved sterile

drug prep solution on the market available for use by healthcare professionals. However, the clinical implications of this sterility, that is, whether or not this would 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 the resistance of removal during the surgical procedure and of improving the adhesion of adhesive-backed incise drapes. A tint provides improved visualization of the surgical area prepped. Based on currently available data, risks appear to be limited to skin irritation, with rare reports of hypersensitivity to chlorhexidine reported in the literature.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> <li>This product is for any condition requiring surgical prep.</li> </ul>	
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> <li>There are numerous preoperative surgical prep solutions on the market.</li> </ul>	
<u>Benefit</u>	<ul style="list-style-type: none"> <li>If the above issues can be adequately addressed, SoluPrep Film-Forming Solution, if approved, would be the first FDA-approved <u>sterile</u> drug prep solution on the market available for use by healthcare professionals. However, the clinical implications of this sterility, that is, whether or not this would 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 the resistance of removal during the surgical procedure and to improving the adhesion of adhesive-backed incise drapes. A tint provides improved visualization of the surgical area prepped.</li> </ul>	
<u>Risk</u>	<ul style="list-style-type: none"> <li>Numerous deficiencies (see summary above)</li> </ul>	Complete Response recommended (see Summary above)

<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<u>Risk Management</u>	<ul style="list-style-type: none"><li>• Complete Response</li></ul>	

## 2. Background

3M Health Care submitted a New Drug Application (NDA) for SoluPrep Film-Forming Sterile Patient Preoperative Skin Preparation (SoluPrep surgical solution) for the following proposed indication:

### Patient Preoperative Skin Preparation

- For preparation of the skin prior to surgery
- Helps reduce bacteria that potentially can cause infection

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. Combinations of CHG and IPA have been used in hospital settings to prevent infections since the early 1990s. Products containing both CHG and IPA have been used extensively in many countries as they are fast-acting antiseptics (due to alcohol) with persistent activity (due to chlorhexidine).

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 of 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, the surgical prep product is processed to a sterility assurance level of (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.

### Regulatory History

The regulatory history of this product is extensively described in Dr. Teresa Podruchny's **Clinical Review**. The original IND (76549) was submitted 09 Nov 2006. The IND was placed on clinical hold and FDA stated in a letter dated 15 Dec 2006 that information on the specific formulation(s) planned for testing in clinical trials and preclinical data to support safe use of these formulation(s) in humans would be required to resolve clinical hold deficiencies. The current clinical program began in 2012 after submission of a complete response to the clinical hold. (b) (4)

(b) (4) Since 2012, there have been numerous communications between the sponsor and FDA to discuss proposed protocols, primary and secondary objectives, trial designs, and statistical analysis plans. Important interactions between 3M Health Care and FDA under IND 76549 included the following:

- 30-May-2012: Complete response submitted by the sponsor. Subsequently, the clinical hold removed (letter date: 29-June-12). FDA identified specific requirements including exposure times, formulations, and test concentrations for the in vitro time kill study and requested an evaluation of the effect of serum on antimicrobial activity. An emergence of resistance study was recommended. FDA requested that studies be done with both the tinted and colorless formulations. FDA recommended the new efficacy requirements, including conducting 2 pivotal abdomen/groin studies and also provided general comments on conducting human safety studies (cumulative irritation, phototoxicity, and photoallergy). Photoallergy and phototoxicity studies were recommended to be conducted on both the tinted and colorless formulations. FDA stated that it does not consider the 3M acrylate copolymer to be a novel excipient as it is “highly similar” to the polymer that is an inactive ingredient in Duraprep.
- 4-June-2013: End-of-Phase 2 (EOP2) meeting conducted via teleconference. FDA requested a study to evaluate the potential for the development of cross-resistance to antibiotics and denied the sponsor’s proposal for waiver for photosensitization and photoallergenicity studies. FDA stated that dry time studies will be required and that mannequin heads could be used. FDA confirmed that a combined cumulative irritation patch test and human repeat insult patch test (HRIPT) in at least 200 evaluable subjects was acceptable. FDA recommended that 3M provide information about whether there is systemic exposure from the drug product/polymer and confirmed that 3M should perform an adhesion study with the final-to-be-marketed formulation.
- Jan/Feb 2014: 3M submitted a Type A meeting request regarding a decision by 3M to place the pivotal clinical study (Study **EM-05-012759**) being conducted at Bioscience Laboratories, Inc (BSL) on hold due to a number of compliance issues identified at the site. At a teleconference on 20-Feb-2014, agreement was reached with FDA to conduct a new study at BSL if BSL could address and correct audit issues. FDA emphasized that for the study to be valid, the test product and active control must meet the performance criteria and the test and active control performances must be superior to the vehicle control.
- April/May 2014: 3M communicated to FDA regarding (b) (4) the addition of a trace amount (b) (4) of HEDTA (b) (4). 3M submitted a revised replacement protocol for the pivotal abdomen/groin study to be conducted at BSL which included an additional arm to compare the non-HEDTA solution with the solution with HEDTA. 3M also stated that the Chloraprep 10.5 mL colorless formulation was being included to enable better blinding of the microbiology staff.
- 20-Jan 2015: Pre-NDA Meeting (face-to-face) held at FDA. Regarding 3M’s proposal to add an arm to the pivotal study at BSL to bridge safety and efficacy formulations with and without a trace amount of HEDTA, FDA stated that this appeared reasonable but whether the product with HEDTA is safe for use in the nonprescription drug setting is a matter of NDA review. FDA also reminded the sponsor “to address safety topics of interest historically associated with the use of topical chlorhexidine-containing products, i.e., anaphylaxis/hypersensitivity reactions and exposure to vulnerable pediatric populations, particularly premature infants and infants less than two months of age..” The

sponsor was also reminded to provide “a review of published literature and a summary of related postmarketing safety data from use of your Avagard™ product.”

- April 2015: FDA provided written feedback (IND 076549 Advice/Information Request, 4-17-15) on the 3M draft replacement pivotal abdomen/groin protocol that had been submitted to FDA in March 2014. FDA stated that it disagreed with 3M’s proposed alternative primary analysis and that in the event that the positive control fails to achieve target threshold, this finding will be a review issue, and a decision on product effectiveness will be made based on the totality of the data submitted. FDA agreed with the proposed primary analysis. However, the sponsor reported that by the time the FDA correspondence was received, the study was completed, and the alternative efficacy analysis was performed.

### 3. Product Quality

The Quality Assessment Team (**Table I** below) conducted the CMC review. In his review, Swapan De, Ph.D., Application Technical Lead, concluded that, “Regarding Chemistry Manufacturing and Controls, the application may not be approved.” He continued, “Drug product and microbiology section of the application are inadequate to support the approval of the application. The drug product impurities, stability of the drug product and sterility assurance of the finished product were found to have significant issues and thus, the application is not recommended for approval.”

**Table I: Quality Assessment Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erika Englund , Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Erin M Kim, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Maria I. Cruz-Fisher, Ph.D.	OPF/DPAII/BranchVI
Facility	Vipulchandra Dholakia, Ph.D.	OPF/DIA/B3
Regulatory Business Process Manager	Thao, Vu	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)	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

(electronically copied and reproduced from Quality Assessment Review; Swapan De, Ph.D.)

SoluPrep surgical solution contains CHG and IPA together with a film-forming polymer and other ingredients to form an antiseptic solution. Experimentation with polymers revealed that a

(b) (4)  
 [REDACTED] for optimum  
 quality of the dried film on skin. Finally, (u) (4) HEDTA was added (b) (4)  
 [REDACTED]

“Sterile solution” was a key design target for the 3M CHG/IPA prep. (b) (4)

The proposed sterile, topical antiseptic product will be supplied in single use applicators containing either 10.5 nL (colorless and tinted) or 26 mL (tinted only) of solution, as shown in the figure below (electronically copied and reproduced from Dr. De’s review). The finished drug product solution is filled into a (b) (4) glass ampoule (primary container) that is housed in a single use (b) (4) plastic applicator. Each plastic applicator has a reticulated foam sponge at one end and is individually sealed in a (b) (4) pouch (b) (4). Each 26 mL applicator is provided with 2 cotton tipped swabs inside the sealed pouch.

**Figure 1: Solupren Applicator System**



The formulation remains in contact with glass only until at the time of application, when the ampoule is broken, then solution flows through the reticulated foam sponge and applies to the skin.

### **Drug Product Quality Review**

During the review cycle, there were several communications between the drug product team and the sponsor, culminating in a tele-conference (t-con) on April 12, 2016. It should be noted that the t-con occurred after the completion of the Quality Assessment Team Reviews. The reader is referred to Dr. Luong’s “Memorandum of Teleconference” (N208288 Tcon letter DARRTS; 4/15/16) for updated information.

Dr. Luong confirmed that the acrylate copolymer in the CHG/IPA formulation has been determined by FDA to be highly similar to the polymer complex in the approved DuraPrep product. Therefore, this copolymer is not considered to be a novel excipient. However, in her review, Dr. Luong also noted that the two degradants, (b) (4) are the most

representative predictors of CHG degradation because they are the major degradation products in the solution. The accelerated (up to 6 months) and long-term (up to 24 months) stability studies conducted on 3M 2%CHG/70% IPA Film Forming Preparation support a 2-year product expiration date when stored at controlled room temperature, and demonstrate that the addition of (b) (4) HEDTA did not alter the stability profile. However, (b) (4) can accelerate the rate of degradation. In response to a drug product information request, 3M proposed specifications (b) (4) based on their stability data. However, both (b) (4) degradants exceed the ICH Q3B limits of <1% when stored at 25°C/60% RH (relative humidity). At t=(b) (4) months, (b) (4) exceeds 1%, and at t=(b) (4) months, (b) (4) exceeds 1.0%, as shown in the figures below (electronically copied and reproduced from Dr. Luong's **Drug Product Review**):



FDA sent an information request (IR) to the sponsor on December 8, 2015 pointing out that it appears that levels of (b) (4) will reach approximately 1.0% at (b) (4) months and levels of (b) (4) will reach 1.0% between (b) (4) months. In the IR, FDA requested that 3M: 1) provide further data for the stability figures; 2) propose tighter specification for both (b) (4) impurities with justification; and 3) revise the level of total impurities from (b) (4) % to a lower limit with adequate justification. 3M responded on December 18, 2015 with a commitment to lowering total impurities specification from (b) (4) % to (b) (4) %. A teleconference (t-con) was held between 3M and FDA toxicology and CMC reviewers on January 12, 2016, at which FDA notified 3M that their approach for deriving acceptance criteria for impurities was unacceptable. 3M proposed to shorten the product shelf-life to (b) (4) months. However, FDA found this unacceptable because the stability data do not support the (b) (4) month shelf-life.

On February 5, 2016, 3M submitted an amendment-16 introducing a response factor (RF) in an attempt to bring down the impurity level of (b) (4). FDA disagreed with use of the RF. Another t-con was held with the sponsor on April 12, 2016 (see “Memorandum of Teleconference”; N208288 Tcon letter DARRTS; 4/15/16). FDA re-iterated that the sponsor’s response factor analytical method was unacceptable. 3M agreed to re-calculate the acceptance criteria specification as instructed at the t-con of 1/12/16 and again at the t-con of 4/12/16. In so doing, total impurities and (b) (4) were calculated to meet specification limit. However, the proposed interim specification of (b) (4) % for impurity (b) (4) would not meet the ICH limit of <1.0% at the proposed interim shelf-life of (b) (4) months. At the t-con, the sponsor asked if the (b) (4) % proposed interim specification would be allowable and approvable, even though it exceeds

the 1.0% qualification threshold per ICH Q3B. Dr. Luong responded that this would be a review issue and deferred further assessment to Pharmacology/Toxicology.

In addition, in her **Drug Product Review Addendum** (March 18, 2016), Dr. Luong wrote, “This NDA has multiple deficiencies from multiple disciplines, including drug product quality. No risk assessment for the facilities has been submitted, comparability protocols listed are considered incomplete; therefore, the change of manufacturers or manufacturing sites as annually reportable is not acceptable. We recommend that the applicant submits complete comparability protocols.”

### **Product Quality Microbiology Review**

The Product Quality Microbiology Review (March 18, 2016) was conducted by Maria Cruz-Fisher, Ph.D. Dr. Cruz-Fisher concluded that, “the submission is **not recommended** for approval on the basis of sterility assurance,” and “the safety risk associated with the microbiology deficiencies is considered high. In her review, Dr. Cruz-Fisher described multiple communications with the sponsor in an effort to obtain additional information and resolve deficiencies. However, in her final analyses, Dr. Cruz-Fisher identified Microbiology deficiencies or inadequacies in: 1) the container closure integrity test (CCIT) validation data and testing method; 2) the requalification (RQ) schedule for the (b) (4); 3) the bioburden testing method; 4) the validation data for the testing of the (b) (4); and 5) several other issues regarding sterility testing. The reader is referred to her review for further details.

## **4. Nonclinical Pharmacology/Toxicology**

The Pharmacology/Toxicology Review was conducted by Wafa Harrouk, Ph.D. Dr. Harrouk recommended a complete response based on the inadequate qualification program for impurities detected during the stability testing of the final product.

Dr. Harrouk noted that no nonclinical safety testing was conducted for the active ingredients, CHG and IPA, because the applicant refers to non-product specific published literature for the general safety and efficacy of these ingredients. Dr. Harrouk also noted that in the earlier phases of the drug development, the applicant proposed to use novel excipients whose safety profiles were not established for drug products, resulting in an IND clinical hold. In the latest formulation, 3M has adjusted the formulation where inactive ingredients which have been used in previously approved drug products have been used. Therefore, no additional testing was needed to demonstrate the nonclinical safety profile of the formulation.

During the early development of this product (under **IND 76549**), the applicant conducted some exploratory nonclinical studies to test the formulations which at the time were thought to contain a new polymer that had not been used in an approved drug product. Dr. Harrouk pointed out that these studies were reviewed by the FDA at the time of their submission. The studies included a skin irritation study in rabbits, a murine local lymph node assay (LLNA) in mice, a systemic toxicity study following repeated dermal application to the rabbit, and a topical primary irritancy and phototoxicity study in hairless mice. These studies demonstrated that the polymer had little or no skin irritation/sensitization and that no systemic toxicity was observed. The polymer was

later considered by the FDA to be “highly similar” to the polymer in DuraPrep, another 3M approved product, and was not considered to be a novel excipient (Letter to the sponsor; IND 76549, Submission #11; July 20, 2012). No further testing for the formulation was required.

During the developmental stages of this sterile formulation, the sponsor identified use of (b) (4) of the 3M™ CHG/IPA Film-Forming Patient Preoperative Skin Preparation. However, as discussed in **Section 3**, it was also discovered that (b) (4) resulted in a number of impurities which were detected during the stability testing under accelerated conditions. Two of the ingredients, (b) (4) exceed the ICH Q3B guideline of <1% when stored at 25°C/60% RH. These impurities appear to be formed continuously and trend towards an increase with time starting at (b) (4) months where (b) (4) exceeds 1.0% and at (b) (4) months where (b) (4) exceeds 1.0%.

3M justified the lack of qualification program for these impurities by citing factors such as a prediction that the newly identified impurities have a similar structure to that of CHG and thus have a similarly low rate of absorption. However, the sponsor did not provide any absorption data for these impurities to allow for an independent comparison between the parent compound, CHG, and the impurities/degradants.

During a teleconference held on January 12, 2016 between representatives of 3M and FDA (Clinical, Pharm/Tox, and CMC), 3M committed to initiating qualification studies (16-day rabbit dermal toxicity study, and local tolerance testing [primary skin irritation in rabbits and sensitization by LLNA). However, no genotoxic testing for the 2 impurities of concern were proposed. Instead, 3M argued that genotoxicity studies are not appropriate for the following reasons:

- No mutagenic potential is expected for (b) (4) based on the QSAR analysis.
- Due to the antimicrobial and cytotoxic nature of CHG and its derivatives, these impurities are likely not to be suitable for point mutation or chromosomal aberration assays.
- The impurities are not commercially available and synthesis would require significant time. The technical challenges are significant and the stability of the impurity is unknown.
- The intended use would typically be no more than 1 to 2 times in a patient’s lifetime as a single-use preoperative skin preparation.

In addition, the sponsor stated that final reports for these studies would not be available until after the deadline for the review cycle of the NDA (approximately June 2016) and committed to submitting the data as a supplement to the approved NDA as soon as the data becomes available. The sponsor still asked for a 24 month expiry date based on the bulleted arguments above. However, during the teleconference, Dr. Harrouk provided the following response to the sponsor:

- The shelf life for this product will have to be supported by the level of impurities and the results of the qualification program that you plan to conduct.

- The qualification program consisting of a rabbit dermal toxicity study (16 days) and local tolerance testing without any genotoxicity testing is not adequate. The sponsor was referred to the qualification program as stated in ICH Q3BR2 guidance which can be found on this link:  
[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q3B\\_R2/Step4/Q3B\\_R2\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2_Guideline.pdf)). The genotoxicity testing aspect is needed for any qualification program even if the intended use of the product is for a single use. If the sponsor finds that conducting an Ames Assay is not feasible for the proposed formulation, the sponsor was referred to S2 R2 guidance for alternative approaches to assess the genotoxicity potential of the detected impurities which can be found on this link:  
<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm074931.pdf> .
- The final reports will have to be submitted during the NDA review cycle since the results of these reports will have a direct impact on the approvability of the NDA.

In conclusion, Dr. Harrouk writes in her review, “At the time of writing this review, the applicant has not submitted an acceptable qualification program or any data that would allow for a timely review of the two impurities, therefore, the Pharm/Tox recommendation is to issue a complete response until the impurities are adequately qualified.

*CDTL Comment: Note that Dr. Harrouk completed her review prior to the t-con held with the sponsor on April 12, 2016 at which time 3M agreed to recalculate the impurity specifications. As a result of the recalculations, it was determined that only one impurity, (b) (4) did not meet ICH Q3B criteria. Thus, at the time of this writing, Dr. Harrouk’s conclusions may only apply to a single impurity. This is a CMC issue. The Pharm/Tox issue is that any impurities that do not have acceptable impurity levels must have an acceptable qualification program.*

## 5. Clinical Pharmacology

No clinical pharmacology data was included in this submission, and therefore, there was no clinical pharmacology review.

## 6. Clinical Microbiology

The Clinical Microbiology NDA Review was conducted by Michelle M. Jackson, Ph.D. Dr. Jackson’s review included Preclinical Studies and Clinical Studies. Preclinical Studies included time kill studies and studies for antimicrobial resistance. Clinical studies included the two pivotal efficacy studies, which will be discussed under **Section 7**. In addition, Dr. Jackson reviewed a Neutralization Validation study and studies of area coverage, dry time, and vapor dissipation.

### In vitro Studies

Dr. Jackson noted that FDA has evaluated numerous broad spectrum antimicrobial activities (minimum inhibitory concentration [MIC]) of chlorhexadine gluconate drug product applications and has concluded that the full battery of organisms described in the 1994 TFM was not needed. Therefore, MIC testing is not necessary to support approval of chlorhexidine gluconate products because FDA has enough information regarding the spectrum of

antimicrobial activity. Instead, a modified *in vitro* time kill study is recommended. Therefore, the sponsor conducted the following studies:

Study EM-05-012770: Assessment of Microbiocidal Activity of Tinted and Colorless 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation Formulation Using a Modified Time Kill Procedure

In this time kill study, ChloroPrep with Tint was used as the active control. Overall, the results of the study indicated that the test SoluPrep™ Film-Forming Prep Tint and SoluPrep™ Film-Forming Prep Colorless achieved a >99.9% reduction in viable microbial cells in 3 and 5 minutes. These results were comparable to those achieved with the active control ChloroPrep with Tint.

Study EM-05-012981: Assessment of Microbiocidal Activity in the Presence of an Organic Challenge of Tinted and Colorless 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation Formulation Using a Modified Time Kill Procedure

In this study, SoluPrep™ Film-Forming Tinted (full strength-1X) and Soluprep™ Film-Forming Prep Colorless (full strength-1X) demonstrated >5 log<sub>10</sub> reductions in the presence of a serum challenge at both the 3-minute and 5-minute time points tested, thus meeting the 3 log<sub>10</sub> reduction to define antimicrobial activity of a time kill. The study demonstrated that chlorhexidine gluconate is not largely inactivated by organic material such as blood or the skin protein. Dr. Jackson pointed out that this residual activity makes this product an attractive choice for skin antisepsis where long-term reduction of microbial flora is desired. I agree.

Importantly, the neutralization validation study results for **EM-05-012770** and **EM-05-012981** demonstrated that the neutralization solution used in the test was not toxic and effectively neutralized the activity of SoluPrep™ Film-Forming Prep Tinted and SoluPrep™ Film-Forming Prep Colorless at various strengths.

Study EM-050-012758: Evaluation of Potential for Development of Antimicrobial Resistance to Tinted 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation Formulation

This study was designed to detect the potential for development of resistance to the chemical test product by sequential passage of a microorganism through increasing concentrations of the antimicrobial included in the culture medium. The study also evaluated potential development of antibiotic cross-resistance. The study did not show any trend toward higher MIC values with clinical isolates compared to ATCC laboratory strains. Overall, there was no evidence of the emergence of resistance, and there was no indication of a change in MIC related to cross-resistance to antibiotics for any of the organism/antibiotic combination tested.

EM-0512985: 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation 26 mL Applicator Area Coverage, Dry Time and Vapor Dissipation Study on Human Skin

In this study, the area coverage results for the 3M™ CHG/IPA Prep with Tint 26 mL applicator was 2499 cm<sup>2</sup> and 387 in<sup>2</sup>. The labeling coverage area states “19.5 in. X 19.5 in. area (approximate from the shoulder to groin in an average full size adult).” This is coverage area size is approximately 2451 cm<sup>2</sup> (380 in<sup>2</sup>). Therefore, Dr. Jackson concluded that the coverage area for the 3M™ CHG/IPA Prep 26 mL applicator is acceptable, and I agree.

In addition, the 3M™ CHG/IPA Prep was considered dry on the average of 1.54 minutes, which is well within the required class flammability labeling of 3 minutes. Furthermore, the labeling for this product states “wait until the solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair).” Therefore, Dr. Jackson concluded that the dry time is acceptable for the 3M™ CHG/IPA Prep 26 mL applicator, and I agree.

EM-05-013337: 3M™ CHG/IPA Film-Forming Preoperative Skin Preparation 10.5 mL Applicator Area Coverage, Dry Time and Vapor Dissipation Study on Human Skin

In this study, the area coverage results for the 3M™ CHG/IPA Prep with Tint 10.5 mL applicator was 1153 cm<sup>2</sup> and 178 in<sup>2</sup>. The labeling coverage area states “13 in. X 13 in. area.” This coverage area size is approximately 1090 cm<sup>2</sup> (169 in<sup>2</sup>). Therefore, Dr. Jackson concluded that the coverage area for the 3M™ CHG/IPA Prep 10.5 mL applicator is acceptable, and I agree.

In addition, the 3M™ CHG/IPA Prep was considered dry on the average of 1.80 minutes, which is well within the required class flammability labeling of 3 minutes. Furthermore, the labeling for this product states “wait until the solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair).” Therefore, Dr. Jackson concluded that the dry time is acceptable for the 3M™ CHG/IPA Prep 10.5 mL applicator, and I agree.

## 7. Clinical/Statistical- Efficacy

Two pivotal clinical simulation studies (**EM-05-012760**: Microbiotest Laboratories; and **EM-05-01360**: BioScience Laboratories) were conducted to evaluate the antimicrobial efficacy of SoluPrep™ Film-Forming Sterile Surgical solution (Tinted and Clear) compared to placebo control saline and active control ChlorPrep with tint on the abdominal and inguinal regions. The procedures used in the pivotal studies were based on the American Society for Testing and Materials (ASTM) E1173-01 (reapproved 2009): Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations and the FDA 1994 Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products (59 FR 31402).

Both studies were entitled, “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.” In general, the study designs of the two pivotal studies were similar. Both studies were randomized (within subject), controlled, third-party blind, single-center studies in healthy volunteers where each subject received 2 of the 4 possible study products on the groin and/or 2 of the 4 possible study products on the abdomen. The study staff performing the bacterial enumeration and the statistician performing the analysis were blinded to the study products. Subjects were excluded if they had any skin disorders on the applicable test areas, skin allergies, significant medical conditions recent systemic or topical exposure to medications such as antibiotics or steroids that might affect the normal microbial flora of the skin, or recent use of antimicrobial soaps, medicated shampoos, medicated lotions, antiperspirants, perfumes or colognes. Pregnant or nursing women were excluded from the study.

Healthy male and female subjects ( $\geq 18$  years of age) who met the inclusion/exclusion criteria were entered into a pre-treatment phase to allow for the removal of antimicrobial agents from the subject's skin and were to refrain from the use of antibacterial agents, antibiotics, contact with chemically treated swimming pools or hot tubs, hot waxes, and depilatories on the test areas during this phase. In addition, subjects were not to shower or bathe for at least 72 hours prior to their scheduled screening appointment. During the Screening Phase, baseline microbial samples were collected from both the left and right sides of the abdominal and/or inguinal regions using a cup scrub technique. For Microbiotest (Study **EM-05-012760**), subjects who had Screening Day baseline counts of  $\geq 3.00 \log_{10}$  per  $\text{cm}^2$  bilaterally on the abdominal region and/or  $\geq 5.00 \log_{10}$  per  $\text{cm}^2$  bilaterally on the inguinal region were eligible for entry into the treatment phase. For Bioscience Laboratories (Study **EM-05-013260**), the criterion was slightly different: subjects who had Screening Day baseline counts of  $\geq 2.5 \log_{10}$  per  $\text{cm}^2$  bilaterally on the abdominal region and/or  $\geq 5.00 \log_{10}$  per  $\text{cm}^2$  bilaterally on the inguinal region were eligible for entry into the treatment phase. On treatment day, subjects were randomized into 1 of 6 treatment groups shown in the following tables (electronically copied and reproduced from Dr. Jackson's review):

**Table II: Subject Treatment Groups (EM-05-012760)**

Treatment Group	Left and Right Treatments
1	3M CHG/IPA Prep 10.5 mL and 3M CHG/IPA Prep 26 mL
2	3M CHG/IPA Prep 10.5 mL and ChloroPrep
3	3M CHG/IPA Prep 26 mL and ChloroPrep
4	3M CHG/IPA Prep 10.5 mL and Saline
5	3M CHG/IPA Prep 26 mL and Saline
6	ChloroPrep and Saline

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloroPrep= ChloroPrep® Patient Preoperative Skin Preparation

**Table III: Subject Treatment Groups (EM-05-013260)**

Treatment Group	Left and Right Treatments
1	3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA
2	3M CHG/IPA Prep and ChloroPrep
3	3M CHG/IPA Prep with HEDTA and ChloroPrep
4	3M CHG/IPA Prep and saline
5	3M CHG/IPA Prep with HEDTA and saline
6	ChloroPrep and saline

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloroPrep= ChloroPrep® Patient Preoperative Skin Preparation; HEDTA=(hydroxyethyl)ethylenediaminetriacetic acid

Following baseline microbial sample collection, contralateral abdominal and inguinal areas were prepped with one of the four study products according to the treatment randomization code assigned to each subject. Microbial samples were collected using the cup scrub technique at 10 minutes post-prep and 6 hours post-prep.

In her review, Dr. Jackson noted that the post application sample collection is standard and acceptable. Dr. Jackson also noted that due to the film-forming component of 3M™ CHG/IPA Prep, a modification of the standard sampling solution (SSS) was required to dissolve the film for bacterial recovery in the two studies. Therefore, all microbial samples were collected using a modified sampling solution that contained triacetin (glyceryl triacetate). The sponsor was informed in an advice letter dated February 7, 2014, that it will need to ensure that Triacetin does not have any antimicrobial activity. The sponsor submitted a neutralization validation study to address this which is included in this submission (see Section 6, page 14).

### **Study Subjects**

**Microbiotest (EM-05-012760):** A total of 406 subjects were randomized to 6 treatment groups for the abdominal region. For the inguinal region, 391 subjects were randomized to 6 treatment groups for the inguinal region.

On the abdominal region, 246 subjects received 3M™ CHG/IPA Prep 10.5 mL, 245 subjects received 3M™ CHG/IPA Prep 26 mL, 247 subjects received ChloroPrep, and 74 subjects received saline. On the inguinal region, 238 subjects received 3M™ CHG/IPA Prep 10.5 mL, 238 subjects received 3M™ CHG/IPA Prep 26 mL, 236 subjects received ChloroPrep, and 70 subjects received saline.

**Bioscience Laboratories (EM-05-013260):** A total of 569 subjects were randomized to 6 treatment groups for the abdominal region. A total of 404 subjects were randomized to 6 treatment groups for the inguinal region.

On the abdominal region, 343 subjects were randomized to receive 3M™ CHG/IPA Prep, 344 subjects were randomized to receive 3M™ CHG/IPA with HEDTA, 347 subjects were randomized to receive ChloroPrep, and 104 subjects were randomized to receive saline. On the inguinal region, 242 subjects were randomized to receive 3M™ CHG/IPA, 244 subjects were randomized to receive 3M™ CHG/IPA with HEDTA, 248 subjects were randomized to receive ChloroPrep, and 74 subjects were randomized to receive saline.

In both studies, the primary objective was to evaluate the antimicrobial efficacy of the test product and demonstrate that the product provided a lower bound of the 95% confidence interval of percent responders that was greater than or equal to 70%. On the abdomen, a responder was defined as a subject with a  $2 \log_{10}/\text{cm}^2$  bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. On the groin, a responder was a subject with a  $3 \log_{10}/\text{cm}^2$  bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours.

However, the two studies differed in the CHG/IPA test product formulations. In study **EM-05-012760**, the antimicrobial efficacy of 3M™ CHG/IPA Prep (10.5 mL and 26 mL tinted

configurations) was evaluated. In contrast, in Study **EM-05-013260**, the antimicrobial efficacy of 3M™ CHG/IPA Prep (10.5 mL colorless) and 3M™ CHG/IPA Prep with HEDTA (10.5 mL colorless) was evaluated. (Tables IV and V below; electronically copied and reproduced from Dr. Jackson’s review).

**Table IV: Description of Test Products in Study EM-05-012760**

Treatment Code	Study Product	Description
10.5	3M CHG/IPA Prep	Contains 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA) in combination with an acrylate copolymer. 10.5-mL applicator, tinted.
26	3M CHG/IPA Prep	Contains 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA) in combination with an acrylate copolymer. 26-mL applicator, tinted.
CP	ChloraPrep	Marketed active control. Contains 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA). 26-mL applicator, Hi-Lite Orange® Tint.
S	Saline	Negative control. Sterile 0.9% saline. 20 mL bottle.

**Table V: Description of Test Products in Study EM-05-013260**

Treatment Code	Study Product	Description
Clear	3M CHG/IPA Prep	Contains 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA) in combination with an acrylate copolymer. 10.5-mL applicator, colorless.
Clear-H	3M CHG/IPA Prep with HEDTA	Contains 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA) in combination with an acrylate copolymer and (hydroxyethyl)ethylenediaminetriacetic acid (HEDTA). 10.5-mL applicator, colorless.
CP	ChloraPrep	Marketed active control. Contains 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA). 10.5-mL applicator, Clear.
S	Saline	Negative control. Sterile 0.9% saline. 20-mL bottle.

## Demographics

There were differences noted in subject demographics between the two study sites. In both the Microbiotest and Bioscience laboratories studies, demographics were similar across treatment groups. However, for Microbiotest, mean age was 36 years and there were approximately 50% women and 50% men. In contrast, for Bioscience Laboratories, mean age was slightly lower at 31 years, and there were significantly more men (~71%) than women (~29%). Furthermore, Microbiotest subjects were much more racially diverse than Bioscience Laboratory subjects. At Microbiotest, subjects were approximately 38% white, 32% Asian, 17% black, and 12% Hispanic/Latino; whereas at Bioscience Laboratories, subjects were approximately 91% white, 4% Hispanic/Latino, 3% Asian 2% other, 1% American Indian or Alaska native, <1% black, and <1% native Hawaiian or other Pacific Islander.

These differences in demographics likely reflect the different demographics of the regions where each study was conducted. In her review, Dr. Jackson wrote, “we do not have any evidence that

race makes a difference in the efficacy of topical antiseptics. These types of products (chlorhexidine gluconate and alcohol) has been marketed in the United States for a number of years and there are no reports in AERS or the literature to suggest that efficacy is affected by specific demographic factors.” I agree. It is unlikely that differences in demographics between the two sites affected efficacy results. Furthermore, efficacy comparisons between treatment arms in each study will not be affected because in each study, demographics were similar across treatment groups for both body regions.

### Efficacy Results

**Microbiotest (EM-05-012760):** As shown in the **Table VI** below (electronically copied and reproduced from Dr. Jackson’s review), the primary efficacy endpoint of achieving  $\geq 70\%$  for the lower bound of the 90% CI for responder rate was met by all active study products in the abdominal and inguinal regions.

**Table VI: Responder Rate (mITT Population, Study EM-05-012760)**

<b>Abdominal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep, 26 mL	ChloroPrep <sup>®</sup>	Saline
N	205	201	198	62
Responder, n (%)	167 (81.5)	175 (87.1)	178 (89.9)	0
95% CI for rate	76.1%, 86.8%	82.4%, 91.7%	85.7%, 94.1%	NA
P-value relative to negative control	<0.001	<0.001	<0.001	NA
<b>Inguinal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep, 26 mL	ChloroPrep <sup>®</sup>	Saline
N	204	203	200	59
Responder, n (%)	168 (82.4)	162 (79.8)	168 (84.0)	4 (6.8)
95% CI for rate	77.1%, 87.6%	74.3%, 85.3%	78.9%, 89.1%	0.4%, 13.2%
P-value relative to negative control	<0.001	<0.001	<0.001	NA

Thus, for both abdominal and inguinal regions, responder rates for all active products were statistically significantly higher than for the saline control ( $p < 0.001$ ). Furthermore, the responder rate following saline treatment was 0% and 6.8% for the abdominal region and inguinal region, respectively. Dr Jackson concluded that “the sponsor has met the primary endpoint recommended requirement for this clinical simulation study.” I agree.

The secondary efficacy analyses were supportive of the primary efficacy results. For the abdominal region, baseline mean bacterial (skin flora) count was approximately  $3.3 \log_{10}$  per  $\text{cm}^2$  across study products. At 10 minutes, all the test products demonstrated  $\geq 2 \log_{10}$  reduction at the abdomen site. For the inguinal region, baseline mean bacterial (skin flora) count was approximately  $5.4 \log_{10}$  per  $\text{cm}^2$  across study products. At 10 minutes, all the test products demonstrated  $\geq 3 \log_{10}$  reduction at the abdomen site. For both the abdominal and inguinal region, all test products did not exceed the baseline counts at 6 hours.

Bioscience Laboratories (**EM-05-13260**): As shown in **Table VII** below (electronically copied and reproduced from Dr. Jackson’s review), the primary efficacy endpoint of achieving  $\geq 70\%$  for the lower bound of the 90% CI for responder rate was met by all active study products in the abdominal region. The responder rates for all active products were higher and statistically significant ( $p < 0.001$ ) compared to the saline control. For the abdominal region, the secondary analysis was supportive of the primary efficacy results. Baseline mean bacterial (skin flora) count was approximately  $3.6 \log_{10}$  per  $\text{cm}^2$  across study products. At 10 minutes, all the test products demonstrated  $\geq 2 \log_{10}$  reduction at the abdomen site, and all test products did not exceed the baseline counts at 6 hours.

However, for the inguinal region, the primary efficacy endpoint of achieving  $\geq 70\%$  for the lower bound of the 90% CI for responder rate was not met by any active product. As shown in the **Table VII**, the lower bound of 95% CI for responder rate was 32.3%, 40.1%, and 46.4% for 3M™ CHG/IPA prep, 3M™ CHG/IPA Prep with HEDTA, and ChloroPrep, respectively. The corresponding responder rates (38.9%, 46.9%, and 53.0%, respectively; bolded in the **Table VII** below) were all higher and statistically significantly different ( $p < 0.001$ ) compared to the saline control (1.6%). However, the active test products did not reach the FDA recommended  $\geq 70\%$  for the inguinal region. Regarding the secondary analyses, only the active control ChloroPrep made the secondary endpoint of  $\geq 3 \log_{10}$  reduction at the inguinal site. All the test products did not exceed the baseline counts at 6 hours.

**Table VII: Responder Rate (mITT Population) Study EM-05-13260**

<b>Abdominal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep with HEDTA, 10.5 mL	ChloroPrep®	Saline
N	196	202	196	59
Responder, n (%)	159 (81.1)	165 (81.7)	163 (83.2)	5 (8.5)
95% CI for rate	75.6%, 86.6%	76.3%, 87.0%	77.9%, 88.4%	NA
P-value relative to negative control	<0.001	<0.001	<0.001	NA
<b>Inguinal Region</b>				
	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep with HEDTA, 10.5 mL	ChloroPrep®	Saline
N	208	209	219	61
Responder, n (%)	81 (38.9)	98 (46.9)	116 (53.0)	1 (1.6)
95% CI for rate	<b>32.3%</b> , 45.6%	<b>40.1%</b> , 53.7%	<b>46.4%</b> , 59.6%	NA
P-value relative to negative control	<0.001	<0.001	<0.001	NA

The sponsor provided an alternative assessment on the primary efficacy requirements that were met for 3M™ CHG/IPA Prep with HEDTA, as shown in the **Table VIII** below (electronically copied and reproduced from D. Jackson’s review): Noninferiority to the 10 minute log reduction of ChloroPrep, no difference in the return to baseline versus ChloroPrep at 6 hours, and

superiority to saline in responder rate. 3M™ CHG/IPA without HEDTA did not meet the non-inferiority portion of the alternative primary efficacy requirements.

**Table VIII: Alternative Primary Efficacy Results for the Inguinal Region: Difference in Log Reduction at 10 Minutes and Difference in Return to Baseline at 6 Hours (mITT Population, Study EM-05-013260)**

	3M CHG/IPA Prep	3M CHG/IPA Prep with HEDTA	ChloroPrep
<b>Inguinal Region</b>			
N	208	209	219
95% CI for the difference in log <sub>10</sub> reduction (ChloroPrep minus 3M CHG/IPA Prep) at the 10-minute time point <sup>a</sup>	(0.103, 0.567)	(-0.041, 0.410)	NA
97.5% CI for the difference in log <sub>10</sub> reduction (ChloroPrep minus 3M CHG/IPA Prep) at the 10-minute time point <sup>a</sup>	NA	(-0.074, 0.443)	NA
N(%) of subjects with skin flora returning to baseline values at the 6-hour time point	0	0	0
P-value for the difference in the percentage of subjects with skin flora returning to baseline values at the 6-hour time point <sup>b</sup>	1.000	1.000	NA

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloroPrep= ChloroPrep® Patient Preoperative Skin Preparation; CI=confidence interval; CSR=clinical study report; HEDTA=(hydroxyethyl)ethylenediaminetriacetic acid; mITT=modified intent-to-treat; NA=not applicable

### Statistical Analyses

The statistical review was conducted by Mushfiqur Rashid, Ph.D., Division of Biometrics IV. Dr. Rashid performed primary efficacy analysis of the two pivotal studies (**EM-05-12760** and **EM-05-13260**) and confirmed that “this reviewer’s primary analysis was consistent with the Applicant’s analysis. Dr. Rashid confirmed the sponsor’s efficacy findings that in Study **EM-05-012760** for both the abdominal and inguinal regions and in Study **EM-05-013260** for the abdominal region only, the primary efficacy endpoint of achieving  $\geq 70\%$  for the lower bound of the 95% CI for responder rate was met by all active study products. In Study **EM-05-013260** for inguinal region only, the primary efficacy endpoint of achieving  $\geq 70\%$  for the lower bound of the 95% CI for responder rate was not met by the two drug products or the *active control* product. Thus, Dr. Rashid wrote, “we have replicative efficacy for the abdominal site and there is nonreplicative efficacy for the inguinal site.” In addition, the active control did not meet primary efficacy criterion in the failed inguinal region study. However, Dr. Rashid also noted that in the failed inguinal region study (**EM-05-01326**), the mean log reduction criteria (secondary endpoint) comes close to the recommended 3 log<sub>10</sub> reduction in the inguinal site: 3M CHG/IPA Prep 10.5 mL (2.87), 3M CHG/IPA Prep with HEDTA 10.5 mL (2.99), and ChloroPrep (3.17). Thus, Dr. Rashid wrote, “there is marginal evidence of the antimicrobial efficacy of the two products for the inguinal site for patient preoperative skin preparation.”

**Table IX: Responder Rate and Mean log Reduction (mITT Population, Study EM-05-012760 and Study EM-05-013260)**

	Study EM-05-012670				Study EM-05--130260			
	Tinted 3M CHG/IPA Prep, 10.5 mL	Tinted 3M CHG/IPA Prep, 26 mL	Tinted ChloroPrep, 26 mL	Saline 20 mL	Clear 3M CHG/IPA Prep, 10.5 mL	Clear 3M CHG/IPA Prep with HEDTA, 10.5 mL	Tinted Chloro Prep 10.5 mL	Saline 20 mL
<b>Abdominal Region</b>								
N	205	201	198	62	196	202	196	59
Responder (%)	167 (81.5)	175 (87.1)	178 (89.9)	NA0	159 (81.1)	165 (81.7)	163 (83.2)	5 (8.5)
95% CI for responder rate	76.1, 86.8	82.4, 91.7	85.7, 94.1	NA	75.6, 86.6	76.3, 87.0	77.9, 88.4	NA
Mean log reduction (SD)	2.66 (0.71)	2.74 (0.64)	2.79 (0.57)	0.64 (0.49)	2.78 (0.935)	2.73 (1.002)	2.75 (0.973)	0.76 (0.814)
95% CI for mean log reduction	2.56, 2.77	2.65, 2.83	2.71, 2.87	0.52, 0.76	2.65, 2.91	2.59, 2.89	2.61, 2.89	0.55, 0.97
<b>Inguinal Region</b>								
N	204	203	200	59	208	209	219	61
Responder (%)	168 (82.4)	162 (79.8)	168 (84.0)	4 (6.8)	81 (38.9)	98 (46.9)	116 (53.0)	1 (1.6)
95% CI for responder rate	77.1, 87.6	74.3, 85.3	78.9, 89.1	0.4, 13.2	32.3, 65.6	40.1, 53.7	46.4, 59.6	NA
Mean log reduction (SD)	3.98 (1.03)	3.89 (0.93)	4.03 (0.97)	1.34 (1.1)	2.84 (1.19)	2.99 (1.13)	3.17 (1.24)	1.01 (0.67)
95% CI for mean log reduction	3.84, 4.12	3.76, 4.01	3.90, 4.16	1.06, 1.62	2.68, 3.00	2.84, 3.14	3.00, 3.33	0.84, 1.18

Note: The 95% CI for responder rate was calculated based on the normal approximation to the binomial distribution.

Electronically copied and reproduced from sponsor's submission: Table 18, page 72, Module 2

In her review, Dr. Jackson recommended that, based on her review of the in vitro and clinical simulation studies, the application be approved for the indication “patient preoperative skin preparation.” She pointed out that although for the inguinal region in Study **EM-05-013260**, the SoluPrep products and the active control (ChloroPrep) did not pass the  $\geq 70\%$  responder rate, the mean log reduction criteria (secondary endpoint) comes close to the recommended  $3 \log_{10}$  reduction. She noted that other antiseptics have had similar problems meeting this criteria, particularly in the BioScience Laboratory. Both test sites (Bioscience and Microbiotest) have passed inspections several times, and the reasons for differing results between the two labs (the only two labs performing these studies in the United States) are unclear. However, Dr. Jackson noted that the two pivotal protocols are identical except for the glass cylinder sampling scrub size used between the two lab facilities and theorized that the resulting differences in surface area sampling size may result in differences in bacterial count. Another inconsistency may be how hard one scrubs the skin using the hollow cylinder with the hollow policeman. However, she also commented that, “In regards to the 3 log reduction in the groin site, forging ahead, we may wish to also consider a final threshold level that would provide some measure of confidence

that a reduction in surgical infection rate would occur. However, a definitive link of decreasing bacterial count on the skin of any order of magnitude to clinical efficacy (reduction in incidence of post-operative infections), has not been made.”

*CDTL Comment: Although Dr. Jackson’s explanation as to why the Bioscience site failed to reach the primary endpoint at the groin site is plausible and raises appropriate concerns regarding the difficulties in reaching the currently approved primary efficacy endpoints, I disagree with her recommendation for approval, because the sponsor has been unable to reach the primary efficacy endpoints for both abdominal and groin sites in two pivotal studies, based upon current FDA standards which were agreed upon by FDA and the sponsor. Furthermore, we cannot rely on secondary endpoints if the primary analysis has failed, and the sponsor’s alternative analysis is a noninferiority analysis and therefore is generally not acceptable. Note that FDA had previously communicated to the sponsor (IND 076549 Advice/Information Request’ 4-17-15) that it disagreed with 3M’s proposed alternative primary analysis and that in the event that the positive control fails to achieve target threshold, this finding will be a review issue, and a decision on product effectiveness will be made based on the totality of the data submitted (see Section 2, page 7).*

## 8. Safety

The safety review was conducted by the Medical Officer, Teresa Podruchny, M.D., and is described in detail in her **Clinical Review** dated March 22, 2016. The safety information submitted by the sponsor included the following:

- Data from clinical trials
- Scientific literature
- Postmarketing safety data from use of the sponsor’s related product, Avagard (2% CHG/61% ethyl alcohol)

The following Table summarizes the trials for which safety data is available (electronically copied and modified from Dr. Podruchny’s review):

**Table X: Studies Used to Evaluate Safety**

<b>Pivotal clinical efficacy studies - single application, exposure about 6 hours*</b>
12760
13260
12759
<b>Persistence of efficacy –single application followed by up to a 72-hour period*</b>
13509
<b>Coverage and Dry Time studies- single application, exposure up to 30 minutes*</b>
12985
13337
<b>Drape Adhesion studies –single application, exposure up to 4 hours*</b>
12680
12794
<b>Safety Challenge Studies- intended to test more extreme conditions</b>
12853- multiple exposures over extended periods of time under dressings
12952 - after exposure to ultraviolet light
13062 - after exposure to ultraviolet light
<b>Other studies that collected AEs and skin irritation data</b>
12635 – non IND pilot study conducted in Romania
13447- sponsor did not intend for the NDA- study of product attributions

The two pivotal studies (**EM-05-12760** and **EM-05-13260**) were described above in **Section 7**. The third pivotal study, Study **EM-05-12759**, was prematurely terminated in agreement with FDA due to technical and data quality issues (See **Section 2**). Thus, there is no efficacy data for review, but the study was included in the safety evaluation.

The persistence of efficacy study, Study **EM-05-13509**, was designed 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 her review, Dr. Jackson noted that in order to demonstrate persistence for a preoperative skin preparation claim, FDA requires that the level of resident microorganisms remain below the 6-hour time point. Furthermore, FDA has advised sponsors that in order to obtain a claim with an associated time-frame greater than 6 hours, it is necessary to show clinical benefit with clinically meaningful outcomes, not just log reductions. Therefore, this study was not reviewed for efficacy. However, it remains part of the safety database.

Dr. Podruchny noted several limitations to the safety data from the clinical trials, including open-label designs, small numbers of subjects, and some recycling of subjects. Dr. Podruchny also noted that most studies were not performed with the final to-be-marketed (TBM) formulation, that is, 3M™ CHG/IPA with HEDTA. A total of 1568 unique subjects were exposed to the NDA product in human trials. However, the only studies that employed the TBM formulation were Studies **EM-05-13260** (461 subjects), **EM-05-13509** (25 subjects), and **EM-05-13447** (21 subjects), for a total of 507 subjects who were exposed to the TBM formulation.

No safety data was integrated. No scheduled clinical laboratory tests were performed in the clinical studies, except for the urine pregnancy testing performed in all female subjects in the safety challenge studies at screening and at final visit. No physical examinations were performed in any of the clinical studies. Vital signs were measured at screening and at final visit in the safety challenge studies (Studies **EM-05-12853**, **EM-05-012952**, and **EM-05-013062**). No clinically significant changes in vital signs were noted during these studies.

There were no deaths and no serious adverse events (SAEs) reported in any clinical study investigating 3M<sup>TM</sup> CHG/IPA Prep. The sponsor reports discontinuation secondary to an adverse event in only two studies (both safety challenge studies). Few adverse events (AEs) were reported. None of the subjects reported AEs in the persistence of efficacy study (**EM-05-013509**), in the coverage area, dry time, and vapor dissipation studies (Studies **EM-05-012985** and **EM-05-013337**), in the drape adhesion studies (**EM-05-012680** and **EM-05-012794**), nor in 2 of the 3 pivotal studies (**EM-05-12760** and **EM-05-12759**). Across all studies, all AEs that were considered related to study products were skin events; all of these events were mild or moderate in severity.

The only pivotal trial reporting adverse events was Study **EM-05-13260** (abdominal region: 5/569 [0.9%] subjects; inguinal region 4/404 subjects [~1%]). All treatment-emergent adverse events (TEAEs) involved the skin. One subject reported moderate skin irritation on both sides of the abdominal and inguinal regions (specifically, dryness and itching on both abdominal sides, and itching on both inguinal sides); all 4 moderate events of skin irritation were considered probably related to the study products on each side (3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA). After treatment on the abdominal region, mild events included an unexpected skin abrasion (1 subject, not related), burning sensation (2 subjects, probably related to ChloroPrep and 3M CHG/IPA Prep, respectively), and allergic reaction (1 subject, probably related to 3M CHG/IPA Prep with HEDTA). After treatment on the inguinal region, mild events included skin abrasion (1 subject, not related), warmth/heat sensation (1 subject, possibly related to 3M CHG/IPA Prep), and burning sensation (1 subject, probably related to 3M CHG/IPA Prep with HEDTA).

## Literature Review

In her review, Dr. Podruchny commented that the literature publications submitted were not optimal. The publications referenced in the the Clinical Summary of Safety (CSS) were, for the most part, not submitted, requiring an information request. When submitted, two of the articles were not in English, requiring another information request. Importantly, upon review of the submitted literature, product specific names were frequently found. Product specific literature cannot be relied upon under this 505(b)2 application. Furthermore, the CSS does not distinguish product-specific from non-product-specific literature, so there was no way for the reviewer to know which is which and how much literature is product specific without reading every article and keeping a record.

Thus, the literature review was limited, but no new safety signals were identified. The sponsor summarized that the search of the published literature found that acute hypersensitivity (anaphylaxis or anaphylactoid reactions) to CHG is rare, although the exact incidence is difficult

to estimate. It appears that the vast majority of anaphylaxis cases were related to use on wounds, broken skin, or mucosa. According to the sponsor, although serious hypersensitivity reactions can occur, they are rare when compared to the large numbers of exposures to CHG over the last 60 years.

The sponsor also summarized the pediatric literature and concluded the major concern with alcohol-based and aqueous chlorhexidine solution was skin irritation. The sponsor also noted that skin irritation, burns, and skin breakdown were limited to premature neonates and the burns were related to gestational age (severe only in “extremely premature neonates”).

## **Dermal Safety**

An evaluation of dermal safety was conducted by Gary Chiang, MD, MPH, Clinical Reviewer, Division of Dermatology and Dental Products (DDDP). Dr. Chiang reviewed the results of the three dermal safety studies conducted by the sponsor, as well as the reported adverse events from the pivotal clinical trials (**EM-05-12750**, **EM-05-12759**, and **EM-05-13260**). The dermal safety studies conducted by the sponsor and reviewed by Dr. Chiang were as follows:

**Study EM-05-12853**: A cumulative skin irritation test entitled, “Cumulative Irritation Patch Test 21-day with Challenge of 3M CHG-IPA Film Forming Skin Prep Colorless and Tint Marketed Active Control Positive Control and Negative Control.” In this single-site, open-label, randomized study, 3M CHG/IPA Prep (tinted and colorless) was compared to Chloraprep tinted (the active marketed control), 0.4% SLS (sodium lauryl sulfate, the positive control), and 0.9% sterile saline (the negative control). The primary objective of the study was to determine, by repetitive contact, the primary or cumulative irritation potential of the test materials compared to the positive control. The secondary objective was to determine the allergic contact sensitization potential of the test material compared to a marketed active control. The design included a cumulative irritation test (CIT; 21-day induction phase) followed by a rest phase and a challenge phase. In this study, 234 subjects received at least 1 treatment, and 205 completed the study. Six subjects withdrew due to AEs (1 with inflammation, edema, burning, contact dermatitis, and skin infection; 1 with erythema and edema; 1 with rash; 1 with allergic reaction; 1 with urinary tract infection; 1 with sinusitis).

The summary cumulative irritation scores are shown in **Table XII** below (electronically copied and reproduced from Dr. Chiang’s review). Dr. Chiang noted in his review that the result category for both the positive control and the negative control were as expected and the result category for the 3M investigational products, both colorless and tinted, were also expected as both CHG are known irritants. However, Dr. Chiang also pointed out that Chloraprep resulted in a lower CIT score than the negative control, which is atypical and unexpected.

**Table XI: Summary of Cumulative Irritation Scores: Study EM-05-12853**

<b>CIT Score</b>	<b>Indications from Test</b>	<b>Description of Responses</b>	<b>Treatment Group Result (all subjects)</b>
<b>0 to 723</b>	Mild material – no experimental irritation	Essentially no evidence of cumulative irritation under conditions of use	ChloraPrep (70.0) Negative control (195.5)
<b>724 to 2939</b>	Probably mild in normal use	Evidence of slight potential for very mild cumulative irritation under conditions of use	3M colorless (1899.5) 3M tinted (2060.0)
<b>2940 to 6610</b>	Possibly mild in normal use	Evidence of moderate potential for mild cumulative irritation under conditions of use	
<b>6611 to 8538</b>	Experimental irritant	Evidence for strong potential for mild-to-moderate primary or cumulative irritation under conditions of use	Positive control (6679.0)
<b>8539 to 9270</b>	Experimental irritant	Evidence of strong potential for moderate-to-marked primary cumulative irritation under conditions of use	

Source: Adapted from Sponsor's submission of Final Report

There were 14 adverse events among 9 subjects and no serious adverse events during the trial. Five of the AEs were judged to be mild and 9 AEs were judged to be moderate in severity. Seven of the AEs were judged to be unlikely related to any investigational materials, which seems a reasonable conclusion. The AEs are listed in **Table XII** below:

**Table XII: Adverse Events - Study EM-05-12853**

<b>Adverse Event*</b>	<b>N (%)</b>
Number of Subjects Enrolled	235
Number of Subjects with Adverse Events	9(3.8%)
Number of Subjects without Adverse Events	226 (96.2%)
<b>Skin &amp; Subcutaneous Tissue Disorders</b>	
Allergic reaction on Abdomen	1(0.4%)
Burning	1(0.4%)
Contact Dermatitis	1(0.4%)
Edema	2(0.9%)
Erythema	1(0.4%)
Inflammation	1(0.4%)
Rash on Torso	1(0.4%)
<b>Infections &amp; Infestations</b>	
Skin Infection	1(0.4%)
Ear Infection	1(0.4%)
Urinary Tract Infection	1(0.4%)
Sinusitis	1(0.4%)
<b>General Disorders</b>	
Malaise	1(0.4%)
<b>Vascular Disorders</b>	
Hypertension	1(0.4%)

Source: Sponsor submission of Final Report EM-05-012853-13-162

Dr. Chiang noted that a review of the conduct of the study (which was performed at an experienced laboratory) did not reveal any issues that could explain the atypically low CIT score for ChloroPrep (which is also a known irritant due to the CHG and IPA ingredients). There were no significant protocol departures that would explain the results. In this submission, the sponsor proposed the following explanation:

*“After review of the study methodology, the difference in product application of the investigational materials (two 3M CHG/IPA Prep products and ChloroPrep) may have had an impact on the lower than expected results for ChloroPrep.”*

Dr. Chiang concluded that, “the sponsor’s analysis appears acceptable. The Division does not recommend repeating the cumulative irritation study. The 3M product should be labeled as an irritant due to the CHG and IPA active ingredients.”

*CDTL Comment: I agree. Although it is not possible to know with certainty, there may be differences in application procedures based on product design that could have impacted the lower than expected Chloraprep results. Regardless, the results of the positive and negative controls indicate that the study was conducted properly, and I accept Dr. Chiang’s analysis that the study appears acceptable and consistent with the known irritant effects of CHG and IPA. The 3M product should be labeled as an irritant.*

**Study EM-05-012952:** A single-site, open-label, randomized study entitled, “Clinical Evaluation to Assess the Phototoxicity Potential of Topically Applied 3M CHG/IPA Film-Forming Skin Prep and a Marketed Active Control.” The primary objective was to determine the phototoxic potential of topically applied 3M CHG/IPA Prep (tinted and colorless) compared to the active marketed control (ChloraPrep tinted) and no treatment, with and without full spectrum UV radiation and UVA radiation. The criterion for positive phototoxic reaction was based on a comparison, on a scale of 0 (no visible skin reaction) to 4 (severe erythema, possible edema, vesiculation, bullae, and/or ulceration), of the skin reactions on a treated, irradiated test site versus skin reactions noted on a treated, non-irradiated test site at the 24- and 48-hour post-irradiation evaluations.

Thirty-seven subjects completed the study. All scores ranged from 0 (no visible skin reaction) to 1 (mild erythema converging most of the test site) on all test sites at all post-treatment time points, as shown in **Table XIII** below.

**Table XIII: Evaluation from the 3 Post-treatment Timepoints; Study EM-05-012952**

Skin Reaction Evaluation Score, n	Treatment							
	3M CHG/IPA Prep, colorless		3M CHG/IPA Prep, tinted		ChloraPrep, tinted		Untreated	
	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated
0	89	106	95	105	95	108	89	109
0.5	20	4	14	5	14	3	20	2
1	2	1	2	1	2	0	2	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloraPrep=ChloraPrep® Patient Preoperative Skin Preparation; CSR=clinical study report

Notes:

Skin reaction evaluation scale: 0=no visible skin reaction; 0.5=barely perceptible or spotty erythema; 1=mild erythema covering most of the test site; 2=moderate erythema, possible presence of mild edema; 3=marked erythema, possible edema; 4=severe erythema, possible edema, vesiculation, bullae, and/or ulceration

Number of evaluations for each treatment: 37 subjects x 3 post-treatment evaluation time points (24 hours post-treatment, 24 hours post-irradiation, and 48 hours post-irradiation) = 111 evaluations

Source: CSR for Study EM-05-012952 in Module 5.3.5

Dr. Chiang concluded that, “As all evaluations remained within the normal limits at all time points, there was no indication of phototoxicity in any of the treatment groups.” I agree with Dr Chiang’s conclusion.

**Study EM-05-13062:** A single-site, open-label, randomized trial entitled, “Clinical Evaluation of Photoallergy Potential.” The primary objective was to determine by

repetitive epidermal contact and UV irradiation, the photoallergic potential topically applied 3M CHG/IPA Prep (tinted and colorless) compared to the active marketed control (ChloraPrep [tinted]) and no treatment when applied to human subjects. The secondary objective was to determine the contact and UV radiation of a photo-irritant potential of the test materials. The study consisted of an induction phase (twice weekly treatment and irradiation for 3 weeks), a rest phase of 10 days, and a challenge phase (treatment and irradiation to virgin sites adjacent to the induction sites). Fifty subjects completed the study. The results of the study are illustrated in **Table XIV** below:

**Table XIV: Evaluations form Post-Treatment Time Points in Each Skin Reaction Evaluation Score Category, by Phase and by Treated and Untreated Sites with and without Irradiation: Study EM-05-013062**

Skin Reaction Evaluation Score, n	Treatment (N=50)							
	3M CHG/IPA Prep, colorless		3M CHG/IPA Prep, tinted		ChloraPrep, tinted		Untreated	
	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated
<b>Induction Phase<sup>a</sup></b>								
0	395	697	371	692	410	694	NA	NA
0.5	191	12	210	15	208	11	NA	NA
1	119	2	124	1	92	6	NA	NA
2	6	0	3	3	1	0	NA	NA
3	0	0	2 <sup>b</sup>	0	0	0	NA	NA
4	0	0	1 <sup>b</sup>	0	0	0	NA	NA
<b>Challenge Phase<sup>a</sup></b>								
0	192	200	191	200	190	200	193	200
0.5	8	0	9	0	10	0	7	0
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloraPrep=ChloraPrep® Patient Preoperative Skin Preparation; CSR=clinical study report; NA=not applicable

Note: Skin reaction evaluation scale: 0=no visible skin reaction; 0.5=barely perceptible or spotty erythema; 1=mild erythema covering most of the test site; 2=moderate erythema, possible presence of mild edema; 3=marked erythema, possible edema; 4=severe erythema, possible edema, vesiculation, bullae, and/or ulceration

<sup>a</sup>For the induction phase, the maximum number of evaluations for each treatment was 711 evaluations. For the challenge phase, the maximum number of evaluations for each treatment was 200 evaluations.

<sup>b</sup>One subject experienced a tape reaction to the occlusive bandage, which spread to the test site, raising scores to 4 (1 evaluation) and 3 (2 evaluations).

Source: CSR for Study EM-05-013062 in Module 5.3.5

Dr. Chiang agreed with the sponsor's conclusion that, under the conditions of the study, 3M CHG/IPA (tinted and colorless) and the marketed active control (ChloraPrep) did not induce a response indicative of irritant contact dermatitis, allergic contact dermatitis, photoallergic contact dermatitis, or phototoxic dermatitis. I agree with Dr. Chiang.

**Clinical Trials:** Dr. Chiang evaluated the dermal safety events in the pivotal trials. In Trials **EM-05-012760** and **EM-05-012759**, no skin irritation score of higher than 1 (mild) was reported for erythema, edema, rash, or dryness, and the incidence of mild skin irritation was low (<4%). In Study **EM-05-013260**, a total of 2 subjects had moderate reactions on the abdomen at 6 hours post-prep (moderate erythema and moderate dryness, respectively); all other skin reactions on both body regions were mild. At 10 minutes post-prep, the highest incidence of any skin reaction in either body region was mild erythema on the inguinal region in 2.0% of subjects in the ChloraPrep group. At 6 hours post-prep, the most commonly reported reaction on the abdomen was mild erythema, in 9.3%, 9.6%, 4.3%, and 5.8% of subjects in the 3M CHG/IPA Prep, 3M CHG/IPA Prep with HEDTA, ChloraPrep, and saline groups, respectively.

On the inguinal region, the most commonly reported reactions were mild erythema and mild rash at 6 hours post-prep, in 6.3% and 5.0% of subjects in the 3M CHG/IPA Prep group; in 9.8% and 5.3% in the 3M CHG/IPA Prep with HEDTA group; in 4.8% and 7.7% in the ChloroPrep group; and in 2.7% and 10.8% in the saline group.

Thus, Dr. Chiang concluded that sufficient safety information was collected in the pivotal trials to supplement the odd results from the Cumulative Irritation Testing (CIT) and provide further evidence that a repeat CIT is not needed.

In conclusion, Dr. Chiang wrote, “the applicant has provided sufficient dermal safety evaluations to satisfy provocative dermal safety testing recommendations typically provided by DDDP. Chlorhexidine Gluconate (CHG)/Isopropyl Alcohol (IPA) products are known irritants and labeling should typically note this effect. The Division of Dermatology and Dental products has identified no issues from our perspective which would affect approval based on the dermal safety data provided by the applicant.” I agree with Dr. Chiang’s conclusions.

*CDTL Comment: In my opinion, the safety data submitted by the sponsor from the clinical trials is adequate for safety review. A total of 1568 unique subjects have been identified. It is true that only 507 unique subjects were exposed to the to-be-marketed formulation, that is, the formulation containing HEDTA. It is not likely that the addition of small amounts of HEDTA would have a significant impact on safety.*

## **9. Advisory Committee Meeting**

At present, no Advisory Committee meeting is planned for this application. However, in her review, Dr. Podruchny, “Given the use of these products as preoperative scrubs and the issues relative to efficacy evaluation..., I recommend consideration of an advisory committee to again address these complex issues.” In my opinion, an Advisory Committee Meeting would not be helpful at present. In the future, after internal discussions and discussions with sponsors have shed more light on the challenges in conducting these clinical simulation studies, an Advisory Committee could be considered.

## **10. Pediatrics**

No pediatric studies were submitted with this application. In her review, under Recommendations for Pediatric Requirements,” Dr. Podruchny wrote, “Consider pediatric studies.” 3M had previously requested a pediatric study waiver because the efficacy of this product as an antimicrobial would not differ between the adult and pediatric population. In healthy term infants, skin barrier function is considered to resemble that of human skin. Proposed product labeling will include, under Warnings and Precautions, “Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.” For the pediatric population greater than 2 months of age, efficacy data will be extrapolated from clinical and microbiological studies in adults. From a safety and efficacy standpoint, I believe that this is adequate and that no pediatric studies to support this application are needed.

## 11. Other Relevant Regulatory Issues

### 505(b)(2) Application

The initial NDA is unclear regarding the sources of information upon which the applicant is relying. The applicant referred to published literature, but the 356h form also cited the listed drug, [REDACTED]<sup>(b) (4)</sup>. The applicant subsequently submitted an amendment dated 7/9/15 where they noted that their NDA is based on nonproduct specific references only and that they are not citing a listed drug. However, review of the referenced literature found that product specific literature is included, as discussed above (see **Section 8, Literature Review**). At the time of this writing, the application is under discussion by the 505(b)(2) Committee.

### Office of Scientific Investigations (OSI) Audits

Three clinical investigator sites were inspected, and four protocols audited. Study **EM-05-12760** (pivotal) and Study **EM-05-13509** (antimicrobial persistence study) were audited at Dr. Bashir's site in Sterling, Virginia (Microbiotest). 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.

### Financial Disclosures

The sponsor provided a Financial Disclosure document which was reviewed by Dr. Podruchny (**Clinical Investigator Financial Disclosure\_208288**). During the course of review, Dr. Podruchny noted several deficiencies in the financial disclosure information, as a result of which there have been several communications with the sponsor to request additional information. Initially, no subinvestigator (SI) information was included. In addition, of the 5 principal investigators (PIs), [REDACTED]<sup>(b) (4)</sup> was identified to be a company employee whose Form 3455 indicates that [REDACTED] "has participated in financial arrangements or holds financial interests" that require disclosure. However, a complete financial disclosure form is not included. [REDACTED]<sup>(b) (6)</sup>

In an email of 4/6/16, the sponsor noted that "clinical study sites were contacted in the past day to confirm/double-check that subinvestigators could certify that they did not have any financial disclosures" and also noted that several SIs were on vacation and others were "former" employees at the site and could no longer be contacted. Furthermore, in an email of 4/7/16, the sponsor noted they do not plan to include personnel on the 3454 forms if they no longer work for "MBT or BSL study sites" because they cannot directly reach them for confirmation of financial certification. At the time of this writing, the submitted financial disclosure information is as shown in **Table XV** below (electronically copied and reproduced from Dr. Podruchny's review):

**Table XV: Financial Disclosure Information (Submitted as of 4/8/16)**

<i>Studies</i>	<i>Financial Disclosure</i>
<i>Pivotal study 12759, discontinued study</i>	<i>PI reported, no SIs</i>
<i>Pivotal study 12760</i>	<i>PI reported, missing up to 50% SI and company appears to not be planning to submit these</i>
<i>Pivotal study 13260</i>	<i>PI reported, missing 1/5 SIs and company appears to not be planning to submit this</i>
<i>Persistence of Efficacy, study 013509</i>	<i>PI reported, appear to missing 6-7 SIs and company appears to not be planning to submit for these</i>
<i>Coverage, Dry Time, study 012985</i>	<i>PI was company employee, email indicates not planning to collect 3454 for this study. There were two SIs per SDN 9 information.</i>
<i>Coverage Dry Time, study 013337</i>	<i>PI reported, no SIs are reported &amp; 4-7 email indicates not planning to collect these. Multiple SIs listed in SDN 9 information.</i>
<i>Drape Adhesion, study 012680</i>	<i>PI was company employee, no SI per SDN 9</i>
<i>Drape Adhesion, study 012794</i>	<i>PI was company employee, no SI per SDN 9</i>
<i>Safety Challenge, study 012853</i>	<i>PI was reported, SIs reported</i>
<i>Safety Challenge, study 012952</i>	<i>PI was reported, SIs reported</i>
<i>Safety Challenge, study 013062</i>	<i>PI was reported, SIs reported</i>
<i>Pilot, non-IND study, study 012635</i>	<i>Not applicable unless using safety data for denominators in label</i>

The sponsor is planning to submit additional information. However, at present, Dr. Podruchny has concluded that these are Complete Response issues. Dr. Podruchny expressed concerns about potential study bias and pointed out that, although the sponsor has described steps taken to minimize bias, bias cannot be ruled out in some of the studies, such as the ones conducted (b) (6)

*CDTL Comment: In my opinion, the financial disclosure information submitted by the sponsor indicates a lack of due diligence. Per FDA Good Clinical Practice Guidance (<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf>), financial information should be documented before the trial starts. This was clearly not done. A separate issue is whether or not significant bias was introduced by investigators who were company employees or by investigators for whom financial disclosure information is unknown. I am not particularly concerned about the coverage and dry time studies, because the sponsor took reasonable measures to minimize bias, and the open-label design was unavoidable due to differences in tint color. Furthermore, it is hard to imagine that bias would result in a significant change in study results (for example, a large change in drying time). In addition, the persistence of efficacy study (EM-05-013509) is not relevant to approval. I am more concerned about the lack of investigator information for the pivotal studies. It is impossible to accurately assess whether the investigators were unbiased and the effect, if any, on efficacy results without further information about each investigator's role in the studies (i.e., number of subjects they studied, role and responsibilities in the study, etc). If this information is available, a sensitivity analysis of pivotal trial results could be done. Regarding safety assessments, it is possible that bias in the open-label studies could have resulted in a better safety profile. However, even in the blinded trials, the incidence*

*of adverse events is low. My concern would be greater if there were a significant safety signal of concern based on drug mechanism of action or based on prior experience with CHG and IPA, but this is not the case. Nevertheless, the sponsor should provide all financial information possible with justification or explanation of any missing information in order to demonstrate due diligence.*

## 12. Labeling

### DMEPA Review

A Label and Labeling Review was conducted by Grace P. Jones, PharmD, BCPS, Division of Medication Error and Analysis (DMEPA). DMEPA observed that the proposed container labels, carton labeling, and information leaflet for SoluPrep follows a similar format as currently marketed DuraPrep. A search was conducted for medication error reports associated with topical preoperative skin preparation products that contain the active ingredients chlorhexidine gluconate, isopropyl alcohol, or contain “prep” in the product name (ChloroPrep, DuraPrep, and Prevantics) to assess for possible postmarketing concerns among similar preoperative preparation products. No postmarketing medication error issues associated with container labels and carton labeling were identified for the currently marketed topical preoperative skin preparation products. Since the proposed labels and labeling for SoluPrep follows the same format as the currently marketed topical preoperative skin preparation products, DMDPA concluded that the proposed labels, labeling, and information leaflet for SoluPrep “are acceptable from a medication error perspective.”

### Labeling Review

In addition, a labeling review was conducted by Michelle Jackson, PhD, IDS Microbiologist, DNDP. The labeling submitted by the sponsor and reviewed by Dr. Jackson is electronically copied and reproduced in **Appendix I** below. Based on her review, Dr. Jackson recommended a Complete Response.

Dr. Jackson noted several deficiencies in the sponsor’s labeling. The major deficiencies are as follows:

1. Dr. Jackson noted 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,” as shown below (electronically copied and reproduced from Dr. Jackson’s review):

### Proposed 10.5-mL Brite Green and Clear

2. The section shown below (electronically copied and reproduced from sponsor's submission) was found to be unacceptable because it is not consistent with class labeling. 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 incorrectly 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.

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

3. In the *Other Information* section shown below (electronically copied and reproduced from Dr. Jackson's review), the statement, "•the tint will slowly fade from the skin. Alcohol may be used to remove the tint if desired," must be removed for the 10.5 mL Clear applicator because there is no tint in the solution; therefore, it is not applicable.

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

4. Additional issues were noted regarding bolding, font size, and barcode.

Therefore, Dr. Jackson recommended the following Complete Response to the sponsor:

### **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.
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.

## **13. Postmarketing Recommendations**

There are several Complete Response issues with this application. Therefore, there are no postmarketing recommendations at present.

## 14. Recommended Comments to the Applicant

I recommend that the following comments be sent to the sponsor in a Complete Response letter. Note that there may be additional comments or editing of existing comments based on further internal discussions. Under Product Quality, I have edited (in track changes), the language proposed by the Product Quality Team, because we would not accept any proposed interim specifications for an interim shelf-life of (b) (4) monthswith an impurity (b) (4) exceeding the ICH limit of  $\leq 1.0\%$ . In addition, at the time of this writing, Dr. Podruchny is completing an addendum to her review on the basis of new financial information disclosure information submitted by the sponsor on April 25, 2016, as a result of which, there may be additional clinical comments (not complete response).

### CLINICAL

1. You have failed to demonstrate replicative efficacy in two pivotal clinical simulation studies, based on the previously agreed upon statistical analyses and primary endpoints. Study **EM-05-012760** (MicroBiotest) passed on all primary efficacy analyses; however, Study **EM-05-013260** (BioScience Laboratories) did not pass the  $\geq 70\%$  responder rate (primary endpoint). Thus, replicative efficacy was demonstrated for the abdominal site, but replicative efficacy was not demonstrated for the inguinal site. We have previously communicated to you (IND 076549, Advice/Information Request, 4-17-15) that your proposed alternative primary efficacy analyses to be conducted in the event that the positive control fails to meet the 70% threshold are not acceptable. Therefore, a repeat study of the inguinal region will be required.
2. Financial disclosure information is not sufficient. Eleven of twenty of the sub investigators listed on the revised 1572 for pivotal study 12760 are missing disclosure information and one in five are missing financial disclosure information in study 13260. Good Clinical Practice Guidance, section 8.2 (<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf>) indicates this information should be documented before the trial starts formally. As you know, financial arrangements between investigators and the sponsor can introduce bias in trial data that may be difficult to evaluate. In addition to the potential impact on efficacy outcome data, this is an issue of study conduct.

In order to evaluate the possible impact on efficacy outcomes, identify how many subjects each sub investigator contributed in each of the named studies. Submit analyses dropping the subjects of all sub investigators without financial disclosure per pivotal trial. Provide datasets for each pivotal trial that allow independent verification of the sensitivity analyses, (i.e. the sub investigator is named for each subject by usubjid in efficacy datasets for each study). As a sub investigator may have participated in more than one trial, for each trial in the NDA indicate whether there is missing sub investigator information, list the missing sub investigator, and provide a listing of all sub investigators in the respective trial. Also, describe your efforts to obtain financial disclosure. Feel free to discuss and provide other strategies you believe may evaluate this issue and to discuss the potential impact on data integrity, especially efficacy data in the pivotal trials.

### NONCLINICAL

Your stability testing detected two impurities which exceed the allowed impurity threshold per FDA guidance and which have not been qualified. We refer you to the meeting minutes from the teleconference held on January 12, 2016 between representatives of your company and the FDA.

In order to resolve this deficiency, you will need to conduct qualification studies for (b) (4) according to the qualification program as stated in ICH Q3B(R2) guidance *Q3B(R2) Impurities in New Drug Products*, which can be found on this link:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf>

## PRODUCT QUALITY

Your proposed limits for two related impurities (b) (4) in the drug product at (b) (4)% exceed ICH Q3B (R2) limits ( $\leq 1\%$ ) and are not acceptable. Based on your quantitative stability data, (b) (4) will reach 1.0% at (b) (4) months, and (b) (4) will exceed 1.0% at (b) (4) months. These degradants continue to rise and accumulate in the drug product throughout the shelf-life. ~~Even though you have proposed interim specifications for an interim shelf life of (b) (4) months, impurity (b) (4) still exceeds the ICH limit of  $\leq 1.0\%$ , we cannot grant it without additional justifications.~~ You will need to conduct qualification studies for (b) (4). Refer to nonclinical comments.

## MICROBIOLOGY

1. The container closure integrity test (CCIT) validation data provided in the submission dated March 10, 2016 demonstrate that the proposed headspace oxygen analysis method has a detection rate of approximately 33% or less for defects that are 50  $\mu\text{m}$  or larger in 10.5 mL drug product (DP) filled ampules. Moreover, you did not detect defects of any size in the 26 ml DP filled ampules. Further, the information presented indicates that your selected test method is only capable of detecting holes of 50  $\mu\text{m}$  or greater, which, per the USP 1207.1 you previously provided, corresponds to an air leak rate of  $> 0.360$  standard cc per second (sccs). Kirsch, et. al. (also referenced in the Parenteral Drug Association's Technical Report 27) demonstrates that a leakage rate that correlates with microbial ingress is approximately  $10^{-5}$  sccs, which is considerably lower than what your results demonstrate. With the low detection rate demonstrated by positive controls, and without further information to correlate your proposed method with the potential for microbial ingress, the method that you propose is not acceptable as a container closure integrity test method. Provide CCIT results from a validated testing method capable of detecting microbial ingress in order to demonstrate the integrity of the proposed container closure system (glass ampules) for the DP.
2. Provide CCIT results for the (b) (4) pouch used to package the DP applicator. Provide a description of methods (and applicable validation information), a description of controls, and a summary of results.

3. Regarding (b) (4) monitoring during production, the December 9, 2015 response (under section Q5) stated that (b) (4)  
(b) (4) Clarify if (b) (4) for the 26.0 mL ampules is the same for the 10.5 mL ampule (b) (4) during commercial production.
4. The information provided for the requalification (RQ) schedule for the (b) (4) (u) (4) ) is acknowledged. However, (b) (4)  
(b) (4) This is not acceptable, (b) (4) Revise (b) (4)  
your SOP to provide a (b) (4)
5. The December 9, 2015 submission stated that two samples from the 46 samples were tested for bioburden, (b) (4) whereas the other 44 samples were taken from ampules that were placed in the stability program. Identify the source of each sample (lot numbers) and please clarify if the 44 samples that were taken from the stability programs were (b) (4)
6. In regard to the bioburden testing per (b) (4) testing method STP00036, address the following concerns:
  - a. Clarify the name of the microorganisms that are used as positive monitors for aerobic bacteria and fungi organisms.
  - b. Clarify any additional rinsing steps (rinse fluid and volume) or neutralization buffers that are used to neutralize the antimicrobial activity of the DP against aerobic bacteria and fungi.
  - c. Provide validation testing data to demonstrate that the STP00036 is capable of recovering aerobic bacteria, fungi, anaerobic bacteria and spores.
7. The information provided in the submission dated August 12, 2015 and November 6, 2015 included validation data for the testing of (b) (4)  
(b) (4) lack clarity, and the report appears to contain discrepancies. Address the following points:
  - a. The significance of the (b) (4) (b) (4) ” procedures described in protocol 201404182 is unclear; further, it is unclear if these were utilized in testing to support the conclusion that the method is validated.



- a. 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.
  - b. 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
  - c. 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
    - a. 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
    - a. 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
    - a. 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).

#### **ADDITIONAL COMMENTS**

We have the following comments/recommendations that are not approvability issues:

## **CLINICAL**

1. For all safety-related proposed labeling statement that are not directly supported by clinical trial data from your development plan, such as conditions of use, “Do Not Use”, pediatric use, and hypersensitivity/anaphylaxis, summarize the literature using only non-product specific literature and provide the literature (or hyperlink to previously submitted literature). If you believe the NDA already separates product-specific literature for each of these areas from non-product specific literature, reference the sections and locations of the NDA and clarify how we can identify the non-product literature without having to check the publication while reading the text summaries.
2. Discuss the drape adhesion study designs as related to real-world use.
3. Describe efforts to minimize or address bias in the small, open-label studies conducted by employees and used to support labeling (e.g. coverage and dry time studies).
4. Submit datasets that correspond to Listings 16.2.8.1 and 16.2.8.2 in the study report for study 13260 such that a comparison of adverse events with and without HEDTA can be verified.
5. The protocol for study 12680 submitted to the NDA on March 15, 2016 in amendment 23 does not appear to contain changes in dwell time noted on page 51/90 (adobe reader page number). Specify which pages of the protocol submitted in amendment 23 contain these changes.
6. Provide a dataset showing adverse events for study 12680 by unique subject id (column variable “usubjid”).

## **CARTON AND CONTAINER LABELING**

7. 10.5 mL Clear Applicator
  - a. 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.

## **Appendix I: Sponsor’s Proposed Labeling**

10 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.**  
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/s/  
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FRANCIS E BECKER  
04/26/2016

**CLINICAL REVIEW**

<b>Application Type</b>	NDA Resubmission after CR
<b>Application Number(s)</b>	208288 SDN 59
<b>Priority or Standard</b>	S
<b>Submit Date(s)</b>	2-09-18
<b>Received Date(s)</b>	2-09-18
<b>PDUFA Goal Date</b>	8-9-18
<b>Division/Office</b>	DNDP/ODE IV
<b>Reviewer Name(s)</b>	Teresa A. Podruchny
<b>Review Completion Date</b>	4-20-18
<b>Established Name</b>	2% w/v chlorhexidine gluconate and 70% isopropyl alcohol
<b>(Proposed) Trade Name</b>	SoluPrep™
<b>Applicant</b>	3M Health Care Business
<b>Formulation(s)</b>	Solution
<b>Dosing Regimen</b>	Single-use
<b>Applicant Proposed Indication(s)/Population(s)</b>	Pre-operative skin preparation
<b>Recommendation on Regulatory Action</b>	Pending review by the Office of Clinical Pharmacology as to the maximal use trial. Otherwise, there are no clinical safety issues in this resubmission that would preclude approval.
<b>Recommended Indication(s)/Population(s)</b> (if applicable)	Adult and pediatric patients ≥ 2 months of age

**Summary:**

This is a resubmission after a Complete Response (CR) and is the second such resubmission. The CR letter, dated September 1, 2017, is based solely on nonclinical deficiencies. There is clinical information in this resubmission as the CR letter included a templated request for a safety update. This document reviews the clinical information in this resubmission. The following paragraphs summarize the clinical review as based on the Sponsor's submission and provide a recommendation on action.

Six new trials have been conducted. [REDACTED] (b) (4) [REDACTED] one is submitted as a maximal use study (MUST), two are related to visibility, and one is a saline challenge. [REDACTED] (b) (4) [REDACTED]

[REDACTED] Per the submission, in the six studies conducted post-NDA resubmission of March 3, 2017, 163 subjects were exposed to the IND product for 15 minutes and up to 100 hours depending on the study design. The Sponsor's response to the CR indicates there have been no significant changes or findings in the safety profile since the resubmission of March 3, 2017.

No patients died in these six trials and there are no reported discontinuations that occurred secondarily to an adverse event. The Sponsor reports a total of four adverse events (rhinitis, upper respiratory infection, dental abscess, and itching). All adverse events are in the study submitted as a maximal use study (MUST), are reported as mild or moderate, and were followed until resolution.

The Sponsor states there has been no new information that suggests a substantial change in the incidence of common but less serious adverse events since the original NDA data.

If approved, the U.S. will be first country to grant marketing approval.

There are no safety findings identified by the Sponsor or presented in this resubmission that preclude approval pending acceptability of CR issues (as these CR issues could represent a safety concern to humans).

**Clinical Safety information submitted:**

- Clinical Overview in module section 2.5 (46 page document)
- Clinical Study Report in section 5.3.3.1 of study EM-05-014226 (MUsT)
- Safety Update Report in section 5.3.5.3 (6 page document)
- Other Study Reports: EM-05-014182, EM-05-014116, EM05-013603

**Review strategy:**

The Clinical Overview mentions the newly conducted pharmacokinetic study (MUsT, Study EM-05-014226) but appears to only summarize safety and efficacy information from trials previously submitted to support efficacy and safety. As these data were previously reviewed, I did not review this Clinical Overview<sup>1</sup>. DNDP determined it was not necessary to request confirmation from the Sponsor that there were no changes to the safety data previously reported in either the initial or previous CR submission.

I reviewed the study reports of the newly conducted IND studies for adverse events and skin irritation scores. For the study EM-05-014226, I also reviewed the vital signs, chemistry and hematology findings, and demographic data. NonIND study reports were not included. DNDP determined it was not necessary to obtain these<sup>2</sup>, indicating there is a long marketing history of drugs with the same active ingredients.

I reviewed the clinical safety information presented in the Safety Update Report section 5.3.3.1.

**Review:**

The Sponsor's table summarizing the six newly conducted studies is duplicated from the submission below. This is followed by a more detailed review of study EM-05-014266 (MUsT) and reviews of the safety of the three (b) (4) studies. Review of the adequacy of the design and conduct of the MUsT and of the pharmacokinetic data is deferred to the Office of Clinical Pharmacology.

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<sup>1</sup> Email communication Dr. Becker to me, 4-9-18 4:00 PM of discussion between Dr. Becker and Dr. Michelle regarding a proposed information request to Sponsor made in email from me to Dr. Becker, 3-29-18 1:23PM

<sup>2</sup> See footnote #1, as well, there was some discussion between Dr. Becker and me

Study EM-05-	Test Location	IND Y/N	Type of Study	N =	Exposure Time	Products Tested	Skin Irritation	Adverse Events (AEs)	Drop Outs
014226	Medpace (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

### Study EM-05-14226- “SoluPrep™ Film-Forming Sterile Surgical Solution Human Pharmacokinetics Maximum Usage Trial to Evaluate Systemic Absorption of Chlorhexidine Gluconate Qualification Level Related Substances”

The study is an open-label prospective study in healthy volunteers with the stated primary objective to evaluate the systemic absorption of the active pharmaceutical ingredient-related degradants for chlorhexidine gluconate (CHG) and topical solution impurities, (b) (4) in a maximal use study (MUST). The study was initiated on November 14, 2017, completed on December 09, 2017, and was conducted at one site in the United States.

Version 1.0 of the protocol, dated October 23, 2017, was amended three times and clarified once.

- A clarification memo dated October 26, 2017 noted inclusion of certain drugs to be tested in the drug of abuse panel at screening, described an approved birth control method for males, and noted conditions for admission of subjects with fake/acrylic nails.
- On November 3 (“administrative revision” #1, with memo dated November 10) 2017, changed that the Medical Dictionary for Regulatory Activities and World Health Organization Drug Dictionary for coding would not be used.
- On November 27, “administrative revision #2” changed how area under the curve plasma concentrations were reported.
- On November 30, 2017, administrative revision #3) allowed re-evaluation of subjects dismissed as screen failures due to insufficient surface area for all four treatment sites.

Subjects were admitted to the study site on Day -1 and had their treatment areas clipped. Study product was administered on Day 1. Blood samples for pharmacokinetic (PK) were collected prior to study drug administration. One 26 mL applicator was applied topically to a surface area mapped to be about 2500 cm<sup>2</sup>. Thus, four 26 mL applicators of 3M SoluPrep were applied topically to about 1550 in<sup>2</sup> (10,000 cm<sup>2</sup>) of the intact skin on the chest/abdomen, upper and lower back, and front and back legs. Product was applied with repeated back-and-forth strokes for two minutes on each treatment area and allowed to dry for three minutes. Applicators were weighed before and after. PK samples were collected. While CHG was not part of the PK variables or statistical analysis, the Sponsor collected CHG data and analyzed it. Subjects remained in-house until the last blood sample was collected at hour 48 post-treatment. Subjects were advised to refrain from showering and vigorous physical activity that might cause sweating and wore loose clothing for the duration with a change of clothes at least once daily.

The safety monitoring was for adverse events, skin irritation (Modified Draize Skin Irritation Scale), physical exam, vital signs, and clinical laboratory assessments (chemistry, hematology, and urinalysis). The schedule for safety measure evaluations is shown below,

Procedure	Screening Days-21 to -2	Admit/clip Day Day -1	Treatment Period			Early Termination Visit
			Day 1	Day 2	Day 3	
Vital Signs	X	X	X	X	X	X
PE	X					X
Symptom based PE		X	X	X	X	
Visual Skin Assessment	X	X	X			
Perform skin irritation rating-prior to study product application and prior to each PK blood draw (2, 4,8, 12, 24, and 48 hours)			X	X	X	X
Safety labs	X	X		X	X	X
Serum pregnancy test	X					
Urine pregnancy test		X				
FSH	X					
HIV, HBV, HCV screen	X					
AE evaluation	X	X	X	X	X	X

Source: CSR for EM-05-014226, p. 27/118, Table 2. Schedule of Procedures, Safety labs were chemistry, hematology, and urinalysis. FSH (=follicle stimulating hormone) was performed on women of non-child bearing potential who were not surgically sterile.

An informed consent was signed by 135 subjects. Twenty-four (24) completed. *Per the study report, 24 subjects were randomized and completed (however, the study is not randomized<sup>3</sup>). About 82% of the consented population was not in the trial. The reason for this is not certain and not provided. One of the*

<sup>3</sup> See Appendix 16.1.7: Randomization Scheme and Codes

*amendments suggests that insufficient area for all four exposure sites may have been contributory, but this is speculative.*

The mean age of the 24 subjects was 36.8 years with a standard deviation (SD) of 10.86 years. Most were male (79.2%) and most were Black or African American (70.8%). The average BMI was in the obese range at 37.55 (SD 5.507).

## **PK**

The study report states that “the PK results suggest there is no systemic absorption of CHG and the active pharmaceutical ingredient-related degradants for CHG, (b) (4)” in the submitted MUsT. The adequacy of this study as a MUsT and conclusions related to PK are deferred to the Office Of Clinical Pharmacology review staff.

## **Safety**

### Adverse events-

Four subjects experienced one adverse event each. The events were rhinitis, upper respiratory infection (URI), dental abscess, and itching. The upper respiratory infection (URI) and dental abscess were rated as moderate and the itching and rhinitis as mild. All events are reported as recovered or resolved<sup>4</sup>. The URI and dental abscess were not treatment emergent<sup>5</sup>. The investigator considered the event of itching related to the study product. There was no drug treatment for the itching<sup>6</sup>. Of the adverse events, the itching on- face seems potentially related and is not unexpected with these products. These events do not alter the safety profile of the product.

### Skin irritation scales-

The Skin Irritation Rating Scale rates events of erythema, edema, rash, and dryness on a scale of zero (0) to three. Zero means no reaction, 1 is mild/and or transient and limited to sensitive area, 2 is moderate and persisting over much of the product-exposed area. Events rated as a level 3 were to be considered adverse events and were considered severe and extending over most, or all, of the product-exposed area.

Listing 14.3.5.1 indicates two pre-dose ratings greater than zero. Both were rated a “1”, were of dryness, were in the same subject<sup>7</sup>, and involved a lower extremity. Otherwise, all pre-dose ratings for edema, rash, and erythema are reported as zero. Per the referenced listing, all 2, 24, and 48 hour ratings are zero (dryness, edema, rash, erythema). At 4, 8, and 12 hours, one subject (b) (6)<sup>8</sup> was rated as “1” for erythema (mild and/or transient). The text in the CSR indicates the grade 1 erythema scores were on the chest/abdomen area. These findings do not alter the safety profile of the product.

### Physical Exam (PE)-

One subject is reported as having a clinically significant PE finding that corresponded with the dental abscess adverse event. Most subjects did not have PE except on screening (based on listing 16.2.9.2). Subject (b) (6) is noted to have had clinically significant dental findings (“several broken teeth, mild

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<sup>4</sup> Adverse Event Listing pdf p.2/2 Listing 16.2.7.1 in module section 5.3.3.1

<sup>5</sup> Listing 16.2.7.1

<sup>6</sup> Listing 16.2.7.1

<sup>7</sup> Listing 16.2.9.5

<sup>8</sup> Listing 16.2.9.5 Other Safety Data:2 pdf, 24 and 48-hour post dose are zero on all parameters.

tenderness to left lower jaw and gum area”) on Days 2 and 3, dates 12-01 and 12-02. These dental findings are unlikely related to the use of this product.

#### Vital Signs (VS)-

Based on Listing 16.2.9.1, subject (b) (6) experienced increased blood pressures compared to screening (114/78 on 11-27-17) on Day -1 (133/85 on 11-29-17) and on treatment (107-157/90-114)<sup>9</sup>. Treatment dates blood pressure measures were 11-30, 12-01, 12-02. This subject had dental abscess recorded as an adverse event beginning on 11-29 and through 12-11<sup>10</sup>. The dental abscess (e.g. pain) may have been contributory to the increase blood pressure. There is not an obvious trend to higher blood pressures in the data and the results are non-contributory.

#### Laboratory Measures-

The Sponsor summarized that in general, no clinically meaningful changes were observed in laboratory parameters. Further, all abnormal values were considered not clinically significant by the Investigator because there were no accompanying clinical symptoms or signs and that such values were able to explained by diet, hydration, and activity levels.

Chemistry- 16 parameter chemistry panel (ALT, Albumin, ALP, AST, bilirubin, Ca, CO<sub>2</sub>, Cl, CK, Cr, est GFR, Glucose, Phosphate, K, Protein, and Na)<sup>11</sup> was obtained at screening, Day -1, Day 2, and Day 3. There were no obvious clinically negative trends in laboratory results based on review of the listing of chemistry data. Datasets were not provided.

Hematology labs were collected on the same days as chemistry labs and included RBC, WBC, differential, Hemoglobin and hematocrit, and platelets. There were no obvious trends related to treatment.

Urinalysis-There were abnormal values but no obvious consistent trends.

This is a small study with no placebo group. Data are of limited interpretation. There are no obvious signals in the laboratory data.

#### **Review of other study reports:**

##### **Visibility studies:**

Studies EM-05-01482 and EM- 05-014116 were visibility studies that enrolled twelve and nine healthy male subjects respectively. The studies were started and completed within a few days. Study EM-05-01482 was conducted from July 17, 2017 to July 19, 2017 and study EM-05-014116 was conducted from May 2, 2017 to May 4, 2017 (last completed). Both study reports indicate that individual involvement was noted as 3 hours or up to 3 hours and exposure time as about two hours for each subject. Safety was assessed in both studies by the incidence of adverse events and skin irritation observation at the test site 30 minutes after the prep was removed.

The study reports of each study state there were no adverse events reported during the study, no clinical laboratory data were collected, and no vital signs or physical examinations were planned or performed. Skin irritation scores at the test sites were assessed 30 min after the test products were removed (with 70% isopropyl alcohol and gauze) in both visibility studies and were evaluated using the

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<sup>9</sup> Listing 16.2.9.1

<sup>10</sup> Listing 16.2.7.1

<sup>11</sup> Listing 16.2.8.1

Modified Draize scale. Both study reports state that “No skin irritation scores were reported.” No listings or datasets of the skin irritation scores are provided for either study (which precluded review of per subject data information).

Visibility results are summarized by the Sponsor for Study EM-05-014182 as follows.

- SoluPrep FF and ChloroPrep were both judged to be easy to see on light and medium skin tones.
- SoluPrep FF was not judged easier to see than ChloroPrep on light or medium skin tones.

For study EM-05-014116, visibility results are summarized by the Sponsor as,

- SoluPrep FF Tints A and B are easy to see on dark skin tones while ChloroPrep Tint was judged difficult to see on dark skin tones.
- SoluPrep FF Tints A and B were judged easier to see than ChloroPrep tint on dark skin tones.
- SoluPrep FF Tint A was judged as easy to see as SoluPrep FF Tint B on dark skin tones.

#### **Saline Challenge-**

Study EM-05-013603 employed the 3M IND product and ChloroPrep after repeat exposure to saline and wiping with the objective of evaluating the film-forming attribute of the product compared to ChloroPrep. High Performance Liquid Chromatography was used to measure chlorhexidine gluconate (CHG). The study was completed in about 9 days (the first subject was consented on April 12, 2017 and the last completed on April 20, 2017). Twenty-one healthy subjects were exposed to study products about 15-30 minutes. Each subject was exposed to both study products, one in each test area (upper and lower back). Safety was based on the incidence of adverse events reported and skin irritation assessments. Skin irritation was evaluated using a modified Draize scale prior to product application and again at 10 minutes after product application just before collecting the pre-challenge CHG samples. No clinical laboratory data, vital signs, or physical examinations were collected/performed. Per the study report, no adverse events were reported and “No skin irritation scores were reported.” This is consistent with a listing of skin irritation scores per subject found in the study report<sup>12</sup> for which all results are “no reaction”.

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<sup>12</sup> Pages 47-56 of the CSR for study EM-05-013603

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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.**  
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/s/  
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TERESA A PODRUCHNY  
04/20/2018

FRANCIS E BECKER  
04/20/2018



## MEMORANDUM

Date: 6-APR-2016

From: Gary Chiang, MD, MPH Clinical Reviewer, DDDP

Through: David Kettl, MD, Clinical Team Lead, DDDP  
Felecia Wilson, RPM, DDDP

To: Celia Peacock, RPM, DNDP  
Teresa Podruchny, MD, Clinical Reviewer, DNDP

Cc: Kendall Marcus, MD, Director DDDP  
Theresa Michele, MD, Director DNDP

Re: Consult #1676, **NDA 208288** SoluPrep Sterile Surgical Solution  
(2%CHG/70%IPA) by 3M Health Care (Infection Prevention Division)

### Materials Reviewed:

- DNDP Consult Request
- Pre-NDA meeting minutes for IND 76549
- NDA 208288 submission package
- Draft Guidance for Industry: *Human Dermal Safety Testing for Topical Drug Products*
- Pre-IND meeting minutes for IND 76549

### Background:

Chlorhexidine Gluconate (CHG)/Isopropyl Alcohol (IPA) Film-Forming Sterile Preoperative Skin Preparation (#M CHG/IPA Prep) is a antimicrobial skin preparation containing 2 active ingredients, 2% weight/volume (w/v) CHG and 70% volume/volume (v/v) IPA, in combination with an acrylate copolymer, (b) (4). The proposed use is to pre-treat the skin around the surgical site prior to surgery to reduce skin flora colony counts and therefore reduce the surgical site infection risk.

Current New Drug Application (NDA) surgical prep products on the market include: ChloraPrep® Patient Preoperative Skin Preparation (ChloraPrep), 3M™ DuraPrep™ Surgical Solution (DuraPrep™), Prevantics® (formerly Chlorascrub™), Sage® CHG Cloths, and Hibiclens®.

The Division (DDDP) was asked to provide comments for the Pre-IND 76549 meeting 4-JUN-2013. The sponsor provided dermal safety protocols for the Agency to review. The Division (DDDP) completed the “Cumulative Irritation Patch Test” protocol on 4-DEC-2014. The sponsor then met with the Agency for the Pre-NDA meeting on 20-JAN-2015. It was noted at the meeting that in the HRIPT/HCIPT study that the result category for both the positive control and the negative control were as expected and the result category for the 3M investigational products, both colorless and tinted, were also as expected as both CHG and IPA are known irritants. However, ChloroPrep resulted in a lower CIT score than the negative control, which is atypical and unexpected.

The Division evaluated the results for the HRIPT/HCIPT provided by the sponsor and commented that:

*“Given the marketing history of ChloroPrep, we do not recommend that a repeat cumulative irritation study be conducted given the information provided. There is no discussion in the briefing document, however, regarding any explanation for the low CIT score for ChloroPrep and whether an evaluation for issues with conduct of the study was undertaken or discovered. In your application, include a discussion of your analysis of the study results and provide an explanation as to why this atypical result occurred, and whether this result has implications for interpretation of other irritation trial results, as well as any implications for eventual product labeling. Your application may include references to dermal safety studies previously conducted with this product to support any recommendations for labeling.”*

The current submission is the NDA application for approval. The Division of Dermatology and Dental Products will review the three dermal safety studies and participate in labeling.

**Review:**

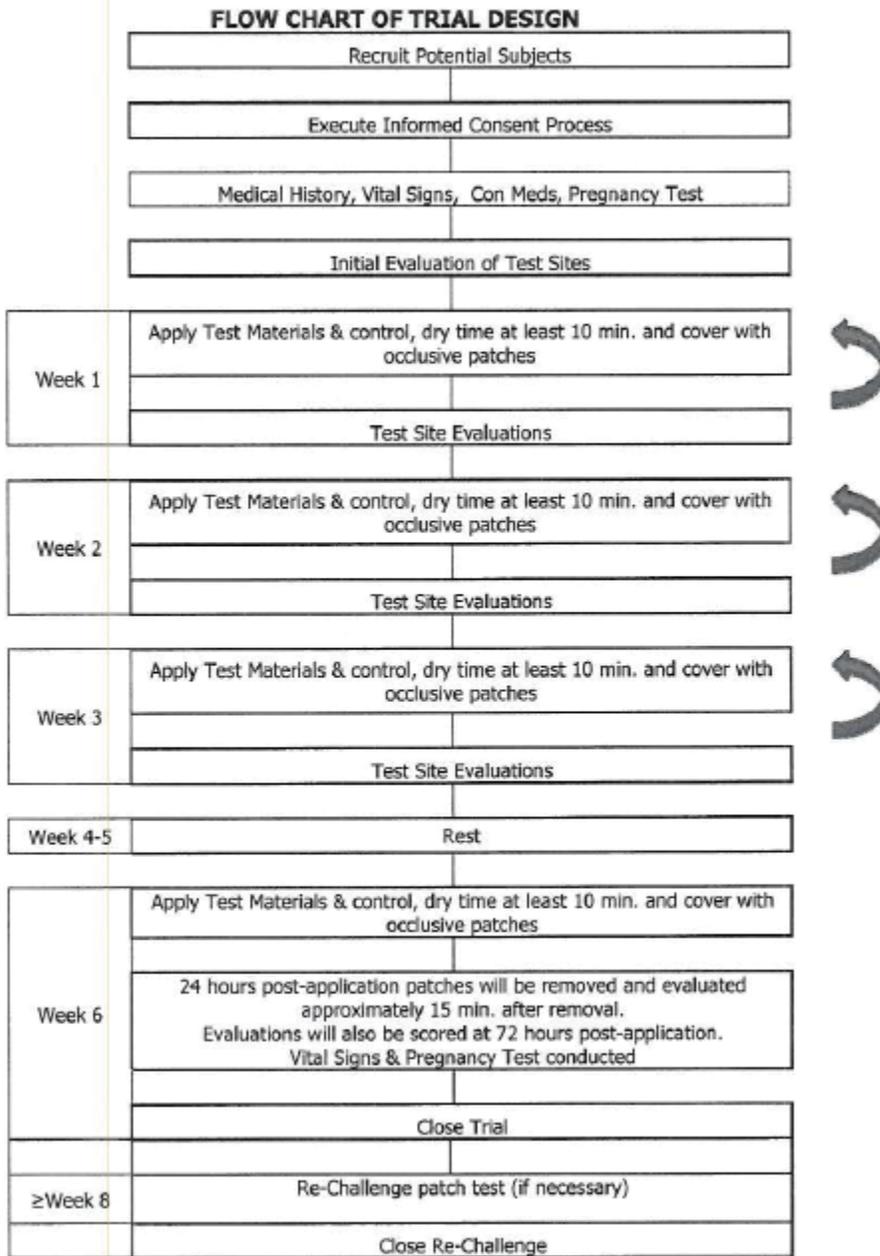
**Title:** Cumulative Irritation Patch Test 21-day with Challenge of 3M CHG-IPA Film Forming Skin Prep Colorless and Tint Marketed Active Control Positive Control and Negative Control.

<b>Sponsor</b>	3M HealthCare, Infection Prevention Division	
<b>Investigational Products</b>	MTDID 25415 3M CHG/IPA Film-forming Skin Prep Colorless Lot# CLIN C  MTDID 25415 3M CHG/IPA Film-forming Skin Prep with Tint Lot # CLIN D  ChloroPrep® with Tint Hi Lite Orange 26 mL Lot: 62910 Exp. 04/2016 (marketed active control)	
<b>Name of Active Ingredients</b>	2% w/v Chlorhexidine Gluconate (CHG) with 70% Isopropanol (IPA)	
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  EM-05-012853 IND 76,549		
<b>Principal Investigator</b>	Michael Caswell, Ph.D., CCRA, CCRC	
<b>Testing Facility</b>	Consumer Product Testing Company, Inc. 70 New Dutch Lane Fairfield NJ 07004 (973) 808-7111	
<b>3M Medical Monitor</b>	Michelle Hulse Stevens, MD 3M Health Care 3M Center Building, 270-4N-01 St. Paul MN 55144-1000 (651) 733-3600	
<b>First Subject's Enrollment Date:</b>	October 14, 2013	<b>Last Subject's Last Observation Date:</b>
		December 10, 2013
<b>Clinical Phase/Study Type:</b>	Phase I/Cumulative Irritation Test with Challenge Safety	<b>Protocol Date:</b>
		September 11, 2013

**Objective:**

The primary objective is to determine, by repetitive epidermal contact, the primary or cumulative irritation potential of the test materials compared to the positive control.

The secondary objective is to determine the allergic contact sensitization potential of the test material compared to a marketed active control.



**Study Plan:**

This is a single site, open-label, randomized study of testing materials. Testing materials will be applied under occlusive dressings. The study is described in the flow chart above.

**Safety:**

Safety was evaluated by any adverse events associated with exposure to the test materials.

**Results:**

A total of 235 subjects were enrolled in the study; of these subjects, 234 received at least 1 treatment, and 205 completed the study and had evaluable data. For the 30 subjects who discontinued from the study, the reasons for discontinuation included withdrawal of consent (23

subjects), AEs (6 subjects: 1 with inflammation, edema, burning, contact dermatitis, and skin infection; 1 with erythema and edema; 1 with rash; 1 with allergic reaction; 1 with a urinary tract infection; 1 with sinusitis), and protocol deviation (1 subject). The mean age of evaluable subjects was 46 years, there were approximately 71% women and 29% men, and the main races/ethnicities were approximately 42% white, 37% Hispanic, 18% black, and 3% other.

***Reviewer’s comment: No further discussion was provided for subjects that withdrew consent. This is not unusual for these types of trials; therefore, these subjects are not followed.***

The summary cumulative irritation scores for all materials tested are provided in the **Table 1**. The result category for both the positive control and the negative control were as expected and the result category for the 3M investigational products, both colorless and tinted, were also as expected as both CHG and IPA are known irritants.

ChloroPrep resulted in a lower CIT score than the negative control, which is atypical and unexpected.

**Table 1: Summary of Cumulative Irritation (CIT) Scores**

<b>CIT Score</b>	<b>Indications from Test</b>	<b>Description of Responses</b>	<b>Treatment Group Result (all subjects)</b>
<b>0 to 723</b>	Mild material – no experimental irritation	Essentially no evidence of cumulative irritation under conditions of use	<b>ChloroPrep (70.0)</b> <b>Negative control (195.5)</b>
<b>724 to 2939</b>	Probably mild in normal use	Evidence of slight potential for very mild cumulative irritation under conditions of use	3M colorless (1899.5) 3M tinted (2060.0)
<b>2940 to 6610</b>	Possibly mild in normal use	Evidence of moderate potential for mild cumulative irritation under conditions of use	
<b>6611 to 8538</b>	Experimental irritant	Evidence for strong potential for mild-to-moderate primary or cumulative irritation under conditions of use	Positive control (6679.0)
<b>8539 to 9270</b>	Experimental irritant	Evidence of strong potential for moderate-to-marked primary cumulative irritation under conditions of use	

Source: Adapted from Sponsor’s submission of Final Report

There were 14 adverse events among 9 subjects and no serious adverse events during the clinical trial. Investigators judged 5 adverse events to be mild in severity and 9 adverse events to be moderate in severity. Investigators judged 7 adverse events to be unlikely related to any investigational material and 7 adverse events to be related to any investigational material.

**Table 2: Adverse Events in HRIPT/HCIPT**

<b>Adverse Event*</b>	<b>N (%)</b>
Number of Subjects Enrolled	235
Number of Subjects with Adverse Events	9(3.8%)
Number of Subjects without Adverse Events	226 (96.2%)
<b>Skin &amp; Subcutaneous Tissue Disorders</b>	
Allergic reaction on Abdomen	1(0.4%)
Burning	1(0.4%)
Contact Dermatitis	1(0.4%)
Edema	2(0.9%)
Erythema	1(0.4%)
Inflammation	1(0.4%)
Rash on Torso	1(0.4%)
<b>Infections &amp; Infestations</b>	
Skin Infection	1(0.4%)
Ear Infection	1(0.4%)
Urinary Tract Infection	1(0.4%)
Sinusitis	1(0.4%)
<b>General Disorders</b>	
Malaise	1(0.4%)
<b>Vascular Disorders</b>	
Hypertension	1(0.4%)

Source: Sponsor submission of Final Report EM-05-012853-13-162

**Discussion:**

The discrepancy due to the atypically low CIT score for ChloroPrep (an irritant due to CHG and IPA) in the study required explanation. A review of the conduct of the study at this experienced laboratory did not reveal any issues, and there were no significant protocol departures that would explain the results. The sponsor proposed:

*“After a review of the study methodology, the difference in product application of the investigational materials (two 3M CHG/IPA Prep products and ChloroPrep) may have had an impact on the lower than expected results for ChloroPrep.”*

**Reviewer’s comment:** *The sponsor’s analysis appears acceptable. The Division does not recommend repeating the cumulative irritation study. The 3M product should be labeled as an irritant due to the CHG and IPA active ingredients. Clinical trial safety evaluation is discussed in a later section.*

**Title:** Clinical Evaluation to Assess the Phototoxicity Potential of Topically Applied 3M CHG/IPA Film-Forming Skin Prep and a Marketed Active Control (EM-05-012952).

**Objective:**

The primary objective is determination “by epidermal contact followed by UV irradiation, the phototoxicity potential of a test material when applied to human subjects.”

**Test Materials:**

<u>Sponsor ID</u>	<u>Description</u>	
3M CHG/IPA	film-forming skin prep colorless	Lot # CLIN C
3M CHG/IPA Tint	film-forming skin prep with tint	Lot # CLIN D
ChloroPrep® with tint	(marketed active control)	

**Study Plan:**

At least 30 subjects were planned for the trial. This is a single-site, open-label, randomized test site trial. A single-port xenon arc solar simulator will be used as the source of the UV radiation. Determination of minimal erythema dose (MED) for each subject is by a sequence of timed UV exposures to full spectrum UV, graduated in 25% increments, to adjacent 1 cm circular sites on the skin of the back. Approximately 24 hours after irradiation, test sites are evaluated for erythema with the following scale:

- 0 = No visible skin reaction
- 0.5 = Barely perceptible or spotty erythema
- 1 = Mild erythema covering most of the test site with clearly defined borders
- 2 = Moderate erythema, possible presence of mild edema
- 3 = Marked erythema, possible edema
- 4 = Severe erythema, possible edema, vesiculation, bullae and/or ulceration

**Safety:**

Each subject will be monitored for the development of any AEs.

**Results:**

All scores ranged from 0 (no visible skin reaction) to 1 (mild erythema covering most of the test site) on all test sites at all post-treatment time points. All irradiated groups, including the untreated sites, had 2 evaluations with a score of 1, 14 to 20 evaluations with a score of 0.5 (barely perceptible or spotty erythema), and 89 to 95 evaluations with a score of 0. In the non-irradiated groups, 1 evaluation in the tinted 3M CHG/IPA Prep group and 1 evaluation in the colorless 3M CHG/IPA Prep group had a score of 1, 2 to 5 evaluations in each group had a score of 0.5, and all other evaluations (105 to 109) had a score of 0. As all evaluations remained within the normal limits at all-time points, there was no indication of phototoxicity in any of the treatment groups.

**Table 3: Evaluations from the 3 Post-treatment Time Points**

Skin Reaction Evaluation Score, n	Treatment							
	3M CHG/IPA Prep, colorless		3M CHG/IPA Prep, tinted		ChloraPrep, tinted		Untreated	
	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated
0	89	106	95	105	95	108	89	109
0.5	20	4	14	5	14	3	20	2
1	2	1	2	1	2	0	2	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloraPrep=ChloraPrep® Patient Preoperative Skin Preparation; CSR=clinical study report

**Notes:**

Skin reaction evaluation scale: 0=no visible skin reaction; 0.5=barely perceptible or spotty erythema; 1=mild erythema covering most of the test site; 2=moderate erythema, possible presence of mild edema; 3=marked erythema, possible edema; 4=severe erythema, possible edema, vesiculation, bullae, and/or ulceration

Number of evaluations for each treatment: 37 subjects x 3 post-treatment evaluation time points (24 hours post-treatment, 24 hours post-irradiation, and 48 hours post-irradiation) = 111 evaluations

Source: CSR for Study EM-05-012952 in Module 5.3.5

**Reviewer's comment:** Sufficient numbers of subjects are exposed with minimal reaction score. This reviewer agrees that there was no indication of phototoxicity in the treatment groups which needs to be captured in product labeling.

**Title:** Clinical Evaluation of Photoallergy Potential EM-05-013062).

**Objective:**

The primary objective is to determine by repetitive epidermal contact and UV irradiation, the photoallergic potential of a test material when applied to human subjects.

The secondary objective is to determine the contact and UV radiation of a photo-irritant potential of the test material

**Test Materials:**

3M CHG/IPA	film-forming skin prep colorless	Lot # CLIN C
3M CHG/IPA Tint	film-forming skin prep with tint	Lot # CLIN D
ChloraPrep® with tint	(marketed active control)	

**Study Plan:**

At least 45 subjects planned for the trial. This is a single-site, open-label, randomized test site trial. A single port xenon arc solar simulator will be used as the source of UV radiation. The determination of minimal erythema dose (MED) will be identical to the study described for phototoxicity above. There will be an induction phase and a challenge phase to this protocol. Subsequently, in the event of a significant reaction occurring during the challenge phase, the investigator may schedule a re-challenge patch test for confirmatory purposes.

**Safety:**

Each subject will be carefully monitored for the development of AEs.

**Results:**

**Table 4: Evaluations from Post-Treatment Time Points in Each Skin Reaction Evaluation Score Category, by Phase and by Treated and Untreated Sites with and Without Irradiation**

Skin Reaction Evaluation Score, n	Treatment (N=50)							
	3M CHG/IPA Prep, colorless		3M CHG/IPA Prep, tinted		ChloroPrep, tinted		Untreated	
	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated	Irradiated	Non-Irradiated
<b>Induction Phase<sup>a</sup></b>								
0	395	697	371	692	410	694	NA	NA
0.5	191	12	210	15	208	11	NA	NA
1	119	2	124	1	92	6	NA	NA
2	6	0	3	3	1	0	NA	NA
3	0	0	2 <sup>b</sup>	0	0	0	NA	NA
4	0	0	1 <sup>b</sup>	0	0	0	NA	NA
<b>Challenge Phase<sup>a</sup></b>								
0	192	200	191	200	190	200	193	200
0.5	8	0	9	0	10	0	7	0
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloroPrep=ChloroPrep® Patient Preoperative Skin Preparation; CSR=clinical study report; NA=not applicable

Note: Skin reaction evaluation scale: 0=no visible skin reaction; 0.5=barely perceptible or spotty erythema; 1=mild erythema covering most of the test site; 2=moderate erythema, possible presence of mild edema; 3=marked erythema, possible edema; 4=severe erythema, possible edema, vesiculation, bullae, and/or ulceration

<sup>a</sup>For the induction phase, the maximum number of evaluations for each treatment was 711 evaluations. For the challenge phase, the maximum number of evaluations for each treatment was 200 evaluations.

<sup>b</sup>One subject experienced a tape reaction to the occlusive bandage, which spread to the test site, raising scores to 4 (1 evaluation) and 3 (2 evaluations).

Source: CSR for Study EM-05-013062 in Module 5.3.5

Induction phase skin reaction scores for the 50 evaluable subjects ranged from 0 (no visible skin reaction) to 4 (severe erythema, possible edema, vesiculation, bullae and/or ulceration) for the treated, irradiated sites, and from 0 to 2 (moderate erythema, possible presence of mild edema) for the treated, non-irradiated sites at all post-treatment time points. However, excluding 1 subject who had a tape reaction (from the occlusive patch) that spread onto the test sites, scores for the treated, irradiated sites ranged from 0 to 2.

Challenge phase scores for evaluable subjects ranged from 0 to 0.5 (barely perceptible or spotty erythema) on the treated and untreated, irradiated test sites; and were 0 on all treated and untreated, non-irradiated test sites at all post-treatment time points.

The applicant conclusion is that, under the conditions of this study, 3M CHG/IPA (tinted and colorless) and the marketed active control (ChloroPrep) did not induce a response indicative of irritant contact dermatitis, allergic contact dermatitis, photoallergic contact dermatitis, or phototoxic contact dermatitis.

**Reviewer's comment:** *Sufficient numbers of subjects are exposed for this study. This reviewer agrees that the drug product did not induce a skin response indicative of irritant contact dermatitis, allergic contact dermatitis, photoallergic contact dermatitis, or phototoxic contact dermatitis.*

### Clinical Trials:

This reviewer evaluated the dermal safety events in the pivotal clinical trials (EM-05-012760 and EM-05-012759). No skin irritation score higher than 1 (mild) was reported for erythema, edema, rash, or dryness and the incidence of mild skin irritation was low (<4%).

In Study EM-05-013260, a total of 2 subjects had moderate reactions on the abdomen at 6 hours post-prep (moderate erythema and moderate dryness, respectively); all other skin reactions on both body regions were mild. At 10 minutes post-prep, the highest incidence of any skin

reaction in either body region was mild erythema on the inguinal region in 2.0% of subjects in the ChloroPrep group. At 6 hours post-prep, the most commonly reported reaction on the abdomen was mild erythema, in 9.3%, 9.6%, 4.3%, and 5.8% of subjects in the 3M CHG/IPA Prep, 3M CHG/IPA Prep with HEDTA, ChloroPrep, and saline groups, respectively.

On the inguinal region, the most commonly reported reactions were mild erythema and mild rash at 6 hours post-prep, in 6.3% and 5.0% of subjects in the 3M CHG/IPA Prep group; in 9.8% and 5.3% in the 3M CHG/IPA Prep with HEDTA group; in 4.8% and 7.7% in the ChloroPrep group; and in 2.7% and 10.8% in the saline group.

***Reviewer's comment:** Determination of safety under actual use conditions are assessed in the clinical trials. Sufficient safety information was collected in the pivotal clinical trials to supplement the odd results from the Cumulative Irritation Testing. This reviewer does not recommend a repeat of the CIT in light of the clinical trial safety results.*

**Conclusions:**

The applicant has provided sufficient dermal safety evaluations to satisfy provocative dermal safety testing recommendations typically provided by DDDP. Chlorhexidine Gluconate (CHG)/Isopropyl Alcohol (IPA) products are known irritants and labeling should typically note this effect. The Division of Dermatology and Dental Products has identified no issues from our perspective which would affect approval based on the dermal safety data provided by the applicant.

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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.**  
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/s/  
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GARY T CHIANG  
04/06/2016

DAVID L KETTL  
04/06/2016

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208288
Priority or Standard	Standard
Submit Date(s)	7-06-15
Received Date(s)	
PDUFA Goal Date	5-6-16
Division / Office	CDER/OND/DNDP
Reviewer Name(s)	Teresa A. Podruchny
Review Completion Date	3-22-16
Established Name	2%w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
(Proposed) Trade Name	SoluPrep™™
Therapeutic Class	Antiseptic
Applicant	3M Health Care Business
Formulation(s)	Solution
Dosing Regimen	Single use
Indication(s)	Pre-operative skin preparation
Intended Population(s)	Adult and pediatric patients ≥ 2 months of age

Template Version: March 6, 2009

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NDA 208288  
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and 70% (v/v) Isopropyl Alcohol

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

My recommendation is limited in that it is based on the data I reviewed and I did not review all critical data (such as the pivotal efficacy studies or the safety challenge studies). Therefore, I do not make an overall recommendation.

My review did not lead to safety findings that would preclude approval unless the different formulations/formulation redesigns used in the development program prohibit support of the safety data that resulted from studies that did not use the final to-be-marketed formulation. Most studies were not conducted with the final to-be-marketed formulation (i.e. with HEDTA but this seems unlikely to be an issue). I defer to the appropriate review disciplines for those determinations. There is some small suggestion of possible differences in the adverse events between the product with HEDTA and that without HEDTA. There are limitations to the studies I reviewed to include that many are small in number and open-label.

The active antiseptic ingredients have been marketed for many years and there appears to be an assumption that the safety profile is relatively well known in terms of major safety issues. As well, the unique features of this product that led to the NDA (versus perhaps an ANDA) are the sterility of the solution and the applicator. It was not, as I understand it, due to the ingredients in the applicator. The literature seems to contain some (maybe few) product specific references for support for areas that are not covered by clinical trial data with this specific product, however similar products are marketed.

I recommend the Division ask the sponsor to provide, as a non-Complete Response issue, discussion/presentation of the support for safety-related areas of labeling that are not supported by trial data, such as conditions of use and non-use. This presentation should not include or be based on literature that is product specific.

### 1.2 Risk Benefit Assessment

I have concerns about the efficacy based on internal discussions and my preparatory work for this NDA. However, I defer a risk – benefit assessment due to lack of full evaluation of the efficacy data and lack of complete review of the safety data.

I did not review the pivotal efficacy data. Review of efficacy is performed by a DNDP microbiology reviewer, Dr. M. Jackson. My review of efficacy was limited to the two drape adhesion studies. These studies are not that large and at least one was open-label. Additionally, I am not sure how closely the design of the drape adhesion studies

mimic real world use and conditions. Some of the other non-drape adhesion, non-pivotal studies are also small in number and open-label. The product seems not easy to remove. The sponsor reported no adverse events secondary to this. Drape adhesion seems somewhat marginal when compared to other products.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

### **1.4 Recommendations for Postmarket Requirements and Commitments**

Consider pediatric studies

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

SoluPrep™ Film-forming Sterile Surgical Solution is 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA) with a film-forming copolymer and other ingredients proposed as an antiseptic for use as a patient preoperative skin preparation.

CHG is a biguanide biocide that targets the bacterial cell wall at low concentrations and the cytoplasmic membrane at higher concentrations<sup>1</sup>. CHG has no activity against spores or mycobacteria. CHG is cationic and binds to skin, mucosa, and other tissues. It is poorly absorbed through intact, adult skin. The antibacterial activity of CHG depends on the positively charged molecule to bind to stratum corneum. Antibacterial actions possibly may be inactivated by negatively charged substances that are found in some hand lotions or creams.

Alcohol is added for immediate bactericidal and viral inactivation. Aqueous products of only CHG rely on a cumulative effect.

### **2.2 Tables of Currently Available Treatments for Proposed Indications**

Antiseptic products are indicated for patient preoperative skin preparations, healthcare personnel handwash, surgical hand scrub, and as general skin and/or wound cleansers.

There are multiple products approved through the NDA process or marketed via the monograph system as patient preoperative skin preparations. In May, 2015 proposed

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<sup>1</sup> Medscape, assessed online 11-19-15, Chlorhexidine in Healthcare: Your Questions Answered, Laura A. Stokowski, RN, MS.

changes to the 1994 proposed Tentative Final Monograph (TFM) for over-the-counter (OTC) antiseptic drug products<sup>2</sup> were published. The May 2015 proposed amendment to the 1994 TFM proposes that additional safety data are necessary to support the safety of antiseptic active ingredients for use by health care professionals. FDA also proposes that all health care antiseptic active ingredients have in vitro data characterizing the ingredient's antimicrobial properties and in vivo clinical simulation studies meeting specified criteria of log reductions in bacterial counts. The interested reader is referred to the Federal Register for additional background on the complex topic of safety and efficacy evaluations of OTC antiseptics.

The 1994 proposed TFM for OTC antiseptic drugs allows marketing of multiple ingredients, including alcohol (60% to 90%), benzalkonium chloride, benzethonium chloride, chloroxylenol, iodine tincture USP, iodine topical solution U.S.P, povidone-iodine (5% to 10%), and isopropyl alcohol as preoperative skin preparations.

The table below is limited to NDA OTC products with an indication of pre-operative skin preparation, which is the claim sought for this product.

**Table 1 NDA OTC Preoperative Skin Preparations**

<b>Brand Name</b>	<b>Active Ingredients</b>
Chloraprep Triple Swabstick (swab)	
Chloraprep Single Swabstick (swab)	2% CHG, 70% IPA
Chloraprep One-Step Sponge (1 mL, a 3mL, & a 10.5mL)	2% CHG, 70% IPA
Chloraprep One-Step SEPP Swab	2% CHG, 70% IPA
Chloraprep One-Step FREPP Sponge	2% CHG, 70% IPA
Chloraprep One-Step Sponge (yellow dye)	2% CHG, 70% IPA
Chloraprep One-Step Sponge (green dye)	2% CHG, 70% IPA
Prevantics Swab ( <i>previously Chlorascrub</i> ) Prevantics Swabstick ( <i>previously Chlorascrub</i> ) Prevantics Maxi Swabstick ( <i>previously Chlorascrub</i> )	3.15 % CHG, 70% IPA
2% Chlorhexidine Gluconate Cloths (Sage)	2% CHG
Dyna-Hex Solution ( <i>previously Exidine</i> )	2% CHG

<sup>2</sup> Federal Register, Vol. 80, No. 84, Friday, May 01, 2015, Department of Health and Human Services, FDA. 21 CFR Part 310. Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record.

Dyna-Hex Solution ( <i>previously Exidine</i> )	4% CHG
HibiClens Solution	4% CHG
MicroDerm Solution	0.75% CHG
Hibitane Tincture Solution	0.5% CHG
Duraprep Surgical Scrub Sponge	Iodine Povacrylex/74% IPA
EZ-Prep Solution*	10% PV-I
Avagard Solution	1% CHG, 61% ETOH
EZ-Scrub Sponge	450 mg HEX
Pre-OP II Sponge and Pre-OP Sponge	450 mg HEX

Data source: Medical Officer's Resource, Safety Review Information on Topical Antiseptics INDs/NDAs, M.M. Jackson, Ph.D. \*=monograph (withdrawal). CHG=chlorhexidine gluconate, IPA=isopropyl alcohol

### 2.3 Availability of Proposed Active Ingredient in the United States

Both active ingredients are available in the U.S. The polymer was deemed by FDA to not be a novel excipient and therefore to not require qualification.<sup>3</sup>

### 2.4 Important Safety Issues With Consideration to Related Drugs

Safety issues with related drugs are generally related to skin irritation, circumstances of use, hypersensitivity reactions, and fire risk. These are discussed more below.

As the sponsor notes in the Clinical Summary of Safety (CSS), it is widely believed that chlorhexidine is minimally or not absorbed through intact, mature skin.<sup>4</sup> Presumably due to differences in skin thickness and function in young neonates and premature infants when compared to older infants and adults, absorption of chlorhexidine has been reported in premature infants, younger gestational ages, and low-birth weight neonates. This is discussed later in this review. Severe burns have been reported with alcohol based chlorhexidine and after use of alcohol-based antiseptics in younger infants.<sup>5</sup> Current labeling for antiseptic products like Avagard contains label language to use with care in premature infants or infants less than 2 months old noting that the products may cause irritation or chemical burns.

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3 Remove Clinical Hold letter, IND 76549, signature date 6-29-12, DARRTS reference ID: 3153117.

4 CSS provided references for a similar statement made in the CSS, a) Case DE. Chlorhexidine. Attempts to detect percutaneous absorption in man. In: Newsom SWB, Caldwell ADS, eds. Problems in the Control of Hospital Infection. London: Royal Society of Medicine International Congress and Symposium Series, No. 23. London:RSM/Academic Press, 1980: 39-43, and b) Karpanen TJ. Worthington T, Conway BR, et al. Penetration of chlorhexidine into human skin. Antimicrob Agents Chemother. 2008;52:3633-3636.

5 CSS provided references the following publications, respectively, Reynolds PR, Banerjee S, Meek, JH. Alcohol burns in extremely low birth weight infants: still occurring. Arch Dis Child Fetal Neonatal Ed 2005;90:10 and Watkins AMC, Keogh EJ. Alcohol burns in the neonate. J Paediatr Child Health. 1992;28:306-308.

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Mancini<sup>6</sup> reports that many topical agents have been associated with systemic toxicity including alcohol and iodine-containing compounds. Transient hypothyroidism has been reported with short term and long term iodine exposure in premature infants<sup>7</sup>. The CSS included a report of a case of transient hypochloremia in a 29 week old who had been exposed to body cleansing with 2% chlorhexidine-gluconate body wash.<sup>8</sup>

ChloraPrep (2% CHG/70% IPA) carries warnings as a “Do not use” for allergy to either product, for lumbar puncture or meningeal contact, and on open wounds or as a general skin cleanser. Labeling also notes that the product might cause serious or permanent injury if permitted to enter and remain and warns to keep out of eyes, ears, and mouth. Irritation, sensitization, and allergic reactions are in the Warnings, as “Stop use and ask a doctor if”. Skin irritation can occur with use.

Hypersensitivity reactions including anaphylaxis have been reported with chlorhexidine containing compounds. On March 11, 1998, FDA issued a “Dear Health Care Professional’ letter for the potential for serious hypersensitivity reactions to chlorhexidine-impregnated medical devices. This alert notes that anaphylactoid and other reactions have been reported with chlorhexidine used topically, as lubricant on urethral catheters, and with chlorhexidine-impregnated catheters.<sup>9</sup>

OTC alcohol based antiseptic products carry a warning for flammability and there are documented cases of fires (e.g. DuraPrep).

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Highlights of the regulatory history are summarized below.

- IND 76549-2006, 3M proposed a (b) (4) % w/w CHG and (b) (4) % alcohol solution with human study (ies). The IND was placed on hold. The hold letter dated 12-15-06 describes the hold reasons as a lack of full description of the formulation to be used on humans and inadequate pre-clinical data to support safe use of a combination of CHG with (b) (4) isopropyl alcohol and the listed excipients.
- IND 76549- 5-30-12, 3M responded to the Full Clinical Hold Letter FDA issued on 12-15-06. Clinical trial EM-05-012680, a drape adhesion study, was allowed to proceed (letter date 6-29-12). The Remove Hold letter includes that from a CMC

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6 Mancini AJ. Skin. Pediatrics 113 (4 Suppl):1114-1119, 2004. Abstract viewed at PubMed.

7 Pediatric neonatal, 2013 Apr; 54 (2): 128-31.

8 Celik IH, Oguz SS, Dilmen U. Chlorhexidine-associated transient hyperchloremia in an infant. Ped Dermatol. 2014;31(1):110-111. Abstract

9 viewed online, FDA internet site, FDA Public Health Notice: Potential Hypersensitivity Reactions to Chlorhexidine-Impregnated Medical Devices. March 11, 1998.

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point-of-view, the acrylate co-polymer in the CHG/IPA formulation was “highly similar” to the polymer that is an inactive ingredient in Duraprep. Unlike in previous advice, FDA did not consider the polymer to be a novel excipient and it would not have to be qualified.

- 3-11-13- A conference call occurred between 3M and FDA focused on the use of Bayesian statistics and how one might perform an interim analysis.
- 5-30-13- A teleconference was held to discuss 3M’s proposed [REDACTED] (b) (4) [REDACTED].
- 6-4-13- An end-of-phase 2 (EOP2) meeting was held to discuss the development plan inclusive of pivotal studies. Originally scheduled earlier in 2013, 3M requested a later date as they planned to revisit their formulation and attempt to improve the adhesion characteristics.

Notable FDA requests related to the EOP2 package included a study to evaluate the potential for the development of cross-resistance to antibiotics. FDA disagreed with the company’s request of a waiver for testing of photosensitization and photoallergenicity. FDA indicated the company also would have to address safety issues historically associated with CHG including anaphylaxis and hypersensitivity as well as pediatric use.

A number of statistical comments were sent and FDA requested submission of the statistical analysis plan. FDA defined criteria for “success” as related to reduction in bacterial counts.

The proposed studies for neutralization validation, vapor dissipation, and dry time were commented upon. FDA recommended that the sponsor provide information on whether there was systemic exposure for the drug product/polymer. FDA informed that an adhesion study, phase 3 studies, and dermal safety studies should use the final to-be-marketed formulation.

The company asked whether FDA would grant an expedited review based on the IND product claim of a sterile solution preoperative product. FDA indicated this decision would be made after receipt of the NDA.

- 2-3-14- Type C Guidance Meeting-Teleconference with the company to discuss plans for validating the product relative to sterility.
- 2-20-14- Type A Meeting-Teleconference about multiple compliance and data integrity issues at BioScience Laboratories (BSL).

In January 2014, 3M notified the Agency of the presence of compliance and data integrity issues at BSL, which BSL had notified the company of on 11-21-13. At the time of the teleconference,

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3M had two ongoing pivotal efficacy studies; one at BSL in Bozeman, Montana, and one at Microbiotest Laboratories (MBT) in Sterling, Virginia. The company wanted FDA advice as to how to proceed.

Meeting minutes note non-compliance with GCP/GLP and “numerous errors with bacterial enumeration and documentation”<sup>10</sup> for the first 27 subjects. 3M asked whether FDA agreed with their recommendation to stop the BSL study. FDA did. FDA agreed to the conduct of a new study at BSL if BSL could address and correct audit issues. There was discussion of a possible laboratory site in Romania and requirements relative to IND and non-IND studies.

3M noted that in one of the pivotal study, its product and ChlorPrep showed similar efficacy and were better than saline but that none of the active products met the current efficacy requirement. FDA advised that for the study to be valid the test product and active control must meet performance criteria and be superior to the control. FDA described the primary analysis as a binomial endpoint and defined this. 3M inquired as to how to obtain (b) (4). FDA noted it may be available publically or by a FOIA request.

The FDA statistical team inquired about analyses performed at MBT and blinding issues such as procedures the company had put in place to prevent operational bias. The sponsor responded in an email in February, 2014. This email noted that the MBT study was ongoing and about 50% enrolled. Blinding was described. 3M stated that no results had been communicated to either study site and that no results were communicated to 3M study personnel outside of the statistical team until three months after the study started.

- 4-11-14- 3M notified FDA of (b) (4) the CHG/IPA film-forming patient prep solution in some stability samples.



- 1-20-15 Pre-NDA, face-to-face meeting to discuss the content and format of the NDA in terms of clinical, statistical, and chemistry sections.

The company proposed that based on disparate study designs and limited safety data, an integrated analysis of safety data would not be performed. Individual study reports were to be in Module 5 and all safety data presented in Module 2, separately by study. FDA agreed that this seemed reasonable. FDA reminded the company of EOP2 comments, specifically, that the

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<sup>10</sup> FDA meeting minutes of 2-20-14 teleconference

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company's need to "address safety topics of interest historically associated with the use of topical chlorhexidine-containing products, i.e., anaphylaxis/hypersensitivity reactions and exposure to vulnerable pediatric populations, particularly premature infants and infants less than 2 months of age. Provide a review of published literature and a summary of related post marketing safety data from use of your Avagard™ product."

3M noted an "HRIPT/HCIPT" study of the 2% CHG/70% IPA film-forming skin prep in both colorless and tinted formulation versus a positive control and a negative control. ChlorPrep was also tested. ChlorPrep showed a lower cumulative irritation test (CIT) score than the negative control. 3M wanted to know if FDA would accept this study regardless of the unexpected ChlorPrep result. In preliminary comments, FDA recommended that given the marketing history of ChlorPrep, a repeat cumulative irritation study was not recommended. FDA noted, however, that the briefing document did not discuss or explain the low CIT scores for ChlorPrep and whether an evaluation of the study conduct had been undertaken. The sponsor was asked to include a discussion of their analysis of the study results and provide an explanation as to why this atypical result occurred and whether the result had implications for interpreting trial results or eventual product labeling. FDA reiterated the need to include a discussion of the atypical results.

3M conducted a pilot in vivo efficacy study (groin only) at a lab test site in Romania. An early formulation was used that was reported as qualitatively similar, but "slightly different quantitatively than", the final current formulation. 3M proposed to include the full report in Module 5 for reference. FDA agreed.

3M referred to the study EM-05-13260 as having about 100 subjects in one arm (*at the meeting the company said this was close to 500 subjects, not 100*) exposed to the formulation with HEDTA in order to compare it to the non-HEDTA solution. 3M expected this could provide efficacy and safety data and "substantiate "the addition of the HEDTA for both a safety and efficacy perspective. 3M inquired whether FDA agreed that adding the arm was sufficient to bridge the safety and efficacy between the formulations with and without the HEDTA and that no additional clinical or safety studies would be required. FDA 's preliminary comments noted it appeared reasonable from a non-clinical point of view but that final determination would require review of the NDA data. (*At the meeting, 3M noted that all of the nonclinical studies were conducted without the HEDTA formulation.*) FDA noted it also appeared reasonable not to conduct additional clinical safety trials before the NDA submission, but that whether the HEDTA ingredient is safe for use in a nonprescription setting is a matter of review. FDA reminded the sponsor of data submission commitments described in the company's July 2, 2014 letter.

Stability data was addressed/discussed in several questions. Sterilization issues were discussed. Review classification (standard or priority) was again discussed and confirmed that this would be determined at NDA submission (upon filing).

## 2.6 Other Relevant Background Information

With the exception of the study conducted as a pilot, non-IND study (Romanian), all studies were conducted under one of four principal investigators:

- Dr. M. Hamid Bashir – 12760, 13509, and 13337

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- Dr. Michelle H. Stevens- 12985, 12680, 12794, and 13447 (all subjects 3M employees). Fifteen subjects participated in more than one of these studies.<sup>11</sup>
- Dr. Michael Caswell- 12853, 12952, and 13062 (all safety challenge studies, subjects recruited for a database of volunteers)-each subject was unique to a specific study<sup>11</sup>
- Dr. Robert R. McCormack-13260 and 12159

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The submission was not optimal. Some case report forms (CRFs) were not readable though perhaps this was due to factors involved in submission and outside of the control of 3M. Datasets were not always submitted and some/many lacked usable define files. It was difficult to independently verify safety data and in some cases, I could not. See the study reviews for additional details.

Not all study reports included protocols. The literature publications referenced in the Clinical Summary of Safety (CSS) literature reviews to support safety were, for the most part, not submitted. When submitted, two of the articles were not in English, requiring another information request.

I found it difficult to tell how many subjects might have participated in more than one trial (i.e. unique subject exposure to the product). This required an information request. The sponsor's response shows there was some "recycling" of subjects in studies conducted on 3M employees (studies 13447, 12680, 12794, and 12985). Studies 12680 and 12794 were Drape Adhesion studies. This reuse of subjects lowered the denominator of subject exposures in these four studies from 101 to 83. If the studies ended up with subjects who frequently volunteer, this could introduce a selection bias because a volunteer who has experienced a reaction on a topical antiseptic might not volunteer for this study or would meet an exclusion criterion. This limits generalizability and could underestimate or under-represent skin effects. The safety challenge studies too recruited from a database of volunteers (Consumer Products Testing Corporation (CPTC). This could lead to selection bias also.

Data quality issues resulted in 3M stopping one of the pivotal trials early (study 12759). Drape Adhesion studies and the flammability studies exposed small numbers of subjects or mannequin heads. Studies were open label/unblinded. How close these

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<sup>11</sup> NDA 208288, SDN 23

trials mimic clinical settings is not clear, such as the weight used in drape adhesion studies.

### **3.2 Compliance with Good Clinical Practices**

The sponsor states that all clinical studies and nonclinical in vitro studies performed to support the NDA were conducted under Good Clinical Practices (GCP) and Good Laboratory Practices (GLP).<sup>12</sup> One could perhaps argue the veracity of this statement given the data integrity issues in study EM-05-012759. Technically study EM-05-012759 was not submitted to support the NDA because it was stopped early due to problems inclusive of data quality. The pilot study (study 12635) GCP statement was worded as “this study was conducted in spirit with the guidelines on Good Clinical Practice for trials on medicinal products in the European Community, and with the Declaration of Helsinki.”

3M wrote the protocols and monitored the studies on-site and electronically by data capture. The responsibility for the statistical analyses was performed by the contract research organization (CRO) (b) (4) under the oversight of 3M. This CRO also wrote the clinical study reports, with oversight by 3M. For the three in vitro studies, MBT was the site of conduct and (b) (4) wrote the protocols, summarized the data, and wrote the final reports.

### **3.3 Financial Disclosures**

One investigator was a company employee. Please see the Financial Disclosure form to be filed separately from this review.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

Chemistry Manufacturing and Controls (CMC) review is deferred to the CMC reviewers. As I understand it from an internal meeting on 3-18-16, CMC will be recommending a Complete Response due primarily to stability issues.

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<sup>12</sup> Clinical Overview, p 11/46, NDA application 7-6-15, module section 2.5

## **4.2 Clinical Microbiology**

## **4.3 Preclinical Pharmacology/Toxicology**

Deferred to the pharmacology/toxicology reviewer.

## **4.4 Clinical Pharmacology**

### **4.4.1 Mechanism of Action**

Please see the review of Dr. M. Jackson (DNNDP microbiologist).

### **4.4.2 Pharmacodynamics**

The product is not intended for systemic use. No clinical pharmacodynamics studies were performed.

### **4.4.3 Pharmacokinetics**

The product is not intended for systemic use.

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

The following table is copied, in a modified form, from the initial NDA submission, module section 5.2. Study 13447 was submitted in SDN 008 and is not in the table below. Study 13447 was a small, open-label study performed to evaluate Health Care Professionals (HCP) ratings of the 3M product compared to an active comparator product with respect to features such as look of prep on the skin and removal.

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**Table 2 Studies to support the NDA**

Study Number	Study Title
<b>Pivotal Clinical Efficacy Studies</b>	
EM-05-012760	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-05-013260	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-05-012759	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
<b>In Vitro Efficacy Studies</b>	
EM-05-012700	Assessment of Microbicidal Activity of Tinted and Colorless 3M CHG/IPA Film-Forming Preoperative Skin Preparation Formulations Using a Modified Time-Kill Procedure
EM-05-012758	Evaluation of Potential for Development of Antimicrobial Resistance to Tinted 3M CHG/IPA Film-Forming Preoperative Skin Preparation Formulation
EM-05-012981	Assessment of Microbicidal Activity in the Presence of an Organic Challenge of Tinted and Colorless 3M CHG/IPA Film-Forming Preoperative Skin Preparation Formulations Using a Modified Time-Kill Procedure
<b>Persistence of Efficacy Study</b>	
EM-05-013509	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
<b>Coverage Area, Dry Time, and Vapor Dissipation Clinical Efficacy Studies</b>	
EM-05-012985	3M CHG/IPA Film-Forming Skin Preparation 26-mL Applicator Area Coverage, Dry Time and Vapor Dissipation Study on Human Skin

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Study Number	Study Title
EM-05-013337	3M CHG/IPA Film-Forming Skin Preparation 10.5-mL Applicator Area Coverage and Dry Time on Human Skin
<b>Drape Adhesion Clinical Efficacy Studies</b>	
EM-05-012680	Evaluation of Adhesion Performance of 3M CHG/IPA Film-Forming Skin Preparation vs. Other Preps Using Ioban Incise Drape in Saline-Challenged and Unchallenged Conditions
EM-05-012794	Evaluation of Adhesion Performance of 3M CHG/IPA Film-Forming Skin Preparation Reformulation Designs vs. Other Preps Using Ioban Incise Drape in Saline-Challenged and Unchallenged Conditions
<b>Safety Challenge Studies</b>	
EM-05-012853	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
EM-05-012952	Clinical Evaluation to Assess the Phototoxicity Potential of Topically Applied 3M CHG/IPA Film-Forming Skin Prep and a Marketed Active Control
EM-05-013062	Clinical Evaluation of Photoallergy Potential
<b>Dry Time in Mannequin Hair Laboratory Study</b>	
EM-05-013430	Determination of 3M CHG/IPA Film-Forming Skin Preparation Solution Drying Time and Vapor Dissipation on Shoulder Length Human Hair (Mannequins) under Normal Surgical Suite Conditions
<b>Neutralization Sampling Solution Studies</b>	
Technical Report 05-256621	Assessment of Neutralization Sampling Solution for 3M CHG/IPA Film-Forming Preoperative Skin Preparation
<b>Pilot Study (non-IND study for information only)</b>	
EM-05-012635	Preoperative Skin Preparation Study Following ASTM – E1173 Methods to Evaluate the Antimicrobial Properties of Five Test Products

Abbreviations: 3M CHG/IPA= 3M™ Chlorhexidine Gluconate/ Isopropyl Alcohol; ASTM=American Society for Testing and Materials; Ioban incise drape=Ioban™ 2 Antimicrobial Incise Drape

## 5.2 Review Strategy

Efficacy review was performed by a DNDP microbiologist, Dr. M. Jackson and by the DNDP statistical review team

My review of data focused on adverse events and skin irritations, which were the safety assessments made in the studies I was to review. I reviewed these types of data from the pivotal trials and in all trials except the challenge studies. The safety data in the challenge studies were reviewed by the Division of Dermatology and Dental Products' (DDDP) reviewer. I reviewed the Drape Adhesion studies and the Flammability study.

I also reviewed the literature reviews and post-marketing data as provided by the sponsor.

The following NDA submissions were utilized in this review:  
SDN 1, 7-6-15

SDN 6, 8-25-15  
SDN 7, 8-27-15  
SDN 8, 11-04-15  
SDN 9, 11-06-15  
SDN 10, 11-18-15  
SDN 20, 3-4-16  
SDN 23, 3-15-16  
SDN 24 3-16-16  
SN 25, 3-18-16

### **5.3 Discussion of Individual Studies/Clinical Trials**

Please see the review of the DNDP microbiologist and the statistical review team.

## **6 Review of Efficacy**

### **Efficacy Summary**

Review in the DNDP of the efficacy data is conducted by microbiology and statistical disciplines. Efficacy evaluations and recommendations are made by the microbiologist and statistical team.

Efficacy endpoints are based on responder rate and bacterial count reductions. The reader is referred to the DNDP microbiology review for a full discussion of efficacy endpoints.

There are discrepant results for the inguinal region when compared to the abdominal region. As I understand it, this type of discrepancy is not new for these products. These issues are discussed in the DNDP microbiology review.

Though there are hypotheses and/or speculations about these discrepant results, the inconsistency remains and the reason(s) remains unknown. Inspections conducted, including those by OSI for this NDA, have not uncovered a clear explanation. In recent internal meetings it has been discussed that perhaps criteria should be a certain threshold of bacterial counts instead of reductions in bacterial counts. Dr. Jackson has some thoughts about the cup size for collection which are discussed in her review. Other possibilities might be different flora in the inguinal than abdominal. This does not offer an explanation *if* there are consistent difference in results between the two labs performing these types of studies, unless some other factor is also happening at one lab (such as male predominance with potentially different flora?). It seems that another plausible explanation for marginal and/or inconsistent results is that maybe the products are not as effective or have marginal efficacy in the groin.

The sponsor reports that “numerous surgical prep products have not met the previous less stringent efficacy requirements per the TFM on the inguinal region (i.e., mean 3-log reductions at 10 minutes)”<sup>13</sup> It is not clear to me whether the sponsor is arguing the criteria is too stringent or is stating observations made. As I understand it, in addition to other products not meeting certain criteria, the criteria remain under consideration.

Given the use of these products as preoperative scrubs and the issues relative to efficacy evaluation (please see Dr. Jackson’s review), I recommend consideration of an advisory committee to again address these complex issues.

## 6.1 Indication

The indication proposed<sup>14</sup> is “for use as a patient preoperative skin preparation, for the preparation of skin prior to surgery and to help reduce bacteria that can potentially cause skin infection”

### 6.1.1 Methods

The primary objective of the pivotal efficacy studies was to evaluate the antimicrobial efficacy of 3M/CHG/IPA Prep when applied to the abdomen and inguinal regions of healthy subjects. ChlorPrep (also 2% CHG, 70% IPA but without the film-forming capability) was used as an active control and sterile 0.9% saline as a negative control.

The final formulation is the 3M CHG/IPA Prep with HEDTA. The only pivotal efficacy study conducted with the to-be-marketed formulation is study 13260. Pre-NDA meeting minutes of 1-20-15 show that there was discussion of whether the arm added to study 13260 (Question 10) would be sufficient to bridge safety and efficacy between the formulations with and without the Trisodium HEDTA without additional clinical and safety studies. The Division response is copied from the pre-NDA minutes below. As a note, 461 subjects were exposed the TBM formulation in study 13260.<sup>15</sup>

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13 Clinical Summary, module 2.7, p 2/70 (adobe reader page number), NDA 208288, SDN 1.

14 Draft labeling text-MS Word, Module 1, 1.14.1.3 NDA submission 7-6-15

15 SDN 23 response to an Information Request

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FDA Preliminary Response to Question 10

*It appears reasonable from a nonclinical perspective. However, final determination of the nonclinical studies required to support your NDA submission will only be determined after completion of review of all data in the NDA submission. In your submission, provide a comprehensive nonclinical review of your proposed product.*

*It also appears reasonable not to conduct additional clinical safety trials prior to NDA submission, but whether your product with the HEDTA ingredient is safe for use in the nonprescription setting is a matter for the review of an NDA. We remind you of your data submission commitments as described in your letter of July 2, 2014 in response to FDA's related questions.*

Meeting Discussion - Question 10

The sponsor clarified that all of the nonclinical studies were conducted with the non-HEDTA formulation. However, one of the pivotal clinical studies is currently being conducted using both the HEDTA formulation and the non-HEDTA formulation. Close to 500 subjects, not 100 as stated in the meeting materials will receive the HEDTA final formulation in this pivotal clinical study from which skin irritation and overall safety data will be gathered.

The following table shows the study products used in each of the pivotal studies.

**Table 3 NDA OTC Topical Preoperative Preparations**

	Description	EM-05-12760	EM-05-013260	EM-05-012759
3M CHG/IPA Prep	2%CHG and 70% IPA with acrylate polymer. 10.5mL, tinted	x		x
3m CHG/IPA Prep	2%CHG and 70% IPA with acrylate polymer. 26 mL, tinted	x		
3M CHG/IPA Prep	2%CHG and 70% IPA with acrylate polymer. 10.5mL, colorless		x	x
3M CHG/IPA Prep- with HEDTA	2%CHG and 70% IPA with acrylate polymer and (hydroxyethyl) ethylenediaminetriacetic acid (HEDTA), 10.5mL, colorless		x	
ChloraPrep	2% CHG and 70% IPA. 26mL, Hi-Lite Orange Tint	x		x
ChloraPrep	2% CHG and 70% IPA. 10.5 mL, clear		x	
Saline	Sterile 0.9% saline, 20 mL bottle	x	x	x

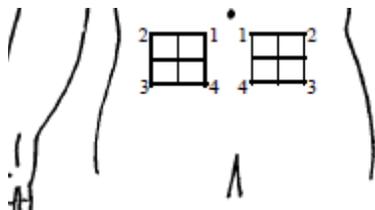
Information from tables in protocols in NDA module 5, Table 3.4.1A in all studies (for study 05-012760, protocol version 2, Study EM-05-013260 version 1, study 05-012759 protocol version 2)

Study 13260 treatment groups were as follows:

- 1- 3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA
- 2- 3M CHG/IPA Prep and ChloraPrep
- 3- 3M CHG/IPA Prep with HEDTA and ChloraPrep
- 4- 3M CHG/IPA Prep and saline
- 5- 3M CHG/IPA Prep with HEDTA and saline
- 6- ChloraPrep and saline

In each pivotal efficacy study (images excerpted from protocols),

**Figure 1 abdominal sites**



**Figure 2 Inguinal sites**



In protocol 05-013260, the protocol indicates that the 3M product and the marketed active control were to be applied topically to intact skin of the abdominal and groin regions of the subject with repeated back-and-forth strokes for 30 seconds on the abdomen or 2 minutes on the groin and allowed to dry for 3 minutes. Protocols 05-012750 and 05-012759 instruct that the Chloraprep (i.e., the marketed active control) would be applied for 30 seconds on the abdomen or 2 minutes on the groin according to the manufacturer's directions and allowed to dry for 3 minutes.

The saline (the negative control) was to be applied with repeated back-and-forth strokes for 30 seconds on the abdomen or 2 minutes on the groin using sterile polyurethane foam applicators, aseptically filled with 20 mL of solution, and allowed to dry for 3 minutes.

There were numerous inclusion and exclusion criteria in each of the pivotal studies. I reviewed the inclusion and exclusion criteria in the sponsor's presentations in the corresponding study report. Inclusion and exclusion criteria were generally similar or identical with the exception of the required baseline abdominal counts at screening. Studies 12759 and 13260 required  $\geq 2.5 \log_{10}/\text{cm}^2$  bilaterally on the abdominal region while study 12760 required  $\geq 3.0 \log_{10}/\text{cm}^2$  bilaterally on the abdominal region. Other, notable differences between the criteria of the three efficacy studies are described, as applicable, below.

Study 12759 Inclusion criteria<sup>16</sup>.

**Inclusion criteria included:**

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16 these criteria are adapted from the Abbreviated Final Clinical Study Report for study EM-05-012759, SDN000, module 5.3.5.1, page 17-19/91. Some wording is verbatim from the sponsor.

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- 1) 18 years of age
- 2) Generally in good health
- 3) Signed informed consent
- 4) Cooperative and willing
- 5) Subjects willing to avoid showering and tub-bathing within 72 hours prior to screening and treatment days ( sponge baths were allowed but were to avoid the lower abdomen and upper thighs).
- 6) Subjects were willing to avoid showering, tub-bathing, swimming, and vigorous physical activity that could cause sweating during the 6.5 hour ( $\pm$ ) period before sampling.
- 7) Studies 12759 and 13260 =Screening Day baseline counts of  $\geq 2.5 \log_{10}/\text{cm}^2$  bilaterally on the abdominal region and/or  $\geq 5.0 \log_{10}/\text{cm}^2$  bilaterally on the inguinal region. Study 12760 criterion was different with respect to the baseline Screening Day counts in the bilateral abdominal area ( $\geq 3.0 \log_{10}/\text{cm}^2$  compared to  $\geq 2.5 \log$ ).
- 8) Subjects who were willing to report to the study facility about 72 hours before Screening Day or Treatment Day sampling for clipping if needed.

### **Exclusion criteria included:**

- 1) Participation in another clinical study in the past 30 days, current participation in another clinical study, or previous participation in this study
- 2) Any tattoos, scars, breaks in the skin, or any form of dermatitis or other skin disorders (including acne) on the applicable test areas
- 3) History of skin allergies
- 4) History of skin cancer within 6 inches of the test areas
- 5) Known sensitivity to actylate, chlorhexidine gluconate, or alcohol –containing products, or to medical tape, metals, natural rubber latex, vinyl, or skin-marking inks
- 6) Medical diagnosis with a physical condition that may put the subject at risk, such as a current or recent severe illness, hepatitis, organ transplan, congestive heart disease, or any immunocompromised conditions, such as acquired immune deficiency or HIV positive status.
- 7) Any medical condition or medication use that should preclude participation, in the opinion of the investigator
- 8) Pregnancy, possible pregnancy, attempting pregnancy, nursing
- 9) Topical antimicrobial exposure within 14 days before Screening and Treatment Day
- 10) Use of systemic or topical antibiotic medications, steroid medications (other than for hormonal contraception or postmenopausal reasons), or any other product known to affect the normal skin microbial flora within 14 days before Screening and Treatment Days
- 11) Exposure of the test area to solvents, acids, bases, strong detergents, fabric-softener-treated clothing, or other household chemicals within 14 days prior to Screening and Treatment Days
- 12) Swimming in chemically treated pools or bathing in hot tubs, spas, or whirlpools within 14 days before Screening and Treatment Days
- 13) Use of tanning beds, hot waxes, or depilatories (in the applicable test sites) within 14 days Screening and Treatment Days
- 14) Bathing or showering within 17 hours before Screening and Treatment Days

**Reviewer comment: Some of these criteria would seem to decrease generalizability to the patient population that might need surgery (e.g. criteria like #10-14).**

### 6.1.2 Demographics

Overall, study 13260's study population was younger (mean and median ages of about 31 years and 36 respectively) than study 12760 (31 and 23 years mean and median ages respectively). Neither study, based on my count, had a large representation of subjects 65 years of age or older (study 13260 about 3.5% and study 12760, ~4.4%). The studies were notably different in sex distribution (study 13260 with 71% male, study 12760 was about 47-50% female) and in racial/ethnic composition (13260 was ~91% White and about 4% Hispanic/Latino with few Blacks/African Americans, study 12760 was ~38% White, 32% Asian, and 16-17% Black/African American).

A description of demographics of the two studies completed as pivotal efficacy trials, as well as of the trial that was terminated early, is below based on information in the respective CSR or referenced dataset. The reader is referred to the microbiology and/or statistical reviews for additional details.

#### Study 13260:

Abdominal (n= 569 total) and inguinal regions (n=404) were similar demographically. The average age was about 31 years ( $\pm$  about 14.7 years). The median age was 23-24 years. The range of ages was 18-80 years. Based on my count using the sponsor-submitted dataset DM.xpt, 22/632 unique subjects were  $\geq$  65 years old (14 were 65-68 years, 7 were 71-79 years, and 1 was 80 years old). Most subjects were male (~71% of abdominal group and 74% of the inguinal group). Most subjects for each body region were white (~91%). The next largest racial/ethnic stratum was Hispanic/Latino (3.7 & 4.2%). About 2.5% were Asian. Only one subject was Black/African American in the inguinal group (0.2 %) and 8 (1.4%) in the abdominal group.

#### Study 12760:

Abdominal (n= 406 total) and inguinal regions (n=391) were similar demographically. The average age was about 36 years ( $\pm$  about 14.5 years). The median age was 31 years. The range of ages was 18-80 years. Based on my count using the sponsor-submitted dataset DM.xpt, 19/426 subjects were  $\geq$  65 years old (7 were 65, 6 were 65-69, 5 were 70's, and 1 was 80 years old) . Around 50% of the abdominal sites were from female subjects compared to about 47% of the inguinal sites. Almost 38% of each body region group was white, about 32% were Asian, 16-17% were Black/African American, and about 12% were Hispanic/Latino.

**Study 12759:**

Abdominal and inguinal regions were similar demographically with 161 and 162 subjects accordingly. The mean age of the abdominal group  $33.6 \pm 14.7$  years, the median age was 28 years. The age range was 18-70. By my count, using the sponsor-submitted dataset ADMB.xpt, three subjects out of 162 were 65 years or older. Most subjects for each body region were male (~73.5%). Racially or ethnically, most subjects were white (87.6% and 87% in the inguinal area). The next largest racial/ethnic stratum was American Indian or Alaskan at around 4%. Black/African American subjects comprised 2.5% and Hispanic/Latino, 2.5% to ~3%.

**6.1.3 Subject Disposition**

Overall, the study reports indicate that a smaller proportion of the consented population had screening data for microbial counts in Study 13260 than in Study 12760 (79.5% compared to 96% for the abdominal region and 81% versus 96% respectively for the inguinal region). Of those categorized as having screening data for microbial counts, a smaller percentage of study 13260, was then randomized into the study in both body regions (overall, about 70% versus about 80%). Most randomized subjects completed the pivotal studies.

**Table 4 Overview of Disposition in Pivotal Efficacy Studies**

	<b>Study 13260</b>	<b>Study 12760</b>	<b>Study 12759*</b>
<b>Consented abdominal</b>	1035	510	419 consented
<b>Had screening data for microbial counts</b>	823 (79.5%)	489 (~96%)	161 randomized
<b>Randomized abdominal</b>	569 (569/823=~69%)	406 (406/489=83%)	
<b>Completed abdominal</b>	568	406	161
<b>Consented inguinal</b>	715		162 randomized inguinal
<b>Had screening data for microbial counts</b>	579/715 (81%)	489 (489/510=~96%)	
<b>Randomized inguinal</b>	404 (404/579=~70%)	391 (391/489=~80%)	162
<b>Completed inguinal</b>	403	391	162

CSR Table 5 of each study and the text preceding it were used for the numbers in this table. For studies 12760 and 13260, Tables 14.1.1.1 and 14.1.1.4 for each study were used as needed. \*Study 12759 terminated early. It is shown here for completeness. It is not being considered for efficacy, some in the Division may consider it for safety data. Study 12759 data source is Table 5 of the CSR.

Since study 13260 is the only pivotal trial with the to-be-marketed formulation defined as the 3M CHG/IPA product with HEDTA, the distribution of subjects with respect to randomized product is (3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA) are duplicated below from the sponsor’s submission. One subject discontinued the study early due to “other”. Due to the design, this impacted several treatment arms. There

were a few deviations from the protocol (subjects who received the wrong product or no product).

### Table 5 Study 13260 Disposition by Study Product

Table 6 Subject Disposition by Study Product (ITT/Safety Population)

Disposition, n (%)	3M CHG/IPA Prep	3M CHG/IPA Prep with HEDTA	ChloraPrep	Saline
<b>Abdominal Region</b>				
Randomized sides	343	344	347	104
mITT population	196 (57.1)	202 (58.7)	196 (56.5)	59 (56.7)
PP population	191 (55.7)	197 (57.3)	191 (55.0)	59 (56.7)
Completed study	343 (100.0)	343 (99.7)	346 (99.7)	104 (100.0)
Discontinued early from study	0	1 (0.3) <sup>a</sup>	1 (0.3) <sup>a</sup>	0
<b>Inguinal Region</b>				
Randomized sides	242	244	248	74
mITT population	208 (86.0)	209 (85.7)	219 (88.3)	61 (82.4)
PP population	204 (84.3)	199 (81.6)	213 (85.9)	56 (75.7)
Completed study	241 (99.6)	244 (100.0)	248 (100.0)	73 (98.6)
Discontinued early from study	1 (0.4) <sup>a</sup>	0	0	1 (1.4) <sup>a</sup>

Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloraPrep= ChloraPrep® Patient Preoperative Skin Preparation; HEDTA=(hydroxyethyl)ethylenediaminetriacetic acid; mITT= modified intent-to-treat; PP=per-protocol  
Note: Percentages are based on the number of randomized treatment sides. Each subject is summarized in more than 1 treatment arm as he/she was treated with more than 1 treatment.

<sup>a</sup>Subject (b)(6) discontinued early from the study due to “other” (“other”=sites were compromised during testing; Listing 16.2.2.3).

Source: End-of-text Tables 14.1.1.3 and 14.1.1.6

For additional discussion of disposition, please see the review of the DNDP microbiology review (Dr. Jackson).

#### 6.1.4 Analysis of Primary Endpoint(s)

The primary analysis for the pivotal efficacy trials was based on the proportion of subjects meeting a “responder” definition. A responder was defined as having a 3-log reduction from baseline on the groin and a 2-log reduction on the abdomen at 10 minutes and for whom the skin flora at 6 hours post-application had not returned to baseline. Both the IND product and the active control had to meet the following criteria:

- Lower bound of the confidence interval (CI) for the responder rate of the test product was to be  $\geq 70\%$
- Lower bound of the 95% CI for the responder rate of the active control was to be  $\geq 70\%$
- Both the test product and the active control were to be superior to the vehicle or negative control

#### 6.1.5 Analysis of Secondary Endpoints(s)

Deferred to the statistical review team.

### **6.1.6 Other Endpoints**

Deferred to the statistical review team

### **6.1.7 Subpopulations**

Deferred to the statistical review team.

The CSR states no subgroup analyses were planned or performed.

### **6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

There were no different dose groups of the IND product in the study. Also, please see the review of Dr. Jackson.

### **6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

The sponsor submitted a persistence of efficacy study, study EM-05-013509. The reader is referred to Dr. M. Jackson's review for discussion of this study as related to efficacy evaluation.

### **6.1.10 Additional Efficacy Issues/Analyses**

Study EM-05-012759 (BSL) was also a pivotal efficacy study. The study was stopped early due to data quality and technical issues. Efficacy analyses were not conducted though the sponsor submitted safety data.

## **7 Review of Safety**

### **Safety Summary**

#### **7.1 Methods**

##### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

The studies are referred to by the last numbers of the studies (e.g. study 12760) or in the format of EM-05-012760.

Adverse events (AEs) and skin irritation rating measures were the main safety assessments collected in the trials shown below.

**Table 6 Studies Used to Evaluate Safety**

	<b>Pivotal clinical efficacy studies</b> - single application, exposure about 6 hours*
1	12760
2	13260
3	12759
	<b>Persistence of efficacy</b> –single application followed by up to a 72-hour period*
4	13509
	<b>Coverage and Dry Time studies</b> - single application, exposure up to 30 minutes*
5	12985
6	13337
	<b>Drape Adhesion studies</b> –single application, exposure up to 4 hours*
7	12680
8	12794
	<b>Safety Challenge Studies</b> - intended to test more extreme conditions
9	12853- multiple exposures over extended periods of time under dressings
10	12952 - after exposure to ultraviolet light
11	13062 - after exposure to ultraviolet light
	<b>Other studies that collected AEs and skin irritation data</b>
12	12635 – non IND pilot study conducted in Romania
13	13447- sponsor did not intend for the NDA- study of product attributions

\* **source: CSS 2.7.4.1.1.1**

Literature was sent to support the safety with respect to issues historically associated with chlorhexidine gluconate.

- Vulnerable pediatric populations
- Hypersensitivity and anaphylaxis

Literature was sent specifically to serve as a bridge for general safety and to support the Target Product Information.

### 7.1.2 Categorization of Adverse Events

In the pivotal studies, an adverse event was defined as “any undesirable clinical occurrence in a subject whether or not it is considered to be drug related.” Serious adverse events were defined as events that were fatal or life-threatening, permanently or significantly disabling/incapacitating, requiring inpatient hospitalization or prolongation of existing hospitalization, or resulting in a congenital anomaly/birth defect. The investigator was responsible for identifying adverse events that occurred on Treatment Day. Adverse events could be also be reported by the subject.

Skin irritation rated as a 3 or more was to be considered an adverse event. The skin irritation rating scale is reproduced from Study 13260 and is the scale used in all pivotal trials and other studies with the possible exception of the challenge studies. The study conducted in Romania also used this scale but discontinued the subject if irritation was at the level 2 or 3.

**Table 7 Skin Irritation Rating Scale**

Skin Irritation Rating Scale (Modified Draize)		
Condition	Rating	Description
Erythema	0	No reaction
	1	Mild and/or transient redness limited to sensitive area
	2	Moderate redness persisting over much of the product-exposed area
	3 <sup>a</sup>	Severe redness extending over most or all of the product-exposed area
Edema	0	No reaction
	1	Mild and/or transient swelling limited to sensitive areas
	2	Moderate swelling persisting over much of the product-exposed area
	3 <sup>a</sup>	Severe swelling extending over most or all of the product-exposed area
Rash	0	No reaction
	1	Mild and/or transient rash limited to sensitive area
	2	Moderate rash persisting over much of the product-exposed area
	3 <sup>a</sup>	Severe rash extending over most or all of the product-exposed area
Dryness	0	No reaction
	1	Mild and/or transient dryness, limited to sensitive area
	2	Moderate dryness persisting over much of the product-exposed area
	3 <sup>a</sup>	Severe dryness extending over most of the product-exposed area

<sup>a</sup> = A rating of 3 on the skin irritation scale will be recorded as an Adverse Event.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were not pooled due to differences in study design.

## 7.2 Adequacy of Safety Assessments

Overall, the studies I reviewed for safety have limitations as noted. These include open-label designs, small numbers, and recycling of subjects. Most studies were not performed with the TBM formulation with the TBM formulation defined as the one with HEDTA. Also, the product's polymer ratio was modified for study 12794, a drape adhesion study. This study was performed between 1-14-13 and 1-24 14, preceding the pivotal trial start dates of,

- 10-9-13 for 12759
- 10-1-13 for 12760 and
- 6-27-14 for 13260.

Therefore, it would seem the product in the pivotal efficacy trials would have used the same polymer as the one in 12794. This is deferred to the Chemistry review team (CMC) for confirmation.

Other than the first drape adhesion study (12680) and the non-IND study (12635), the other studies with human safety data have start dates after the completion date of study 12794, based on the Clinical Study Report (CSR) of each of those studies. The study report for the mannequin study was not dated but includes a copy of the protocol. The protocol is dated 3-19-15 and approval of the study was in January-February of 2015. Therefore, it would seem these studies used the product with the final polymer (presumed final polymer used in the second drape adhesion study). CMC should confirm this.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The sponsor indicates that a total of 1568 unique subjects were exposed to the NDA product in human trials<sup>17</sup>. The sponsor listed the trials by number. The list shows all of the studies in the table shown in 7.1.1 above except study 12635.

The only studies that employed the to-be-marketed formulation (TBM), meaning the 3M CGH/IPA product with HEDTA, are study 13260, study 13509, and study 13447<sup>18</sup>.

- Study 13260-pivotal study, 461 subjects exposed
- Study 13509-persistence of efficacy study-25 subjects exposed
- Study 13447-not sent in support of the application-21 subjects exposed
- Total exposure=507 to the TBM formulation.

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17 SDN 25 to the NDA, 3-18-16

18 SDN 23 to the NDA, 3-15-16

Based on Target Product Information, the target population is preoperative patients (not for use in lumbar puncture or procedures in contact with meninges) with no known allergies to chlorhexidine gluconate or isopropyl alcohol who are preferably older than two months of age. The product is a single use applicator. Technically, this means one use but in reality people may have more than one surgical procedure or even multiple procedures in relatively short time frames.

### **7.2.2 Explorations for Dose Response**

Not performed.

### **7.2.3 Special Animal and/or In Vitro Testing**

Please see the reviews of the nonclinical reviewer and of Dr. Jackson (DNDP microbiology).

### **7.2.4 Routine Clinical Testing**

Per the CSS, no routine clinical testing was performed in any of the clinical studies except for urine pregnancy testing in the safety challenge studies at screening and at the final visit. Per the CSS, physical exams were not performed in any of the clinical studies investigating 3M CHG/IPA

Vital signs were measured only in the safety challenge studies (EM-05-12853, EM-05-12952, and EM-05-013062).

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Not addressed. Probably not applicable based on current thinking of minimal absorption.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Pivotal trials included a comparator though the low number of AEs limits interpretability. Also, only one of the pivotal studies included the final, to-be-marketed formulation (13260). Study 13260 did include ChlorPrep, which is a 2% CHG-70% IPA solution in an applicator but the solution does not have the polymer that the proposed product contains and is not sterile.

### 7.3 Major Safety Results

This presentation is incomplete as it does not incorporate adverse events and skin irritation from the safety challenge studies. The reader is deferred to the review by medical officer in the Division of Dermatology and Dental Products.

Few AEs were reported. In the pivotal trials, none were serious. I did not review the Safety Challenge Studies but would expect to see more events in these studies.

**Table 8 Overview of Incidence of AEs in the Clinical Program**

Study Number	Death	SAE	Discontinuation 2 <sup>nd</sup> to an AE	Number subjects with AE/total # (%)
<b>Pivotal clinical efficacy studies</b>				
12760	0	0	0	
13260	0	0	0	5 in abdominal (569=<1%) 4 in groin (4/404=~1%)
12759	0	0	0	
<b>Persistence of efficacy</b>				
13509	0	0	0	0
<b>Coverage and Dry Time studies</b>				
12985	0	0	0	0
13337	0	0	0	0
<b>Drape Adhesion studies</b>				
12680	0	0	0	0
12794	0	0	0	0
<b>Safety Challenge studies</b>				
12853	0	0	6	9
12952	0	0	0	0
13062	0	0	1	6
<b>Other studies</b>				
12635	0	0	0	0 or 1 (appears discrepant)
13447	0	0	0	0

Source: Unnumbered overview summary table submitted in SDN 9 for studies with 0 AEs. Also, CSR summaries were utilized to cross-reference/audit. Study 13260 data from SDN 9. For SDN 13447, information is from SDN 10 to the NDA 11-18-15. For study 12635 data is from text on page 43/240 of the CSR.

There were no skin irritation scores of “severe” in the pivotal trials. In study 13260, there were two subjects with moderate skin reactions on the abdomen at 6 hours. One of these subjects experienced reactions of moderate erythema with both of the 3M

products (the one with HEDTA and the one without HEDTA). The other subject experienced moderate dryness after exposure to ChlorPrep.

The following table provides highlights of skin irritation. The reader is referred to the details of the study results.

**Table 9 Highlights of Skin Irritation Scales**

	<b>Pivotal clinical efficacy studies -</b>
1	<b>Study 12760</b> no reactions reported
2	<b>Study 13260</b> -2 subjects with moderate events (one was CP), of mild, more subjects with mild erythema in 3M with HEDTA on abdomen and inguinal than 3M without HEDTA, CP and saline, about 1.5 x to 2x over CP. More saline subjects with rash at 6 hours followed by CP.
3	<b>Study 12759</b> -reports no scores higher than mild
	<b>Persistence of efficacy –</b>
4	<b>Study 13509</b> all reactions reported as “no reaction”
	<b>Coverage/ Dry Time studies-</b> not use TBM formulation defined as with HEDTA
5	<b>Study 12985</b> - all reported as “no reaction”, not clear if parameters limited to erythema
6	<b>Study 13337</b> - all reported as “no reaction”, not clear if parameters limited to erythema
	<b>Drape Adhesion studies –</b> not use TBM formulation defined as with HEDTA
7	<b>Study 12680</b> - 3M product numerically does not look worse on skin irritation measures when compared to CP and DP. Sponsor reports CP significantly higher edema and erythema at 24-72 hours in Dry Conditions.
8	<b>Study 12794</b> -tested 4 experimental formulation redesigns of 3M product – one of the lots (A1) generally not worse, numerically, than CP except at follow-up in Wet Conditions and Dry Condition for erythema (also statistical separation). More mild edema with 3M products than CP or DP at follow-up. No rashes at removal. CP no rashes at follow-up but 3M product 1 rash (6.7%). 3M product not worse, numerically, than CP. DP worse than 3M lot A1. A1 reported to have easiest removability.
	<b>Safety Challenge Studies-</b> see review of DDDP
9	<b>Study 12853</b>
10	<b>Study 12952</b>
11	<b>Study 13062</b>
	<b>Other studies that collected AEs and skin irritation data</b>
12	<b>Study 12635</b> – “no reports of erythema, edema, rash, or dryness for any test materials
13	<b>Study 13447</b> - no reports with 3M product. One slight redness with comparator

Sources- detailed study reviews, CSRs. CP=ChlorPrep, DP=Duraprep

Adhesion-lower than company expected on saline challenged. Company attributed this to the polymer ratio and used the next drape adhesion study (12794) to evaluate modifications of the polymer ratio components. Study 12794 results indicated that compared to ChlorPrep, all 3M lots (formulations) were lower than ChlorPrep in Dry Condition and all 3M lots were similar to Duraprep and higher than ChlorPrep in Wet.

Prep removability rating - in study 12985, all 3M rated as moderate compared to controls which were rated as easy. In study 13337, 3M rated as difficult in the majority of subjects (56%) and moderate in the remaining subjects (44%).

The product was reported to not ignite when sparked.

### **7.3.1 Deaths**

3M reports that no deaths occurred in any clinical study investigating 3M CHG/IPA Prep.

### **7.3.2 Nonfatal Serious Adverse Events**

3M reports that no non-fatal serious adverse events occurred in any clinical study investigating 3M CHG/IPA Prep.

### **7.3.3 Dropouts and/or Discontinuations**

Per the sponsor's table shown in section 7.2 of this review, no subjects in the pivotal studies discontinued secondary to an adverse event. This is consistent with pivotal trial study report summaries.

The sponsor reports discontinuations secondary to an adverse event in only two studies (both safety challenge studies) of 10 clinical trials reported in the initial NDA submission). Please see the review of the DDDP reviewer for review of these trials.

To evaluate whether drop-outs not coded as adverse event related may have been due to an adverse event, I looked at the drop-outs in study 13260. The study report indicates that only one randomized subject did not complete (subject (b) (6)). The reason is reported as "other", "sites were compromised during testing-not all data were collected;"<sup>19</sup> This subject does not appear to have experienced an adverse event based on data in the ADAE.xpt dataset.

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<sup>19</sup> Page 46 bottom right hand of CSR for EM-05-13260 or page 38/104, adobe reader number –CSR submitted with initial NDA in SDN 1, July 2015. Based on information in the dataset ADSR.xpt, subject (b) (6) is usubjid (b) (6).

### 7.3.4 Significant Adverse Events

#### Pivotal trials:

The only pivotal trial reporting adverse events was study 13260. Two events characterized as “moderate” in severity were reported in one subject

- Subject (b) (6) (usubjid (b) (6)) experienced two “moderate” events; one in the abdomen and one in groin sites bilaterally. The events were of skin irritation, itching, dryness in testing sites on the abdomen and itching sensation in the bilateral groin sites. Based on the information in the referenced dataset the subject reported that symptoms began after she got home on testing day. Symptoms were reported to the lab at the 6-hour return visit. The subject was called the next day and reported symptoms resolved during the night and after soaking in a tub. The subject was exposed to 3M product with HEDTA and 3M product without HEDTA (Listing 16.2.7.1 and Listing 16.2.7.2)
- Subject (b) (6) (usubjid (b) (6)) experienced an event characterized as mild event and coded as an allergic reaction, on the abdomen. This subject had a consult with a physician and the outcome is listed as not recovered/not resolved. Comments in this dataset indicate the subject reported itching, redness, and bumps to the left abdomen test site beginning on 3-10-15. The Nurse Practitioner saw the subject on 3-10-15 and recommended over-the-counter cortisone cream and Benadryl. As of 3-18-15, the subject reported the event as ongoing off and on. The CSR reports that subsequently it was confirmed with the Investigator that the event resolved (p.61/104 reader number). The subject was exposed to 3M product with HEDTA (Listing 16.2.7.1).

### 7.3.5 Submission Specific Primary Safety Concerns

This is a 505b2. The sponsor reports depending on the general literature, non-product specific, to support the safety.

- A response as to the scientific bridge was in SDN 7 to the NDA. This response states that the data presented in the NDA demonstrate safety/tolerability and efficacy of the proposed 3M NDA product. The sponsor elaborates that the polymer is the “same” as the one used in their product, DuraPrep, “aside from a (b) (4) 20”. The sponsor also provided a listing of key references from non-clinical and clinical sources. References that were non-product specific were noted to be linked to the bibliography. I saw four links in the literature reference list, section 2.6.7, of this submission (references #3, 11, 36, and 37 in section 2.6.7). Reference #3 is a review type article of chlorhexidine that does not allow independent assessment and is not very

detailed in the safety descriptions. Reference #11 focuses on efficacy of alcohols. Reference #37 is about chlorhexidine and its diacetate and digluconate salts. It contains literature review level safety descriptions and was published 23 years ago. I did not follow the link to reference #36 primarily because of a security type prompt to connect to the site and based on the title, it seems unlikely to be helpful in terms of safety support. A 2001 publication was submitted that is a review type article which does include some discussion of safety, but is a review.

- A response to the scientific bridge was included in SDN 9. This referred back to the Modules 2.6 and 2.7 and provided the actual publications that were not submitted with the initial NDA (about 94 publications). Module 2.7 included the discussion of pediatric literature and anaphylaxis/hypersensitivity. These topics are discussed in sections 7.3.6 and 7.3.7 of this review. Some of the publications referenced by the sponsor use brand names.
- I looked at the Target Product information in SDN 9. Four publications are used to support “Do Not Use” information. Two are nonclinical. Neither of the other two is product specific but one is of questionnaire distributed to health care workers regarding skin symptoms with occupational exposure and reported 4 cases of IgE-mediated chlorhexidine allergy. The other is a report of large case series of contact allergy.
- The sponsor references older, non-clinical publications to support the do not use in lumbar puncture or contact with meninges. I am not advocating that such should be done. It is noted, however, that in at least one publication submitted by the sponsor, the authors concluded that their results of a review of cases support the hypothesis that CHG can be used for skin antisepsis before spinal placement without increasing the risk of neurologic complications attributed to the spinal anesthetic.<sup>21</sup>

Comment: I recommend the Division ask the sponsor to resubmit the literature review, specifically for the pediatric literature and for the clinical literature intended to support use and “Do not Use” sections of labeling or any sections requiring literature support other than anaphylaxis and hypersensitivity. This resubmission would be filtered to exclude all product specific literature (i.e. include only non-product specific literature).

### **7.3.6 Literature on Vulnerable Pediatric populations**

None of the clinical studies of 3M CHG/IPA Prep were performed on subjects less than 18 years of age.

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21 Sviggum et al, Regional anesthesia and Pain Medicine 2012 Mar/Apr; 37(2): 139-144)

## Clinical Review

Teresa A. Podruchny

NDA 208288

SoluPrep™ Film-forming Sterile Surgical Solution (2% w/v Chlorhexidine Gluconate and 70% (v/v) Isopropyl Alcohol)

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In section 2.7.4.5.1 of the CSS, the sponsor describes that a 1999 publication<sup>22</sup> indicates that the skin of the pediatric population from 2 months old up to 18 years of age is essentially the same as adult skin. The vulnerable pediatric population is infants less than 2 months old and premature infants due to thinner and less developed skin and may be more easily irritated from surgical preparation solutions.

The sponsor searched EMBASE, Medline, Biosis, and Chemical Abstracts databases for topical chlorhexidine products used in the pediatric population. The terms used were chlorhexidine or CHG combined with indexing terms for topical or skin dermatitis. The sponsor then describes the properties of infant skin and the results of the literature search described.

Neonate skin is described as having skin that is 40-60% thinner than an adult and that a premature neonate's skin is "markedly thinner" than that of a full-term infant (p.26/62 of the CSS). The stratum corneum is the major barrier of the skin to the passage of drugs (not the deeper layers of the epidermis and dermis). Premature infants less than 28 weeks gestation have no or incompetent epidermal barriers at birth<sup>23</sup>. The stratum corneum starts to develop at 34 weeks gestation and then thickens (CSS information). The CSS indicates the epidermis of a 2 week old premature infant, histologically, shows increased epidermal thickness and a well-formed stratum corneum.<sup>24</sup> Skin maturation accelerates after birth.<sup>25</sup> The CSS summarizes that postnatal and gestational age are important in the assessment of an infant's skin. Full term babies generally have a stratum corneum that functions comparably to an adult though the skin is still adjusting. The sponsor reports that several studies indicate that, depending on gestational age, it can take up to two month for skin maturity and full barrier function.

The sponsor discusses the difference in ratio of surface area to weight in babies as 3 to 5 times that of an adult. This places the baby at increased risk for percutaneous absorption. The sponsor searched the literature for chlorhexidine absorption in infants and related symptoms. The sponsor's conclusions of the literature reviewed,

- absorption of chlorhexidine in full term babies was minimal, but was reported in pre-terms and increases with lower gestational age.
- Detectable chlorhexidine concentrations have been reported but that no toxicity or systemic adverse events have been reported due to this in the more than 5 decades of use in children (the clinical relevance is not known)

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22Lund C, Kuller J, Lane A. Neonatal skin care: the scientific basis for practice. Neonatal Netw. 1999;18(4):15-27

23 CSS references to Rutter, N. The immature skin. Brit Med Bull. 1988;44(4):957-970

24 CSS references to Evans NH, Rutter N. Development of the epidermis in the newborn. Biol Neonate. 1986;49:74-80.

25 CSS references Hardaway CA, Eichenfield LF. Neonatal dermatology. Curr probl dermatol. 2000;12(3):115-117

## Clinical Review

Teresa A. Podruchny

NDA 208288

SoluPrep™ Film-forming Sterile Surgical Solution (2% w/v Chlorhexidine Gluconate and 70% (v/v) Isopropyl Alcohol)

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- Tens of thousands of children have been bathed in chlorhexidine solutions without reports of side effects.
- It seems reasonable to conclude that toxicity would be apparent by now.

The sponsor's literature includes an abstract of a case of transient hyperchloremia in infant born at 29 week gestational age who experienced 7 episodes of sepsis before age 58 days<sup>26</sup>. After the last septic episode, he was bathed with 2% CHG body wash, whole body, on alternate days for 2 weeks. After CHG therapy was discontinued, sodium chloride levels returned to normal in 48 hours.

The following table is from my read of publications references in this section of the CSS. This read was not a comprehensive review but rather was in part to ascertain how detailed the safety information was reported. It appears that though these publications varied, there is some evidence of accumulation in the literature after CHG exposure in premature infants. No obvious serious skin reactions are noted in these publications.

**Table 10 Literature review Pediatric**

	Miscellaneous	
Chapman et al, 2013 <sup>27</sup>	Sage Cloth (2% aqueous CHG impregnated cloth)  Infants older than 48hrs of life	CHG detected in blood of premature infants receiving CHG antiseptics for PICC insertion, highest at 2-3 days after exposure. Authors say suggest could be delayed or ongoing cumulative absorption in premature infants. Did not find evidence of CHG-related skin irritation
Garland et al 2009 <sup>28</sup>	10% IPA or 2% CHG Randomized  N=48 neonates Neonates > 1500 g and At least 1 week old  CSS indicates CP used but	Publication notes FDA limited trial to larger & older neonates due to 6% experiencing serious contact dermatitis in previous work by this group.  7/24 with detectable CHG levels  Possible suggestion of accumulation "no significant systemic side effects"

26 Celik IH, Oguz SS, Dilmen U. Chlorhexidine-associated transient hyperchloremia in an infant. *Ped Dermatol.* 2014;31(1):110-111. Abstract

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

28 Garland JS, Alex CP, Uhing MR. Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antiseptics for central venous catheter placement in neonates. *J Perinatol.* 2009;29(12):808-813.

	publication indicates CHG in ampules used	"failed to detect contact dermatitis following cutaneous antiseptics with 2% CHG before PICC insertion.
Mullany et al <sup>29</sup> 2008	Dilutions of 20%w/v CHG in water Critically ill infants ≥1500 g and ≥ 7 days old Full body skin cleansing in Nepal, India	286 infants randomized to 1 of 3 solutions  No instances of skin irritation No differences between 3 CHG solutions  About 1/3 with detectable levels in 1% group  The sponsor's summary table (Table 24 in the CSS, page 59/62 reader) states that body temperature was minimally reduced.
Blumer et al <sup>30</sup> 1982	Abstract Full body bathing Full term newborns Randomized to Hibiclens (4%) or soap	No percutaneous absorption first 3 days No increase in adverse clinical reactions compared with castile soap
O'Neill et al <sup>31</sup> 1982	Hibiclens 4% diluted 1:10 aqueous 51 infants in study, treated 41 full term neonates with various regimens	No chlorhexidine detected in blood by gas-liquid chromatography Publication-"no treatment related side effects" reported during exposure or during 1 year follow-up
Aggett et al <sup>32</sup> 1981	1% solution chlorhexidine in ethanol, dusting powder with 1% chlorhexidine and 3% zinc oxide	Publication summary indicates percutaneous absorption in preterm neonates with the solution, but not in term or preterm infants with dusting powder
Cowen <sup>33</sup> 1979	Hibiscrub 34 newborn infants bathed	From publication-Low levels in blood of all 10 babies sampled by heel prick & 5/24 venous. Detection varied "greatly" with method & timing of sample. No correlation with gestational or postnatal age and chlorhexidine levels. "No unusual effects which could be attributed to chlorhexidine absorption were noted."

29 Mullany LC, Khattry SK, Sherchand JB, et al. A randomized controlled trial of the impact of chlorhexidine skin cleansing on bacterial colonization of hospital-born infants in Nepal. *Pediatr Infect Dis.* 2008;27(6):505-11

30 Blumer JL, Husak MP, Wiltshire J, et al. Antibacterial efficacy and safety of neonatal bathing with Hibiclens. *Pediatr Res.* 1982;16(4):148A

31 O'Neill J, Hosmer M, Challop R, et al. Percutaneous absorption potential of chlorhexidine in neonates. *Current Therap Res.* 1982;31(3):485-489

32 Aggett PJ, Cooper LV, Ellis SH, et al. Percutaneous absorption of chlorhexidine in neonatal cord care. *Arch Dis Childhood.* 1981;56:878-880

33 Cowen J, Ellis SH, McAinsh J. Absorption of chlorhexidine from the intact skin of newborn infants. *Arch Dis Childhood.* 1979;54:379-383

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The sponsor reports that three safety studies using a 2%/70% CHG-IPA formulation were published in the pediatric literature.

- One<sup>34</sup> describes bathing of infants in two neonatal intensive care units (NICU). Skin preparations were used before intravenous catheter insertions and phlebotomy and during dressing changes. Two cases of skin breakdown were reported in infants < 1000g. This prompted a change in the NICU protocol with restriction of use of the 2%CHG/70% IPA to infants > 1000 g or 2 weeks of age.
- One describes a multicenter, prospective pilot trial to compare tolerance of CHG to PVP-I antiseptics for PICC placement in neonates.<sup>35</sup> Primary outcome measures were contact dermatitis, catheter colonization, and chlorhexidine absorption. 48 critically infants, weighing ≥ 1500 g and 7 days of age or more but less than 2 months old were randomized to either 2%CHG/70% IPA (ChloraPrep) or 10% PVP-I. The goal was to enroll 150 neonates but it was terminated after 2 years and only 48 neonates due to parental refusal and difficult entry criteria. There was an insufficient number for power. Severe contact dermatitis did not occur in either group and reportedly, only PVP-I catheter sites had signs of dermatitis. Five neonates of 10 neonates had measurable serum concentrations (>10 ng/mL) after the first application of ChloraPrep. Seven neonates had concentrations of 13-100 ng/mL sometime during catheterization. The highest concentration (100 ng/mL) occurred after the third dressing change in a 27 day old born at 28 weeks gestation.
- One describes the effects of 2%CHG/70% IPA (ChloraPrep) on skin inflammation and stratum corneum integrity at PICC sites in NICU patients.<sup>36</sup> Application of ChloraPrep to the PICC site did not visibly increase erythema. The referenced abstract states that the “dressings used to secure PICC lines contribute to the observed skin compromise at CHG- treated skin sites and may affect skin barrier development in similar populations of neonates. The dressing was a transparent, semi-permeable adhesive (Tegaderm). The publication reports that their sample size in the age range for premature infants was small (14), erythema differed for all sites at week 1 when compared to control and was higher than control at weeks 2 and 3. PICC skin dryness was higher than control at week 2.

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34 CSS references to Pettit J, Sharpe E. The safety of chlorhexidine gluconate as a skin antiseptic in neonates & young infants. Poster. Presented at Association for Vascular Access (AVA) Annual Scientific Meeting, 2010. National Harbor, MD; Sep 24-26, 2010

35 Garland JS, Alex CP, Uhing MR. Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antiseptics for central venous catheter placement in neonates. *J Perinatol.* 2009;29(12):808-813.

36 CSS references to Visscher M, deCastro MV, Combs L, et al. Effect of chlorhexidine gluconate on the skin integrity at PICC line sites. *J Perinatol.* 2009;29(12):802-7.

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The sponsor summarized that low birth weight infants are at increased risk of skin irritation and this risk is higher in the first weeks after birth. Based on these publications, one of the three reports (NICU study of Petit) reported skin breakdown/erythema that led to a restriction of use of 2% CHG/70% IPA to infants >1000g or 2 weeks of age.

The sponsor provides a discussion of case reports and surveys. The sponsor divided the presentation into a summary paragraph of alcohol-based chlorhexidine skin antiseptics and a summary paragraph of aqueous chlorhexidine skin antiseptics.

Burns characterized in the CSS for the alcohol based cases reports and surveys include

- “sustained extensive burns” in premature infants,
- “extensive chemical burns” in a neonate born at 26 weeks cleansed with 0.5% CHG/70% IPA (instead of saline accidentally),
- extensive abdominal burns with umbilical catheter insertion, and
- hemorrhagic skin necrosis associated with umbilical artery catheterization in an extremely premature infant attributed to 0.5% CHG/70% alcohol.

For the aqueous based chlorhexidine skin antiseptic case reports and surveys, the CSS shows one case linking use of 2% aqueous chlorhexidine on an “extremely premature” infant to chemical burns. The sponsor indicates that analysis of safety data in Table 24 suggests aqueous chlorhexidine is tolerated well in all age groups except very premature neonates. The sponsor notes that one study reported skin irritation with the aqueous based chlorhexidine in a subset of premature neonates (severe skin irritation) but no skin reactions in mature neonates and older infants treated with alcohol-based chlorhexidine.

The CSS describes (and references) a NICU survey that did not differentiate between aqueous and alcohol-based chlorhexidine preparations showed report of adverse events with CHG in 51% of 55 NICUS that responded to the survey. All were skin reaction and included burns (61%), erythema (32%) and erosions.

As well, a multiple page table summarizes the pediatric literature. This table summarizes 15 alcohol based chlorhexidine publications and 10 aqueous based chlorhexidine publications. Many of these have been discussed briefly in this review.

The sponsor concluded that reports and analyses of safety data from clinical efficacy and/or safety studies in Table 24 of the CSS found the major concern with alcohol-based and aqueous chlorhexidine solution was skin irritation. The sponsor summarizes that skin irritation, burns, and skin breakdown were limited to premature neonates and the burns were related to gestational age (severe only in “extremely premature neonates”). The sponsor states that no adverse skin reactions or other adverse events were reported in full term neonates and older children. The sponsor qualifies that post-

natal age for the studies in their Table 24 was not always give. The sponsor concluded that aqueous chlorhexidine was “usually well tolerated” in neonates with rare cases of burns in very low birth weight infants with solution applied during the first 2 weeks of life. Also, the sponsor concludes that alcohol-based chlorhexidine can cause skin irritation ranging from erythema to severe burns in neonate and that is related to the gestational age with highest risk in lowest-weight newborns with immature skin.

Based on the information in their presentation, the sponsor suggests that the 3M IND product be used with care in premature infants or infants under 2 months of age.

From a regulatory point of view, it is unclear how many of these publications can be used to support the safety as a few are noted to be branded. The sponsor can be asked to list how many of these studies/reports referenced a specific product and possibly to re-submit a presentation of this that only uses non-product specific literature.

### **7.3.7 Literature about Anaphylaxis and Hypersensitivity**

The CSS describes that a literature search for hypersensitivity was conducted in Medline, Embase, Biosis, and Chemical Abstracts. The strategy used was to search for the indexing terms or chemical registry numbers for chlorhexidine or CHG. These terms were combined with the indexing terms for hypersensitivity or anaphylaxis. The sponsor summarized the study reports and review articles and stated they presented all cases reports of anaphylaxis published between 2008 and April 2015.

1. A 2014 publication by LaChapelle<sup>37</sup> compared the irritant and allergenic properties of antiseptics. The following discussion of this publication is from the publication. This author noted and referenced that allergic contact dermatitis to chlorhexidine is well known since first published in 1962. The author also reports that large studies show sensitization rate of 2%, “mainly after repeated applications. The author notes it is also generally considered a “rather common” event in terms of relevance. In most cases, the reaction is limited to the application site but it can extend to other areas of the skin. In exceptional cases, it can cause photosensitivity or even a fixed drug eruption which can be confirmed by patch testing and/or photo-patch testing. The author notes that chlorhexidine in leg ulcers is listed in allergen catalogues but that it is particularly important when chlorhexidine is used under occlusion.

The author also notes that occupationally-related allergic contact dermatitis cases have been reported. Immunologic cases of contact urticaria and anaphylactic reactions are reported as “well documented”. The author notes that even if the reported case numbers are “rather low”, the problem is of great concern. The author describes a

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37 LaChapelle J-M. A comparison of the irritant and allergenic properties of antiseptics. Eur J Dermatol. 2014;24(1):3-9.

chapter in a Dermatotoxicology textbook<sup>38</sup> devoted to these reactions. This textbook is noted to describe anaphylactic, life-threatening reactions under different circumstances such as application to damaged skin (e.g. wounds, burns, dermabrasion), venous puncture, application on mucous membranes, intra-urethral application prior to cystoscopy, chlorhexidine-containing lubricant applied intravaginally, and chlorhexidine impregnated devices. The author cites a recent paper<sup>39</sup> in which anesthesiologist emphasized that in a series of 344 patients with perioperative anaphylaxis, 7% could be “incriminated to chlorhexidine”. The author states that determining whether these are immediate-type reactions can be proven with prick testing.

The author notes the FDA alert about impregnated medical devices as well as an alert paper from Switzerland. The author notes this is considered a new occupational hazard with urticaria, angioedema, and anaphylaxis reported in health care workers<sup>40</sup>. The author posits that increased awareness and easier access to chlorhexidine-specific IgE serologic testing should facilitate early diagnosis and reduce future risk of severe allergic reactions.

The conclusions of the authors included that allergic contact dermatitis is common when compared to other major antiseptics (octenidine, polyhexanide, and povidone-iodine) but it considered a relatively rare and weak allergen, however, it is troublesome for dermatologist because it can cause immunological contact urticaria and life-threatening anaphylaxis.

2. Krishna<sup>41</sup> et al reported results of a multi-center retrospective survey in the United Kingdom to evaluate the etiology and diagnostic utility of tryptase in anaphylaxis in general surgery. Retrospective data from 2005-2012 from 161 patients referred to four regional centers were reviewed. Patients were evaluated systemically by an allergy specialist. Inspection of anesthesia and drug charges, perioperative vital signs, clinical features and temporal association were evaluated. Though neuromuscular blocking agents (NMBA) were the most common cause (38%) and antibiotics, the second most common cause (8%), chlorhexidine (5%) and patent blue dye emerged (6%) emerged as causes of IgE mediated anaphylaxis. Latex allergy was only found in patient (0.6% of the total cases). No cause was found in 30% of cases. The authors assert that chlorhexidine and patent blue dye are emerging health-care associated allergens that

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38 The text is Marzulli and Maibach's Textbook of Dermatotoxicology

39 The reference is Leysen J, Bridts C, Sabato V, Vercauteren M, Ebo D. Anaphylaxis during general anaesthesia: ten-year survey from a Belgian allergyclinic. *European Academy of Allergy and Clinical Immunology*, 16-20 June 2012, Geneva (poster 291).

40 The reference is Nagendran V, Wickin J, Ekbote A, et al. IgE-mediated chlorhexidine allergy: a new occupational hazard? *Occup Med (Lond)* 2009; 59: 270-2.

41 Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Experiment Immunol*. 2014;178(2):399-404.

may result in anaphylaxis. They state that elevated serum tryptase is highly predictive of IgE-mediated anaphylaxis and that both methods used were comparable.

3. A 2014 publication by Obstrup<sup>42</sup> et al investigated data of all patients evaluated for perioperative allergic reactions in a Danish allergy center between 2004 and 2012. The following is based on the publication. The objectives were to estimate the prevalence of chlorhexidine allergy in preoperative allergy and characterize the specificity and sensitivity of diagnostic tests for chlorhexidine allergy. The severity of the allergic reactions was classified on a scale of 1-4 (mild to cardiac arrest, 3 was severe, life-threatening, usually multiorgan involvement). Perioperative allergic symptoms ranged in severity from rash to anaphylactic shock, and there were cases of cardiac arrest. The authors report that all patients underwent a systematic individualized investigation protocol for all drugs exposed to before the reaction by criteria, essentially, of intravenous drugs given within an hour and most other routes of administration, within two hours. All patients were also tested for allergy to chlorhexidine, latex, and ethylene oxide as all had been exposed to these. Other frequently tested drugs included opioids and anesthetic drugs.

The authors defined chlorhexidine allergy as with a minimum of two positive diagnostic tests in combination with and at least one relevant allergic reaction. The authors' results were that 9.6 % (22/228) of patients met the definition of chlorhexidine allergy. Estimated sensitivity and specificity for specific IgE were 100% and 95% respectively. They recommended that all patients with perioperative allergic reactions be tested with chlorhexidine and for use of tests like the specific IgE test and skin prick test at a minimum for investigation of chlorhexidine allergy.

3Arochena<sup>43</sup> et al, abstract from 2014, is a report of a retrospective nature of all patients referred to their allergy center through a pathway from September 2011 to August 2013. Skin prick, intradermal and drug provocation testing were conducted as deemed appropriate. Their rationale was that allergic reactions during general anesthesia are frequent and usually secondary to one of several pharmaceutical agents. Eighteen patients with various surgeries (largest stratum, orthopedic) with a mean age of 58 years of age were seen. Allergy was confirmed in 9 patients, demographics "impeded study in 2, pharmacologic cause in 1, and cause not identified in six. Causes were "NMBAs" in 5 patients, midazolam in 3, chlorhexidine in 2 and one each from ondansetron or povidone iodine.

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42 Opstrup MS, Malling H-J, Kroigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy – a large single-centre evaluation. *Allergy*. 2014;69(10):1390-1396.

43 Abstract, *J. Allergy Clin Immunol* February 2014.

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4. Malihol<sup>44</sup> et al, 2009, evaluated the risk of sensitization associated with topical dermatitis treatment. For a 10-year period between January 1997-January 2007, 641 consecutive children less than 16 years old with atopic dermatitis (AD) were referred by a doctor for multidisciplinary clinical and allergic evaluation. The median age was 3.4 years and 48% were male. The authors conclude that the study showed that the prevalence of contact allergy to AD treatment in children is not negligible and antiseptics and emollients appear to be the most frequent allergen (based on patch test). Chlorhexidine seemed to be the most frequent allergen (42.5 % compared to emollients (47.5%).

5. McNeill<sup>45</sup> et al , 2008, retrospectively analyzed patients referred to the Immunology Unit for evaluation of a specific hospital between June 2000 and February 2007 after experiencing anaphylaxis or an anaphylactoid reaction during general anesthesia. Patients were evaluated by an immunologist with the review by a senior anesthetist. Fifty patients were referred. Patients were between 14 and 80 years with a mean age of 46 years. Sixty percent (60%) were female. 39 had severe reactions, four were moderate, and six were mild. Acute serum tryptase levels were available in 56% of patients (n=28). All sixteen patients with increased tryptase values had experienced severe reactions. A cause was identified in 40 patients (80%). Of these, NMBA were implicated in 19 patients (38%). The authors report (with references) that sensitization to chlorhexidine has been responsible both for anaphylaxis and for cases of oral allergy syndrome, contact, dermatitis, and local urticaria. Two severe cases had large skin prick wheals (>10 mm). The authors recommend adding chlorhexidine testing to prevent unrecognized reactions to this.

6. Chong<sup>46</sup> et al retrospectively reviewed twenty-three consecutive adult patients who experienced anaphylaxis during anesthesia from March 1, 2005 to February 28, 2006. Twelve were female and the mean age was 53 ± ~16 years. Fifteen had positive skin tests to NMBA and all showed cross-sensitivity to with one or more NMBA. The next most common agent in this series was the opioids (3=13%). One patient each showed positive testing to povidone-iodine and chlorhexidine. The patient with chlorhexidine allergy was exposed during an orthopedic procedure. Re-questioning indicated he had a medical history of mouth pruritus and lip swelling upon use of a chlorhexidine mouthwash many years before. The authors note there is also evidence that

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44 Mailhol C, Lauwers-Cances V, Rance F, et al. Prevalence and risk factors for allergic contact dermatitis to topical treatment in atopic dermatitis: a study in 641 children. *Allergy*. 2009;64:801-806.

45 McNeill O, Kerridge RK, Boyle MJ. Review of procedures for investigation of anaesthesia-associated anaphylaxis in Newcastle, Australia. *Anaesth Intensive Care*. 2008;36(2):201-207.

46 Chong YY, Caballero MR, Lukawska J, et al. Anaphylaxis during general anaesthesia: one-year survey from a British allergy clinic. *Singapore Med J*. 2008;49(6):483.

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anaphylaxis to chlorhexidine could be preceded by chlorhexidine-induced contact dermatitis<sup>47</sup>.

7. A book chapter authored by Heinemann, Sinaiko, and Maibach<sup>48</sup> reviewed the literature using PubMed for “chlorhexidine anaphylaxis”, “chlorhexidine contact urticaria” and “chlorhexidine allergy”. Sources for the chapter were bibliographic citations of relevance were reviewed when possible and standard textbooks of allergy and dermatology were screened for information about chlorhexidine. Also, reports from an alert paper from the World Health Organization, Japanese and Swiss journals about anaphylactic shock secondary to chlorhexidine-coated venous catheters were not “studied” in detail. The authors reviewed 72 case reports of chlorhexidine immediate type reactions. Only 15% were female. Twenty-one (21) occurred when chlorhexidine was used on damaged skin (10 case) or when the skin barrier was broken after application (n=9, e.g. surgery, venous puncture). 32 patients showed an immediate type reaction with application of chlorhexidine to mucous membranes. Most occurred after use of intraurethral instillation of urethral jelly before cystoscopy or catheterization. Three were after use as a lubricant intravaginally during gynecologic examination, and one was case each was from lip application to a wound, after an ophthalmic wash solution, and after use of a dental gel containing chlorhexidine. The authors note only three cases of immediate type reactions after use of chlorhexidine on “more or less unbroken skin” though in these cases, chlorhexidine was applied to pre-existing hand dermatitis, to acne lesions, or to erythematous skin after friction trauma from riding a horse.

8. A review by Lim and Kam<sup>49</sup> summarizes that the incidence of contact dermatitis to chlorhexidine in atopic patients is 2.5 to 5.4%. The review is broad, covering microbiology, pharmacology, clinical applications, and adverse effects. The adverse effects section of this review states that adverse effect of chlorhexidine are rare with 50 reports to the Japanese Ministry of Welfare between 1967 and 1984, 26 to the Danish Medicines Agency between 1968 and 2000, and 182 to the Committee on Safety of Medicines in the United Kingdom between 1965 and 1996. Of the 50 reports to the Japanese authority, nine were anaphylaxis. All were associated with mucosal application.

The authors note that oral ingestion is usually well tolerated due to negligible systemic absorption but reference a publication of five babies accidentally fed formula made with

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47 The authors reference this to Ebo DG, Stevens WJ, Bridts CH, Matthieu L. Contact allergic dermatitis and life-threatening anaphylaxis to chlorhexidine. *J Allergy Clin Immunol* 1998; 101(1 pt 1):128-9.

48 Heinemann C, Sinaiko R, Maibach HI. Contact urticaria and anaphylaxis to chlorhexidine. In: Marzulli and Maibach's *Dermatotoxicology*. 7th edn. Zhai H, Wilhelm K-P, Maibach HI, eds. CRC Press, Boca Raton FL, 2008; 485-495

49 Lim KS and Kam PCA. Chlorhexidine – pharmacology and clinical applications. *Anaesth Intensive Care*. 2008;36:502-512.

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chlorhexidine 0.05% instead of sterile water. Four developed tongue edema and oral ulcers and one had acute pulmonary edema. An 80 year old woman who accidentally ingested 10 g of chlorhexidine died (developed acute respiratory distress syndrome). A suicide attempt of 30g ingestion resulted in diffuse fatty degeneration of the liver and lobular hepatitis. Several other exposure types (e.g. corneal, intravenous, otic) are described. Skin reactions are discussed.

The authors discuss published findings from a randomized, controlled trial of chlorhexidine gluconate impregnated dressing with povidone iodine for central venous catheter site care. Contact dermatitis is noted. There were nine reported skin reactions in 300 babies. The authors state that the incidence of anaphylaxis is difficult to estimate. Nine were reported in Japan in a 17 year period (see above), 11 in Australia between the years of 1985-1994, and 3 in Finland up to 1999. 36 subjects who experienced anaphylactoid reactions were referred to the Danish Anaesthesia Allergy Centre, established in 1998, up to July 2001. Four of 21 patients (who had positive tests to various agents preoperatively) showed positive reactions to chlorhexidine. Intra-operative anaphylaxis to chlorhexidine with application to skin have been reported. Cases with urethral gels used in catheterization are noted (n=22). The authors note that wound dressings have been reported to cause anaphylaxis (Bactigras™, 0.5 g chlorhexidine acetate per 100g and paraffin).

The authors state that the risk of sensitization to health care workers is small. The authors also state that acute hypersensitivity reactions are often not recognized and may be underreported.

9. Beaudouin<sup>50</sup> et al, 2004, reviewed chlorhexidine. These authors summarized that immediate hypersensitivity reactions with chlorhexidine can occur from contact with skin or mucosa. They note 50 case reports published worldwide of chlorhexidine-related anaphylaxis over the past 10 years of which fifteen occurred during surgery. The occurrence was characterized as rare but to be kept in mind. Signs were noted to appear 15-45 minutes after starting anesthesia. The authors recommended prick-tests or intradermal reaction techniques if there is any suspicion of immediate allergy to chlorhexidine. The authors note that over 100 medical products on the French market contain chlorhexidine.

The CSS contains brief discussion of thirteen additional publications under a section titled, "Case Reports of Anaphylaxis". Based on review of the information in this section of the CSS, anaphylaxis cases have been reported in various settings, many as noted in the earlier literature above. Somewhat unique case reports are,

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50 Beaudouin E, Kanny G, Morisset M, et al. Immediate hypersensitivity to chlorhexidine: Literature review. *Europ Ann Allerg Clin Immunol.* 2004;36(4):123-126.

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- In the catheterization lab precipitated by an intravenous cannula through chlorhexidine-prepped skin and additional cleaning of the port with chlorhexidine in a patient with a history of prior exposure to chlorhexidine.<sup>51</sup>
- In cardiac surgery due to chlorhexidine-impregnated central venous catheters<sup>52</sup>
- Anaphylaxis after use of chlorhexidine –containing urethral lubricant in a 74-year old patient<sup>53</sup>. The CSS summarizes that the data from a local immunology service found two of nineteen cases of anaphylaxis over a 15-year period attributable to chlorhexidine. The authors also reference other publications as centers reporting that 13-44% of anesthetic-related incidences of suspected anaphylaxis test positive for chlorhexidine sensitivity.

The sponsor summarizes that a search of the published medical literature found that acute hypersensitivity (anaphylaxis or anaphylactoid reactions) to chlorhexidine is rare but incidence is difficult to estimate. The sponsor notes some suggests 4% and 7% of perioperative anaphylaxis may be related to chlorhexidine use and that the incidence appears higher in atopic patients and higher in the Japanese population.

The sponsor summarizes that the vast majority of anaphylaxis cases were related to use on wounds, broken skin, or mucosa. They posit that it appears to be the contact of chlorhexidine that causes the IgE-mediated hypersensitivity reaction. The sponsor asserts that although serious hypersensitivity reaction can occur, they are rare when compared to the large numbers of exposures over the last 60 years to chlorhexidine.

*Reviewer-note that some of the literature may have mentioned brand names, such as the Beatty publication of the 74 year old with anaphylaxis after a urethral lubricant was used. The precut was brand Instillagel.*

### 7.3.8 Skin Irritation Assessments in Pivotal Trials

#### 7.3.8.1 EM – 012760

Evaluation of skin irritation was as follows, based on the protocol included in NDA submission 0000<sup>54</sup>, before collection of the baseline, and 10-minute, and 6-hour post-

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51 Msonthi A, Morrison C, Nasr I, et al. Chlorhexidine allergy. Clin Exp Allerg. 2015;45:492-540. Abstract P.25.

52 Guleri A, Kumar A, Morgan R, et al. Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature. Surg Infect. 2012;13(3):171-174

53 Beatty P, Kumar N, Ronald A. Correspondence: A complicated case of chlorhexidine-associated anaphylaxis. Anaesthesia. 2011;66:60-61.

54 Clinical study protocol, version 2, issue date 10/1/2013 6:58:36PM, EM-05-012760 p.23/54 (adobe reader page numbers).

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prep samples. As noted previously, a rating of 3 in any category during the 10-minute and 6-hour post-prep samples was considered to represent significant irritation and qualified as an adverse event. Any area with a rating of 3 was not to be sampled.

The study report states that no erythema, edema, rash, or dryness was reported on either body region during the study. Data in Table 14.1.1.2 and dataset ADSR.xpt are consistent with this statement as well as an audit of subject data in Listings 16.2.8.1.

### 7.3.8.2 EM-013260

The skin irritation scale used in study 13260 is the same as the one in study 12760. The CSR reports that two subjects had moderate reactions on the abdomen at 6 hours post-prep

- Subject (b) (6) and subject (b) (6). Subject (b) (6) experienced moderate erythema on the left abdominal site with the 3M IND product that has HEDTA and on the right abdominal site with the 3M IND product without the HEDTA.
- Subject (b) (6) experienced moderate dryness on the right with exposure to ChloraPrep.

Based on the CSR Table duplicated below, of the mild reactions,

- The highest incidence of any skin reaction in either body region at 10 minutes was erythema on the inguinal region in 2% of subjects with ChloraPrep (n=5).
- Of the mild reactions, no edema was reported in abdominal area sites at any time point. One edema was reported in the inguinal region. This was at 10 minutes and was a ChloraPrep subject.
- Rash was reported in the abdominal sites only at 6 hours. The 3M product with HEDTA reported more subjects with rash at 6 hours than the other products (2% compared to 1.4% ChloraPrep, 1.2% 3M without HEDTA, and 1% Saline. Rash was reported in the inguinal sites in about the same number of subjects relative to the HEDTA ( 5% of 3M CHG/IPA and 5.3% of CHG/IPA Prep with HEDTA) compared to 7.7% of ChloraPrep, and 10.8 % of Saline subjects at 6 hours. Rash was not reported at earlier time points. *(Note to the reader: These summary data were not verified by listings or the dataset due to the size of the listings and the lack of a dataset similar to the listings for the skin reactions or an adequate define file. As this is to be a bridge for safety between the 3M product with and with HEDTA, we might consider asking the sponsor to submit a dataset formatted like Listing 16.2.8.1 and 16.2.8.2.)*
- Dryness in the abdominal area was reported only at hour 6 and in more 3M CHG with HEDTA subjects than with other preps (4.1% compared to 2.6% 3M product without HEDTA, and 2.9% each for ChloraPrep and Saline). In the inguinal area, Dryness was reported only at hour 6 and by more ChloraPrep subjects than with other preps (2.8% compared to 1.6%, and 1.4% for 3M with HEDTA and Saline respectively, and 0.8% with the 3M product without HEDTA.

**Table 11 Study 13260 Incidence Mild Skin Irritations**

**Table 11 Subjects with a Mild Skin Irritation Score (ITT/Safety Population)**

Skin Irritation n (%)	Sampling Time Point	3M CHG/IPA Prep	3M CHG/IPA Prep with HEDTA	ChloroPrep	Saline
<b>Abdominal Region</b>					
N		343	343	347	104
Erythema	Baseline	3 (0.9)	1 (0.3)	0	0
	10 Minutes	2 (0.6)	1 (0.3)	2 (0.6)	0
	6 Hours	32 (9.3)	33 (9.6)	15 (4.3)	6 (5.8)
Edema	Baseline	0	0	0	0
	10 Minutes	0	0	0	0
	6 Hours	0	0	0	0
Rash	Baseline	0	0	0	0
	10 Minutes	0	0	0	0

Skin Irritation n (%)	Sampling Time Point	3M CHG/IPA Prep	3M CHG/IPA Prep with HEDTA	ChloroPrep	Saline
	6 Hours	4 (1.2)	7 (2.0)	5 (1.4)	1 (1.0)
Dryness	Baseline	0	0	0	0
	10 Minutes	0	0	0	0
	6 Hours	9 (2.6)	14 (4.1)	10 (2.9)	3 (2.9)
<b>Inguinal Region</b>					
N		240	245	248	74
Erythema	Baseline	1 (0.4)	1 (0.4)	1 (0.4)	0
	10 Minutes	2 (0.8)	2 (0.8)	5 (2.0)	1 (1.4)
	6 Hours	15 (6.3)	24 (9.8)	12 (4.8)	2 (2.7)
Edema	Baseline	0	0	0	0
	10 Minutes	0	0	1 (0.4)	0
	6 Hours	0	0	0	0
Rash	Baseline	0	0	0	0
	10 Minutes	0	0	0	0
	6 Hours	12 (5.0)	13 (5.3)	19 (7.7)	8 (10.8)
Dryness	Baseline	0	0	0	0
	10 Minutes	0	0	0	1 (1.4)
	6 Hours	2 (0.8)	4 (1.6)	7 (2.8)	1 (1.4)
Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloroPrep=ChloroPrep® Patient Preoperative Skin Preparation; HEDTA=(hydroxyethyl)ethylenediaminetriacetic acid Source: End-of-text Tables 14.2.1.14 and 14.2.1.15					

Data auditing: The dataset ADSR.xpt<sup>55</sup> (variable SRORRES) displays the skin reaction data. Listings 16.2.8.1 and 16.2.8.2 display skin irritation scale data by subject for

55 This appears to be the skin reaction dataset but the define file is not adequate to verify.

## Clinical Review

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NDA 208288

SoluPrep™ Film-forming Sterile Surgical Solution (2% w/v Chlorhexidine Gluconate and 70% (v/v) Isopropyl Alcohol)

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abdominal and inguinal regions respectively (dataset search for “mode” and “seve” after check to see that it was searchable). These sources were used to verify the CSR reported moderate events. The dataset and listing were consistent for the two subjects who experienced moderate events and that all other events were mild (282 lines of data). Most (23,031 lines of data) are recorded as “no reaction” in the referenced dataset. This is consistent with the CSR report that all other skin reactions were mild on both body areas.

Table 11 from the sponsor’s CSR shows the incidence of mild irritation per the score system.

### 7.3.8.3 Study 12759

The protocol included with NDA indicates same skin irritation scale used as was used in the other pivotal efficacy studies. The CSR states that no skin irritation scale score was higher than 1 (mild) for erythema, edema, rash, or dryness on either body region during the study.

Two subjects experienced treatment emergent irritations on the abdomen (subjects (b) (6) reportedly experienced mild erythema on the abdomen at 10 minutes post-prep with colorless 3M CHG/IPA Prep, which reportedly resolved by 6 hours post-prep.)

Four (4) subjects had treatment-emergent skin irritations on the groin. One subject experienced mild rash (8-117) in the groin at 10 minutes post-prep with colorless 3M CHG/IPA prep (resolved by 6 hours post-prep). Subject (b) (6) and (b) (6) experienced mild erythema at 6 hours post-prep with tinted 3M CHG/IPA prep. Subject (b) (6) experienced mild erythema at 10 minutes post-prep with colorless 3M CHG/IPA Prep reportedly resolved by 6 hours post-prep.

The sponsor’s summary table showing these results is displayed review. I checked this table against a sponsor –submitted dataset of skin reactions, ADSR.jmp<sup>56</sup>. No reactions in this dataset are more than mild.

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56 Variables SRORES, SRSTRESC, SRSTRESN

**Table 12 Study 12759 Incidence Mild Irritation**

**Table 9 Subjects with a Mild Skin Irritation Score (ITT/Safety Population)**

Skin Irritation [n (%)]	Sampling Time Point	3M CHG/IPA Prep, Tinted	3M CHG/IPA Prep, Colorless	ChloraPrep	Saline
<b>Abdominal Region</b>					
Randomized N		93	101	96	32
Erythema	Baseline	3 (3.2)	2 (2.0)	0	1 (3.1)
	10 Minutes	2 (2.2)	3 (3.0)	0	1 (3.1)
	6 Hours	0	0	0	0
Edema	Baseline	0	0	0	0
	10 Minutes	0	0	0	0
	6 Hours	0	0	0	0
Rash	Baseline	0	0	0	0
	10 Minutes	0	0	0	0
	6 Hours	0	0	0	0
Dryness	Baseline	0	0	0	0
	10 Minutes	0	0	0	0
	6 Hours	0	0	0	0
<b>Inguinal Region</b>					
Randomized N		99	97	97	31
Erythema	Baseline	2 (2.0)	0	1 (1.0)	1 (3.2)
	10 Minutes	2 (2.0)	1 (1.0)	1 (1.0)	1 (3.2)
	6 Hours	3 (3.0)	0	0	1 (3.2)
Edema	Baseline	1 (1.0)	0	1 (1.0)	0
	10 Minutes	1 (1.0)	0	1 (1.0)	0
	6 Hours	0	0	0	0
Rash	Baseline	2 (2.0)	0	1 (1.0)	1 (3.2)
	10 Minutes	2 (2.0)	1 (1.0)	1 (1.0)	1 (3.2)
	6 Hours	0	0	0	0
Dryness	Baseline	2 (2.0)	0	1 (1.0)	1 (3.2)
	10 Minutes	2 (2.0)	0	1 (1.0)	1 (3.2)
	6 Hours	0	0	0	0
Abbreviations: 3M CHG/IPA Prep=3M™ Chlorhexidine Gluconate/Isopropyl Alcohol Film-Forming Preoperative Skin Preparation; ChloraPrep= ChloraPrep® Patient Preoperative Skin Preparation, ITT=intent-to-treat					
Note: Skin reactions with a skin irritation score higher than 1 (mild) were not reported in the study.					
Source: End-of-text Tables 14.2.1.1 and 14.2.1.2					

Other studies evaluating skin irritation are presented in section 7.4.7 for study 12635 and section 7.5 of this review.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

In the pivotal efficacy and safety studies, inclusive of the study that terminated early (012759), only study EM-013260 reports the occurrence of any adverse events. The only other studies in the initial NDA submission reporting AEs are the safety challenge studies which are reviewed by DDDP and are not described in this review.

EM-013260

EM-013260- Due to on-face discrepancies between the IND annual report for IND 76549 submitted on 2-13-15 and amended on 9-9-15 description of adverse events and the adverse event presentation in the CSR, the sponsor was queried in the 74-Day Letter. The sponsor's response was submitted in SDN 9 to the NDA. The sponsor reported that the apparent discrepancy was that the NDA table (Table 12) was of treatment-emergent adverse events while the IND annual report included all adverse events.

The CSR states that a total of 5 subjects (5.569=0.9%) experienced six treatment-emergent adverse events after exposure on the abdominal area and 4/404 (1%) experienced 5 treatment emergent adverse events after exposure on the inguinal area. The CSR states that all treatment-emergent adverse events were recorded as resolved except for the allergic reaction of subject (b) (6) (usubjid (b) (6)). Information in dataset ADAE.xpt indicates all were resolved except the subject (b) (6) and that Subject (b) (6) was evaluated by the nurse practitioner who recommended over-the-counter Cortisone cream and Benadryl. Eight days later the subject reported the event was ongoing off and on.

The following table shows the adverse event terms and unique subjects for subjects who experienced adverse events<sup>57</sup>

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57 Listings 16.2.7.1 and 16.2.7.2 were used to identify the subjects with treatment-emergent adverse events on the abdominal and inguinal areas respectively (based on information recorded in column, "Treatment", with blank assumed to be non-treatment emergent. The define file was not adequate for variable identification, thus the dataset was used only to make a more succinct listing of adverse events.

**Table 13 Study 13260 Adverse Events**

	USUBJID	TRTA	SEX	RACE	AETERM	AELOC
1	(b) (6)	CH	M	WHITE	Abrasion, left inguinal crease	GROIN
2	(b) (6)	CH	M	WHITE	Skin abrasion, right upper abdomen	ABDOMEN
3	(b) (6)	CP	M	WHITE	Burning sensation, left lower/mid-back	ABDOMEN
4	(b) (6)	CL, CH	F	WHITE	Abdominal skin irritation, dryness and itching in testin...	ABDOMEN
5	(b) (6)	CL, CH	F	WHITE	Itching sensation in bilateral groin testing areas	GROIN
5	(b) (6)	CL	F	WHITE	Warmth/heat sensation at genital area	GROIN
7	(b) (6)	CH	M		Burning sensation, left groin	GROIN
3	(b) (6)	CL	M		Burning sensation, right abdomen	ABDOMEN
3	(b) (6)	CH	F	WHITE	Allergic reaction to left abdomen test area	ABDOMEN

Treatment codes are presumed to be the same as used in the subject data listing legend listing 16.2.7.1 and 16.2.7.2. CL=3M CHG/IPA Prep, Clear, CH=3M CHG/IPA Prep Clear-H, CP=ChloraPrep, S=saline

The table indicates that 2 subjects had AEs with both of the 3M products (unique subject ids (b) (6) and (b) (6)), 3 subjects with 3M + HEDTA s had an AE (unique subject ids (b) (6)), 1 subject each with the 3M product without HDTA and with ChloraPrep (unique subject ids (b) (6)). This appears consistent with Data Listing 16.2.71 and 16.2.7.2 with the caveat that a blank under the “Treatment” column was assumed not attributed to a treatment though the legend for these tables says, “Treatment(s) listed are those reported as applied on the specific site where the AE occurred; subjects may have received additional treatments.”

I looked in the skin reaction dataset (ADSR.xpt) for the subjects in the table above. Five of the subjects from the table had a skin reaction. Two did not have a reaction. Most of the reactions were mild. The type of reactions for subject (b) (6) was dryness and for the three other subjects ((b) (6)) was erythema. Subject (b) (6) had two skin reactions characterized as “moderate”.

#### 7.4.2 Laboratory Findings

Other than pregnancy testing, routine laboratory data were not collected in the clinical studies.

#### 7.4.3 Vital Signs

Vital signs were collected in the safety challenge studies. Listings were provided for the studies but datasets were not. I tend to think the vital sign data are non-contributory (i.e. non-informative) given what appears to be a widely held belief that there is negligible or absent percutaneous absorption in the study population recruited into these studies. Additionally, the studies are open-label and studies 12952 and 13062 are relatively

small. The sponsor was not required to measure laboratory data, vital signs, or electrocardiograms in pivotal trials.

The data presentations submitted do not provide data analyses or discussions more typical of an NDA product.

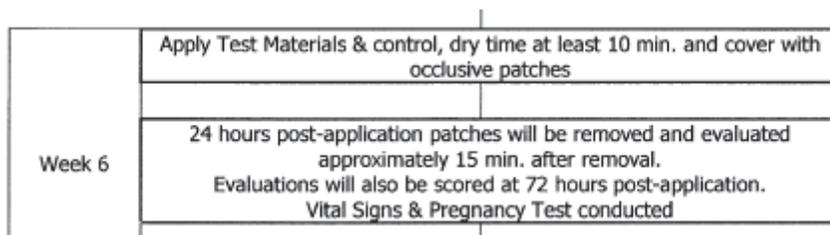
The sponsor reports in the CSS that no clinically significant changes in vital signs were noted during challenge studies.

At the request of my Team Leader, the following limited review of the vital signs is included in this review.

#### 7.4.3.1 Study 12853

Vital signs were collected twice in the study and are called initial and final. It is unclear exactly when the final vital signs were taken. The flow chart in the protocol issued on 4/24/15 appears to indicate it was 72 hours after application in week 6 (see cut and paste from the protocol, page 11/29 using adobe reader numbers) and the flow chart in the CSR (9.5, p.18/50 adobe reader numbers) indicates that Vital signs were taken on Day 1 and again on Day 36/39.

#### Figure 3 Study 12853 Vital Sign Assessment



The study enrolled 235, evaluable 205 (completed trial). 22 withdrew consent after one treatment, 7 discontinued by PI after at least one treatment each.

The tables below are from the CSR. For the table of evaluable subjects, evaluable subjects were defined as meeting all the inclusion and exclusion criteria, completing all visits to the Testing Facility, which included test material and control material application to test sites, and have all test sites evaluated.

The vital sign data is summarized by the sponsor as “no clinically significant changes in vital signs during the course of the trial”.

From a look at the listings in Appendix 16.4.4, it appears a number of people had high blood pressures at initial visit (>140 systolic or > 90 diastolic) and/or the final visit.

**Table 14 Summary Initial Vital Signs All Subjects**

**Table 12.5.1 Summary of Initial Vital Signs for All Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	18	96	30	58	16
Max	79	200	118	100	24
Average	45.4	130.3	83.4	74.5	18.2
StdDev	14.8	19.9	11.3	9.4	1.9
Median	46	128	80	74	18

Source: [Appendix 16.4.1 Initial Vital Signs for All Subjects](#)

**Table 15 Summary Final Vital Signs All Subjects**

**Table 12.5.3 Summary of Final Vital Signs for All Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	18	98	60	58	16
Max	79	210	110	100	24
Average	45.4	127.8	80.1	75.4	18.6
StdDev	14.8	21.1	9.6	9.3	2.0
Median	46	126	80	76	18

Source: [Appendix 16.4.2 Final Vital Signs for All Subjects](#)

**Table 16 Summary Initial Vital Signs Evaluable Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	18	96	62	58	16
Max	79	200	118	100	24
Average	46.0	130.5	83.7	74.3	18.1
StdDev	14.7	20.6	10.6	9.4	1.9
Median	47	127	80	74	18

Source: [Appendix 16.4.3 Initial Vital Signs for Evaluable Subjects](#)

**Table 17 Summary Final Vital Signs Evaluable Subjects**

**Table 12.5.4 Summary of Final Vital Signs for Evaluable Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	18	98	60	58	16
Max	79	210	110	100	24
Average	46.0	128.8	80.5	75.0	18.5
StdDev	14.7	21.3	9.6	9.1	2.0
Median	47	128	80	76	18

Source: Appendix 16.4.4 Final Vital Signs for Evaluable Subjects

7.4.3.2 Study EM-05-12952

38 subjects were enrolled and 37 completed and provided data. The average age was about 45 years and about 60% were female. Over 97% were Caucasian. The CSR indicates that the Initial vital signs were taken at day 1 and Final vital signs were taken at day 4. Some tables are copied directly from the CSR.

**Table 18 Study 12952 Vital Signs All Subjects**

<b>All Subjects</b>		<b>Initial</b>	<b>Final</b>	<b>Initial</b>	<b>Final</b>
	Age	Systolic Blood pressure		Diastolic Blood Pressure	
range	20-65	100-180	100-180	60-110	62-110
Mean	45.1± 12.9	129.4 ±19.3	129.5 ±19.5	81.2 ± 9.9	80.9 ± 8.7
Median	48	130	129	80	80
<b>All Subjects</b>		<b>Initial</b>	<b>Final</b>	<b>Initial</b>	<b>Final</b>
		Pulse		respiration	
range		60-88	64-100	16-20	16-24
Mean		72.4 ± 8.6	77.1 ± 6.9	17.3 ±1.3	19.1 ±2
Median		73	78	18	20

Source: Summary Table from CSR, Tables 12.5.1 and 12.5.3.

**Table 19 Study 12952 Initial Vital Signs Evaluable Subjects**

**Table 12.5.2 Summary of Initial Vital Signs for Evaluable Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	20	100	60	60	16
Max	65	180	110	88	20
Average	45.4	129.4	81.2	72.6	17.3
StDev	12.9	19.5	10.0	8.6	1.3
Median	48	130	80	74	18

Source: Listing 16.4.2 Initial Vital Signs for Evaluable Subjects

**Table 20 Study 12952 Final Vital Signs Evaluable Subjects**

**Table 12.5.4 Summary of Final Vital Signs for Evaluable Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	20	100	62	64	16
Max	65	180	110	100	24
Average	45.4	130.1	81.1	77.1	19.1
StDev	12.9	19.3	8.7	7.0	2.0
Median	48	130	80	78	20

Source: Listing 16.4.4 Final Vital Signs for Evaluable Subjects

7.4.3.2 Study EM-05-013062

The CSR indicates 60 subjects enrolled and 50 provided evaluable data. Table 14.1.1 indicates that the about 70% of subjects were female, mean ages were about 42-43 years old. The CSR indicates vital signs were measured on Day 1 before any exposures and Day 5.

Six dc due to adverse events-1 dc due to pyoderma. One subject positive pregnancy test at the end of the trial (this subject was lost to follow-up, subject # (b) (6)).  
3 for prohibited medications-1 used hydrocortisone for test site pruritus.

Vital signs as copied from the CSR.

**Table 21 Summary Initial Vital Signs All Subjects Study 13062**

**Table 12.5.1 Summary of Initial Vital Signs for All Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	20	98	62	60	16
Max	65	190	110	100	26
Average	42.9	129.0	83.0	75.5	18.3
StdDev	13.5	20.6	9.8	9.6	2.1
Median	47	122	83	76	18

**Table 22 Summary Final Vital Signs All Subjects Study 13062**

**Table 12.5.3 Summary of Final Vital Signs for All Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	20	94	68	58	16
Max	65	200	112	110	24
Average	42.9	127.4	81.8	75.1	17.8
StDev	13.5	25.1	10.1	11.9	2.0
Median	47	120	80	76	18

Source: Listing 16.4.3 Final Vital Signs for All Subjects

**Table 23 Summary Initial Vital Signs Evaluable Subjects Study 13062**

**Table 12.5.2 Summary of Initial Vital Signs for Evaluable Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	20	98	62	60	16
Max	62	180	100	98	24
Average	42.1	129.0	83.3	75.6	18.2
StDev	13.1	19.7	9.2	9.3	2.0
Median	47	122	84	76	18

Source: Listing 16.4.2 Initial Vital Signs for Evaluable Subjects

**Table 24 Summary Final Vital Signs Evaluable Subjects Study 13062**

**Table 12.5.2 Summary of Final Vital Signs for Evaluable Subjects**

	Age	Blood Pressure		Pulse	Respiration
		Systolic	Diastolic		
Min	20	94	68	58	16
Max	62	200	104	110	22
Average	42.1	125.7	81.2	73.9	17.6
StDev	13.1	23.8	9.3	11.1	1.6
Median	47	120	80	72	18

Source: Listing 16.4.4 Final Vital Signs for Evaluable Subjects

#### 7.4.4 Electrocardiograms (ECGs)

It appears these were not collected in any trial.

#### 7.4.5 Special Safety Studies/Clinical Trials

Three safety challenge studies designed to assess exaggerated application conditions of the test product were conducted.

- Study EM-05-012853- multiple applications over extended periods of time
- Study EM-05-012952- applications after ultraviolet light exposure
- Study EM-05-013062- applications after ultraviolet light exposure

Review of these studies is deferred to the prescription review division.

Other studies of issues unique to topical preoperative preparations were performed:

- a study characterized as Persistence of Efficacy
- Two studies intended to evaluate coverage area, dry time and vapor dissipation
- Two studies intended to evaluate drape adhesion qualities
- A flammability study

Adverse events, skin irritation from these studies are discussed in the section below, 7.5, Other Safety Explorations. Efficacy review of the two coverage and dry time studies is performed by the DNDP microbiologist.

#### 7.4.6 Immunogenicity

Not performed.

#### 7.4.7 Non-IND pilot study

##### Study EM-05-012635

Title: Preoperative Skin Preparation Study Following ATM-E1173 Methods to Evaluate the Antimicrobial Properties of Five Test Products

This study was conducted in Romania and is reported as a pilot, non-IND study. The study report states it was conducted “in spirit with Good Laboratory Practice standards and Good Clinical Practice standards (ICH E6) with the following exception: test article preparations were not analyzed at LABORATORY to confirm chemical composition, concentration, purity, stability, or homogeneity.” (p. 30/240 CSR).

This study is not submitted to support efficacy for reasons. The CSR notes that shortly after completing the study, there was a change in the formulation based on the results of the drape adhesion study. The CSR reports that “while working with the new formulation, it was determined [REDACTED] (b) (6)

[REDACTED] p.44/240, adobe reader page number) and therefore, the antimicrobial efficacy data could not be validated.

This lab is not known to the Agency as a site that conducts these trials (i.e. there is no history) and the study was not conducted under the IND. As I understand it, FDA would not use these data anyway without validation of the laboratory and testing procedures.

Reviewer: I consider that this study can only be used for safety if there is a safety finding. This might trigger additional exploration of the reported event and the trial methods and formulation. The absence of findings in a lab with which we have no history in terms of OSI audits and assessments of technique is not necessarily informative.

The study was randomized, included controls, and was blinded only to the principal investigators performing bacterial enumerations. The study objective was to evaluate the antimicrobial properties and safety of five test products. The study evaluated the immediate and persistent antimicrobial efficacy of a preoperative skin preparation containing 2% CHG-70% IPA (3M tinted product and tinted ChloroPrep) based on samples taken from sites within 30 seconds post-application, and at 10 minutes and 24 hours post- application.

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Healthy subjects aged 18 years to 70 years were admitted. Subjects were to be free of clinically evident dermatoses or injuries and meet baseline inguinal criteria ( $\geq 5 \log_{10}$  CFU/cm<sup>2</sup>). There were a number of inclusion and exclusion criteria reported in the CSR, many similar to the ones in the pivotal efficacy studies submitted in support of the efficacy of the IND product.

### Results 12635:

180 subjects were admitted to the testing portion of the study and 161, ages 19-68 years old (median 50 years) received product. Twenty-four % of subjects receiving product were male. All subjects were White/Caucasian. Clinical laboratories were not performed and “The recording of vital signs, physical findings, and other observations was not applicable to this study.” (p.44/240). Page 58/240 is from the protocol and indicates that the center has a general panel of subjects constantly renewed and that study subject would be selected from this general panel based on meeting criteria and willingness to abide by the protocol. Subjects would then be selected after specific questioning and clinical examination. Using professional subjects could select out those with previous exposure to either component of test products and underestimate skin irritation and adverse events in a naïve population.

No adverse events were recorded per the CSR (p.43/240) in contrast to CSR page 44/240 which reports that one adverse event was reported by the sub-investigator as mild and resolving without sequel. Skin irritation scores are reported as “no reports of erythema, edema, rash or dryness for any of the materials tested.” (p.44/240 CSR). The skin irritation scale used in this study is the same as the one used in the pivotal efficacy studies submitted to this NDA. However, reactions graded as 2 and 3 were noted to represent significant irritation and to require removal from the study. In the other pivotal efficacy studies, a 3 was considered to be an adverse event (as it was in this study, but the 2’s in the NDA studies did not lead to discontinuation per protocol).

Skin irritation assessments were made on D-21 at the beginning of the washout period, D-7 at the Screening Day, before baseline sampling, after product application, and before the 24-hour post-treatment sampling. The sponsor summarizes (p43/240) that “skin irritation scores showed no reports of erythema, edema, rash or dryness for any of the materials tested.” There were no line listings to audit or check and no datasets submitted with the NDA.

## 7.5 Other Safety Explorations

### 7.5.1 Study 13509 Persistence of efficacy

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SoluPrep™ Film-forming Sterile Surgical Solution (2% w/v Chlorhexidine Gluconate and 70% (v/v) Isopropyl Alcohol)

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This study was a randomized, controlled, third-party blind, single-center study in healthy volunteers in which subjects received both study protocols on the abdomen and/or the groin.

There is one protocol amendment, dated 3-27-15, which is described as changing a sentence to add that dressings were to be applied within 15 minutes of completion of 3-minute drying time. The full amended-protocol was not submitted with the NDA. The protocol for study EM-05-013509, dated 3/23/15, is the basis for most of the background information below though the Clinical Study Report was also used. There are no datasets or listings of individual skin irritation scores, thus the safety information is from the CSR.

The study enrolled healthy males and females, 18 years old or older, with no dermatologic conditions or known history of sensitivity to acrylate, CHG, or alcohol-containing products, medical tapes, or natural rubber latex. Subjects were to avoid showering and tub-bathing within 72 hours before Screening or Treatment Day sampling for clipping, if needed and to avoid these activities once the products had been applied. As well, subjects were to be willing to avoid vigorous physical exercise that may cause sweating. There were a number of exclusion criteria including “any medical condition or use of any medications that, in the opinion of the Investigator, should preclude participation.” and swimming in chemically treated pools within 14 days (protocol, p.16/41 reader page number).

This review does not address the intended primary objective of the study. This review is limited to review of the safety generated from this study. The description of inclusion and exclusion criteria are noted as these may limit generalizability to the population of surgical patients, especially in acute or emergent situations, and thus potentially impact safety assessments, such as skin irritation.

The goal was to enroll enough to obtain a minimum of 20 treatment sites per anatomical region, per collection that met the baseline requirements ( $\geq 3.0 \log_{10}$  CFU/cm<sup>2</sup> on the abdomen and  $\geq 5.0 \log_{10}$  CFU/cm<sup>2</sup> on the groin) on treatment day and have an intact dressing at the collection time. The stated primary objective was to evaluate the antimicrobial persistence of 3M CHG/IPA Prep (26 mL tinted) on the abdomen and groin at 48 and 72 hours. Sterile 0.9% saline was used as a negative control. Safety evaluation was based on adverse event reporting during the study and evaluation of skin irritation using a skin irritation scale.

Subjects who met the inclusion/exclusion criteria were to undergo a minimum 14-day pretreatment phase during which subjects were to refrain from the use of products containing antimicrobial agents. Subjects were given nonantimicrobial products for use during this period. Hair removal to facilitate sample collection might have been performed. During the pre-treatment phase, subjects were asked to refrain from

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swimming and hot tubs and were to not shower or bathe for 72 hours before their scheduled screening appointment. Subjects could sponge bathe but were to avoid the inguinal and abdominal areas. In the Treatment Phase, Triacetin, a triglyceride, was used to dissolve the film for bacterial recovery. Subjects were randomized to receive either the 3M CHG/IPA Prep on the right side and saline on the left side or vice-versa. After the application of the study products, a sterile semi-occlusive dressing was to be secured over the remaining sample sites to allow restricted mobility and protect the sites from contamination between sampling times. Subjects were allowed to leave the clinical test facility as long as they returned for the 48-hour and 72-hour procedures.

The Clinical Study report for the protocol EM-05-013509 is the basis for the following information. The Investigator and study staff performing product application, sample assessment, and skin assessment were not blinded due to the differences in applicator design, color, and other physical characteristics. The study staff performing the bacterial enumeration was not involved in product application or sample collection. The statistician was blinded.

The same skin irritation scale was used in this study as in the pivotal efficacy trials (Modified Draize). Skin irritation was evaluated before collection of baseline, 48-hour, and 72-hour samples.

### **Safety Results:**

35 subjects signed an informed consent. Six subjects did not meet microbial criterion for the abdominal region and eight did not pass the microbial bacteria criterion for the inguinal region. Four subjects did not show up on Treatment Day for the abdominal region and four did not show up for the inguinal region on Treatment Day. Thus, twenty-five (25) were randomized and exposed to study drug on the abdominal region and twenty-three (23) subjects on the inguinal region.

Abdominal region demographics: The mean age of the 25 subjects was about 33 years ( $\pm 16$  years), the range was 19-74 years. 80% were male. 48% were Asian, 36% were White, 12% were Black or African American, and one person (4%) was Hispanic/Latino.

Inguinal region demographics: The mean age of the 23 subjects was about 36 years ( $\pm 17$  years), the range was 19-74 years. About 87% were male. About 48% were Asian, 35% were White and 17% (n=4) were Black or African-American.

All skin irritation scores are reported as “no reaction” for all measures (erythema, edema, dryness, and rash) for both 3M CHG/IPA Prep and the negative control on both the abdomen and groin at all assessment times. No adverse events were reported during the study per the study report. No datasets or data listings are provided, therefore, no audit of skin irritation scores could be performed.

## 7.5.2 Coverage, Dry Time, and Vapor Dissipation

Studies to evaluate coverage area, dry time and vapor dissipation (EM-05-012985 and EM-05-013337). Of these one also evaluated coverage and Vapor Dissipation (EM-05-013337).

Neither of these studies was performed with the TBM formulation (noted in response in SDN 23). It is not clear to me how close these simulate typical procedure in a surgical setting, how adequate the designs are to address the endpoints or whether the statistical analyses are optimal.

### 7.5.2.1 Study EM-05-012985

3M CHG/IPA Film-forming Skin Prep 26-mL Applicator Area Coverage, Dry Time, and Vapor Dissipation Study on Human Skin

Investigator: Dr. M. Stevens

The study protocol included in the initial NDA section 5.3.5.1, version 1, was used for the trial description.

The study was open-label, non-randomized. The study consented the first subject on 1-24-14 and completed the last observation on 1-30-14.

Twenty healthy 3M employees were the volunteers. Volunteers were to be aged 18 or older. It appears from the study report (p.11/68) that all subjects were male.

There were multiple exclusion criteria (copied from the CSR below. CSR and protocol displayed the same criteria, the CSR was more readable).

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- Subject had been a participant in another clinical study that involved his back, legs or arms at the test site within the last 2 weeks,
- Subject had taken antihistamines, immunosuppressant, or oral steroids in the previous 48 hours,
- Subject had a sensitivity/allergy to acrylates,
- Subject had a sensitivity to chlorhexidine gluconate (CHG),
- Subject had psoriasis,
- Subject had active dermatitis (rash), sunburn, blemishes, broken skin or cuts, or skin infection on his back, legs, or arms,
- Subject had a history of diabetes,
- Subject had used moisturizers or other skin contact materials on the test sites in the 24 hour period prior to participation in the study.

The primary objective was to assess the coverage area of 3M CHG/IPA Film-forming Preoperative Skin Preparation. Dry time was to be measured after the application and vapor collection used to confirm dryness. Removability of the prep with isopropyl alcohol was the secondary objective. 70% isopropyl alcohol was used as a positive control and 0.9% sterile saline as a negative control.

Drape application was performed by the same trained professional for all subjects. The In-house study coordinator assessed dryness and removability. The first enrolled subject was to be assigned to the vapor collection device calibration with the positive control. The next two subjects were to be assigned to the vapor collection device with the investigational product. The 4<sup>th</sup> subject was to be assigned to the vapor collection device with the negative control. The remaining sixteen (16) subjects were to be assigned to the area coverage and dry time portion of the study.

18 subjects received 3M CHG/IPA Prep from 26mL applicators (tinted product per the CSR), one subject received 70% IPA (26 mL applied with a foam applicator) or 9% sterile, 26 mL applied with a gauze sponge.

Vapor collection was performed on four subjects. The methods described in the protocol were not reviewed. Average Coverage Time and Dry Time was performed on 16 subjects. The procedure is not reviewed in this review.

Skin irritation was assessed for erythema 30 minutes on 18 subjects after the prep was removed using a modified Draize protocol. As with other protocols, any score of 3

qualified as an adverse event. The reporting and collection of adverse events may have been limited to skin irritation (it is not clear to me from the protocol, p.15/22).

Dry time-data from the four subjects in the vapor collection calibration portion were used to quantify the IPA concentration during the time that the prep solution and controls were drying. One subject had pooling of product that was “not able to be seen by the person applying the product” (p. 19/68). The analysis was repeated to exclude that subject.

### Study 12985 results

Adverse Events and Skin irritation:

The duration of exposure to study products was about 15-30 minutes. The CSR states there were no adverse events reported during the study. No laboratory or vital signs were collected. Skin irritation assessments are reported as “no reaction” for any subject on any treated section. I checked this against skin reactions (data from listings p.40.68 CSR in which the data is shown for sections 1, 2, and 3 skin assessments). All are either listed as no reaction or not applicable. It is not clear whether all parameters were evaluated or whether only erythema was.

Coverage and dry time parameters are noted below as reported by the sponsor.

The average coverage was

- In  $\text{cm}^2$ ,  $2499.8 \pm 206$ , range 2150-2923 for 16 subjects
- In  $\text{in}^2$ ,  $387.5 \pm 32$ , range 333-453 for 2 subjects

The average dry time in minutes (p.21/68 CSR) for all of the subjects was about 1.54 minutes with a range of 1 minute to a little over 4 minutes ( $1.54 \pm 0.79$ , 1.08-4.33). The mean value was not very different without the subject who pooled ( $1.35 \pm 0.26$ , 1.08 – 1.97).

Maximum alcohol concentration after the prep was judged to be dry:

- Mean of 16 subjects was  $18.6 \pm 26.3$ , 0-98

Net weight delivered:

- ranged from almost 5 to about 9.25 for the 3M product, 21.29 for the saline, and 5.43 for the isopropyl alcohol. Subject 9's net weight was 7.26. (data from subject listings 16.2 in the CSR).

Prep removability: (subject data listings 16.2, p.37/68 CSR)

- The CSR indicates that 18 considered prep removability as moderate. The data listing referenced appears to show this and to show that both isopropyl alcohol and sterile saline were the controls.

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- subjects 1 and 2- controls-were considered “easy”
- subjects 3-20 were all considered “moderate”

Vapor collection of IPA gas reportedly showed all concentrations “well below” the lower flammability limit.

The sponsor concluded the following (copied from the synopsis submitted with the initial NDA).

### Conclusions:

#### For the 3M CHG/IPA Prep:

- The dry time, on average, was 1.54 minutes (92 seconds). Excluding one subject who had a pooled area of solution that was not noticed during application, the dry time, on average was 1.35 minutes (81 seconds).
- The coverage area, on average, was 2499.8 cm<sup>2</sup> (387.5 in<sup>2</sup>).
- Total prep delivered weighed, on average, 8.00 grams.
- The prep covered, on average, 314.5 cm<sup>2</sup>/gram (48.74 in<sup>2</sup>/gram).
- Vapor collection of IPA gas shows all concentration values are well below the lower flammability limit (LFL).
- Removability was judged to be moderate on 100% of the subjects.
- Prep was well-tolerated by the study population. From the skin irritation scores no erythema was reported by the study population. No AEs were reported during this study.

### 7.5.2.2 Study EM-05-01337

PI: M.H. Bashir, M.D. CCRP, MicroBio Test

Medical Monitor: M.Hulse Stevens, M.D.

The study consented the first subject on 11-20-14 and completed the last observation on 11-25-14. This was an open-label study performed with the tinted 10.5 mL applicator.

The primary objective was to assess the coverage area of 3M IND product with tint in the 10.5 mL applicator. The secondary objective was removability of the prep with isopropyl alcohol. As in study 012985, the same trained professional applied the preps for all subjects. The room environmental conditions were the same as those in IND 12985 (air exchange 15/hour minimum, temperature 68-73° F, and humidity of 30-60%.)

Subjects were males only, 18 years of age or older. Subjects were asked to not use lotion or moisturizing products on their legs, back, and arms for 24 hours before the visit for the procedure. Exclusion criteria are the same as in study 012985.

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The main safety measure was skin irritation at the test site 30 minutes after the prep was removed. Skin irritation was rated on a modified Draize scale (the same as used in study 12985). A skin event rated 3 or more was to qualify as an adverse event.

Results:

The study report states that all 16 subjects were assigned to the same treatment and data collected from all subjects were used to evaluate coverage area and dry time. Study product was only used on the back with the noting that legs and arms were not needed since the visual difference in the coating intensity was achieved on the back.

The study report indicates there were no protocol deviations. The only demographic data collected was age.

Per the sponsor's study report (I rounded some numbers for ease of reading.)

Average coverage-

- in cm<sup>2</sup>,  $1153.7 \pm 109$ , range 966-1397. (n=16)

- in in<sup>2</sup>  $178.8 \pm 17$ , range ~150-217 (n=16)

Average Dry time in minutes (p.19/34 CSR):

- n=16 subjects  $1.80 \pm 0.48$ , 0.92-2.9

Mean Net weight delivered in grams:

- n=16 subjects  $3.5 \pm 0.25$ , 3.1-3.9.

Prep removability: 7 were rated as moderate and 9 as difficult.

Skin listings on page 33/34 only describe erythema and all 16 are reported as "no reaction". The study report states there were no adverse events reported during the study. No clinical laboratory data or vital signs were measured. Prep removability was rated difficult for 56% of subjects and moderate for 44%.

### 7.5.3 Studies of Drape Adhesion

Two studies were performed to evaluate the adhesion performance of 3M CHG/IPA film-forming skin preparation when compared to other preps using Ioban Incise Drape in Saline-Challenged and Unchallenged studies (EM-05-012680 and EM-05-012794). Study 12680 did not yield desirable results. The polymer was modified and various formulation designs were used in study 12794. The studies are described in more detail below.

*Neither of the Drape Adhesion studies was performed with the TBM formulation, defined as the 3M product that contains HEDTA (confirmed in sponsor's response in SDN 23).*

As I understand it, HEDTA is considered acceptable to add and is essentially

considered non-active. If this is the case, it is not clear that DNDP will require a drape adhesion test be performed with the formulation that has HEDTA.

Per the CSS, exposure time to the product depended on whether the drape condition was Dry or Saline-Challenged. For subjects in the Dry Condition, the exposure to the 3M Prep was 4 hours and for subjects in the Saline-Challenged Condition, the exposure to the 3M Prep ranged from 35-50 minutes (CSS, p.14/62).

#### 7.5.3.1 Study EM-05-12680

**PI: Michelle Hulse Stevens, M.D.**

This study initiated on 7-31-12 and completed on 8-24-12.

The study was to evaluate the adhesion performance of 3M CHG/IPA Film-forming skin preparation compared to ChlorPrep and to DuraPrep using loban Incise Drape in Saline-Challenged and Unchallenged conditions. The 10.5 mL foam tipped applicator of the tinted 3M product was used in this study. The 10.5 mL foam tipped applicator of ChlorPrep was used. The 3M DuraPrep solution was used.

The CSR notes that the study was amended to add a 10 minute loban dwell time and a 20 minute loban dwell time before the saline challenge (versus 5 minute dwell time).

No protocol is included with the initial NDA submission. This was requested and received in SDN 24. The cover letter of SDN 24 indicates the last version of the protocol was in amended protocol #2. The amendment changes are described as adding a 10 minute loban dwell time and a 20 minute loban dwell time before the saline challenge.

***Reviewer comment: I looked at the protocols to better familiarize myself with the study regarding this amendment. Based on my read of the protocols in SDN 24 it is not clear that the latest protocol submitted in SDN (dates that are in July 2014, version 1, top right corner) included instruction in the protocol for 10 and 20 minutes dwell times. If the instructions were not clear, this might contribute to the finding of no difference between prep dwell times.***

The primary objective was to evaluate the adhesion performance of the 3M product compared to ChlorPrep and DuraPrep using loban incise drape in saline-challenged conditions and unchallenged conditions. An automated Pull-Peel Tester with the arm at 90° was to be used. The safety was to be evaluated under both conditions with all of the preps. Safety assessments were performed post adhesion and 24-72 hours post sample removal. The subjects were blinded to identity of the preps on their backs. The coordinator was not blinded. The skin irritation scoring scale was the same as the one in the pivotal efficacy trials (Modified Draize).

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All 32 subjects were 3M employees, male or female, 18 years of age or older. Inclusion and exclusion criteria were similar to that in the Dry Time and Coverage studies except the subjects' backs also had to be large enough to fit 24 loban samples.

The inclusion and exclusion criteria are copied from the CSR below for the interested reader.

### 6.3.1 Inclusion criteria

1. 3M employees, males or females 18 years of age or older,
2. Subject signed the Informed Consent form,
3. Subject exhibited compliance with requirements of the study,
4. Subject's back was of sufficient size and free of blemishes to comfortably fit 24 Ioban samples.

### 6.3.2 Exclusion criteria

1. Subject was a participant in a clinical study that involved his or her back as the test site within the last two weeks,
2. Subject has a sensitivity/allergy to adhesive products, ie, medical tapes, acrylates, or propylene glycol,
3. Subject has a sensitivity to isopropyl alcohol (IPA) or to antimicrobial agents chlorhexidine gluconate (CHG) or iodine,
4. Subject has psoriasis, a history of dermatitis, or skin conditions that might be exacerbated by the action of removing adhesive materials,
5. Subject has active dermatitis (rash), sunburn, blemishes, broken skin or cuts, or skin infection on his or her back,
6. Subject was pregnant, thinks she may be pregnant, or nursing,
7. Subject has a history of diabetes and/or thyroid disease,  
Subject was using moisturizers or other skin contact materials on the test sites in the 24 hour period prior to participation in the study.

The skin prep instructions are summarized or repeated verbatim from the CSR. These application stroke techniques for the comparator products appear similar to those with the labeling seen online at DailyMed, for the intended site except the Daily Med DuraPrep language included discussion of cleaning the umbilicus with swabs when applicable.

- 3M product-apply using repeated overlapping strokes for 30 seconds covering the test section. Allow each prepped test section to dry for three minutes.
- ChlorPrep- use repeated back-and-forth strokes with the applicator for 30 seconds, completely wetting the test section with the prep. Allow prepped section to dry for three minutes.
- DuraPrep – start at the center and work toward the edges of the test section. Paint a single uniform coat of solution to the skin using light pressure. Do not scrub or go back over a prepped area. Allow prep to dry for three minutes. After three minutes of prep dry-time, dryness was to be confirmed at the perimeter of each prepped section to loban strip adhesion would not be affected.

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Each subject's back was divided into six (6) test sections of about 4 inches wide x 3 inches long. The sections were numbered 1-6. The three preps were randomized to duplicate sections on all subjects. Hair was clipped with a surgical hair clipper if needed. After the strips were applied, **a 4.5 pound roller was rolled over the samples to promote consistent drape adhesion.**

10 subjects were assigned to each of the two conditions,

--Test Condition A/ Unchallenged-subject's back was prepped and loban strips applied. The subjects resumed normal work activities for four hours while wearing the test materials. The loban strips were removed using a calibrated, peel tester with a 90 degree arm mechanism, at 12 inches per minute. The test sites were evaluated immediately for skin irritation and again 24-72 hours later.

--Test Condition B/ Saline-challenged- subject's back was prepped and loban strips applied. The loban strips stayed in place for 5 minutes to "build adhesion". Saline-soaked gauze was placed on top of the loban strips while the subject remained prone for 30 minutes. The strips were then removed using the peel mechanism described in Test Condition A. The test sites were evaluated immediately for skin irritation and again 24-72 hours later.

The description of the application of loban strips is copied from the protocol (version 1, submitted in SDN 24, p.65/90) below,

### Application of Loban Strips

- Loban samples will be pre-cut into ½-inch x 3-inch strips.
- Apply four loban samples to each prepped test section.
- Immediately after the loban strips have been placed on the test sites, roll a 4.5-lb roller over each loban strip back and forth one time, using no additional pressure.
- Allow the loban strips to build adhesion for five (5) minutes +/- 30 seconds before any further procedure.

12 subjects were assigned to the treatment described in the amended protocol. The subject's back was prepped and loban strips applied as described previously. The loban strips stayed in place on the right or left side of the back depending on the randomization for 10 minutes ± 30 seconds or 20 minutes ± 30 seconds to "build adhesion" (CSR). Saline-soaked gauze was placed on top of the loban strips while the subject remained prone for 30 minutes. The strips then were removed using the peel mechanism described in Test Condition A above. The test sites were evaluated immediately for skin irritation and again 24-72 hours later.

Results:

*Under the original protocol-*

**Adhesion** -Five minute adhesion time results are shown below.

**Table 25 Study 12680 Adhesion Based on Original Protocol**

Condition	Prep	n	Mean ±Std dev	Median	Min-Max
T30 Wet	3M	80	63.41± 22.9	62.2	10-136
	CP	80	67.1 ± 24.7	62.3	27-152
	DP	80	95.0 ± 21.5	93.6	36-142
T4 Dry	3M	80	94.54 ± 53.2	77.2	21-253
	CP	80	140.9 ± ~44	138.5	58-229
	DP	80	131.2 ± 34.6	123.1	53-206

Data source: Table 1 (CSR). 3M=3M CHG/IPA Film-forming preparation, CP=ChloraPrep, DP=DuraPrep. Some Numbers are rounded.

The sponsor's analyses of the least square data is copied below from the CSR,

**Table 26 Study 12680 Original Protocol Adhesion Analyses**

TABLE 2								
Differences of Least Squares Means for T30 Wet								
Prep	Prep	Estimate	Standard Error	DF	Adjustment	Adj P	Adj Lower	Adj Upper
3M CHG/IPA	ChloraPrep	-3.6878	5.7036	18	Tukey-Kramer	0.7966	-18.2443	10.8688
3M CHG/IPA	DuraPrep	-31.6126	5.7036	18	Tukey-Kramer	<.0001	-46.1691	-17.0560
ChloraPrep	DuraPrep	-27.9248	5.7036	18	Tukey-Kramer	0.0003	-42.4814	-13.3683

TABLE 3								
Differences of Least Squares Means for T4 Dry								
Prep	Prep	Estimate	Standard Error	DF	Adjustment	Adj P	Adj Lower	Adj Upper
3M CHG/IPA	ChloraPrep	-46.3814	9.7508	18	Tukey-Kramer	0.0004	-71.2671	-21.4956
3M CHG/IPA	DuraPrep	-36.6299	9.7508	18	Tukey-Kramer	0.0039	-61.5157	-11.7442
ChloraPrep	DuraPrep	9.7514	9.7508	18	Tukey-Kramer	0.5862	-15.1343	34.6371

The sponsor's conclusions of the analysis of least square mean data is copied from the study report below.

#### **Saline-challenge**

DuraPrep had higher mean adhesion than both 3M CHG/IPA Film-forming Preparation and ChlorPrep (p-values of <0.0001 and 0.0001, respectively). The 95% confidence intervals are shown in Table 2. The estimated differences were about 30 grams for both comparisons.

#### **Unchallenged**

3M CHG/IPA Film-forming Preparation had lower mean adhesion than both ChlorPrep and DuraPrep (p-values of 0.0004 and 0.004, respectively). The 95% confidence intervals are shown in Table 3. The estimated differences between the CHG/IPA Film-forming Preparation and the other skin preps were between about 35 and 45 grams.

**Edge lift** in the original protocol was assessed just before the removal of the loban test strips for both the unchallenged (dry) and saline-challenged (wet) conditions. The sponsor states there were no reports of edge lift for any of the skin prep and test conditions during the original protocol.

**Residue**-assessments were made immediately after removal of the loban strips for both the unchallenged and saline-challenged conditions. The sponsor states there were no reports of residue for any of the skin prep and test conditions.

*Results from evaluations conducted under the amended protocol:*

#### **Adhesion -**

Adhesion results following adhesive dwell times of 10 and 20 minutes before the saline challenge, is summarized by the sponsor as follows (p.19/71 of CSR). "DuraPrep was associated with significantly higher mean adhesion compared to both the 3M CHG/IPA Film-forming Preparation (p<0.001) and ChlorPrep (p<0.001)." The sponsor states there was a lack of significant skin prep by dwell time interaction suggesting that the difference between preps was consistent for both dwell times and there was no statistically significant difference between the overall mean adhesion associated with different dwell times.

The sponsor's presentations of the summary statistics and analysis of least squares means data are copied from the CSR below for the interested reader.

#### **Table 27 Study 12680 Sponsor's Summary Statistics Adhesion Dwell Times 10 and 20 minutes**

DWELL TIME /SKIN PREP		TABLE 4 SUMMARY OF ADHESION (GM/0.5 INCH)- SALINE-CHALLENGE TEST CONDITION					
		N	Mean	Std	Median	Min	Max
10 Minutes	3M CHG/IPA	48	48.63	22.633	44.3	11.4	87.4
	ChloroPrep	48	56.06	20.082	53.9	21.9	109.7
	DuraPrep	48	85.22	24.147	84.2	5.1	128.4
20 Minutes	3M CHG/IPA	48	61.07	31.396	55.8	14.1	158.7
	ChloroPrep	48	63.06	23.103	67.2	14.4	99.4
	DuraPrep	48	91.26	37.185	82.4	47.9	205.8
All		288	67.55	30.972	66.7	5.1	205.8

**Table 28 Study 12680 Sponsor's Summary of Analyses Comparing Products for Adhesion**

TABLE 5 Differences of Least Squares Means											
Effect	Prep	Dwell	Prep	Dwell	Estimate	Standard Error	DF	t Value	Pr >  t	Adjustment	Adj P
Prep	3M CHG/IPA		ChloroPrep		-4.7064	5.6582	22	-0.83	0.4145	Tukey-Kramer	0.6877
Prep	3M CHG/IPA		DuraPrep		-33.3873	5.6582	22	-5.90	<.0001	Tukey-Kramer	<.0001
Prep	ChloroPrep		DuraPrep		-28.6809	5.6582	22	-5.07	<.0001	Tukey-Kramer	0.0001
Dwell		10		20	-8.4907	5.4233	11	-1.57	0.1457	N/A	N/A

**Edge lift** in the amended protocol was assessed also prior to removal of the loban test strips following the saline-challenge conditions with dwell times of 10 and 20 minutes. The sponsor reports there were no reports of edge lift for any of the skin prep and test conditions using the amended protocol.

**Residue**-assessments were made also after removal of the loban test strips following the saline – challenged conditions with dwell times of 10 and 20 minutes. The sponsor reports there were no reports of residue for any of the skin prep and test conditions.

**Safety-**

The CSR states there were no adverse events during the treatment or assessments of this study.

Five subjects failed to show up for the 24-72 hour follow-up assessment. The skin assessments for these subjects at this follow-up was considered to be “no reaction” (p.22/71 CSR).

Audit of the data below was limited by a lack of a dataset. Therefore, the audit was limited to a search of data listings provided in 11.1, Tabulation of Individual Response Data for the word “severe” and the word fragment, “sever”. No instances of these were found. (The document appeared searchable as it rendered findings of the word, “moderate”).

*Under the original protocol:*

- 1) Erythema- assessed after removal of the loban strips and 24-72 hours after removal of the strips.
  - Under the Dry Condition, (Unchallenged), the sponsor reports there was no significant difference between skin prep conditions immediately following removal of the test strips. At 24-72 hours, the sponsor reports that the ChlorPrep sites had significantly higher erythema ratings than the 3M IND product and higher than DuraPrep. The sponsor’s table of the frequency of erythema (Table 7) is duplicated below after the text that follows.

Based on data in Table 7, under the Dry Condition, the initial readings for all products showed that most had a reaction to the prep regardless of the type of prep and that DuraPrep had a higher frequency of moderate reactions (70% than either ChlorPrep (60%) or the 3M IND product (55%). At follow-up for the Dry Condition, the 3M product is reported to have had no reactions while most DuraPrep and ChlorPrep showed either a mild or moderate reaction with DuraPrep having more moderate reactions (16.7% vs 8.3%). It should be noted that the five no-shows were considered as no reaction

- Under the Wet conditions (saline-challenged), the maximum erythema score for any of the test strips at each observation time was recorded in the database. The sponsor summarizes that there were no significant differences between preps in the erythema ratings immediately after removal of the test strips. The sponsor states there were no reports of erythema associated with any of the skin prepped test sites at 24-72 hour follow-up visit.

From the sponsor’s Table 7, duplicated from the submission below, under wet conditions, the initial readings for all products showed that most had a reaction to the prep regardless of the type of prep and that most of the reactions were moderate. DuraPrep had a higher frequency of moderate reactions (95% than either the 3M IND product (75%) or ChlorPrep (70%). At follow-up, reportedly, no reactions were noted for any product. It should be noted that the five subjects who did not show-up for the follow-up evaluation were counted as no reaction.

**Table 29 Study 12680 Frequency of Erythema**

VISIT / CONDITION / SKIN PREP			TABLE 7 FREQUENCY OF ERYTHEMA					
			No reaction		Mild		Moderate	
			N	PctN	N	PctN	N	PctN
Initial	Dry	CHG/IPA	1	5.0	8	40.0	11	55.0
		ChloraPrep	0	0	8	40.0	12	60.0
		DuraPrep	0	0	6	30.0	14	70.0
	Wet	CHG/IPA	0	0	5	25.0	15	75.0
		ChloraPrep	0	0	6	30.0	14	70.0
		DuraPrep	0	0	1	5.0	19	95.0
Follow-up	Dry	CHG/IPA	12	100.0	0	0	0	0
		ChloraPrep	2	16.7	9	75.0	1	8.3
		DuraPrep	8	66.7	2	16.7	2	16.7
	Wet	CHG/IPA	18	100.0	0	0	0	0
		ChloraPrep	18	100.0	0	0	0	0
		DuraPrep	18	100.0	0	0	0	0
<b>All</b>			<b>77</b>	<b>36.7</b>	<b>45</b>	<b>21.4</b>	<b>88</b>	<b>41.9</b>

2) Edema

CSR Table 9, not reproduced in this review, displays summarized data in a format similar to Table 7. Table 9 data indicates that no subject in either the Dry or Wet Condition had a skin reaction to any product initially.

At follow-up, Table 9 reports that for the Dry Condition, the 3M IND product all had “no reactions”. ChloraPrep data shows most having mild reactions (n=8, 66.7%) , 1 having a moderate edema (8.3%), and 3 having “no reaction” compared to DuraPrep, with most as “no reaction” (66.7%) and both mild and moderate reactions as 16.7%. At follow-up for the Wet Condition, Table 9 indicates that all subjects (all preps) had “no reaction”.

The sponsor summarized that ChloraPrep was associated with significantly higher ratings of edema as compared to the 3M CHG/IPA product in Dry conditions at the 24-72 hour follow-up.

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- 3) Rash-The sponsor states there were no reports of rash for any of the test sites immediately following removal of the test strips or at the 24-72 hour visit for either the Wet or Dry Condition.
- 4) Dryness- The sponsor states there were no reports of dryness for any of the test sites immediately following removal of the test strips or at the 24-72 hour visit for either the Wet or Dry Condition.

*Under the Amended Protocol:*

- 1) Erythema- Erythema was assessed immediately after loban strip removal and again at 24-72 hours after loban strip removal. The Sponsor reports that the difference in erythema ratings between skin preps immediately after removal of the test strips (initial) were not statistically significantly different after either the 10 minute dwell time or the 20 minute dwell time. The sponsor reports there were no instances of erythema at any test site at 24-72 hours post-test strip removal.

Based on the sponsor's table, as reproduced below (Table 8), initial ratings after the 10 minute dwell time indicate most had reactions and most were mild. Duraprep had notably more moderate reactions (~42% compared to ~17% for each of the other two products). Initial ratings after the 20 minute dwell time indicates that though most reactions were still mild. There were more moderate reactions than when compared to the 10 minute dwell time for each product. Follow-up ratings are reported as no reactions for all preps. It is noted that the five subjects who did not return for follow-up were considered no reaction (if they were in this set of conditions).

**Table 30 Frequency of Erythema Amended Protocol**

VISIT / DWELL TIME / SKIN PREP			TABLE 8 FREQUENCY OF ERYTHEMA					
			No reaction		Mild		Moderate	
			N	PctN	N	PctN	N	PctN
Initial	10 min	CHG/IPA	1	8.3	9	75.0	2	16.7
		ChlorPrep	0	0	10	83.3	2	16.7
		DuraPrep	1	8.3	6	50.0	5	41.7
	20 min	CHG/IPA	0	0	7	58.3	5	41.7
		ChlorPrep	2	16.7	6	50.0	4	33.3
		DuraPrep	1	8.3	4	33.3	7	58.3
Follow-up	10 min	CHG/IPA	12	100.0	0	0	0	0
		ChlorPrep	12	100.0	0	0	0	0
		DuraPrep	12	100.0	0	0	0	0
	20 min	CHG/IPA	12	100.0	0	0	0	0
		ChlorPrep	12	100.0	0	0	0	0
		DuraPrep	12	100.0	0	0	0	0
<b>All</b>			<b>77</b>	<b>53.5</b>	<b>42</b>	<b>29.2</b>	<b>25</b>	<b>17.4</b>

- 2) Edema-The sponsor states there were no reports for any test sites at either assessment time-point for the saline-challenged test conditions.
- 3) Rash- The sponsor states there were no reports for any test sites at either assessment time-point for the saline-challenged test conditions.
- 4) Dryness- The sponsor states there were no reports for any test sites at either assessment time-point for the saline-challenged test conditions.

**Reviewer:**

- The summarized data could not be efficiently referenced back to the listing in the tabulation and there were no datasets. Thus, the review is based on the sponsor’s summary tables and audit was limited to search for severe events as noted above.

- **One limitation of the skin irritation scale assessments is that if the subjects are professional volunteers (they are recruited from 3M employees), those with skin reactions to topical products may be selected out. In that case, the reactions here could be different than one might expect in the general population.**
- **The study does not appear to have had blinded readers, though this is not clear.**
- **The subjects who did not show up are considered as “no reaction”.**
- **There is no information as to outcome in those with reactions present at the follow-up visit.**
- ***Based on my read of the protocols in SDN 24 it is not clear that the latest protocol submitted in SDN (dates that are in July 2014, version 1, top right corner) instructed in the protocol for 10 and 20 minutes dwell times versus 5 for the saline condition. If the instructions were not clear, this might contribute to a finding of no difference between prep dwell time. However, it is possible I misread the protocol or that the last protocol in SDN 24 is not the final one.***

***I recommend asking the sponsor to clarify though the response may be more important for quality issues than for study results as it seems the formulation used in this drape adhesion study may not have been the one carried forward. I defer to CMC to confirm or not. The reason it seems this was not the formulation carried forward is that essentially , the sponsor was not satisfied with some of the performance of the product and a second drape adhesion tried different formulations. It seems likely the one (A1) in that study may have been the final formulation, or final except for the HEDTA, which appears would not have been added before January 2014 (based on the date of the notification to FDA (b) (4)).***

#### 7.5.3.2 Study EM-05-12794

**PI: Michelle Hulse Stevens, M.D.**

The study initiated on 1-14-13 and completed on 1-24-13.

Study was to evaluate the adhesion performance of 3M CHG/IPA Film-forming skin preparation compared to ChlorPrep and to DuraPrep using loban Incise Drape in Saline-Challenged and Unchallenged conditions.

This drape adhesion study was performed about 6 months after study 12680. The CSR notes that the adhesion results in study 12680 were lower than expected on saline-challenged loban strips. This was attributed to the polymer ratio of the polymer used in

the previous study<sup>58</sup>. The sponsor reported this polymer ratio in the prep did not show saline-challenge adhesion values that were expected to be desirable for wound edge contact in a surgical setting. (b) (4)

(b) (4). The CSR notes the (b) (4) polymer content was used in all experimental formulations.

(b) (4)

The primary objective was to evaluate the incise drape adhesion-to-skin performance using various reformulations of the 3M IND product. The performance of the IND skin prep reformulation designs were compared with two commercially available skin preps, ChlorPrep and DuraPrep. A commercially available loban incise drape was to be used with each skin prep to assess adhesion-to-skin characteristics of the prep and incise drape under unchallenged and saline-challenged test conditions.

The secondary objective was to compare dermal safety under both test conditions. Removability of the preps with the use of warm, soapy water was also evaluated by the coordinator as easy, moderate, or difficult to remove.

The study was randomized and open-label. The back of each subject was prepped with six preoperative skin preps; four with the 3M IND product designs and two with the commercially available comparator preps. loban was used in combination with each skin prep to evaluate adhesion-to-skin characteristics of the prep and drape incision. A calibrated peel testing instrument was used to remove the samples in a consistent manner.

The four experimental preps (b) (4)  
(b) (4) Tinted formulations in 10.5 mL foam tipped applicators were used. ChlorPrep was a tint preparation in a 10.5 mL foam tipped applicator and DuraPrep was solution.

(b) (4)

The inclusion criteria were the same as study 12680. The exclusion criteria were similar, though not identical. In study 12794, a history of having had psoriasis was exclusionary. Sensitivity to alcohol and adhesive tapes were not specifically listed in the exclusion criteria of this study but were in study 12680.

The procedures for the administration of treatments for the Unchallenged (Dry) and Saline-Challenged (Wet) conditions appear similar to those in study 12680 (ioban strips on the back for 5 minutes in the Wet condition. Page 12/115 of the CSR describes a 5 min dwell time. Page 14/115 indicates that extra saline was added at 10 minutes  $\pm$  2 minutes and 20 minutes  $\pm$  2 minutes during the challenge period to the test sections saturated. The mechanical removal of the loban strips used an angle of about 90 degrees and pull rate of 12 inches/min. This is similar to 12680.

Similar to study 12680 subjects were blinded. The coordinator was not.

The skin prep application appears the same as that in study 12680.

Skin irritation was measured by the Modified Draize with a level 3 event considered an adverse event. The skin irritation scale is the same one used in the pivotal studies and was shown previously in this review. Skin irritation measures were performed immediately after removal of loban strips and at 24 hours post-sample removal for all subjects except subject (b) (6). Subject (b) (6) was re-evaluated at 48 hours due to work issues. Subject (b) (6) was one of two protocol deviations.

### **Study 12794 results:**

Adhesion:

Adhesion is given in grams per ½ inch. The sponsor states that overall p values were <0.0001 for both 4 hour and 30 minutes Wet. The sponsor compared adhesion of loban drapes on ChloraPrep to adhesion on the experimental preps and between adhesion of loban drapes on DuraPrep to adhesion on the experimental preps for the Dry condition for the 4 hour time and for the Wet condition for at 30 minutes. These tables are not shown in this review.

The sponsor's summary table of mean adhesion in the Wet and Dry condition is shown below as reproduced from the sponsor. In Dry conditions, with 60 samples, the CHG/IPA Lot A1 product had the lowest mean adhesion. In Wet conditions, ChlorPrep did. In the Dry condition, the mean and median was lower for 3M Lot A1 than for other 3M lots and was lower than both ChlorPrep and DuraPrep. In the Wet Condition, the mean adhesion for 3M Lot A1 was lower than all products except ChlorPrep

**Table 31 Study 12794 Mean Adhesion**

CONDITION/SAMPLE		TABLE 8.4.1.1 SUMMARY OF MEAN ADHESION					
		N	Mean	Std	Median	Min	Max
Dry	CHG/IPA Lot A1	60	80.76	44.497	76.7	24.3	201.8
	CHG/IPA Lot A2	60	144.65	51.535	137.2	63.9	292.7
	CHG/IPA Lot A3	60	159.49	45.523	161.6	63.0	260.7
	CHG/IPA Lot A4	60	192.74	45.563	182.9	119.0	295.6
	ChloraPrep	60	152.94	35.550	148.5	82.3	248.6
	DuraPrep	60	128.13	48.494	123.1	38.8	261.2
Wet	CHG/IPA Lot A1	60	113.03	40.718	105.5	39.8	192.8
	CHG/IPA Lot A2	60	132.03	28.834	125.7	78.7	203.9
	CHG/IPA Lot A3	60	131.81	37.254	132.2	46.4	215.8
	CHG/IPA Lot A4	60	152.74	43.446	164.8	36.4	221.0
	ChloraPrep	60	65.03	24.735	64.4	22.6	127.2
	DuraPrep	60	124.88	41.761	125.8	27.1	218.8

The sponsor reports no edge lift was observed for any drape sample on any prep for either condition (Wet or Dry).

**Ease of removal-**

Based on the sponsor's Table 8.4.1.5, ChloraPrep was rated "easy" to remove 100% of the time compared to 0-40% of the time with CHG/IPA Lots A1-A4 and 0% of the time for Duraprep. The CHG/IPA Lot A1 was rated easy more often than the other CHG/IPA Lots (40%).

In Wet Condition, ChloraPrep was rated "easy" 86.7 % and was never "difficult". DuraPrep was always "difficult". CHG/IPA Lot A1 –Lot A4 were generally rated difficult (66.7% -93.3%, not in order of respective lot numbering).

**Table 32 Study 12794 Frequency of Ratings of Ease of Prep Removability**

CONDITION/SAMPLE		TABLE 8.4.1.5 FREQUENCY REMOVABILITY					
		Easy		Moderate		Difficult	
		N	PctN	N	PctN	N	PctN
<b>Dry</b>	<b>CHG/IPA Lot A1</b>	6	40.0	7	46.7	2	13.3
	<b>CHG/IPA Lot A2</b>	4	26.7	9	60.0	2	13.3
	<b>CHG/IPA Lot A3</b>	5	33.3	6	40.0	4	26.7
	<b>CHG/IPA Lot A4</b>	0	0	4	26.7	11	73.3
	<b>ChloraPrep</b>	15	100.0	0	0	0	0
	<b>DuraPrep</b>	0	0	0	0	15	100.0
<b>Wet</b>	<b>CHG/IPA Lot A1</b>	2	13.3	3	20.0	10	66.7
	<b>CHG/IPA Lot A2</b>	0	0	4	26.7	11	73.3
	<b>CHG/IPA Lot A3</b>	0	0	1	6.7	14	93.3
	<b>CHG/IPA Lot A4</b>	0	0	3	20.0	12	80.0
	<b>ChloraPrep</b>	13	86.7	2	13.3	0	0
	<b>DuraPrep</b>	0	0	0	0	15	100.0

Based on the sponsor's Table 8.4.1.4, duplicated below, ChloraPrep's mean score was the lowest at 1.0 and DuraPrep's mean was the highest (3.0) in the Dry Condition. CHG/IPA Lots A1-A4 were around 2 with the Lot A4 the highest (2.73) and Lot A1 the lowest (1.73). In the Wet condition, ChloraPrep had the lowest mean (1.13 and the lowest maximum (2). DuraPrep had the highest mean and maximum (3). CHG/IPA Lots A1-A4 means were between 2.53 and 2.93 with maximums of 3. CHG/IPA Lot A1 had the lowest mean (2.53 with a range of 1-3).

**Table 33 Study 12794 Summary of Removability**

CONDITION/SAMPLE		TABLE 8.4.1.4 SUMMARY OF REMOVABILITY					
		N	Mean	Std	Median	Min	Max
Dry	CHG/IPA Lot A1	15	1.73	0.704	2.0	1.0	3.0
	CHG/IPA Lot A2	15	1.87	0.640	2.0	1.0	3.0
	CHG/IPA Lot A3	15	1.93	0.799	2.0	1.0	3.0
	CHG/IPA Lot A4	15	2.73	0.458	3.0	2.0	3.0
	ChloraPrep	15	1.00	0.000	1.0	1.0	1.0
	DuraPrep	15	3.00	0.000	3.0	3.0	3.0
Wet	CHG/IPA Lot A1	15	2.53	0.743	3.0	1.0	3.0
	CHG/IPA Lot A2	15	2.73	0.458	3.0	2.0	3.0
	CHG/IPA Lot A3	15	2.93	0.258	3.0	2.0	3.0
	CHG/IPA Lot A4	15	2.80	0.414	3.0	2.0	3.0
	ChloraPrep	15	1.13	0.352	1.0	1.0	2.0
	DuraPrep	15	3.00	0.000	3.0	3.0	3.0

APPEARS THIS WAY ON ORIGINAL

**Study 12794 safety:**

Thirty subjects were exposed to study product for a maximum of about 4.5 hours. The CSR reports states there were no adverse events “during the treatment or assessments of this study.” There were two protocol violations. One was subject (b) (6) who had follow-up at 48 hours instead of 24 due to being called out of town. The other was subject (b) (6) in which randomization was not followed.

**Skin irritation:**

1) Erythema

At removal, the skin irritation scales, as summarized by the sponsor in Table 9.5.1 (duplicated from the CSR below) provide that under Dry conditions, most reactions were mild for CHG/IPA Lots (though not for Lot 4A) and ChloraPrep compared to the majority “moderate” for DuraPrep.

At removal, the skin irritation scales, as summarized by the sponsor in Table 9.5.1 (duplicated from the CSR below) show that under Wet conditions, most were mild for CHG/IPA Lots and ChloraPrep compared to the majority “moderate” for DuraPrep.

**Table 34 Study 12794 Sponsor Summary Frequency of Erythema at Removal**

CONDITION/SAMPLE		TABLE 9.5.1 FREQUENCY OF ERYTHEMA at removal					
		(0) No reaction		(1) Mild and/or transient redness limited to sensitive area		(2) Moderate redness persisting over much of the product-exposed area	
		N	PctN	N	PctN	N	PctN
		Dry	CHG/IPA Lot A1	3	20.0	8	53.3
CHG/IPA Lot A2	0		0	8	53.3	7	46.7
CHG/IPA Lot A3	0		0	9	60.0	6	40.0
CHG/IPA Lot A4	1		6.7	6	40.0	8	53.3
ChloraPrep	0		0	8	53.3	7	46.7
DuraPrep	1		6.7	4	26.7	10	66.7
Wet	CHG/IPA Lot A1	1	6.7	9	60.0	5	33.3
	CHG/IPA Lot A2	0	0	9	60.0	6	40.0
	CHG/IPA Lot A3	1	6.7	7	46.7	7	46.7
	CHG/IPA Lot A4	0	0	9	60.0	6	40.0
	ChloraPrep	1	6.7	9	60.0	5	33.3
	DuraPrep	0	0	4	26.7	11	73.3

APPEARS THIS WAY ON ORIGINAL

At follow-up, in the Dry Condition, about 93% of CHG/IPA Lot A1 and ChloraPrep had no reaction and the remainder mild. All of DuraPrep had no reaction. There was one moderate reaction in the Dry Condition at follow-up. This was lot A4 of the 3M product.

At follow-up in the Wet Condition, ChloraPrep had no reactions in 93.3% and mild in 1 (6.7%). DuraPrep had no reactions in 53.3% , mild in 33.3%, and moderate in 13.3%. CHG/IPA Lots A1-A4 varied within themselves in terms of reactions. CHG/IPA Lot A1 had the largest percentage of “no reaction” (46.7%) as well as the lowest of the lots for moderate reaction (13.3%). Forty percent (40%) of CHG/IPA Lot A1 were rated mild reaction.

**Table 35 Frequency of Erythema at Follow-up**

CONDITION/SAMPLE		TABLE 9.5.2 FREQUENCY OF ERYTHEMA at follow-up					
		(0) No reaction		(1) Mild and/or transient redness limited to sensitive area		(2) Moderate redness persisting over much of the product-exposed area	
		N	PctN	N	PctN	N	PctN
Dry	CHG/IPA Lot A1	14	93.3	1	6.7	0	0
	CHG/IPA Lot A2	15	100.0	0	0	0	0
	CHG/IPA Lot A3	14	93.3	1	6.7	0	0
	CHG/IPA Lot A4	10	66.7	4	26.7	1	6.7
	ChloraPrep	14	93.3	1	6.7	0	0
	DuraPrep	15	100.0	0	0	0	0
Wet	CHG/IPA Lot A1	7	46.7	6	40.0	2	13.3
	CHG/IPA Lot A2	5	33.3	7	46.7	3	20.0
	CHG/IPA Lot A3	5	33.3	7	46.7	3	20.0
	CHG/IPA Lot A4	4	26.7	6	40.0	5	33.3
	ChloraPrep	14	93.3	1	6.7	0	0
	DuraPrep	8	53.3	5	33.3	2	13.3
<b>All</b>		125	69.4	39	21.7	16	8.9

APPEARS THIS WAY ON ORIGINAL

2) Edema-

At removal, the sponsor reports there was no edema.

At 24 hours, the sponsor's Table 9.5.7, duplicated below, indicates

- All were “no reaction” with all preps in the Dry Condition with the exception of CHG/IPA Lot A4 which had one (6.7%) mild reaction.
- In the Wet Condition, all ChloraPrep and DuraPrep ratings were “no reaction”. Most CHG/IPA Lots were no reaction (93.3% no reaction in Lots A1-A4). All other with the 3M product were “mild”.

The sponsor states that overall p-values were 0.42 for 4 hours dry 24 hours post-removal and 0.26 for 30 minutes wet 24 hours post-removal.

**Table 36 Study 12794 Frequency of Edema**

CONDITION/SAMPLE		TABLE 9.5.7 FREQUENCY OF EDEMA at follow-up			
		(0) No reaction		(1) Mild and/or transient swelling limited to sensitive area	
		N	PctN	N	PctN
Dry	CHG/TPA Lot A1	15	100.0	0	0
	CHG/TPA Lot A2	15	100.0	0	0
	CHG/TPA Lot A3	15	100.0	0	0
	CHG/TPA Lot A4	14	93.3	1	6.7
	ChloraPrep	15	100.0	0	0
	DuraPrep	15	100.0	0	0
Wet	CHG/TPA Lot A1	14	93.3	1	6.7
	CHG/TPA Lot A2	14	93.3	1	6.7
	CHG/TPA Lot A3	14	93.3	1	6.7
	CHG/TPA Lot A4	13	86.7	2	13.3
	ChloraPrep	15	100.0	0	0
	DuraPrep	15	100.0	0	0
<b>All</b>		<b>174</b>	<b>96.7</b>	<b>6</b>	<b>3.3</b>

APPEARS THIS WAY ON ORIGINAL

3) Rash-

At removal, the sponsor reports there was no rash observed. At 24 hours, the sponsor's Table 9.5.8, table not shown, indicates that all were "no reaction" with all preps in the Dry Condition. In the Wet Condition, all ChloraPrep ratings were "no reaction". Most CHG/TPA Lots and DuraPrep were no reaction (93.3%). All others were "mild". The sponsor reports that the overall p-value was 0.42 for 30 minutes wet 24-hours after removal and for 4 hours dry was 1.

4) Dryness

At removal in the Dry Condition, the sponsor's Table 9.5.9 (not shown) reports that all CHG/TPA Lot A1 showed no reaction compared to Lot A3 with 93.3% no reaction and one moderate reaction (6.7%), ChloraPrep with 80% no reaction, and DuraPrep with 73.3% no reaction. The only product with a moderate reaction was CHG/TPA Lot A3.

At removal in the Wet Conditions, the sponsor's Table 9.5.9 reports that 100% of all preps recorded no reaction.

At follow-up in the Dry Condition, the sponsor's Table 9.5.10 (not shown) reports that all preps had "no reaction".

At follow-up in the Wet Condition, the sponsor's Table 9.5.10 (not shown) reports that all preps except CHG/IPA Lot A3 and DuraPrep had "no reaction". CHG/IPA Lot A3 and DuraPrep had "no reaction" 93.3% and each had one (6.7%) mild reaction. No moderate reactions were reported.

The sponsor's overall conclusion is copied from the CSR below,

Overall Conclusion

The incise drape adhesion performance of 3M CHG/IPA Film-forming Prep formulations A1 and A2 are both acceptable under the unchallenged and saline-challenged test conditions.

3M CHG/IPA Film-forming Prep formulation A1 shows the easiest removability of the four investigational formulations.

There were no significant safety issues with the use of any of the formulations.

The sponsor's

A) Study for Dry Time and Flammability

This study *may not have been* performed with the HEDTA 3M product<sup>59</sup>.

### 7.5.5 EM-05-01340 Flammability

***Reviewer note: The units in the tables that appear to be the primary data are in ppmv not ppm. I am not certain how this differs from ppm and based the vapor review as if this were ppm.***

*The date of the study is not on the report but company approval signatures are dated in January-February of 2015.*

Title: Determination of 3M CHG/IPA Film Forming Skin Preparation Solution Drying Time and Vapor Dissipation on Shoulder Length Human Hair (Mannequins) Under Normal Surgical Suite Conditions  
Investigator: Brandon Archibald

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<sup>59</sup> Based on information in SDN 23 to the NDA.

## Clinical Review

Teresa A. Podruchny

NDA 208288

SoluPrep™ Film-forming Sterile Surgical Solution (2% w/v Chlorhexidine Gluconate and 70% (v/v) Isopropyl Alcohol)

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The information below is from the CSR.

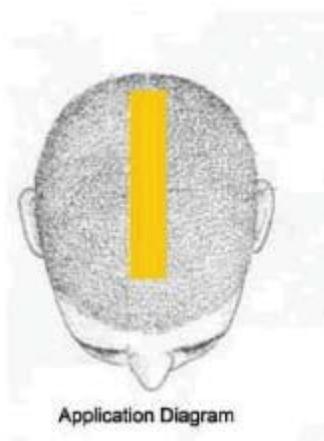
The study was not a clinical study (no humans were exposed) and was non-randomized, open-label, non-controlled.

The objectives

- To measure the drying time of human head hair on mannequins of 3M CHG/IPA Film-forming Preoperative Skin Preparation solution dispensed from the 10.5 mL applicator, based on measurement of isopropyl alcohol vapors for an hour and wiping the hair with a Kim wipe until there was no prep transfer to the tissue.
- Similar to the first objective except the 26 mL applicator was used
- Confirm that prep dried hair is not flammable by testing 1 prepped and dried mannequin head from each applicator for ignition capabilities

12 human hair mannequins (6 per applicator size) were used in room conditions of 15/hour minimum air exchange, 68-73% F, and 30-60% relative humidity. Heads were placed horizontally, face-up with support at the neck. Per the protocol included in the CSR (p.78/86), the hair was straight and cut to shoulder length. The hair was parted on the top. The CHG/IPA solution (tinted per protocol p. 79/86) was applied one applicator per mannequin. Effort was made to use as much of each applicator to the hair as could be transferred. The sponsor's diagram showing the application is copied from the protocol below.

**Figure 4 Study 013430 Diagram of application**



Drying time began immediately following the completed application. Dry time determination began 20 minutes after the application was completed, continued every 5 minutes until hair appeared close to dry, and every minute after that until it was determined to be dry based on the absence of Kim wipe transfer. Vapor dissipation measure with FTIR Spectrometer from the beginning of the process. Alcohol volatiles were drawn into the FTIR Spectrometer for quantification by a collection device placed

over the coated area and using a pump. Measurement continued at least until the readings were below 23, 000 ppm (sponsor reports this is the flammability limit of isopropyl alcohol. Elapsed times of the CHG/IPA prep application was recorded by a timer.

Flammability assessment was made on a single mannequin head for each applicator size that had prep solution and dry determined with blotting. In a fire safe environment, a sparking device meant to simulate operating room suite electrocautery was applied to the hair to see if it could be ignited.

**Study 013430 Results:**

Review of the methodology of the FITR spectrometer and other technical features of the protocol are outside of the expertise of clinical review. Therefore, conclusions such as those on page 47/86 (validity of the extractive FTIR method) were not evaluated by this reviewer.

The sponsor’s presentation indicates about 3 g of the 10.5mL solution and 9 grams of the 26 mL solution were on the delivered to the mannequin heads.  
Net weight of solution delivered

**Table 37 Postmarketing Avagard Literature**

	N	Mean ± Std Dev (gram)	Range (grams)
10.5 mL	6	2.95 ± 0.42	2.16 - 3.26
26 mL	6	9.16 ± 0.89	7.86 – 10.41

Source: Table 1 in the CSR  
Study 13430-

Dry time-The mean dry time for the 10.5 mL applicator exposure was about 29 minutes (± ~2) and about 41±3.8 minutes for the 26 mL applicator. The range of dry times was 25 - 30 minutes for the smaller applicator and 35 – 45 minutes for the larger applicator. (data source, CSR Table 2).

Isopropyl alcohol vapor concentration-Vapor concentration measurement began after solution application. The sponsor’s Table 3 (not shown in this review) reports that all mean measurements were below 23,000 ppm.

I reviewed the mannequin head listings in Table 1 of Appendix 7.5 (pps. 12- 23) looking to verify that all measures were <23,000 ppm (searched using “Find” and “23,” and “22, “ Though the pages were noted as searchable, a search of a number (1,131 on page

19/86) did not capture the number. Therefore, I also manually reviewed the values reported on the referenced pages under “IPA concentration ppmv). I did not see any values to manual scan above 23,000 but the units were ppmv, not ppm.

Flammability- The sixth mannequin head for each applicator size was prepped, allowed to dry until it was considered “apparently dry” with the Kim method. It was bagged and taken to a hood where ignition was tried. The sponsor states that the “hair did not ignite with multiple attempts using the sparking device”.

### **7.5.1 Dose Dependency for Adverse Events**

Not applicable

### **7.5.2 Time Dependency for Adverse Events**

Not performed.

### **7.5.3 Drug-Demographic Interactions**

Not evaluated.

### **7.5.4 Drug-Disease Interactions**

Not evaluated. With some exception (such as burn victims, premature infants), this is probably not applicable due to presumed low absorption.

### **7.5.5 Drug-Drug Interactions**

Not evaluated.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

Not performed.

### **7.6.2 Human Reproduction and Pregnancy Data**

The topical antiseptics are thought to have negligible percutaneous absorption through intact adult skin. Also, the product will be single use and is not expected to be used in a chronic intermittent matter. Pregnancy was exclusionary in the trials.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not addressed.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not expected to have a drug abuse given the indication. Overdose likely would not be expected in intact skin though perhaps there is an overdose or overexposure in premature neonates, especially low birth weight or damaged skin. These situations can be addressed in labeling.

## 7.7 Additional Submissions / Safety Issues

November 6, 2015 (SDN 9) -We requested a literature review and discussion of the overall safety. The sponsor reports searching EMBASE, Chemical Abstracts, and Medline for the terms chlorhexidine or CHG or the chemical registry numbers and limited to keywords for skin prep or anti-infective agents used in surgery and in humans and in English, with a publication date since 2007.

In SDN 9, 1.11.14, the sponsor reports a total of 68 studies were identified. Of these, eleven were identified as clinical studies that included the use of CHG-IPA as a skin preparation agent for preoperative surgical skin antisepsis. The sponsor notes that five did not comment on adverse events. Neurologic, genitourinary, and skin body systems were noted to be described in the remaining studies.

- One was a review of cases, retrospectively identified, of patient prep for patients undergoing placement of spinal catheters performed at the Mayo Clinic between 2006 and 2010. This publication was noted elsewhere in this review. The authors concluded that the results supported the hypothesis that CHG can be used for skin antisepsis before spinal placement without increasing the risk of complications (neurologic) attributed to the anesthetic. There were 5 complications possibly related to be from the spinal anesthetic.
- A study that assessed safety of patients being prepped for genitourinary prostheses. The Sponsor reports there was no dysuria or “genital complications (skin irritation)” noted immediately in the perioperative period or at 1 and 6 months.
- Per the sponsor, skin complications were noted in three publications. One of these identified three patients with an adverse event around the surgical wound (pruritus, erythema, or both).
- The sponsor reports that no serious adverse events “were related” to study drugs. One study had two discontinuations but the reasons for discontinuation were reportedly not described.
- The sponsor’s table (included in SDN, page 20/88) notes that one publication is a query of prospectively collected data to test the hypothesis that ChlorPrep is

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more effective at reducing surgical site infections and 30 day readmission when compared to DuraPrep. The submission information reports there was no comment on CHG AEs but 30 day readmission was “marginally significantly increased for ChlorPrep compared with DuraPrep.” The numbers were considered too small to have power and the readmission reasons were not described.

SDN 10 was a resubmission of the 120-day safety update. It was a single page safety-update essentially noting there was no new safety information that would alter the draft labeling submitted in July.

Study 13447, a study that rated product attributes by health care professionals, was noted to be complete after the filing date. As a note, this study employed the TBM formulation. The sponsor stated they had not planned this study to be part of the NDA review since it was not designed as a full safety or efficacy study and did not provide new safety information. The sponsor states exposure time was 15-30 minutes and reports there were no adverse events. Twenty-one subjects had the 3M product (the TBM formulation) and ChlorPrep applied to their knees and back. The final CSR notes a skin irritation assessment of “slight redness” on the test site where the comparator product was. This was noted to resolve within 24 hours.

## 8 Postmarket Experience

There is no postmarket experience with this product as it is not marketed.

Minutes of the January 20, 2015 pre-NDA meeting indicate that the sponsor was asked to provide a review of published literature and a summary of postmarketing safety data from use of their Avagard product. Avagard is approved as a surgical and healthcare personnel handwash, NDA 21074. It is my opinion that ChlorPrep (2% CHG- 70% IPA) shares more in common with the proposed NDA product than Avagard (2% CHG - 61% ethyl alcohol) though neither of these products has a polymer.

The sponsor’s presentation of Avagard’s postmarketing data is minimal and does not allow independent confirmation.

The sponsor reports that 5 adverse drug experiences were considered serious, anticipated, and “covered” by current labeling. These were described in a 3.5 page table (Table 23). I verbatim reproduced some of the narratives in the table or summarize/abbreviated other parts.

**Table 38 Post marketing Serious Adverse Events**

LCAM-9J9KEN	4-7-2014	OR technician developed sores on his forearm. Prescribed topical and oral steroids. "Pockmarks" on his arms at assumed site of sores as of 4-18-14 information. Previous use of Avagard Surgical Scrub for 2 years without problem.
USEN-9HXRTE	3-1-14	64 year old OR technician. A month before report, noticed an increase in spots on his forearms and increase in temperature for weeks. He "alleged" that he had open sores on his wrists to elbows and described as if a layer of skin was removed. He stopped using Avagard Surgical Scrub which he had used for about 2 years before this event. He was prescribed topical and oral steroids. Follow-up indicates he did not rinse the Avagard, that he occasionally applied product directly to wounds. He reported he had pockmarks on his arms.
LCAN-9J9KBV	10-7-13	Customer reported that surgeon reported developing open sores on his forearms about 6 months earlier. Sores were not blisters. Surgeon went to GP who prescribed topical and oral steroids. Sores appears to have had some pockmark scarring but the report is inconsistent.
LJMP-98TRJM	2-8-13	Customer reported a NICU nurse who claims allergy to latex and CHG who developed redness, blisters, rash, itching, burning on hands and forearms. Nurse treated with EpiPen due to shortness of breath. Reportedly nurse scrubs for 3 minutes in morning with soap and water, Betadine, or CHG and uses Avagard Hand Antiseptics up to the elbows between patients, washes with soap and water every 2-3 applications after use of Avagard Hand Antiseptic.
USEN-935NJ6	12-19-12	Male customer who always wears face shield accidental squirted under the shield into his eye. He rinsed with cold water and went to ER. They seem to have put something in his eye and irrigated with "IV solution". "Reportedly is fine."

Table 23 pages 121-124 of the CSS. OR =operating room. "alleged" is the sponsor's wording.

The sponsor reports a total 145 adverse drug experiences considered non-serious, anticipated, and covered by approved labeling. All were in the body system, Skin and Appendages/Application Site Reactions. The sponsor lists included reactions as rash, cracked skin, blisters welts, inflammation, contact dermatitis, itching, and swelling. The sponsor shows a listing per year from 2010 to 2014 and a number of complaints per million doses (CMD). The lowest number of non-serious, anticipated, and labeled events is 2010 with 10 events and a CMD of 0.17. The highest number of events, and highest CMD, is 2013 with 92 such events (82 from the same facility).

The sponsor concludes that "Avagard has been found to be safe when used as intended and according to the label directions" (p.42/62 of the CSS).

Sponsor’s review of the published literature on Avagard:

The sponsor notes that the following literature seven abstracts included were taken directly from the literature. No cumulative synthesis of these abstracts was made by the sponsor. Based mostly on the abstracts, my review indicates that four of the abstracts did not address safety (outside of overlap with efficacy or effectiveness as an antiseptic).

Three of the abstracts contained some mention or degree of safety outside of effectiveness though they are non-contributory in a meaningful way to evaluating the safety of this product. One was of interest, though not definitively interpretable in terms of conclusions. This is the first publication in the table below. This describes that an institution was investigating a three consecutive quarter increase in surgical site infection rates. Eighteen months prior to this cluster, Avagard had been introduced in the operating rooms. It was thought that (mis) use of Avagard was associated with the increased rates of SSI. The product was removed from the operating rooms and other changes as well as staff education was performed. The SSI rates dropped at or below previous levels. The article is not conclusive in causality to Avagard misuse, given other changes made. It is suggestive that if product labeling is not followed, this can contribute to increased infection rates.

**Table 39 Post marketing Avagard literature**

<p><b>Haessler S, Connelly NR, Kanter G, et al. A surgical site infection cluster: the process and outcome of an investigation--the impact of an alcohol-based surgical antiseptis product and human behavior. <i>Anesth Analg.</i> 2010;110(4):1044-8</b></p>	<p>An institution investigated an increase in surgical site infection (SSI) rate for 3 consecutive quarters in 2007(over their usual). The abstract reports that it was thought that “(mis)use of an alcohol-based hand antiseptic product was associated with the increased infection rate.” The article indicates that Avagard had been introduced 18 months before this SSI cluster. The product was removed from the ORs and personnel underwent education and it seems other changes were made. SSI rate ↓.</p>
<p><b>Weight CJ, Lee MC, Palmer JS. Avagard hand antiseptis vs. traditional scrub in 3600 pediatric urologic procedures. <i>Urology.</i> 2010;76(1):15-7</b></p>	<p>The abstract states that no side effects for the patients or surgeon were noted, including skin irritations or allergic reactions in either group. Conclusions included that the Avagard provided comparable hand antiseptis to traditional scrub in pediatric urological procedures.</p>
<p><b>Vergara-Fernández O, Morales-Olivera JM, Ponce-de-León-Rosales S, et al. Niveles de satisfaccion del equipo quiuirgico entre dos metodos de lavado de mano. [Surgical team</b></p>	<p>Abstract indicates the objective was to evaluate washing times, safety, cost and amount of water between two surgical scrub techniques. Article indicates traditional was 4% CHG with brush, rub</p>

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<p><b>satisfaction levels between two preoperative hand-washing methods]. Rev Invest Clin. Nov-Dec 2010;62(6):532-7.</b></p>	<p>with sterile sponge and rinse with water. The other group washed with Avagard with no rubbing or brushing. N=100 surgeries (50 per group). Dryness 6.5% traditional and 2% in non-brush scrub (Avagard).</p>
<p><b>Olson LK, Morse DJ, Duley C, Savell BK. Prospective, randomized in vivo comparison of a dual-active waterless antiseptic versus two alcohol-only waterless antiseptics for surgical hand antisepsis. Am J Infect Control. 2012;40(2):155-9</b></p>	<p>The abstract describes that the study aimed to demonstrate the value of adding an active level of persistent antimicrobial agent such as CHG to an alcohol based hand antiseptic. The abstract does not describe safety of use of the product outside of the effectiveness of adding CHG.</p>
<p><b>Lai KW, Foo TL, Low W, Naidu G. Surgical Hand Antisepsis-A Pilot Study comparing Povidone Iodine Hand Scrub and Alcohol-based Chlorhexidine Gluconate Hand Rub. Ann Acad Med Singapore. 2012;41(1):12-6</b></p>	<p>Abstract describes pilot study comparing PVI-P to Avagard scrubs. Outcome measure was efficacy (cultures). No safety results are described.</p>
<p><b>Burch TM, Stanger B, Mizuguchi A, Zurakowski D, Reid SD. Is Alcohol-Based Hand Disinfection Equivalent to Surgical Scrub Before Placing a Central Venous Catheter? Anesth Analg. 2012;114(3):622-5</b></p>	<p>Abstract does not describe safety information. The hypothesis for the study was effectiveness of disinfection before placing a central venous catheter.</p>
<p><b>Chen C-F, Han C-L, Kan C-P, Chen S-G, Hung PW. Effect of surgical site infections with waterless and traditional hand scrubbing protocols on bacterial growth. Am J Infect Control. 2012;40(4):e15-7.</b></p>	<p>Study to evaluate effect of surgical site infections with waterless and traditional hand scrubbing on bacterial growth. Safety of the product outside of the overlap with effectiveness in SSI was not described in the abstract.</p>

Source: Information from pages 125-128 CSS. PVP-I=povidone iodine, CHG=chlorhexidine gluconate.

## **9 Appendices**

### **9.1 Literature Review/References**

See section 7.3.6 and 7.3.7.

### **9.2 Labeling Recommendations**

As I understand it, this product is likely to receive a Complete Response Letter. Label recommendations are deferred.

### **9.3 Advisory Committee Meeting**

There has been no Advisory Committee Meeting for this product.

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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.**  
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/s/  
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TERESA A PODRUCHNY  
03/22/2016

FRANCIS E BECKER  
03/22/2016

For further comments and recommendations, please refer to the CDTL Review, which will be completed after submission of all primary and secondary reviews.