CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 30, 2018
From	Francis E. Becker, M.D., F.A.C.P.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 207964
Applicant	Medline Industries
Date of Submission	October 20, 2017
PDUFA Goal Date	November 20, 2018
Proprietary Name	ReadyPrep CHG
Established or Proper Name	2% chlorhexidine gluconate (CHG) cloth
Dosage Form(s)	Cloth
Applicant Proposed Indication(s)/Population(s)	Presurgical skin preparation • For preparation of the skin prior to surgery • Helps reduce bacteria that potentially can cause skin infection
Applicant Proposed Dosing Regimen(s)	Dry surgical sites (such as abdomen or arm) • Use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Moist surgical sites (such as inguinal fold) • Use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub back and forth for 3 minutes, completely wetting treatment area, then discard. Allow to dry for one (1) minute. Do not rinse.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Presurgical skin preparation Use with care in premature infants or infants under 2 months of age.
Recommended Dosing Regimen(s) (if applicable)	Same as applicant proposed dosing regimen

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

I recommend approval of Ready Prep CHG cloth for use as a preoperative skin preparation. In two randomized, vehicle and active controlled, evaluator-blinded clinical simulation studies, ReadyPrep Cloth met the effectiveness criteria outlined in the 2015 proposed rule, with the lower bound of the 95% Confidence Interval (CI) of the responder rate greater than 70% at 10 minutes (primary objective). The ReadyPrep CHG cloth demonstrated statistical superiority (based on average treatment effects) to both Dyna-Hex 2 (a 2% CHG solution) and the vehicle (placebo cloth) at 10 minutes, in both the abdomen and groin body regions. At the 6-hour timepoint in both studies, the ReadyPrep CHG cloth demonstrated 100% responder rate (secondary objective), responder being defined as a subject with skin flora counts at 6 hours below baseline, either in groin or abdomen. Thus persistence of effect at 6 hours at 6 hours was demonstrated for the ReadyPrep product.

The Centers for Disease Control and Prevention (CDC) note that the human and financial cost of treating surgical site infections (SSIs) are increasing and estimates that approximately half of SSIs are preventable.[1] A 2016 Surgical Site Infection Guidelines from the American College of Surgeons and Surgical Infection Society, states that SSIs are the most common hospital-acquired infections accounting for 20% of all hospital acquired infections. SSIs are associated with morbidity, increased length of hospital stay and an annual cost in the billions of dollars.[2] Prevention of SSI is increasingly important as the number of surgical procedures performed in the US continues to rise. Prevention of SSIs is a critical focus in patient care.

ReadyPrep CHG cloth will provide an additional option for preoperative skin preparation. In vitro studies demonsrate effectiveness against a broad range of Gram-positive and Gram-negative bacteria, facultative anaerobes, aerobes, and yeast. The addition of preservatives to the formulation which may prevent growth of Burkholdia cepacia, may also prove beneficial.

In general the safety profile of ReadyPrep CHG was consistent with that of other CHG-containing products, and no new safety signals were identified. In the clinical studies, adverse events associated with ReadyPrep CHG occurred in less than 1% of subjects (26 of 1931 treated) and consisted of mild skin reactions (pruritis, irritation, rash, and pain at application site). Allergic reactions, including anaphylaxis, have been associated with topical CHG products. Class labeling, which will be included in the Sponsor's labeling, addresses this concern in an ***Allergy Alert*** under **Warnings**, which identifies signs of a severe allergic reaction (wheezing/difficulty breathing,shock, facial swelling, hives, rash) and advises that "*If an allergic reaction occurs, stop use and seek medical help right away."* Due to its irritant properties, CHG-containing products are contraindicated for lumbar puncture or in contact with the meninges, or on open skin woulds or as a general skin cleanser, and it is not to be used around the eyes, ears or mouth. These warnings are adequately addressed in class

[1] Berríos-Torres, S.I., Umscheid, C.A., Bratzler, D.W., et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg.* 2017;152(8):784-791. doi:10.1001/jamasurg. https://www.cdc.gov/infectioncontrol/guidelines/ssi/index.html

[2] Ban, K.A., Minei, J.P., Laronga, C., et al American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update.pdf http://dx.doi.org/10.1016/j.jamcollsurg.2016.10.029

labeling. Premature infants or infants less than 2 months of age have an increased risk of chemical burns, and there is concern that CHG absorption through the skin is increased in younger infants due to differences in skin thickness and function in this age group. This risk is also adequately addressed in class labeling and in the proposed label which states, "*use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.*" It is important to note that CHG-containing products may still remain the best option for infants requiring surgery. 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.

In conclusion, the Benefit-Risk assessment remains favorable for approval of ReadyPrep CHG 2% cloth for preoperative skin preparation.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Prevention of surgical site infections (SSIs) is increasingly important as the number of surgical procedures in the United States continues to rise. • SSIs are the most common hospital-acquired infections • Estimated annual incidence of SSIs in the US ranges from 160,000 to 300,000; annual cost of 3.5 to 10 billion; increased length of hospitalization by 9.7 days	Prevention of SSIs is a critical focus in patient care with far-reaching implications
Current Treatment Options	• There are numerous preoperative preparations containing chlorhexidine (1-4%) alone or in combination with alcohol or isopropyl alcohol on the market • Dosage forms vary: CHG 2% is available in cloth and solution • CHG products have been demonstrated to help reduce bacteria that can cause skin infection. They are generally well-tolerated but are known skin irritants and can be associated with allergic reactions, including anaphylaxis.	In vitro time-kill studies and clinical in vivo simulatin studies demonstrating statistically significant decrease in baseline bacterial counts provides the basis for it use. Safety profile is well-understood and with appropriate labeling, is acceptable.
Benefit	• The results of the two pivotal Clinical Simulation studies, supported by three pilot studies and invitro time-kill studies are adequate to demonstrate efficacy of ReadyPrep CHG 2% cloth for the proposed indication: "helps reduce bacteria that can potentially cause skin infection; for preparation of the skin prior to surgery." In addition, the results of the time-kill studies provided by the Sponsor indicate that (b) (4) has no impact on the antiseptic effectiveness of the ReadyPrep CHG formulation. • The product will provide an additional option for preoperative skin preparation • Product excipients may prevent Burkholdia cepacia (B. cepacia) contamination	Insert text as concise paragraphs

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety profile of CHG is well known. • No new safety signals were identified in the clinical studies, postmarketing databases, or published literature • CHG is a known skin irritant • Common AEs are generally mild and include pruritis, irritation, rash and pain at the application site • Allergic reactiions (anaphylaxis) has been associated with CHG • Use with care in premature infants or infants under 2 months of age because risk of skin irritation and chemical burns in this group is increased.I n addition, absorption through the skin in this group may be increased, the consequences of which are not know.	In general, adverse events are mild and resolve with little or no treatment. The risk of anaphylaxis is addressed in labeling. Class labeling includes precaution about use in infants. However, at present CHG may be the best option for infants who must have surgery. 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.

2. Background

Medline Industries (Medline; the Sponsor) is seeking approval of a New Drug Application (NDA) for ReadyPrep CHG, a 2% chlorhexidine gluconate (CHG) cloth, under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed indication for ReadyPrep CHG is for use as a preoperative skin preparation. The product is formulated as a 2% CHG (that delivers up to 500 mg of the active moiety, CHG, per cloth and application), an inactive incipient profile, and a polyester cloth. CHG is applied through a single application, consisting of a 3-minute vigorous rub followed by a 1-minute dry time, at the therapeutic site of action.

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). On 20 December, 2017, FDA published its HealthCare Antiseptic Final Rule (82 FR 60474). Products containing CHG, such as ReadyPrep CHG, do not fall under the monograph and must be submitted as NDAs. NDA drugs include a variety of CHG products, including CHG alone, and CHG/alcohol or isopropyl alcohol (IPA). Iodine/IPA products are also available under NDAs. Products available under the OTC drug monograph include a number of different ingredients, including alcohol (ethyl alcohol), benzalkonium chloride, benzethonium chloride, iodine, and IPA.

Chlorhexidine gluconate is approved for preoperative use in the United States at concentrations ranging from 1-4% and in a variety of formulations, including topical cloth, topical solution, topical sponge, and topical swab (see **Table 1** below). It is also approved for use in dental products for the treatment of gingivitis. Because CHG is generally poorly absorbed through the skin, the general safety profile of a topical 2% CHG solution includes skin reactions such as irritation and rash with specific warnings not to be used around eyes and ears. However, hypersensitivity reactions, including anaphylaxis, have been reported with CHG containing compounds. Consequently, the ***Warnings*** section of the Drug Facts Labeling for CHG-containing products generally contain an **Allergy Allert** which includes a description of allergy symptoms (wheezing, difficulty breathing, shock, facial swelling, hives, and rash) and the statement, "if an allergic reaction occurs, stop use and seek medical help right away." In addition, severe burns have been reported with alcohol-based CHG products in younger infants, and there is concern that CHG absorption through the skin is increased in younger infants due to differences in skin thickness and function in this age group. As a result, class labeling for these products includes directions to "use with care in premature infants or infants under 2 months of age. These products may cause chemical irritation or chemical burns." ReadyPrep CHG is not approved for for use anywhere in the world at the present time.

Table 1: Current Skin Preoperative Preparation Products

Brand Name	Active Ingredient(s)
ChloraPrep Single Swabstick ChloraPrep Triple Swabstick ChloraPrep One-Step Sponge ChloraPrep One-Step Sponge SEPP Swab ChloraPrep One-Step Sponge FREPP Sponge ChloraPrep One-Step Sponge (yellow or green tint)	2% CHG, 70% IPA
SoluPrep Film-forming Sterile Solution)	2% CHG, 70% IPA

Prevantics Swab Prevantics Swabstick Prevantics Maxi Swabstick (all previously Chlorascrub)	3.15% CHG, 70% IPA
Chlorhexidine 2% CHG Cloths (Sage)	2% CHG
Dyna-Hex2 Solution	2% CHG
Dyna-Hex Solution	4% CHG
Hibiclens (15 mL single use packet)	4% CHG
PRE-OP II and PRE-OP Sponge	480 HEX
DuraPrep Surgical Scrub Sponge	Iodine Povacrylex/74% IPA

CHG=chlorhexidine gluconate, IPA=isopropyl alcohol, ETOH=ethyl alcohol,
HEX= Hexachlorophene
Source: FDA Orange Book
https://www.pharmacompass.com/fda-orange-book/chlorhexidine-gluconate
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The ReadyPrep CHG IND (**107899**) was submitted on 23 December 2013. Key meetings that took place during the ReadyPrep development program are listed in the **Table 2** below. Important discussions relevant to the current submission include discussion at the Pre-IND meeting of 19 September 2012, at which time (b) (4) At the meeting, FDA stated that (b) (4)

(b) (4)

FDA also agreed in written comments to the Sponsor that it is reasonable to request a waiver for the phototoxicity and photoallergy studies for this product in the NDA submission, although whether the waiver will be granted will be a review issue.[4]

Table 2:Overview of Key Interactions Held Between FDA and Medline

Meeting Type	Meeting Date	Date Minutes Issued	Reference
Pre-IND	13 December 2011	11 January 2012	3070490
Pre-IND	19 September 2012	15 October 2012	3203245
Type A Refusal to File	23 May 2016	21 June 2016	3949172
Advice Request	29 June 2016	14 September 2016	3983558
Type C	(Written Responses)	6 December 2016	4023755
Type C	(Written Responses)	3 March 2017	4064254

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Medline first submitted the ReadyPrep NDA on 9 February 2016, and a Refusal to File (RTF) action was taken by FDA (notification received by the Sponsor on 8 April 2016). The RTF letter noted that the application was deemed incomplete for the following reasons (the actions taken by the Sponsor in the current submission to address these deficiencies are italicized):

[3] PIND 107899 PIND Meeting Minutes; 19 September 2012
[4] NDA 207964 Type C written Responses Only; 3 March 2017

- "The application fails to address the safety of [redacted]

[redacted]

- "The application is incomplete because Clinical Study Reports in module 5 of the eCTD (Electronic Common Technical Document) do not contain a section on subgroup analysis."

Medline has amended the clinical study reports with the requested subgroup analyses.

- "The application does not contain an appropriate patent certification as required under 21 CFR 314.50(i)."

References to chlorhexidine gluconate listed drugs other than Hibiclens (NDA 017768) have been removed from the application; there are no patents associated with Hibiclens, therefore Medline has provided a Paragraph 1 patent certification.

While not related to the refusal to file, the RTF letter also identified Clinical, CMC, Microbiology, Statistical, and Labeling issues that the Sponsor "should address" if the application is resubmitted. In addition, as agreed to in the Type A meeting of 23 May 2016, due to concerns over study integrity, the Sponsor has removed efficacy data from Study **R13-052** from the Integrated Summary of Efficacy but has included the safety data and study report in the current submission.

During the current review cycle, FDA inspection of one pivotal study site (Study **R15-029**, discussed in the sections below), which occurred on 26 March 2018, identified many previously unreported protocol deviations, as a result of which the Sponsor submitted an amended clinical study report on 13 June 2018. The submitted response qualified as a major amendment. Therefore, the PDUFA clock was extended 3 months.

3. Product Quality

ReadyPrep CHG is comprised of a polyester cloth saturated with 2% chlorhexidine gluconate topical solution, USP. The product is packaged in a single-use, unit-dose presentation consisting of two cloths sealed in a [redacted] pouch, which provides the equivalent of 500 mg of chlorhexidine gluconate per cloth and corresponds to [redacted] g of liquid per cloth. The product is nonsterile. The cloth is 100% polyester with an average thickness of 1.50 mm and an absorption capacity of [redacted] L/m^2. The cloth material is provided [redacted] to a size of [redacted] cm. The liquid application to the cloth is manufactured as [redacted] The finished product is packaged in a primary container closure system and is a [redacted] pouch made from a [redacted] The composition of the final formulation of ReadyPrep CHG is provided in **Table 3** below:

Table 3: Composition of Final Formulation of ReadyPrep CHG

Component	Function	Quantity (% w/w)	Quantity (% w/v) [a]
Chlorhexidine Gluconate	Active Ingredient / Antiseptic	2 [b]	2 [b]
Glycerin	(b) (4)		
Propylene Glycol			
Isopropyl Alcohol			
Dimethicone (b) (4)			
Benzalkonium Chloride			
(b) (4)			
Purified Water			
(b) (4)			

Source: NDA 207964 Section 2.7.1 Summary of Biopharmaceutic Studies; Table 1, page 5.

The product quality assessment was conducted by the Quality Review Team listed in **Table 4** below. For a detailed review, the reader is referred to the Quality Team Combined Review.[5]

Table 4: Qualtiy Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Friedrich Burnett, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Tarun Mehta	OPF/DPAII/BranchVI
Microbiology	Denise Miller, Ph.D.	OPF/DPAII/BranchVI
Facility	Carl Lee	OPF/DIA/B3
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Teshara Bouie	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA) and Labeling	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

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In his summary review, Swapan De, PhD, Application Technical Lead, recommended that, "Regarding Chemistry Manufacturing and Controls, the application may be approved." He continued, "Regarding quality aspects of the resubmitted application the drug substance, drug product, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application…The drug product is granted a 24-month shelf life when stored at 25°C/60%RH."

[5] NDA 207964 IQA combined OPQ reviews; Quality Assessment; 12 October 2018.

Dr. De noted that, although the current application, submitted in February 2016 was not filed mainly due to clinical and non-clinical issues, the letter of 8 April 2016 included advice not related to "refuse to file" to address some CMC issues. In the current submission, the Sponsor included a response to the CMC comments. Dr. De reported that "all quality-related (drug substance, drug product, manufacturing process, microbiology and facility) issues are resolved during this review cycle." Facility review with "acceptable recommendation" was completed on 5 October 2018.

In addition, Elise Luong, PhD, performed a labeling assessment and concluded that the drug established name and CMC information in the provided labeling are accurate. Therefore, no labeling changes were recommended from CMC perspective.

4. Nonclinical Pharmacology/Toxicology

As noted above, FDA stated in the RTF letter that the application failed to address the safety of (b) (4) (b) (4) In the current submission, to bridge to the nonclinical and clinical safety and efficacy data, the Sponsor performed a comparative in vitro time-kill study to compare the antimicrobial properties of the ReadyPrep CHG formulation (b) (4) (Study **R17-004**). In addition, PubMed was searched in June 2017 for nonclinical literature related to chlorhexidine.

Nonclinical Pharmacology/Toxicology Review[6] was conducted by D. Charles Thompson, RPh, PhD, DABT (Team Leader: Jane Sohn, PhD.). No original nonclinical data was submitted in support of the current application. Dr. Thompson noted that the proposed drug product formulation contains no novel excipients. Furthermore, all proposed excipients are listed in the Inactive Ingredient Database (IID) as having previously been used in approved drugs of a comparable dosage form, route of administration, and use concentration. Therefore, Dr. Thompson concluded the proposed formulation does not raise nonclinical safety concerns. Regarding impurities and degradants, Dr. Thompson reported that the Sponsor proposes a finished product specification of NMT (b) (4) ppm (b) (4) for (b) (4) He noted that this specification is consistent with (equal or less than) levels that DNDP has previously approved for OTC CHG topical products and is "acceptable from a nonclinical perspective." Dr. Thompson also noted that no other impurities/degradants of concern were identified by the CMC team.

As noted above, the Sponsor submitted and summarized available published literature to support the nonclinical safety of CHG for the proposed indications. As Dr. Thompson pointed out in his review, the primary deficiency that was the basis for the RTF action was (b) (4) (b) (4) The NDA submission provided a patent certification for the original NDA 017768 (Hibiclens, 4% topical solution, approved in 1976); however, the Sponsor indicated that they "will not be relying on the FDA's findings of safety and/or effectiveness for any listed drugs."[7] Dr. Thompson reported that "these published data are lacking by current regulatory standards." Furthermore, "the data and information provided by the Sponsor from the published literature "have little relevance for a new drug product with an acute-use indication that is applied by the topical dermal route of administration. The cited publications provide little, if anything, beyond brief summary information and do

[6] NDA 207964; Pharmacology/Toxicology NDA Review and Evaluation; NDA 207964; 19 June 2018.
[7] NDA 207964, Section 2.2, Introduction to Summary, Table 6, page 8/10

not afford FDA an opportunity for a full and independent evaluation of the original data." However, Dr. Thompson concluded that, "in the context of the existing substantial prior history of safe use of CHG in the marketplace, these published nonclinical data are considered sufficient and adequate to support approvability of the application from a nonclinical perspective."

Nonclinical Review Addendum

Following further internal discussion and communication with the Sponsor informing them of the inadequacy of referencing the nonclinical published literature, the Sponsor proposed to proposed "to rely on FDA's findings of nonclinical safety for Hibiclens, a 4.0% w/v chlorhexidine gluconate (CHG) topical solution (NDA 017768; Molnlyche Health Care US, LLC; Approval Date 17 September 1976."[8] Subsequently, Dr. Thompson completed an addendum to his initial review[9]. He wrote:

> *Following internal evaluation of this information, it is concluded that the estimated dose and duration for the Hibiclens® product supports the proposed product with respect to anticipated exposures to the CHG active ingredient. It is also concluded that the Sponsor's previously submitted literature survey and summary are supportive but not pivotal to supporting the safety of CHG. The application remains approvable from a from a nonclinical perspective*.

5. Clinical Pharmacology

Clinical Pharmacology review was conducted by Kunyi Wu, PharmD, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology 4 (DCP4) (OCP Team Leader: Seong H. Jang, PhD). Dr. Wu concluded that "The clinical pharmacology information provided by the Applicant in support of the 505(b)(2) application is acceptable and supports the approval of ReadyPrep CHG pending the safety review and an agreement on the labeling."[10]

Dr. Wu's review focused on the clinical pharmacokinetic (PK) study (Study **R17-023**) and the published literature provided by the Sponsor. Study **R17-023** was a randomized, single-dose, laboratory-blinded, 3-period, 3-sequence, crossover, pharmacokinetic (PK) study to assess systemic exposure of CHG from ReadyPrep CHG. Each of 12 subjects was scheduled to receive one abdominal application (Treatment 1) of Readyprep CHG, one groin application (Treatment 2) of ReadyPrep CHG, and one control treatment (Treatment 3) with no application (the same procedures as Treatment 1 and 2 were performed, but without application of ReadyPrep CHG), randomized to one of the three study sequences shown in **Table 5** below.

Table 5: Study R17-023 Sequences

	Period 1	Period 2	Period 3
Sequence 1 (n=4)	Treatment-1	Treatment-2	Treatment-3
Sequence 2 (n=4)	Treatment-2	Treatment-3	Treatment-1
Sequence 3 (n=4)	Treatment-3	Treatment-1	Treatment-2

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[8] NDA 207964 SDN-37; received 28 September 2018.
[9] NDA 207964; Memorandum to File, Addendum to Nonclinical Pharmacology/Toxicology Review; 4 October 2018.
[10] NDA 207964 Clinical Pharmacology Review: 12 October 2018.

ReadyPrep CHG was applied with a 3-minute vigorous rub followed by a 1-minute dry time, as is specified for the proposed product if approved for marketing. Ten of the 12 subjects completed all three periods of the study. Two subjects withdrew due to schedule conflicts. Blood samples were collected at 10, 2, and 0.5 hours prior to each treatment, and 1, 2, 3, 4, 5, 6, 8, and 12 hours following each treatment. CHG plasma concentrations were measured using a validated bioanalytical method; the lower limit of quantitation and upper limit of quantitation were 200 pg/mL and 7500 pg/mL, respectively. CHG was not detectable in any blood samples, demonstrating no to negligible systemic exposure to CHG in adults from a single usage of ReadyPrep CHG as instructed in the draft label.

Because the clinical PK study (**R17-023**) was conducted in adults only, the Sponsor provided a literature summary of CHG products in pediatric patients. Dr. Wu reviewed the submitted literature and concluded that, "Literature indicated that chlorhexidine can be absorbed even after a single topical application of chlorhexidine products in pediatric patients from birth to < 18 years. However, no adverse events related to chlorhexidine systemic exposure were observed in the studies conducted in pediatric patients." In his review, Dr. Wu focused on the three studies shown in the **Table 6** below. Importantly, Dr. Wu also noted that the formulations of CHG used in these studies were different from ReadyPrep CHG.

Table 6: Dosing Regimen and Treatment Duration of CHG Products in Pediatric Populations from the Published Literature

Reference	Age	Subject number	Dosing regimen	Treatment duration
Chapman et al[3]., 2013	Preterm neonates (< 32 weeks)	20	Skin wiped with 2% CHG cloth prior to placement of PICC line	Single dose
Cowen et al[4]., 1979	0-3 months; term and preterm infants	34	Full body baths in 4% CHG solution	Single dose; or up to 32 days
Lee et al[1]., 2011	3 months to < 18 years	12	Daily baths with 2% CHG cloths	Up to 30 days

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In the study by Chapmn et al.[11], enrolled infants had their skin cleansed prior to placement of a peripherally inserted central catheter (PICC) with a 2% aqueous CHG-impregnated cloth (Sage Products Inc., Cary, IL, USA). Each cloth contains 500 mg CHG. A CHG cloth was folded into quarters and one quarter was used to cleanse the infant's extremity to limit the total dose exposure. The extremity was cleaned with the CHG cloth using an up and down motion. The skin site was then allowed to dry for one minute prior to PICC insertion attempt. The CHG was not wiped or washed off of the skin prior to PICC insertion attempt. Blood samples were collected 1–2 hours and 6–12 hours after CHG exposure. Residual blood samples collected for other purposes up to > 72 hours, if available, were also used for CHG serum concentration measurement. The limit of quantitation was 12.5 ng/mL for Group 1 (first 11 infants). Based on concentrations detected in Group 1 infants, the assay was recalibrated to have a better sensitivity with respect to limit of quantification.

[11] Chapman, A.K., Aucott, S.W., Gilmore, M.M., Advani, S., Clarke, W., and Milstone, A.M. (2013). Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonates. J.Perinatol. 33, 768-771.

Consequently, the limit of quantitation is 1.06 ng/mL for Group 2 (second 9 infants). In Group 1, 5 of 30 samples (4 of 11 subjects) had detectable chlorhexidine and concentrations ranged from 16 to 274 ng/mL. In Group 2, 13 of 34 samples (6 of 9 subjects) had detectable chlorhexidine and concentrations ranged from 1.6 to 54.4 ng/ml.

In the study conducted by Cowen et al[12], blood samples were collected by heel prick (n = 10) or from venous blood (n = 24) from 34 newborn preterm infants that were bathed (full body) in 4% CHG solution (Hibiscrub). For the heel prick group, chlorhexidine was detected at 1 h (n = 10) and 4 h (n = 8) after first bath, ranging from 31 to 1021 ng/mL. Of the 24 infants that gave venous blood, 5 had positive samples, ranging from 4 to 460 ng/mL.

In the study conducted by Lee et al.[13], blood samples were collected from 12 pediatric subjects (7 males, 5 females; patients aged 3 months to 17 years) that underwent daily baths (median 9 days, range 1-30 days) with 2% CHG cloths. Of the 27 post-exposure samples, 4 (15%) had CHG concentrations above the limit of detection (LOD) (4.5 ng/mL). Of those 4 samples, 3 were below the limit of quantitation (LOQ) (17 ng/mL) and one was at 57 ng/mL. The 4 positive samples came from 4 different patients with varying exposures (4 – 22 days of baths; blood samples drawn 8 to 24 hrs after bath) to CHG. No subject had more than 1 positive sample and no evidence of accumulation was found. The patients with positive samples were aged 9 months, 2 years, 5 years, and 10 years.

Dr. Wu concluded that the clinical relevance of CHG systemic absorption in pediatric patients is unknown and that there appears to be no CHG systemic exposure related adverse events in the studies conducted in pediatric patients.

CDTL Comment: Pediatric use remains an important consideration for CHG-containing products. As noted above, some literature indicates that 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.

The publication by Lee et al, discussed above, raised the possibility that topically applied CHG may be absorbed through the skin in older children. This study was conducted in a 16-bed pediatric intensive care unit. Twelve subjects were selected from participants in an ongoing trial investigating the impact of daily bathing with 2% CHG-impregnated cloth wipes in preventing hospital-acquired bloodstream infections. The subjects had a mean age of 6.8 years (range: 3 months to 17 years). Blood samples were obtained: (1) directly

[12] Cowen, J., Ellis, S.H., and McAinsh, J. (1979). Absorption of chlorhexidine from the intact skin of newborn infants. Arch. Dis. Child 54, 379-383.

[13] Lee, A., Harlan, R., Breaud, A.R., Speck, K., Perl, T.M., Clarke, W., and Milstone, A.M. (2011). Blood concentrations of chlorhexidine in hospitalized children undergoing daily chlorhexidine bathing. Infection Control and Hospital Epidemiology 32, 395-397.

from a central line in conjunction with daily clinical blood draws, or (2) from residual blood from routine testing available in the clinical laboratory. When possible, baseline samples were obtained before the first bath. Subsequent samples were obtained on approximately days 1, 4, 7 after daily bathing had begun and once weekly thereafter. The mean number of daily baths for enrolled subjects was 9 (range: 1-30).

Thirty-four blood samples were collected and analyzed, 7 before exposure and 27 after exposure to CHG. All baseline samples had serum CHG concentrations below the lower limit of detection (LOD; 4.5 ng/mL). Of the 27 postexposure samples, 23 (85%) had a CHG concentration below the LOD and 4 (15%) had concentrations of CHG above the LOD. Of those samples above the LOD, 3 samples (75%) had CHG concentrations concentrations below the limit of quantitation (LOQ; 17 ng/mL). One sample (25%), collected from a 5-year-old child after 14 days of CHG bathing, tested above the LOQ at 57 ng/mL. All 4 samples with positive concentrations of CHG came from different individuals with varying levels of exposure. Of the 4 subjects with detectable CHG concentrations, 2 had subsequent samples collected, including the subject with aconcentration of 57 ng/mL, and both subsequent samples had no detectable CHG. There was not a trend of increasing CHG concentrations with repeated exposures.

*The authors compared the CHG concentrations against several factors that may have affected the detection of CHG in the blood. As shown in **Table 7** below, no relationship was found when examining the length of time that had elapsed between the most recent CHG bath and blood sample collection, the total number of baths the subject had received prior to sample collection, or the age of the subject. There was no evidence of accumulation over time with repeated exposure, as no subject had more than one sample with a positive concentration.*

Table 7: Distribution of Blood Samples Tested for Detectable Levels of CHG

Variable	No. of samples, by CHG concentration		
	<4.5 ng/mL	4.5–16.9 ng/mL	≥17 ng/mL
Age of subjects			
<1 year	3	1	0
1–3 years	3	1	0
4–9 years	6	0	1
≥10 years	11	1	0
Time from CHG bath to sample collection			
0–6 hours	8	0	0
7–12 hours	4	1	1
13–18 hours	5	1	0
>18 hours	6	1	0
Total number of CHG baths			
1–6 baths	10	1	0
7–12 baths	5	0	1
13–18 baths	4	1	0
18–24 baths	2	1	0
≥25 baths	2	0	0

Electronically copied and reproduced: Lee, A., Harlan, R., Breaud, A.R., Speck, K., Perl, T.M., Clarke, W., and Milstone, A.M. (2011). Blood concentrations of chlorhexidine in hospitalized children undergoing daily chlorhexidine bathing. Infection Control and Hospital Epidemiology 32, 395-397, Table 1.

Thus, it is difficult to make firm conclusions about the risk of CHG absorption in children based on the results of this study. As the authors pointed out, the sample size of the study was limited by the duration of the parent clinical trial and the availability of subjects with a projected ICU stay of at least 7 days, precluding application of statistical tests to formally assess the correlation between selected variables and CHG absorption. In addition, in order to minimize risk and harm to subjects, blood collection was timed with clinical blood draws, so there was no standardized timing. Since the CHG baths were left on (not washed off), contamination of the blood samples is always a possibility and might explain the seemingly lack of correlation between detectable CHG concentrations and length of time from last CHG bath, the total number of baths, or the age of the subject. Lastly, although it is apparent that some hospital ICUs are using CHG baths in an effort to decrease hospital-acquired infections, this is an "off-label" use of CHG products. Daily baths over the entire body for several days would result in cumulative application of much greater amounts of CHG than would occur as a preoperative antiseptic. Considering the importance of CHG-containing antiseptics for the preoperative indication in this age group, I do not recommend revisions to labeling based on the results of this study. Further studies are needed.

6. Clinical Microbiology

Clinical Microbiology Review was conducted by Michelle M. Jackson, PhD, Interdisciplinary Science Microbiologist, DNDP (Team Leader: Francisco Martinez-Murillo, PhD.). Based on her review, Dr. Jackson recommended "that the in vitro and clinical simulation studies in this application be approved for the indication 'patient preoperative skin preparation.'"

For details of the microbiology data submitted by the Sponsor, please see Dr. Jackson's thorough review.[14] Briefly, Dr. Jackson reviewed the results of three in vitro studies (**R14-013**, **R17-004**, and **R14-012**), three pilot in vivo studies (**R13-042**, **R14-015**, and **R15-028**), two pivotal clinical simulation studies (**R15-029** and **R13-053**), and one in vivo coverage area study (**R16-034**) as shown in **Table 8** below.

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[14] NDA 207964 Clinical Microbiology NDA Review; 10 September 2018.

Table 8: NDA 207964 Microbiology Studies

Study No.	Title of Study
	Nonclinical Microbiology In Vitro Evaluations
R14-013	Study R14-013 Microbiological Time-Kill Study on Medline 2% Chlorhexidine Gluconate Solution
R17-004	Study R17-004 Comparative In Vitro Time-Kill Study on Medline 2% Chlorhexidine Gluconate Solution
R14-012	Study R14-012 Evaluation of Potential for Development of Antimicrobial Resistance Study
	Clinical In Vivo Microbiology Evaluations
R13-053	Assessment of the Antimicrobial Efficacy of Medline 2% Chlorhexidine Gluconate Cloth Preoperative Skin Preparation (MicroBioTest)
R15-029	Assessment of the Antimicrobial Efficacy of Medline 2% Chlorhexidine Gluconate Cloth Preoperative Skin Preparation (Evic Romania)
R13-042	Pilot Trial Assessment of the Antimicrobial Efficacy of Medline 2% Chlorhexidine Gluconate Cloth Preoperative Skin Preparation (MicroBioTest)
R14-015	Pilot Trial II Assessment of the Antimicrobial Efficacy of Medline 2% Chlorhexidine Gluconate Cloth Preoperative Skin Preparation (BioScience)
R15-028	Pilot Trial III Assessment of the Antimicrobial Efficacy of Medline 2% Chlorhexidine Gluconate Cloth Preoperative Skin Preparation (Evic Romania)
R16-034	Evaluation of the Area Covered by Medline 2% Chlorhexidine Gluconate Cloth Preoperative Skin Preparation

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This section will discuss Dr. Jackson's review of the in vitro studies (**R14-013**, **R17-004**, and **R14-012**) and the in vivo coverage and drying time study (**R16-034**). For discussion of the pivotal clinical simulation studies (**R13-053** and **R15-029**) and a brief discussion of the Phase II pilot studies (**R13-042**, **R14-015**, and **R15-028**), the reader is referred to **Section 7** of this review.

In Vitro Studies

As Dr. Jackson pointed out in her review, because CHG is a well-known anti-microbial agent with broad spectrum activity, FDA accepts a modified in vitro testing scheme. This acceptable in vitro time-kill study includes the following modifications: a limited number of organisms, rather than requiring the full battery of organisms (four ATCC strains instead of 25, and 12 representative clinical isolates instead of 25); and

specification to test three concentrations of the final formulation (actual use concentration, another concentration in the active range, and an inactive concentration). In addition, minimum inhibitory concentration is no longer required.

Study R14-013: Microbiological Time-Kill Study on Medline 2% Chlorhexidine Gluconate Solution

Dr. Jackson reported that this time-kill study showed that Medline 2% CHG solution (full strength-1X), secondary concentration within the active range (0.5X), and the active control, Dyna-Hex 2®, produced ≥3 log_{10} reduction (>99.9%) killing effect in 6 minutes and 10 minutes in all the organisms tested. When Medline 2% CHG Solution was diluted to half its strength (0.5X) it still produced ≥5 log_{10} reduction (>99.9%) killing effect in 6 minutes and 10 minutes in most of the organisms tested. The killing effect or antimicrobial activity of a drug for a particular microorganism needs to be ≥3 log_{10} reduction to be considered an active ingredient. When Medline 2% CHG solution was diluted to 0.01% (0.0001X), it produced ≤1 log_{10} reduction killing effect in 6 minutes and 10 minutes in most of the organisms tested. This is an inactive concentration. Dr. Jackson concluded that, overall, the results of the time-kill studies provided by the Sponsor indicate that the test product Medline 2% CHG solution achieved a >99.9% reduction in viable microbial cells in 6 and 10 minutes. In addition, she observed that these results are comparable to those achieved with the active control, Dyna-Hex 2®. Lastly, Dr. Jackson confirmed that the neutralization validation study results for **R14-013** showed that the neutralization solution used in the test was non-toxic and effectively neutralized the activity of Medline 2% CHG solution at various strengths.

Vehicle (inactive) assessment:

A vehicle control [redacted] was also evaluated (time-kill testing) in Study **R14-013**. Dr. Jackson pointed out that, as this vehicle solution was utilized [redacted] within the pivotal studies for use on human subjects, ingredients with [redacted] Dr. Jackson noted that, considering previous outbreaks of Burkholderia cepacia microorganisms in Sage CHG Cloth[15], this was a good idea. Dr. Jackson observed that benzalkonium chloride [redacted] is used as a [redacted] in this formulation (see **Table 9**), however, benzalkonium chloride used at this concentration is also considered an antiseptic under the 1994 TFM for health care topical antiseptics in the range between [redacted] Nevertheless, similarly to isopropyl alcohol, based on the study results using the product vehicle, Dr. Jackson concluded that benzalkonium chloride does not significantly contribute to the activity of this product. She reported that, according to the FDA inactive ingredient database for approved drug products, benzalkonium chloride [redacted] has also been used as an excipient in at least one approved [redacted] product.[16]

Dr. Jackson reported that the vehicle demonstrated some antimicrobial activity, although less than the 2% CHG containing products. ReadyPrep™ CHG and Dyna-Hex 2® produced comparable log_{10} reductions on the same microorganisms tested. These two CHG containing products had generally log_{10} reductions greater than 5 log_{10}. Dr. Jackson concluded that the activity observed with the vehicle did not affect the antimicrobial effectiveness of the ReadyPrep™ CHG, when compared to Dyna- Hex 2® on the same microorganisms evaluated. The log_{10} reductions for the vehicle solution were mostly ≤3 log_{10} reduction, indicating no significant activity. There were two microorganisms, *Serratia marcescens* and *Streptococcus pneumoniae,* that

[15] FDA safety alert, 2016, Sage Products Expands Voluntary Worldwide Recall of Specific Lots of Topical skin Products Due to Potential Microbial contamination – Second Expansion, available at https://www.fda.gov/safety/recalls/ucm517547.htm

[16] FDA inactive ingredient database, available at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=BasicSearch.page

showed a 3 log10 reduction at 6 and 10 minutes. Dr. Jackson observed that this is not surprising, due to the inactive ingredients such as isopropyl alcohol and benzalkonium chloride, which are otherwise commonly used as antimicrobial preservatives in topical products to prevent bacterial growth. Benzalkonium chloride, like alcohol, is also used as (b) (4) Dr. Jackson concluded that, overall, the ReadyPrep™ CHG formulation was efficacious at reducing the level of ATCC repository and clinical isolate organisms within the 6- and 10-minute evaluations. Log10 reductions observed with the ReadyPrep™ CHG were similar to the comparator, Dyna- Hex 2®. The vehicle did not significantly contribute to the overall antimicrobial activity of ReadyPrep™ CHG formulation.

Table 9: Composition of ReadyPrep™ 2% CHG Solution

Component	Quality Standard	Function	Amount (% w/w)
Purified Water	USP	(b) (4)	
Chlorhexidine Gluconate Solution	DMF (b) (4) USP	Drug Substance	(b) (4)
Glycerin	USP	(b) (4)	
Propylene Glycol	USP		
(b) (4) Dimethicone (b) (4) Emulsion	DMF (b) (4)		
Isopropyl Alcohol	USP		
(b) (4) Benzalkonium Chloride Solution	NF		

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Study R17-004: Assessment of Microbial Activity of Two Medline ReadyPrep™ CHG Solution Formulations Using a Modified Time-Kill Procedure

Per agreement with FDA during the Type A meeting discussion on May 23, 2016, the Sponsor planned to demonstrate the similarity in effectiveness of ReadyPrep™ CHG as an antimicrobial cloth between its proposed New formulation (b) (4) and the Old formulation (b) (4) to support the scientific bridge to the clinical safety and efficacy data and to the quality data supporting the prior information. The Sponsor employed the modified in vitro time-kill study to evaluate the susceptibility of bacteria to the "New" and "Old" ReadyPrep™ CHG formulations. Dr. Jackson reported that the time-kill study showed that both ReadyPrep™ CHG products ("Old" and "New" formulation) produced ≥3 $\log_{10}$ reduction (>99.9%) killing effect in 6 minutes and 10 minutes for most organisms tested. In addition, the testing showed less than 3 log10 reduction for some specific organism, such as *Enterococcus faecalis* and *Staphylococcus aureus*. Dr. Jackson concluded that, overall, the results of the time-kill studies provided by the Sponsor indicate that (b) (4) has no impact on the antiseptic effectiveness of the "New" ReadyPrep™ CHG formulation.

Study R14-012: Evaluation of Potential for Development of Antimicrobial Resistance to ReadyPrep™ CHG Solution

Dr. Jackson reported that this study did not show any trend toward higher MIC values with clinical isolates compared to ATCC laboratory strains. She concluded that, overall, in relation to the emergence of resistance, the MIC did not increase for any of the strains evaluated; therefore, the product is not considered to have the

potential for the development of resistance. Furthermore, an evaluation of the potential for cross-resistance was done by comparing the MIC of several antibiotics both before and after extended exposure to sublethal levels of the antiseptic. Dr. Jackson concluded that, overall, the cross-resistance to antibiotics study showed no indication of a change in MIC related to cross-resistance observed for any of the organism/antibiotic combination tested.

Clinical (In Vivo) Studies

Study R16-034: Evaluation of the Area Covered by Medline 2% Chlorhexidine Gluconate Cloth Preoperative Skin Preparation

Dr. Jackson reported that this study assessed the coverage area of Medline 2% CHG cloth as well as the drying time when applied to 30 healthy volunteers. The amount of product applied was determined by subtracting the final weight of the cloth plus packaging from the initial weight.

The area coverage results for the Medline 2% CHG cloth was 3.66 g/ 0.0081 g/cm^2 = 451 cm^2. The average coverage in square inches is 70 in^2 (10 x 7 inches). The labeling coverage for the dry site (i.e. abdomen) states "use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared," and for the moist site (i.e. groin), the labeling states, "use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared." In addition, the labeling for the Medline 2% CHG cloth also states, "After package has been opened discard any unused cloths." Dr. Jackson concluded that the coverage area for the Medline 2% CHG cloth is acceptable.

The Medline 2% CHG cloth was considered dried on the average of 1.10 minutes (70 seconds), excluding one subject who had a 6.15 minutes (369 seconds) dry time on average. The Sponsor stated that this outlier was considered extreme enough that it would make the numerical results of the drying time analyses suspect or invalid if it were included. Dr. Jackson reported that that this is an unusually high drying time that can be considered an error with an undetermined root cause. Therefore, the drying time from this subject was excluded from further analyses. The drying time on the proposed label states, "Allow area to dry for one (1) minute." Dr. Jackson noted that, since the active ingredient is only CHG (does not include an alcohol combination), flammability labeling is not required. Dr. Jackson concluded that the drying time of one minute is acceptable for the Medline 2% CHG cloth labeling.

7. Clinical/Statistical- Efficacy

In addition to Dr. Jackson's review and assessment of the Clinical Simulation Studies, Statistical Review of the submitted efficacy data was performed by Elande Baro, PhD, Division of Biometrics 7, DNDP (Team Leader Rima Izem, PhD). Dr. Baro concluded that, "from a statistical standpoint, there is sufficient evidence that Medline 2% CHG is effective and adds benefits beyond those of Dyna-Hex 2 and the placebo cloth." Specifically, as detailed in her review[17], Dr. Baro concluded that both pivotal studies (**R15-029** and **R13-053**) demonstrated that:

- Medline cloth meets the effectiveness criteria outlined in the 2015 Proposed Rule, with the lower bound of the 95% CI of the responder rate greater than 70% at 10 minutes.

[17] NDA 207964 Statistical Review and Evaluation; 15 October 2018.

- Medline cloth is statistically superior (based on average treatment effects) to both Dyna-Hex 2 and the vehicle at 10 minutes, in both body regions.

However, Dr. Baro also acknowledged that the Sponsor failed to validate the study conduct to assure that the expected results are produced, as Dyna-Hex 2 did not meet the 70% responder rate criteria.

Clinical Simulation Studies

Phase II Pilot Studies

Dr. Jackson noted that the Sponsor included an 8-hour time point in three of its phase II pilot studies. The pilot studies were used to determine the test article application procedure and to evaluate the efficacy level at endpoints of 10-minutes, 6-hours, and 8-hours post-treatment using the test and positive control articles. The data of the pilot studies were used to determine the appropriate application time and determine if the 8-hour endpoint time was achievable. The results would then be used to calculate the number of subjects required to meet the FDA criteria for efficacy. If the 8-hour endpoint remains below the treatment day baseline, the Sponsor proposed that this endpoint would be included in the pivotal studies, in addition to the 10-minutes and 6-hours posttreatment endpoints. The Sponsor included the 8-hour time point in the pivotal studies. (b) (4)

(b) (4)

Pivotal Simulation Studies

Two pivotal clinical simulation studies (**R13-053**: MicroBioTest and **R15-029**: Evic Romania) were designed to evaluate the antimicrobial efficacy and safety of Medline 2% CHG Cloth, Vehicle Cloth control, and active control Dyna-Hex 2 on the abdominal and inguinal regions. The procedures used in these 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).

There was one additional pivotal study (**R13-052**) that was conducted at BioScience Laboratories that was discontinued prematurely due to low enrollment issues. There were also concerns related to performance, blinding, and handling of missing data in this study. Thus, efficacy data were not evaluable, and only safety data were reported from this study.

As shown in **Table 10** below, the two pivotal studies, **R13-053** and **R15-029**, were both randomized, vehicle and active controlled, third-party blind (staff performing bacterial enumeration), single-center studies. For a detailed review of the study designs, please see Dr. Jackson's review. Briefly, both studies enrolled healthy volunteers who had no dermatological conditions or known history of sensitivity to natural rubber lates, adhesive skin products, or CHG. Study **R15-029** allowed subjects 18 years of age or older to participate, whereas **R13-053** allowed subjects as young as 16 years of age to participate.

Table 10: Description of Pivotal Efficacy Studies

Study number	Design	Treatment arms/Sample size	Primary endpoint/analysis
R13-053 (Virginia)	Randomized, vehicle and active controlled, evaluator blinded (8 hours of treatment)	Test product: Medline 2% CHG Cloth (groin 254, abdomen 252) Active comparator: Dyna-Hex 2 (groin 249, abdomen 254) Vehicle control: Medline placebo (groin 48, abdomen 48)	(1) Primary endpoint: At 10mns, the responder rate for Medline 2% CHG cloth is significantly higher than 70%. (2) Check for study validity: At 10mns, Dyna-Hex 2 responder rate is significantly higher than 70% and both active substances are statistically superior to the vehicle.
R15-029 (Romania)	Randomized, vehicle and active controlled, evaluator blinded (8 hours of treatment)	Test product: Medline 2% CHG Cloth (groin 252, abdomen 241) Active comparator: Dyna-Hex 2 (groin 259, abdomen 253) Vehicle control: Medline placebo (groin 52, abdomen 50)	(1) Primary endpoint: At 10mns, the responder rate for Medline 2% CHG cloth is significantly higher than 70%. (2) Check for study validity: At 10mns, Dyna-Hex 2 responder rate is significantly higher than 70% and both active substances are statistically superior to the vehicle.

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The primary objective of both studies was to show a 70% responder rate of the test product at 10 minutes (lower bound of the two sided 95% Confidence Interval (CI) of percent responders greater than or equal to 70%). On the abdomen, a responder was defined as a subject with a 2 $\log_{10}/cm^2$ bacterial reduction at 10 minutes. On the groin region, a responder was a subject with a 3 $\log_{10}/cm^2$ bacterial reduction at 10 minutes.

Secondary study objectives for the test product were to show:

- A 100% responder rate at 6 hours. At the 6 hours sample, a responder is a subject with skin flora counts at 6 hours below baseline, either in groin or abdomen.
- Statistical superiority to the vehicle.

To check study validity, the active control was also evaluated.

Both studies included three treatment arms (Medline 2% CHG cloth, Dyna-Hex 2, and Medline placebo solution cloth), as described in **Table 11** below, and planned 5:5:1 randomization ratio in a paired-comparison design where each subject receives two of the planned treatments.

Table 11: Treatments, Anatomical Sites of Evaluation, Application and Dry Times and Coverage Areas

Treatment (Quantity/Volume)	Body Site	Application Time	Dry Time	Area of Coverage
Medline 2% CHG cloth (one cloth per body site)	Abdomen (sebaceous poor)	3 minutes total	1 minute	5" x 5"
	Groin (sebaceous rich)	3 minutes total	1 minute	2" x 5"
Medline placebo solution cloth (one cloth per body site)	Abdomen (sebaceous poor)	3 minutes total	1 minute	5" x 5"
	Groin (sebaceous rich)	3 minutes total	1 minute	2" x 5"
Dyna-Hex 2	Abdomen (sebaceous poor)	2 x 2 minutes (4 minutes total)	After wiping off second application	5" x 5"
	Groin (sebaceous rich)	2 x 2 minutes (4 minutes total)	After wiping off second application	2" x 5"

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Each subject received two different treatments, one on the right side of the body, one on the left, such that there were three possible combinations of treatments:

- Medline 2% CHG and Medline placebo solution
- Medline 2% CHG and Dyna-Hex 2
- Medline placebo solution and Dyna-Hex 2

Each study consisted of 3 phases: a pre-treatment phase (14-day washout to allow for the removal of any antimicrobial agents from the subject's skin), a screening phase, and a treatment phase (scheduled at least 72 hours after screening baseline collection). Subjects were required to refrain from bathing or showering for 48 hours prior to both the Screening Day and Treatment Day. At Screening, a baseline sample was collected from each test area within each anatomical region, using the Williamson-Kligman scrub technique. For inclusion in the study, subjects were required to have Screening Day baseline counts of at least 1.3×10^3 CFU/cm^2 per abdominal site (left and right) and 1.0×10^5 CFU/ cm^2 per groin site (left and right).

As illustrated in **Figure 1** below, on Treatment Day, using a 5" x 5" template, the corners of each test area were marked directly on the skin using a nontoxic marker, and the four sampling sites were numbered. The four sampling sites within each abdominal test area represented one baseline (preprep) site, and two or three postprep samples sites (10-minutes, 6-hours, 8-hours). Similar test area marking was done for the groin sites using a 2" x 5" sterile template.

Figure 1: Sampling Sites: Abdominal and Groin Test Areas

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Microbial samples were collected at 10 minutes (±30 seconds), 6 hours (±30 minutes) and 8 hours (±30 minutes) post treatment application for both the abdomen and the groin regions. Post application timing begins upon completion of the treatment material application, including drying time. Microbial samples were collected using the scrub cup technique. After the 10-minute samples have been collected, a piece of sterile gauze and a nonocclusive dressing was secured over the remaining sample sites to allow subjects restricted mobility and to protect the sites from contamination between sampling times. The subjects were allowed to leave the clinical test facility but had to return 6 hours (±30 minutes) post treatment application, for post application sample collection. A skin irritation assessment was performed.

The study materials were not blinded from the Investigator or other study staff performing the study material application or bacterial sample collections. Since the application techniques for Medline 2% CHG and Dyna-Hex 2 products are different per labeling, this is not surprising. The staff member(s) performing the bacterial enumeration was blinded from the identification of treatment assignment.

Dr. Jackson noted that the microbial sample collection and the scrub cup techniques are standard and acceptable. However, the MicroBioTest facility (Study **R13-053**) used a scrub cup size of 2.20 cm I.D. (3.80 cm^2) and the Evic Romania facility (Study **R15-029**) used a scrub cup size of 2.10 cm I.D. (3.46 cm^2). The TFM does not specify the diameter of the sampling cup to be used except to state, "Useful sizes range from approximately 2.5 to 4.0 centimeters."

Subject Disposition

In Study **R13-053**, a total of 489 subjects were consented and 458 subjects were screened. Among the screened subjects, 357 passed screening day baseline and 347 were randomized and treated. Among the randomized subjects, 326 passed treatment baseline criteria and were included in the main analyses.

In Study **R15-029**, a total of 486 subjects were consented and 461 subjects were screened. Among the screened subjects, 344 passed screening day baseline and 340 were randomized and treated. Among the randomized subjects, 323 passed treatment baseline criteria and were included in the main analyses.

For each study, the treatments and number of subjects in the as-treated population are shown in **Table 12** below.

Table 12: Number of Applications

	R13-053		R15-029	
Treatment	Abdomen	Groin	Abdomen	Groin
Medline 2% CHG Cloth (test product)	252	254	241	252
Dyna Hex 2 (active control)	254	249	253	259
Medline Placebo Cloth (vehicle control)	48	48	50	52

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Demographic Characteristics

Within each study and body region, the distributions of age, sex, and race were similar between the three treatment arms. However, Dr. Jackson and Dr. Baro both observed that there were some differences in demographic characteristics between the two studies, with Study **R13-053** enrolling younger subjects, more males, and fewer Caucasians that Study **R15-029**, as shown in **Table 13** below.

Table 13: Demographic Characteristics – Studies R13-053 and R15-029

		R13-053			R15-029		
		Medline 2% CHG cloth	Dyna-Hex 2	Placebo cloth	Medline 2% CHG cloth	Dyna-Hex 2	Placebo cloth
Abdominal Region							
Number Analyzed		252	254	48	241	253	50
Age	Mean (SD)	35.9 (14.4)	35.5 (14.1)	36.2 (15.4)	51.0 (12.0)	51.1 (11.9)	48.5 (13.1)
	Minimum	16	16	18	18	18	19
	Median	32	32	31.5	54	55	51
	Maximum	79	72	79	69	69	68
Sex	Male	57.9%	59.5%	60.4%	47.7%	49.0%	46.0%
	Female	42.1%	40.5%	39.6%	52.3%	51.0%	54.0%
Race	White/Caucasian	42.9%	41.0%	39.6%	100%	100%	100%
	Black/African American	21.4%	21.6%	10.4%	0	0	00
	Hispanic	10.7%	11.4%	14.6%	0	0	0
	Asian	22.6%	23.6%	27.1%	0	0	0
	Other	2.4%	2.4%	8.3%	0	0	0
Groin Region							
Number Analyzed		254	249	48	252	259	52
Age	Mean (SD)	36.4 (14.7)	35.7 (14.3)	34.7 (16.0)	51.9 (11.6)	51.9 (11.7)	48.6 (13.1)
	Minimum	16	16	16	18	18	19
	Median	32	32	30	56	56	51.5
	Maximum	79	72	79	69	69	68
Sex	Male	63.8%	65.5%	66.7%	45.6%	48.3%	38.5%
	Female	36.2%	34.5%	33.3%	54.4%	51.7%	61.5%
Race	White/Caucasian	44.1%	44.2%	39.6%	100%	100%	100%
	Black/African American	19.3%	19.7%	14.6%	0	0	0
	Hispanic	11.8%	10.4%	14.6%	0	0	0
	Asian	23.2%	23.7%	25.0%	0	0	0
	Other	1.6%	2.0%	6.2%	0	0	0

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However, as Dr. Jackson pointed out in her review, "we do not have any evidence that race makes a difference in the efficacy of topical antispetics. These types of products (CHG) has been marketed in the United States for several years and there are no reports in AERS or the literature to suggest that effiacy is affected by specific demographic factors."

Results at 10 Minutes

For each study, responder rates at 10 minutes for each treatment are summarized in **Table 14** and **Table 15** below. For Medline 2% CHG, the lower bound of the 95% CI for responder rate was greater than 70% for all body regions, in both studies. For Dyna-Hex 2, the lower bound of the 95% CI for responder rate was greater than 70% only in Study **R13-053** at the abdomen.

Table 14: Study R13-053: Responder Rates at 10 Minutes

Body Area	Treatment	10 Minute Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	85.04% (216 of 254)	0.8005 to 0.8919
Abdomen	Medline Cloth	93.25% (235 of 252)	0.8942 to 0.9602
Abdomen	Vehicle Cloth	50.00% (24 of 48)	0.3523 to 0.6477
Groin	Dyna-Hex 2	65.06% (162 of 249)	0.5879 to 0.7097
Groin	Medline Cloth	85.83% (218 of 254)	0.8092 to 0.8987
Groin	Vehicle Cloth	25.00% (12 of 48)	0.1364 to 0.3960

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Table 15: Study R15-029: Responder Rates at 10 Minutes

Body Area	Treatment	10 Minute Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	71.54% (181 of 253)	0.6555 to 0.7702
Abdomen	Medline Cloth	80.50% (194 of 241)	0.7492 to 0.8530
Abdomen	Vehicle Cloth	50.00% (25 of 50)	0.3553 to 0.6447
Groin	Dyna-Hex 2	72.97% (189 of 259)	0.6713 to 0.7828
Groin	Medline Cloth	84.52% (213 of 252)	0.7946 to 0.8876
Groin	Vehicle Cloth	55.77% (29 of 52)	0.4133 to 0.6953

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Dr. Baro also evaluated average treatment effects at 10 minutes, as shown in **Table 16** and **Table 17** below. Dr. Baro reported, "these tables suggest that Medline 2% CHG cloth is statistically superior to both Dyna-Hex 2 and the vehicle at 10 minutes, in both body regions and studies. Dyna-Hex 2 was statistically superior to the vehicle in both studies at the abdomen, but only in **R13-053** at the groin.

Table 16: Study R13-053: Differences in Log_{10} CFU/cm^2 Changes from Baseline at 10 Minutes between Treatments

Body Region	Treatment Comparison	10 Minute log10 CFU/cm2 Reductions	
		Difference	95% Confidence Interval
Abdomen	Medline Cloth – Dyna-Hex 2	-0.26	-0.39 to -0.13
	Vehicle - Medline Cloth	1.22	0.99 to 1.46
	Vehicle - Dyna-Hex 2	0.97	0.74 to 1.20
Groin	Medline Cloth – Dyna-Hex 2	-0.60	-0.80 to -0.41
	Vehicle - Medline Cloth	1.80	1.45 to 2.14
	Vehicle - Dyna-Hex 2	1.19	0.85 to 1.54

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Table 17: Study R15-029: Differences in Log_{10} CFU/cm^2 Changes from Baseline at 10 Minutes between Treatments

Body Region	Treatment Comparison	10 Minute log10 CFU/cm2 Reductions	
		Difference	95% Confidence Interval
Abdomen	Medline Cloth – Dyna-Hex 2	-0.34	-0.52 to -0.16
	Vehicle - Medline Cloth	0.81	0.50 to 1.12
	Vehicle - Dyna-Hex 2	0.47	0.17 to 0.78
Groin	Medline Cloth – Dyna-Hex 2	-0.90	-1.12 to -0.68
	Vehicle - Medline Cloth	0.93	0.55 to 1.33
	Vehicle - Dyna-Hex 2	0.04	-0.35 to 0.42

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Results at 6 hours

Responder rates at 6 hours for each treatment are summarized in **Table 18** and **Table 19** below. While Medline cloth showed 100% responder rates for each body region at 6 hours in both studies, Dyna-Hex 2 observed a 100% responder rate at 6 hours in all body regions for Study **R13-053** but only at the groin in Study **R15-029**.

Table 18: Study R13-053: Responder Rates at 6 Hours

Body Area	Treatment	6 Hour Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	100.00% (254 of 254)	0.9856 to 1.0000
Abdomen	Medline Cloth	100.00% (252 of 252)	0.9855 to 1.0000
Abdomen	Vehicle Cloth	97.92% (47 of 48)	0.8893 to 0.9995
Groin	Dyna-Hex 2	100.00% (249 of 249)	0.9853 to 1.0000
Groin	Medline Cloth	100.00% (254 of 254)	0.9856 to 1.0000
Groin	Vehicle Cloth	100.00% (48 of 48)	0.9260 to 1.0000

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Table 19: Study R15-029: Responder Rates at 6 Hours

Body Area	Treatment	6 Hour Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	98.81% (250 of 253)	0.9657 to 0.9975
Abdomen	Medline Cloth	100.00% (241 of 241)	0.9848 to 1.0000
Abdomen	Vehicle Cloth	96.00% (48 of 50)	0.8629 to 0.9951
Groin	Dyna-Hex 2	100.00% (259 of 259)	0.9859 to 1.0000
Groin	Medline Cloth	100.00% (252 of 252)	0.9855 to 1.0000
Groin	Vehicle Cloth	100.00% (52 of 52)	0.9315 to 1.0000

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Dr. Jackson reported that it is not surprising that, for both pivotal studies, the results of the Vehicle Cloth control showed some effectiveness results. The Vehicle Cloth contained the following excipients: purified water (b) (4)%, glycerin (b) (4)%, propylene glycol (b) (4)%, dimethicone NF emulsion (b) (4)%, isopropyl alcohol (b) (4)%, and benzalkonium chloride (b) (4)%. Dr. Jackson noted that these excipients showed limited activity in the in vitro assay testing results. In addition, she noted that the application of the vehicle cloth itself may cause mechanical elimination of bacterial cells, with a corresponding observation of bacterial log reduction.

Protocol Deviations and Sensitivity Analyses

In the Clinical Study Report for Study **R13-053** (9 February 2016), 7 protocol deviations were listed (3 product application deviations, 3 pregnancy tests not performed, and 1 groin result recorded on the abdomen page). In the Clinical Study Report for Study **R15-029**, 4 product application deviations, 1 bacterial counting entry data deviation, and many sampling time deviations were listed. Dr. Baro reported that in response to several information requests (21 December 2017 and 16 May 2018), the Sponsor submitted amendments on 15 March 2018 and 30 May 2018 where a few additional errors were reported. For Study **R13-053**, one groin region should have been excluded as a treatment day baseline failure but was not. For Study **R15-029**, the Sponsor reported 16 subjects with treatment received incorrectly recorded in the dataset.

In addition, FDA inspection of the Romania Site (Study **R15-029**), which occurred on 26 March 2018, identified many deviations (see also **Section 11** below). The inspector stated that "the site reported many time deviations that did not occur, and did not report many time deviations that did occur." Following the inspection, the Sponsor reported updated sampling time deviations for Study **R15-029** in an amended clinical study report submitted on 13 June 2018 in response to an Information Request. The submitted response qualified as a major amendment. Therefore, the PDUFA clock was extended 3 months.

Dr. Baro observed that, overall, deviations in Study **R15-029** were as follows: 160 sampling time deviations, 105 time recording deviations, 23 treatment day baseline count deviations, 17 screening day baseline count deviations, 13 product application time deviations, 4 sample plating deviations, and 2 incubation time deviations. In addition, the study site did not replace 23 treatment day baseline count deviations. As a result, the Sponsor's statistical analyst excluded these deviations at analysis stage. **Table 20** below shows the number of deviations by treatment group and body region for sampling time, time recording, treatment day failures, and screening day failures, which were associated with the largest number of deviations.

Table 20: Percentage of Each Deviation by Treatment Group in Study R15-029

	Abdominal Regions			Groin Regions		
	Medline 2% CHG (N=311)	Dyna Hex 2 (N=311)	Medline Placebo (N=58)	Medline 2% CHG (N=290)	Dyna Hex 2 (N=294)	Medline Placebo (N=56)
Screening Day Baseline Count Deviation	10 (3.2%)	6 (1.9%)	0	0	1 (0.3%)	0
Treatment Day Baseline Count Deviation	14 (4.5%)	7 (2.3%)	1 (1.7%)	1 (0.3%)	0	0
Product Application Time < 4 min	0	2 (0.6%)	1 (1.7%)	4 (1.4%)	5 (1.7%)	1 (1.8%)
10 Min Sampling Time < 9Min 30 Sec or > 10 Min 30 Sec	17 (5.5%)	34 (10.9%)	4 (6.9%)	22 (7.6%)	25 (8.5%)	6 (10.7%)
6 Hour Sampling Time < 5 Hour 30 Min or > 6 Hour 30 Min	2 (0.6%)	4 (1.3%)	0	1 (0.3%)	5 (1.7%)	0
8 Hour Sampling Time < 7 Hour 30 Min or > 8 Hour 30 Min	8 (2.6%)	12 (3.9%)	0	7 (2.4%)	13 (4.4%)	0
Inconsistent Time Recording at Baseline[1]	4 (1.3%)	5 (1.6%)	2 (3.4%)	3 (1.0%)	10 (3.4%)	2 (3.6%)
Inconsistent Time Recording at 10 Min Sampling[1]	6 (1.9%)	3 (1.0%)	2 (3.4%)	8 (2.8%)	4 (1.4%)	4 (7.1%)
Inconsistent Time Recording at 6 Hour Sampling[1]	5 (1.6%)	5 (1.6%)	0	5 (1.7%)	5 (1.7%)	1 (1.8%)
Inconsistent Time Recording at 8 Hour Sampling[1]	6 (1.9%)	10 (3.2%)	3 (5.2%)	7 (2.4%)	5 (1.7%)	0

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Dr. Baro agreed that the large number of deviations raised concerns about the quality of the study conduct. However, she noted that **Table 20** above suggests that except for sampling time, there is a small difference in the proportions of deviations across treatment groups, which is reasusuring. For sampling time, **Table 20**

generally shows a larger proportion of deviations for Dyna-Hex 2 regardless of time point and body region. However, as noted above, the staff performing the bacterial sample collections were not blinded.

To further assesss the acceptability of the study results, Dr. Baro conducted sensitivity analyses using different analysis sets (as-treated [AT], intent-to-treat [ITT], and modified intent to treat [mITT]). Dr. Baro reported that the sensitivity analyses using these different analyses sets led to similar conclusions as the primary analysis (modified as-treated population [mAT]). Specifically:

- Although the ITT population had a considerably larger sample size, as shown in **Table 21** below, than the primary analysis that excluded treatment day baseline failures, the same conclusion holds: Medline 2% CHG always meets the 70% responder rate criteria, while Dyna-Hex 2 does not (**Table 22**)
- The results for the AT analysis were almost identical to the results of the ITT analysis, as the two analysis sets differed only by a few subjects (**Table 21**).
- The results between the primary analysis and the mITT analysis were almost identical, as the two analysis sets differed only by a few subjects (**Table 21**)

Table 21: Number of Body Regions analysed in Different Analyses Populations

Population	R13-053			R15-029		
	Medline 2% CHG Cloth	Dyna Hex 2	Placebo Cloth	Medline 2% CHG Cloth	Dyna Hex 2	Placebo Cloth
Abdomen						
As-Treated	284	283	59	311	311	58
Intent-To-Treat	284	283	59	311	311	58
Modified As-Treated	252	254	48	241	253	50
Modified Intent-To-Treat	252	254	48	241	253	50
Groin						
As-Treated	297	292	59	290	294	56
Intent-To-Treat	297	292	59	291	294	55
Modified As-Treated	254	249	48	252	259	52
Modified Intent-To-Treat	254	249	48	253	259	51

- As-treated population includes all subjects randomized and analysis uses treated received.
- Modified intent to treat population includes all subjects randomized except for treatment day baseline failures and analysis uses treatment randomized.
- Intent-to-treat population includes all subjects randomized and analysis uses treatment randomized.

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Table 22: Responder Rates in R13-053 and R15-029 in ITT Analysis

	R13-053		R15-029	
	% (counts)	95% CI	% (counts)	95% CI
Abdomen				
Dyna-Hex 2	82% (233 of 283)	(0.77, 0.86)	69% (213 of 311)	(0.63, 0.74)
Medline Cloth	91% (259 of 284)	(0.88, 0.94)	77% (238 of 311)	(0.71, 0.81)
Placebo	42% (25 of 59)	(0.30, 0.56)	52% (30 of 58)	(0.38, 0.65)
Groin				
Dyna-Hex 2	65% (191 of 292)	(0.60, 0.71)	67% (197 of 294)	(0.61, 0.72)
Medline Cloth	87% (257 of 297)	(0.82, 0.90)	80% (233 of 291)	(0.75,0.85)
Placebo	27% (16 of 59)	(0.16, 0.40)	55% (30 of 55)	(0.41, 0.68)

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*CDTL Commnent: In summary, the results of the two pivotal Clinical Simulation studies, supported by three pilot studies and in vitro time-kill studies are adequate to demonstrate efficacy of ReadyPrep CHG 2% cloth for the proposed indication: "helps reduce bacteria that can potentially cause skin infection; for preparation of the skin prior to surgery." Although the active control, Dyna-Hex 2, failed to validate the study conduct to assure that the expected results are produced, it was statistically superior to the vehicle in both studies at the abdomen, and in **R13-053** at the groin. Overall, the pivotal clinical simulation studies adequately demonstrated efficacy of the ReadyPrep CHG product. In addition, the results of the time-kill studies provided by the Sponsor indicate that* (b) (4) *has no impact on the antiseptic effectiveness of the ReadyPrep CHG formulation.*

8. Safety

The safety of ReadyPrep CHG cloth was evaluated in single and multiple applications as part of nine clinical studies in healthy subjects:

- Two pivotal safety and efficacy studies to assess antimicrobial efficacy of the ReadyPrep CHG cloth product, in comparison to an active control (Studies **R15-029** and **R13-053**)
- Three additional safety and efficacy pilot studies to assess antimicrobial efficacy of the ReadyPrep CHG cloth product, in comparison to an active control (Studies **R13-042**, **R14-015**, and **R15-028**)
- One additional controlled study (Study **R13-052**), not being relied upon for efficacy findings to support this application, as agreed upon by FDA (see General Advice Letter…….)
- One pharmacokinetic bioavailability study (Study **R17-023**)
- One skin coverage study (Study **R16-034**)
- One cumulative irritation and contact sensitization study of the ReadyPrep CHG cloth product (Study **R13-051**)

In these studies, the safety of ReadyPrep CHG cloth was compared to Vehicle cloth and Dyna-Hex 2 (currently marketed, 2% CHG solution). The Vehicle cloth consisted of the same polyester cloth and excipients as the ReadyPrep CHG cloth, with the exception of CHG. The ReadyPrep CHG cloth used in most

of the above studies included [redacted] (b) (4) as per discussion with FDA at the Type C Meeting of 7 December 2016. The two formulations were bridged in Study **R17-004**. The new formulation, [redacted] (b) (4) was used in Study **R17-023** (pharmacokinetics) and Study **R16-034** (skin coverage).

One thousand, nine hundred and thirty-one (1931) subjects were exposed to ReadyPrep CHG cloth or solution. Approximately 87% (1682) of subjects were treated with the therapeutic application (single dose) of ReadyPrep CHG, and the remaining 13% (249) of subjects were exposed to multiple applications over a 21 day period. As shown in the **Table 23** and **Table 24** below, the majority of subjects were Caucasian (79.2%) and were between 18-40 (56%) and 41-64 (37%) years of age. Pediatric subjects (16-17 years old) represented less than 2% and geriatric subjects (>65 years of age) represented slightly more than 5% of subjects.

Table 23: Study-based Ethnicity Distribution

Sex	Pivotal Studies (N)		Non-Pivotal Safety Study (N)	Skin Cover Study (N)	PK Study (N)	Sensitization/ Irritation Studies (N)		Pilot Studies (N)		
Study Number	R13-053	R15-029	R13-052	R16-034	R17-023	R13-051*		R13-042	R14-015	R15-028
Caucasian	139, (40%)	340, (100%)	785, (89%)	7, (23%)	8, (67%)	194, (92%)	35, (90%)	7, (26%)	30, (91%)	14, (100%)
African-American	66, (19%)	0, (0%)	20, (2%)	7, (23%)	1, (8%)	4, (2%)	2, (5%)	1, (4%)	0, (0%)	0, (0%)
Hispanic	45, (13%)	0, (0%)	12, (1%)	2, (7%)	0, (0%)	2, (1%)	0, (0%)	2, (7%)	1, (3%)	0, (0%)
Native American	0, (0%)	0, (0%)	29, (3%)	0, (0%)	1, (8%)	6, (3%)	2, (5%)	0, (0%)	0, (0%)	0, (0%)
Asian	87, (25%)	0, (0%)	11, (1%)	11, (37%)	1, (8%)	1, (0.5%)	0, (0%)	17, (63%)	1, (3%)	0, (0%)
Other	10, (3%)	0, (0%)	22, (3%)	3, (10%)	1, (8%)	3, (1%)	0, (0%)	0, (0%)	1, (3%)	0, (0%)
Total	**347**	**340**	**879**	**30**	**12**	**210**	**39**	**27**	**33**	**14**

* R13-051 was an irritation and sensitization study (Multiple applications); other studies were efficacy and safety studies (Therapeutic applications) based on TFM-1994 designs. Demographics for all studies included all treated subjects. % based on per study.

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Table 24: Study-based Age Distribution

Sex	Pivotal Studies (N)		Non-Pivotal Safety Study (N)	Non-Pivotal Safety Study (N)	Skin Cover Study (N)	Sensitization/ Irritation Studies (N)		Pilot Studies (N)		
Study Number	R13-053	R15-029	R13-052	R16-034	R17-023	R13-051*		R13-042	R14-015	R15-028
16-17	12, (3%)	0, (0%)	13, (1%)	0, (0%)	0, (0%)	7, (3%)	1, (3%)	1, (4%)	0, (0%)	0, (0%)
18-40	218, (63%)	80, (23%)	577, (66%)	22, (73%)	11, (92%)	113, (54%)	23, (59%)	15, (56%)	13, (39%)	1, (7%)
41-64	99, (29%)	234, (69%)	252, (29%)	7, (23%)	1, (8%)	77, (37%)	13, (33%)	9, (33%)	17, (52%)	11, (79%)
65-74	16, (5%)	26, (8%)	27, (3%)	0, (0%)	0, (0%)	11, (5%)	1, (3%)	2, (7%)	3, (9%)	2, (14%)
>74	2, (0.6%)	0, (0%)	10, (1%)	1, (3%)	0, (0%)	2, (1%)	1, (3%)	0, (0%)	0, (0%)	0, (0%)
Total	**347**	**340**	**879**	**30**	**12**	**210**	**39**	**27**	**33**	**14**

* R13-051 was an irritation and sensitization study (Multiple applications); other studies were efficacy and safety studies (Therapeutic applications) based on TFM-1994 designs. Demographics for all studies included all treated subjects. % based on per study.

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Safety Review was conducted by Martha Lenhart, M.D., PhD, Medical Officer, DNDP. The incidences of adverse events (AEs) across the submitted studies is shown in **Table 25** below. Dr. Lenhart reviewed eight of the nine clinical studies. Study **R13-051**, an irritation and sensitization study, was reviewed by the Division of Dermatology and Dental Products (DDDP).

In the two pivotal (**R13-053** and **R15-029**), three pilot (**R13-042**, **R14-015**, and **R15-028**), and one additional discontinued controlled study (**R13-052**), skin irritation rated as 3, based on the scoring scale in **Table 25** below was considered a reportable AE. In the skin coverage study (**R16-034**), an expanded scale was used, as shown in **Table 26** below.

Table 25: Scoring Scale for Skin Conditions in the Therapeutic Application Regimen*

Rating	Description of Reaction
0	None
1	Mild or Transient
2[a]	Moderate
3[b]	Severe

[a] Significant irritation in any category may have required subject's removal from the study

[b] A rating of 3 in any category was recorded as an adverse event and required subject's removal from study.

*Studies R13-053, R15-029, R13-042, R15-015, R15-029, R13-052.

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Table 26: Scoring Scale for Skin Conditions in the Skin Coverage Study (R16-034)

Skin Irritation Rating Scale			
Condition	**Rating**	**Description**	
Erythema	0	No reaction	
	1	Mild and/or transient redness	Represents irritation and requires subject's removal from study
	2	Moderate redness	
	3	Severe redness	
Edema	0	No reaction	
	1	Mild and/or transient swelling	Represents irritation and requires subject's removal from study
	2	Moderate swelling	
	3	Severe swelling	
Rash	0	No reaction	
	1	Mild and/or transient rash	Represents irritation and requires subject's removal from study
	2	Moderate rash	
	3	Severe rash	
Dryness	0	No reaction	
	1	Mild and/or transient dryness	Represents irritation and requires subject's removal from study
	2	Moderate dryness	
	3	Severe dryness	

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Dr. Lenhart reported that, as shown in **Table 27**, in six of the eight studies involving a single therapeutic application, no AEs were reported. There were no reported AEs or skin reactions in the pivotal studies (**R13-053**, **R15-029**), the three pilot studies (**R13-042**, **R14-015**, **R15-028**), or the skin coverage study (**R16-034**). In the pharmacokinetic (PK) study (**R17-023**), three subjects reported five AEs (one subject reported two application site reactions: pain and pruritis following groin site CHG application). The majority of AEs occurred in Study **R13-052**, in which 23 of 879 subjects reported 25 adverse events. Dr. Lenhart reported that the most common AEs were skin and subcutaneous disorders, such as pruritis, irritation, and rash, and general disorders and pain at the administration site.

Table 27: Incidence of Adverse Events in Submitted Clinical Studies

Protocol Number	Number of treated subjects	Number of Subjects Reported AE	ReadyPrep CHG	Dyna-Hex 2	Vehicle	Saline (Negative control)	Sodium Lauryl S (Positive control)	Not related or unknown
Therapeutic Applications								
R16-034	30	0 (0%)	0 (0%)	NA	NA	NA	NA	0 (0%)
R17-023	12	3 (25%)	3 (25%)	NA	2 (17%)	NA	NA	3 (25%)
R13-053	347	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA	0 (0%)
R15-029	340	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA	0 (0%)
R13-052	879	23 (3%)	14 (2%)	7 (1%)	2 (<1%)	NA	NA	7 (1%)
R13-042	27	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA	0 (0%)
R14-015	33	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA	0 (0%)
R15-028	14	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA	0 (0%)
Multiple Applications								
R13-051 Sensitization	210	36 (17%)	3 (1%)	12 (6%)	0 (0%)	0 (0%)	NA	21 (10%)
R13-051 Irritation	39	10 (26%)	2 (5%)	3 (8%)	0 (0%)	0 (0%)	1 (3%)	6 (15%)

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In Study **R13-052**, 23 subjects out of 879 tested reported 25 AEs. Seventeen subjects reported AEs after treatment with ReadyPrep CHG cloth, 9 subjects reported AEs with Dyna-Hex 2, and 4 reported AEs with Vehicle cloth, as shown in **Table 28** below. The most common AEs reported for all treatments in Study **R13-052** were related to skin and subcutaneous disorders (pruritis, irritation, and rash) and general and administrative site conditions (pain) at the test site. The Sponsor reported that all AEs resolved satisfactorally, and the skin irritation onserved consisted of expected reactions observed 10 minutes following scrubbing the sites and subsided in severity at subsequent sample times. All AEs were mild in severity.

Table 28: Adverse Events Summary for Therapeutic Applications (Study R13-052)

	Subjects with Adverse Events[a] (N [%])			
System Organ Class Preferred Term	**ReadyPrep CHG**	**Dyna-Hex 2**	**Vehicle**	**Total Subjects Affected**
Skin and Subcutaneous Tissue Disorders				
Pruritus	9 (0.5%)	3 (0.2%)	1 (<0.1%)	10 (0.6%)
Irritation Skin	0	1 (<0.1%)	1 (<0.1%)	2 (0.1%)
Rash	0	1 (<0.1%)	0	2 (0.1%)
General Disorders and Administrative Site Conditions				
Pain	5 (0.3%)	2 (0.1%)	0	5 (0.3%)
Nervous System Disorders				
Dizziness	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)
Injury, Poisoning, and Procedural Complications				
Joint Injury	0	0	0	2 (0.1)
Skin Abrasion	0	0	1 (<0.1%)	1 (<0.1%)
Other				
Car Accident	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)

[b]All Adverse Events were mild in severity. Percentages were based on all subjects (N=1640) receiving any treatment from the Therapeutic application regimen.

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During the PK study (**R17-023**), 3 subjects out of 12 reported AEs (25%), as shown in **Table 29** below. Two AEs were related to ReadyPrep CHG cloth. The other AEs were considered not related to the treatment product or the relationship was unknown.

Table 29: Adverse Events Summary for PK Study R17-023

System Organ Class Preferred Term	ReadyPrep CHG	Negative Control	Not Related or Unknown	Total Subjects Affected
Application Site Pain	1 (8.3%)	0	0	1 (8.3%)
Application Site Pruritis	1 (8.3%)	0	0	1 (8.3%)
Headache	0	0	1 (8.3%)	1 (8.3%)
Nasal Congestion	0	0	1 (8.3%)	1 (8.3%)
Oropharyngeal Pain	0	0	1 (8.3%)	1 (8.3%)

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Regarding subgroup analyses, Dr. Lenhart concluded that there "is no apparent statistical evidence of adverse events occurring at different frequencies by age, gender or ethnicity for the therapeutic applications." I agree.

CDTL Comment: In summary, subjects treated with ReadyPrep CHG cloth or solution had an overall incidence of <1% adverse reactions at the treatment site. No deaths or serious adverse events were reported. Safety profile of the ReadyPrep CHG observed in the clinical development program conducted by Medline to support this application appears to be within the expected safety profile of topical drug products containing 2% CHG.

Postmarketing Safety Data

Dr. Lenhart reviewed the following postmarketing safety databases and literature submitted by the Sponsor:

- FDA Adverse Events Reporting System (FAERS) database search from 2009-2016 with break-outs by year of reporting, patient age, and outcome code
- World Health Organization (WHO) VigiAcess search from 1969-2016 with break-outs by year of reporting, patient age, and geographic location
- Drug Abuse Warning Network (DAWN)
- Published medical literature for safety issues associated with CHG

FAERS

From the FAERS database, for the time period assessed (2009-2016), 1384 events were reported representing 308 patients. Note that not all FAERS reports list route of administration, and this may underrepresent adverse events by topical administration. However, 318 were reported after topical and cutaneous administration of CHG representing 88 patients. For topical administration routes, adverse events occurring in ≥ 2% of reported events included anaphylactic reaction (n=24, 7.6%), hypotension (n=14, 4.4%), procedural hypotension (n=9, 2.8%), urticaria (n=9, 2.8%), blister (n=8, 2.5%), rash (n=8, 2.5%), erythema (n=8, 2.5%), and B. cepacia infection (n=7, 2.2%). Eighteen deaths occurred in 7 years. **Table 30** below lists the ten most commonly reported adverse events for topical chlorhexidine administration.

Table 30: Ten Most Commonly Reported AEs for Topical CHG (FAERS Database)

Adverse Event	Number of Events (%)
Anaphylactic reaction	24 (7.6)
Hypotension	14 (4.4)
Procedural hypotension	9 (2.8)
Urticaria	9 (2.8)
Blister	8 (2.5)
Rash	8 (2.5)
Erythema	8 (2.5)
Burkholderia cepacia complex infection	7 (2.2)
Procedural complication	6 (1.9)
Circulatory collapse	6 (1.9)

Electronically copied and reproduced from Sponsor's submission: Integrated Summary of Safety, Table 25, page 50.

From the FAERS data assessment where CHG was considered the primary suspect, 18 death outcomes were reported. Of these, 5 deaths were reported in patients receiving topical or cutaneous administration of CHG:

- Subject # (b) (6) (year (b) (6) was a 35 year old female. She had been administered 2% topical chlorhexidine gluconate. Death was reported due to anaphylactic reaction, dysgeusia, and resuscitation.
- Subject # (b) (6) (year (b) (6) was a 24 year old female. She had been administered topical chlorhexidine gluconate. Death was reported due to bronchopulmonary dysplasia, erythema, excoriation, skin disorder, skin exfoliation, and staphylococcal infection.
- Subject # (b) (6) (also reported as # (b) (6), year (b) (6) was a 57 year old male. He had been administered cutaneous chlorhexidine. Death was reported due to blood immunoglobulin E increased and anaphylactic shock, allergy to chemicals, and cardiac arrest.
- Subject # (b) (6) (year (b) (6) was a 69 year old female. She had been administered 4% chlorhexidine gluconate surgical scrub. Death was reported due to accidental exposure and wrong drug administered.
- Subject # (b) (6) (year (b) (6) was a female (age unspecified). She was administered topical chlorhexidine. Death was reported due to chemical injury.

Dr. Lenhart observed that there were no increasing or decreasing trends during the reporting period (2009-2016).

CDTL Comment: I agree with Dr. Lenhart's assessment that there are no increasing or decreasing trends. Regarding the five reported deaths, information is limited. There is no analysis of confounding factors or of time of CHG exposure relative to time of death (causal association). However, anaphylaxis (Subjects (b) (6) and (b) (6)) is a known potential adverse event associated with CHG and is identified on the Drug Facts label. Subject (b) (6) likely had confounding factors (eg, bronchopulmonary dysplasia, staphylococcal infection). For Subjects (b) (6) and (b) (6) the limited information preclude assessment of causality.

WHO Database

The Sponsor searched the WHO VigiAccess database for CHG containing products. A total of 9837 events representing 4743 records were reported for Hibiclens (4% CHG) and 1710 events representing 603 records for Chloraprep (2% CHG, 70% IPA).

For Hibiclens, adverse events reported in ≥2% of total events were rash (n=429, 4.4%), pruritus (n=340, 3.5%), anaphylactic reaction (n=254, 2.6%), urticaria (n=253, 2.6%), stomatitis (n=237, 2.4%), medication error (n=234, 2.4%), and wrong drug administered (n=208, 2.1%), as shown in **Table 31** below.

Table 31: Ten Most Commonly Reported Adverse Events for Hibiclens (WHO Database)

Adverse Event	Number of Events (%)
Rash	429 (4.4)
Pruritus	340 (3.5)
Anaphylactic reaction	254 (2.6)
Urticaria	253 (2.6)
Stomatitis	237 (2.4)
Medication error	234 (2.4)
Wrong drug administered	208 (2.1)
Application site reaction	183 (1.9)
Dysgeusia	163 (1.7)
Hypersensitivity	152 (1.6)

Electronically copied and reproduced from Sponsor's submission: Integrated Summary of Safety, Table 30, page 53.

ChloraPrep adverse events reported as ≥2% of events (of 1710 events in 603 records) were skin irritation (n=78, 4.6%), application site rash (n=59, 3.4%), anaphylactic reaction (n=43, 2.5%), occupational exposure to product (n=40, 2.3%), application site erythema (n=39, 2.3%), erythema (n=39, 2.3%), and pruritus (n=39, 2.3%), as shown in **Table 32** below.

Table 32: Ten Most Commonly Reported Adverse Events for ChloraPrep (WHO Database)

Adverse Event	Number of Events (%)
Skin irritation	78 (4.6)
Application site rash	59 (3.4)
Anaphylactic reaction	43 (2.5)
Occupational exposure to product	40 (2.3)
Application site erythema	39 (2.3)
Erythema	39 (2.3)
Pruritus	39 (2.3)
Laceration	34 (2.0)
Rash	34 (2.0)
Application site vesicles	30 (1.8)

Electronically copied and reproduced from Sponsor's submission: Integrated Summary of Safety, Table 31, page 53.

Thirteen deaths ("Death," n=12, 0.12%; "Death neonatal," n=1, 0.01%) were reported as adverse events for Hibiclens. Four deaths ("Death," n=3, 0.18%; "Death neonatal," n=1, 0.06%) were reported for ChloraPrep. Further details regarding these cases are not available through VigiAccess.

Dr. Lenhart reported that, overall, adverse events reported by WHO were similar to FAERS, with the most common related to allergy or hypersensitivity and a gender distribution showing a higher percentage of AE reports in females, as shown in **Table 33** below.

Table 33: Gender Distribution of Adverse Events for CHG Products (WHO Database)

Gender	Number of records (%)	
	Hibiclens®	Chloraprep®
Female	2661 (56)	325 (54)
Male	1776 (37)	185 (31)
Unknown	306 (6)	93 (15)
Total	**4743 (100)**	**603 (100)**

Electronically copied and reproduced from Sponsor's submission: Integrated Summary of Safety, Table 34, page 54

DAWN Database

The DAWN database search included years 2004 to 2011, terminated at system discontinuation, and used the closest related product class of "antiseptic and germicide." Chlorhexidine-specific products are not described in DAWN resulting in extremely limited information on abuse or misuse of antiseptic and germicide products. The number of emergency room visits attributable to chlorhexidine is undetermined.

Literature

The Sponsor conducted a PubMed search for published literature supporting the safety of chlorhexidine gluconate. Search terms included "chlorhexidine gluconate" with limits of "humans" and "clinical trials," and a publication range from 12 September 2011 through 31 May 2017. The search identified fifteen randomized, controlled studies using topical chlorhexidine gluconate (CHG) on at least 3699 patients. Concentrations of CHG ranged from 0.5% – 4% for durations of single administrations up to 6 months. Publication reported side effects following use of CHG included tingling, irritation, macular erythema, maculopapular erythema, dermatitis, skin rash, and mild redness. Seven of the publications stated no adverse events were observed.

Two publications identified in the 120-day safety update noted adverse events in neonates. In the report of five case studies, all five preterm neonates experienced serious chemical burns of the skin, with one case resulting in death. In the other study, three of 148 preterm infants (gestational age <31 weeks) exposed to CHG as preparation for central venous catheter insertion had unspecified skin reactions, all of which resolved without treatment.

CDTL Comment: In summary, skin-related events accounted for 20% of all adverse events reported in the FAERS database, including hypersensitivity, rash, and erythema. Data collected from the WHO database were similar to FAERS and most commonly related to allergy and hypersensitivity. Evidence from DAWN was limited due to insufficient CHG-related descriptions. Risk of abuse or misuse of chlorhexidine products is unlikely. Dr. Lenhart concluded that the adverse events reported in the searched databases are consistent with the known safety profile of CHG and that no new trends were identified, and I agree.

*Dr. Lenhart also observed that, in the clinical studies, although female enrollment was half that of males, the incidence of AEs in females was 4% (8 subjects or 3% ReadyPrep CHG related); twice that of males, as shown in **Table 34** below.*

Table 34: Incidence of AEs by Gender in Clinical Studies

Gender	Number of Subjects Treated[a]	Number of Subjects Reporting Adverse Events[b]	Medline CHG Cloth[b]	Dyna-Hex 2[b]	Medline vehicle[b]	Not Related or Unknown[b]
Therapeutic/Single Application[c]						
Female	281 (32%)	10 (04%)	8 (03%)	3 (01%)	1 (00%)	1 (00%)
Male	598 (68%)	13 (02%)	9 (02%)	5 (01%)	3 (01%)	2 (00%)

[a] Percentages are percent of the total number of treated subjects of the indicated ethnicity.
[b] Percentages are percentage of the indicated ethnicity reporting an adverse event for the test substances.
[c] Nine subjects had one AE related to two different test substances; for the purposes of this table, the AEs were attributed to both test substances.

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Furthermore, gender distribution in the WHO database search demonstrated a similar higher percentage of AE reports related to females. In addition, Dr. Lenhart reported that the Sponsor's 120-day safety update identified two deaths associated with topical CHG anaphylaxis in 2017. Dr. Lenhart concluded that "these two areas, female predominance and anaphylaxis, may merit additional monitoring." However, as you can see in ***Table 34****, Dr. Lenhart is referring to a single study (****R13-052****),which was the study discontinued prematurely for low enrollment issues. In this study, for the Medline CHG product, the incidence of AEs is 3% (n=8) for females and 2% (n=9) for males. Nevertheless, it is possible that there is a reporting bias at work in the WHO data, but this is speculative. Regarding anaphylaxis, it is a known potential AE associated with CHG and is addressed in labeling. We will continue to monitor.*

Division of Dermatology and Dental Products Review of Dermal Safety Studies

Assessment of the potential of ReadyPrep CHG for cumulative skin irritation, contact sensitizing potential, phototoxicity, and photoallergenicity was conducted by Carol Langley, MD, MPH, Medical Officer, Division of Dermatology and Dental Products (DDDP). Dr. Langley reviewed the following materials:

- Study **R13-051**: A randomized and observer-blinded study to evaluate the cumulative irritation and contact sensitizing potential of one finished test product
- Documents related to phototoxicity and photoallergenicity potential of investigational product: the Sponsor's waiver request, two FDA information requests (IRs), and the Sponsor's responses to IRs.

Dr. Langley concluded that Study **R13-051** was adequate in design and conduct, and that the study results "indicate that significant irritation occurred with this product; however, contact sensitization was not observed in the study." Regarding phototoxicity and photoallergenicity, Dr. Langley concluded that, although the Sponsor demonstrated that CHG in the test product absorbs light between (b) (4) and (b) (4) nm and documented that the molar extinction coefficient (MEC) exceeds the ICH S10 threshold, "given that extensive exposure to topical CHG products over a period of more than four decades has failed to show evidence of phototoxicity or photoallergenicity, and given that the product is intended for use as a preoperative skin preparation, such that exposure to natural light should be minimal, the Agency supports granting the applicant's request for a waiver of phototoxicity and photoallergenicity studies."

Study R13-051:

Study **R13-051** was entitled, "A randomized and observer-blinded study to evaluate the cumulative irritation and contact sensitizing potential of one finished test product" and was a Phase 1, single center, double-blind,

randomized, vehicle and reference-controlled study. The study involved healthy subjects at least 16 years of age as follows:

- Cumulative Irritation Evaluation: 52 subjects were consented; 33 subjects completed this evaluation.
- Sensitization Evaluation: 222 subjects were consented for the Sensitization Evaluation; 161 subjects completed this evaluation.
- All 33 subjects who completed the Cumulative Irritation Evaluation portion of the study also completed the Sensitization Evaluation portion.

Test products:

- Medline 2% Chlorhexidine Gluconate Cloth (Test Product)
- Medline Cloth (b) (4) (Vehicle)
- Dyna-Hex® (Reference Product)
- 0.9% Physiological Saline, USP (Negative Control)
- 0.1 % Sodium Lauryl Sulfate (Positive Control) (Cumulative Irritation Evaluation only)

Cumulative Irritation Evaluation

For a detailed discussion of the study design, please see Dr. Langley's review. Briefly, for the Cumulative Irritation Evaluation, approximately 0.02 mL of the Test Product, Vehicle, Reference Product, the Negative Control material, and the Positive Control material was applied to specific areas of the parascapular region of the back. The occlusive patches were applied to randomized sites on each subject's back for a twenty-three (23) hours ± 1 hour period of exposure, after which they were removed, and the sites evaluated and scored for irritancy. The procedures were repeated on the same test sites daily for a total of 21 days to determine the irritation potential of each test material.

Sensitization Evaluation

The sensitization study consisted of three phases: Induction, Rest, and Challenge Phases. During the Induction Phase, the occlusive patches were applied to designated sites on each subject's back for a 48-hour ± 1 hour period of exposure, after which the patches were removed, and the sites scored for irritancy. On the weekends, the patches remained in place for 72 hours ± 1 hour. The assessment/application procedures were repeated on the same test sites a total of nine times (three times a week over a three-week period); subjects returned for patch removal and a final evaluation on the last day of the Induction Phase. The Induction Phase was followed by a 2-week Rest Phase during which no products or patches were applied. The day following the end of the Rest Phase, the subjects began the Challenge Phase. Patches were applied on the skin of each subject's back opposite the side used during the Induction Phase. Patches remained in place for 48 hours. Following the 48-hour exposures, patches were removed, and the sites scored for skin irritation by a blinded evaluator 30 minutes, 24 hours, 48 hours, and 72 hours following removal.

The following 8-point scale was used for evaluation of skin reactions during the irritation and sensitization evaluations.

Table 35: Skin Irritation and Sensitization Scale

GRADE	DESCRIPTION
0	no evidence of irritation
1	minimal erythema, barely perceptible
2	definite erythema, readily visible; minimal edema or minimal papular response
3[1, 3]	erythema and papules
4[1]	definite edema
5[1]	erythema, edema, and papules
6[1, 2]	vesicular eruption
7[1, 2]	strong reaction spreading beyond test site

[1] Product application re-sited once during the Cumulative Irritation Evaluation and Sensitization Phase or discontinued if reaction recurred on second site. The positive control material was not re-sited.
[2] Adverse Event, subject discontinued from testing
[3] Adverse Event if no improvement after 48 hours of detection.
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Study Results

The Reference Product, Dyna-Hex® (Dyna-Hex 2; 2% Chlorhexidine Gluconate) was found to be highly irritating to most of the subjects during the Cumulative Irritation evaluation and Induction Phase, with multiple subjects experiencing high-grade reactions and irritation-related adverse events. Due to this high degree of irritation, the Study Protocol was amended to remove the Reference Product from all testing; all subjects continuing in the study had Reference Product patches removed during Evaluation 14 of the Cumulative Irritation Evaluation and in Evaluation 6 of the Induction Phase.

Table 36 shows the results of the Cumulative Irritation Evaluation for each product tested, including minimum, maximum and mean values for the Daily Dermal Response Score, summarizing results for the 21 day duration of the study across all 33 subjects. The table also shows the Total Cumulative Irritation Score for each product.

Table 36: Cumulative Irritation Results – Study R13-051

Product	Daily Dermal Response Score – Minimum	Daily Dermal Response Score – Maximum	Daily Dermal Response Score – Mean (range)	Total Cumulative Irritation Score
Test Product (CHG)	0	4	0.46 – 2.97	52.94
Vehicle	0	4	0.39 – 1.91	23.36
Negative Control	0	3	0.48 – 1.21	17.42
Positive Control	0	3	0.49 – 3.00	43.91
Reference Product	0	4	0.46 – 3.31	58.12

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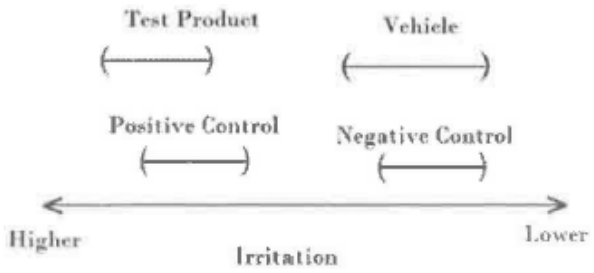
Thus, the Test Product (Medline 2% Chlorhexidine Gluconate Cloth) produced an equivalent level of irritation compared to the Positive Control (0.1 % Sodium Lauryl Sulfate). The Test Product produced a greater level of

irritation compared to the Vehicle (b) (4) and the Negative Control (0.9% Physiological Saline, USP). See **Figure 2** below.

Figure 2: Comparative Irritation Scores – Study R13-051



Test Product = Positive Control > Vehicle = Negative Control

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Sensitization was not observed with any of the products tested. The Test Product (Medline 2% Chlorhexidine Gluconate cloth) was not a skin sensitizing agent based upon the 161 subjects who completed the Challenge Phase of the study. The Test Product was determined to demonstrate irritancy in the Induction Phase and Cumulative Irritation Phase of the study and the Challenge Phase of the study. All observed irritancy decreased in degree of severity over the 72-hour period following patch removal.

Dr. Langley noted the following:

- Although this study evaluated an earlier formulation of the test product, including two excipients not in the final to-be-marketed product, DDDP agrees with prior responses from FDA that additional testing is not required at this point.
- FDA generally recommends testing a minimum of 200 individuals to assess contact sensitization; in the study evaluated here, only 161 subjects completed the study. However, though the sample size is not optimal, this is still within a relatively reasonable range, and would not invalidate the study.
- Topical chlorhexidine gluconate products have been associated with hypersensitivity reactions, anaphylaxis and a number of deaths, along with chemical burns and skin irritation in neonates. However, no new signals have been identified in the Sponsor's review of FAERS and recent published literature. Labeling language should adequately reflect these risks. DDDP agrees with the ***Warnings*** in proposed labeling regarding allergy alert and irritation/sensitization, and the ***Directions*** in labeling recommending "use with care in premature infants or infants under 2 months":

Warnings

Allergy alert

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

- *wheezing/difficulty breathing*
- *shock*
- *facial swelling*

- *hives*
- *rash*

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

Do not use

- *on patients allergic to chlorhexidine gluconate or any other ingredient in this product*
- *for lumbar punctures or in contact with the meninges*
- *on open skin wounds or as a general skin cleanser*

Stop use and ask a doctor if

irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition.

…..

Directions

- *use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.*

Request for Waiver of Requirement for Phototoxicity and Photoallergenicity Studies

The NDA submission included a Request for Waiver of Requirement for Phototoxicity and Photoallergenecity Studies.

In the "NDA 207964 Filing Communication – No Filing Review Issues Identified" letter dated 21 December 2017, FDA provided the following information request:

To evaluate your waiver request for phototoxicity and photoallergenicity studies as discussed in section 1.12.13 of the application, provide the molar extinction coefficient data for your chlorhexidine product, as discussed in the ICH S10 guidance "Photosafety Evaluation of Pharmaceuticals":

"The initial consideration for assessment of photoreactive potential is whether a compound absorbs photons at any wavelength between 290 and 700 nm. A compound that does not have a molar extinction coefficient (MEC) greater than 1000 L mol-1 cm-1 at any wavelength between 290 and 700 nm (Ref. 3) is not considered to be sufficiently photoreactive to result in direct phototoxicity (see Note 3 for further details)."

Dr. Langley pointed out that, since then, the Sponsor submitted contradictory statements regarding whether ReadyPrep CHG absorbs light at any wavelength between 290 and 700 nm. On at least two different occasions (Type C meeting minutes, Question 7, dated 6 Dec 2016 and NDA Resubmission, Section 1.12.13, Request for Waiver of Requirement for Phototoxicity and Photoallergenicity Studies, received 20 Oct 2017), the Sponsor stated that "… no components of the ReadyPrep® drug product absorb light corresponding to wavelengths of 290 nm to 700 nm (UVB, UBA and visible)."

However, in the Sponsor's response to FDA's information request on this issue, dated 8 June 2018, the Sponsor included the following statement:

> "In accordance with ICH S10 "Photosafety Evaluation of Pharmaceuticals", Medline Industries, Inc. (the Sponsor) used a tiered approach to assess the phototoxicity potential of the drug product ReadyPrep, CHG (herein referred to as CHG), which contains the drug substance chlorhexidine gluconate.
>
> "CHG was found to absorb UV/Visible light between approximately (b) (4) and (b) (4) nm. Therefore, the molar extinction coefficient (MEC) was assessed. At (b) (4) nm the MEC was ~1000 L mol-1 cm-1 (b) (4) L mol-1 cm-1 at (b) (4) nm, which exceeded the ICH S10 threshold."

Given contradictory responses from the Sponsor about whether the test product absorbs light between 290 and 700 nm, another IR was sent to the Sponsor on 17 Oct 2018 asking for clarification. The Sponsor responded on 22 Oct 2018, submitting an Information Amendment and a revised waiver request stating that CHG was found to absorb UV/Visible light between (b) (4) and (b) (4) nm:

> "The correct absorption spectrum data were stated in the information amendment dated 8 June 2018: "CHG was found to absorb UV/Visible light between approximately (b) (4) and (b) (4) nm.
>
> "The correct data were also provided in the original Waiver of Requirement of Phototoxicity and Photoallergenicity (NDA Resubmission received 20 October 2017), but were incorrectly described as demonstrating no absorption between 290 and 700 nm (Figure 1 from original Waiver). (b) (4) This misinterpretation is the cause of the discrepancy in reported absorption spectrum data."

Given that CHG in the test product absorbs light between (b) (4) and (b) (4) nm, and given that the molar extinction coefficient (MEC) exceeds the ICH S10 threshold, the Sponsor conducted an in vitro 3T3 neutral red update (NRU) phototoxicity test with CHG to determine its phototoxicity potential. In brief, CHG did not exhibit phototoxic potential in the in vitro 3T3 Neutral Red Uptake assay; per the Sponsor, this suggests low potential for phototoxicity.

Dr. Langley noted that there are concerns about how well this in vitro testing correlates with in vivo clinical response. She pointed out that, in general, FDA has not accepted a negative result from this in vitro test as adequate, in and of itself, to support a waiver. However, she acknowledged that there are a number of mitigating factors favoring granting the request for a waiver of phototoxicity and photoallergenicity studies. CHG has been available in various topical formulations since 1976 and is widely used as a topical antimicrobial agent and antiseptic. Despite this extensive exposure, phototoxicity and photoallergenicity reactions following topical application of CHG have not been reported in the published literature, or in clinical studies conducted by Medline. Further, the drug product, ReadyPrep CHG, is intended for use as a preoperative skin preparation; therefore, as also noted by the Sponsor, it is unlikely that significant light exposure would occur, aside from the lighting in the surgical suite. Given these factors, she concluded that DDDP supports granting the Sponsor's request for a waiver of phototoxicity and photoallergenicity studies.

*CDTL Comment: I agree with Dr. Langley's conclusions that Study **R13-051** was adequate in design and conduct, and that the study results "indicate that significant irritation occurred with this product; however, contact sensitization was not observed in the study." Regarding phototoxicity and photoallergenicity, Dr. Langley's conclusion that, given that extensive exposure to topical CHG products over a period of more than four decades has failed to show evidence of phototoxicity or photoallergenicity, and given that the product is*

intended for use as a preoperative skin preparation, such that exposure to natural light will be minimal, granting the Sponsor's request for a waiver of phototoxicity and photoallergenicity studies is reasonable.

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, with the following precaution for use in children younger thatn 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." This language is included in the Sponsor's proposed DFL.

As the application does not include a new active ingredient, PREA is not triggered.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) Audits

The Office of Scientific Investigation (OSI) conducted an inspection of one foreign clinical investigator (CI) site (Dr. Rozalia Olsavszky, Romania) for Protocol **R15-029**/ER15/050, " Assessment of the antimicrobial efficacy of Medline 2% CHG cloth preoperative skin preparation." In her review[18], Sharon Gershon, PhD, reported, "Although GCP violations were observed during the inspection of the clinical investigator, Dr. Rozalia Olsavszky, they are unlikely to substantially impact the determination of efficacy and safety of the product. The final compliance classification for the inspection is Voluntary Action Indicated (VAI)."

Table 37: Study Site Audited

Name of CI, Address	Protocol #, Site #, and # of Subjects Enrolled	Inspection Dates	Final Classification
Rozalia Olsavszky, M.D. Evic Romania / S.C. Bio High Tech S.R.L. 64-66, Marasesti Blvd, 040256 Bucharest, Romania	Eurofins Evic Romania Protocol: ER15/050 Medline Protocol: 15-29 340 subjects	3/26/2018 – 4/05/2018	VAI

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The site was selected for audit because, although an inspection of Dr. Olsavszky was conducted in December 2017 under NDA 021524 S012, Prevantics Swabstick, DNDP requested a re-inspection because these were

[18] Clinical Inspection Summary; NDA 207964; 27 August 2018.

two very different types of studies using different methods and with different outcome measures. The Prevantics study was a drying time study with results important for labeling. In contrast, the study under NDA 207964 assessed bacterial log reductions at different pivotal time points that were important for approval. Very few sites conduct these types of studies, and since the site in Romania is likely to conduct more types of these studies in the future, DNDP wishes to understand and clarify study conduct practices at this site.

OSI judged the following to be the main deficiencies:

- Discrepancies between source records and data listings with respect to bacterial sample collection times and scrub application times.
- Microbial sample collections were outside the protocol specified timeframes.
- Enrollment of subjects who did not meet the baseline CFU counts.

For details of the inspection, please see Dr. Gershon's review. Briefly, the inspection included a comprehensive review for 38 subjects, comparing data in the subjects' source records with data recorded in the Case Report Forms (CRFs). In addition, the inspector reviewed source records for 73 subjects for sample application (scrub) times and microbial sampling times and found discrepancies between source records and data listings. The inspector also found that for many subjects the scrub times and the sample collection times fell outside the protocol specified timeframes (out of window; OOW). To better understand these discrepancies, the inspector created an Excel spreadsheet of the data for these subjects. The site's explanation for the discrepancies was because the site transferred data from the source records and Case Report Forms to an Excel spreadsheet as an intermediate step and transcription errors occurred in the process. It was the data from the Excel spreadsheet with noted transcription errors that was submitted to the Sponsor. The Sponsor then submitted this data to the FDA. The field investigator noted that the site reported most discrepancies as protocol deviations to the Sponsor.

The following regulatory violations were identified:

1. Failure to follow the investigational plan.
    a. The ORA investigator found instances where the application scrub times were less than or more than the required time. For example, for Subject (b) (6), the treatment application of Dyna-Hex 2 (positive control) on the left groin began at 09:34 and was completed at 09:36:50, a total time of 2 minutes and 50 seconds. It should have been two minutes. For the treatment application of the Medline 2% CHG cloth, the treatment application began at 10:04:30 and ended at 10:06:00 for a total scrub time of 1 minute and 30 seconds. It should have been three minutes.

       However, Dr. Gershon concluded that, "This isolated finding is unlikely to have a significant impact on the efficacy evaluation."

    b. The protocol required that each test product remain on the treatment area for 8 hours (±30 min). Post-treatment microbial samples were to be collected at 10-minutes (±30 sec), 6-hours (±30 min), and 8 hours (±30 min). For 73 of 340 records reviewed, the field investigator identified subjects whose 10- minute (±30 seconds) sample collection time fell outside this window (OOW).

       Dr. Gershon concluded that "the OOW range was 15 seconds to two minutes, and it is unlikely to have a significant impact on the efficacy outcome. The site reported these deviations to the sponsor."

a. The protocol specified that only the subjects who met the screening log bacterial counts be randomized into the study. The bacterial sample collection done at screening must be at least 1.0×10^5 CFU/cm^2 in the groin region and at least 1.3×10^3 CFU/cm^2 on the abdominal region. The field investigator identified 33 subjects who failed screening bacterial log counts: 13 screen failures at the left abdominal site, and 20 screen failures at the right abdominal site. These subjects were allowed to have Treatment Day bacterial counts and be enrolled into the study.

Dr. Gershon reported that baseline sample collection was done at screening and on treatment day. Only subjects who met the screening day log bacterial counts were to be randomized into the study. The investigator found that the site followed Protocol Section 5.2.3 that instructed on the formula to convert the log 10 counts to CFU at screening baseline.

The Sponsor identified 17 subjects that were screening day failures for bacterial counts and were randomized. The field investigator identified 33 subjects who should have been screening day failures, but they were based on CFU count conversion and not on the log10 counts.

Dr. Gershon wrote "the review division asked if the proportion of screening day failure protocol deviations differ between the 3 treatment groups, and based on that analysis did not think these were large differences, although the proportions were smaller for the vehicle. They also asked if there were any differences in baseline CFU values between those screening failures who failed to be excluded and those who did not. Again, there was not much difference for abdomen screen day failures and the remainder of the data, and for groin screen day failure deviations and the remainder of the data."

2. Failure to maintain accurate records.

This was reflected by the discrepancies between source documents and the data listings with respect to 10-minute sample collection times and scrub application times.

Dr. Gershon reported that most of these discrepancies were reported to the NDA as protocol violations. The discrepancies were minor and transcription errors that happened when the site transferred data from source records to an Excel spreadsheet. Dr. Gershon concluded that "these errors are unlikely to impact the integrity of the data."

After the inspection, an exit interview was held with Dr. Olsavszky. Concurrence was reached with Dr. Olsavzky with all deficiencies, and Dr. Olsavszky agreed to a corrective action plan.

CDTL Comment: I agree with the OSI assessment that, although GCP violations were observed during the inspection of the clinical investigator, they are unlikely to substantially impact the determination of efficacy and safety of the product. This was confirmed by the sensitivity analysis conducted by Dr. Baro (see ***Section 7****).*

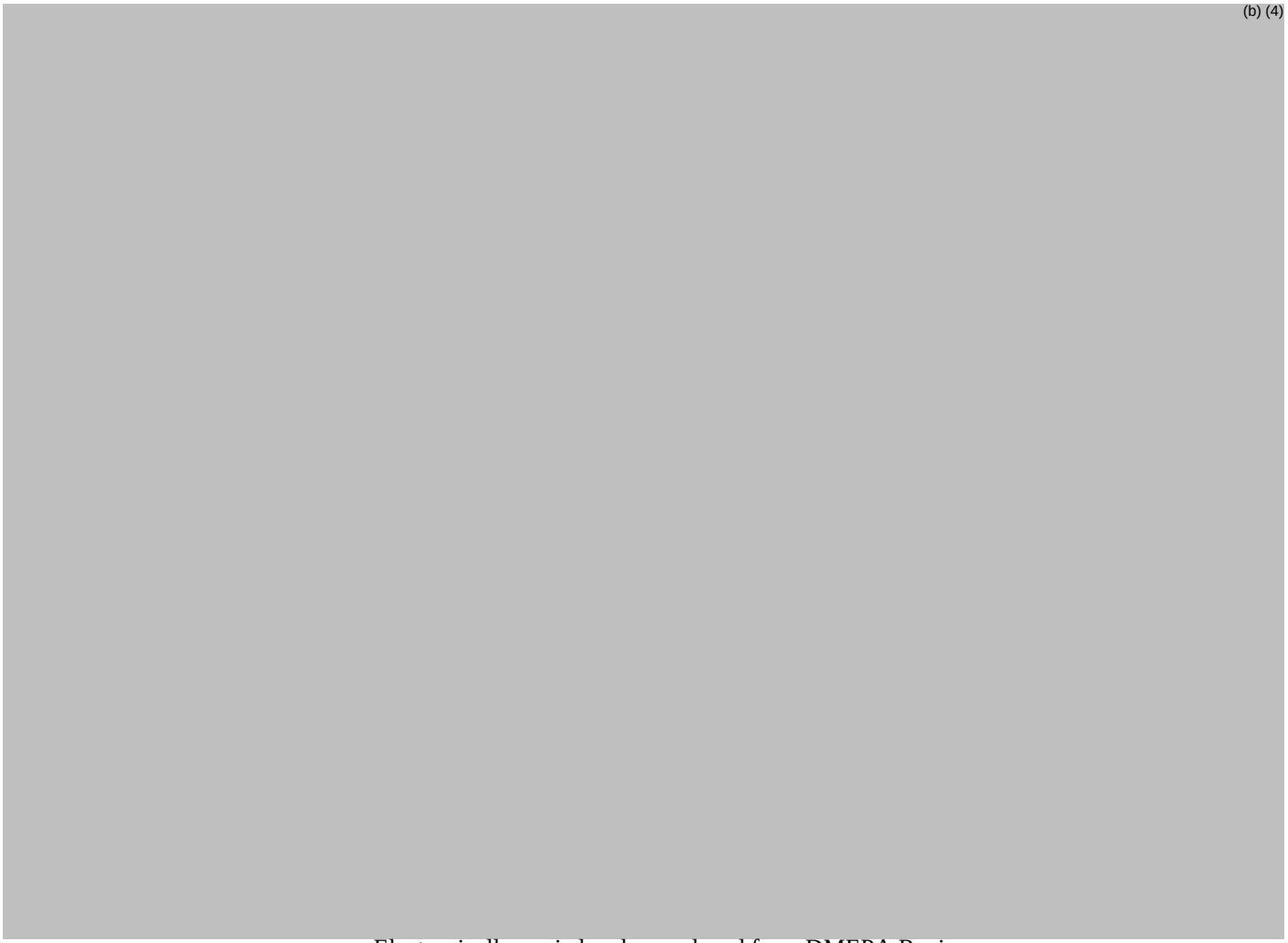
12. Labeling

Division of Medication Error Prevention and Analysis (DMEPA) Human Factors, Label and Labeling Review

The Division of Medication Error Prevention and Analysis (DMEPA) team (Grace P. Jones, PharmD, BCPS, Safety Evaluator; Chi-Ming (Alice) Tu, PharmD, BCPS, Team leader; Quynh Nhu Nguyen, MS, Assocaite Director for Human Factors; and Danielle Harris, PharmD, BCPS, Deputy Director), conducted a review[19] of the proposed container label and carton labeling for areas of vulnerability that could lead to medication errors.

The DMEPA team observed that the Sponsor had indicated on the proposed ReadyPrep CHG container label and carton labeling submitted on 30 March 2018 (See **Figure 3** and **Figure 4** below) that the expiration date would be imprinted at the time of manufacture. However, the Sponsor did not provide the exact format of the expiration date. Therefore, DMEPA provided recommendations on the presentation of the expiration date for container label and carton labeling.

(b) (4)



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[19] Human Factors, Label and Labeling Review, Division of Medication Error Prevention and Analysis (DMEPA); NDA 207964; 13 June 2018.

(b) (4)

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The DMEPA team also reported that on 19 March 2018, DMEPA requested that the Sponsor provide a comprehensive risk analysis and justification for not performing a human factors (HF) study for the proposed combination product.[20] On 30 March 2018, the Sponsor submitted a response.[21] Although the Sponsor did not provide a comprehensive use-related analysis, they provided their justification for not performing HF studies. Relevant product information submitted by the Sponsor on 30 March 2018 is provided in **Table 38** below. As a preoperative skin preparation product, this proposed chlorhexidine gluconate cloth combination product would be used in hospital surgical room environments by healthcare professional (HCP) end users, and use of the proposed product involves tearing the container packaging at the labeled notch to open, and then using the cloth to cleanse the surgical site. In their review, DMEPA wrote, "The risks associated with use of this product are well understood and we have not identified any additional or unique considerations that would warrant the need for additional data at this time. Therefore, we determined that a HF study is not necessary at this time."

[20] Peacock, C. Information Request for NDA 207964 Chlorhexidine Gluconate; Medline Industries, Inc. 2018 MAR 19.

[21] Quality/Response to Information Request; Labeling/Container-Carton Draft for NDA 207964 Chlorhexidine Gluconate; Medline Industries, Inc. 2018 MAR 30. \\cdsesub1\evsprod\nda207964\0025\m1\us\1113-info-amen-30mar2018.pdf

Table 38: Relevant Product Information for Readyprep CHG received on 30 March 2018 from Medline Industries, Inc

Table 2. Relevant Product Information for ReadyPrep CHG	
Initial Approval Date	N/A
Active Ingredient	Chlorhexidine gluconate
Indication	Drug Facts Label Uses: • Helps reduce bacteria that can potentially cause skin infection • For preparation of skin prior to surgery
Route of Administration	Topical
Dosage Form	Topical Cloth
Strength	2%
Dose and Frequency	Drug Facts Label Directions: • Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns. • Do not microwave • Product and packaging are not sterile. Follow your hospital policy for skin preparation with non-sterile products. • Use first cloth to prepare the skin area indicated for a moist or dry site, making certain to keep the second cloth where it will not be contaminated. Use second cloth to prepare larger areas. • Discard each cloth after a single use. • After package has been opened, discard any unused cloths. Top open package • identify the tear notch labeled on the front of the package • grasp with hands on both sides of the tear notch and tear to expose cloth • transfer contents onto prep table, avoiding contact between cloth and outside of package to reduce risk of cloth contamination • Dry surgical sites (such as abdomen or arm): use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to dry for one (1) minute. Do not rinse. • Moist surgical sites (such as inguinal fold): use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to dry for one (1) minute. Do not rinse.
How Supplied	2-count immediate container 24-count carton
Storage	• Store product flat • Store between 20-25°C (68-77°F) • Avoid excessive heat above 40°C (104°F)
Container Closure	(b) (4)

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In summary, the DMEPA team concluded that: 1) a human factors validation study is not needed for this product, and; 2) the format of the expiration date for the proposed product may be improved to increase clarity and promote safe use of the proposed product.

The DMEPA team recommended the following comments to the Sponsor:

A. Container Label and Carton Labeling
    1. As currently presented, the format for the expiration date is not defined on the container label and carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.We recommend using a format such as MMMYYYY (e.g., JAN2019) orMMMDDYYYY (e.g., JAN312019).

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

In addition to the human factors, label, and labeling review discussed above, the DMEPA team conducted a proprietary name review.[22] DMEPA evaluated the proposed proprietary name, ReadyPrep CHG, from a safety and misbranding perspective. DMEPA noted that, "in response to our initial OSE, November 15, 2017 email, the Division of Nonprescription Drug Products (DNDP) had no concerns relating to the proposed proprietary name, ReadyPrep CHG. DMEPA concurs with DNDP's assessment at initial review and concludes that the proposed proprietary name does not misbrand the proposed product." DMEPA concluded that the proposed proprietary name is acceptable and recommended the following comments to the Sponsor:

> *We have completed our review of the proposed proprietary name, ReadyPrep CHG, and have concluded that this name is acceptable.*
>
> *If any of the proposed product characteristics as stated in your October 26, 2017 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.*

Interdisciplinary Science (IDS) Labeling Review

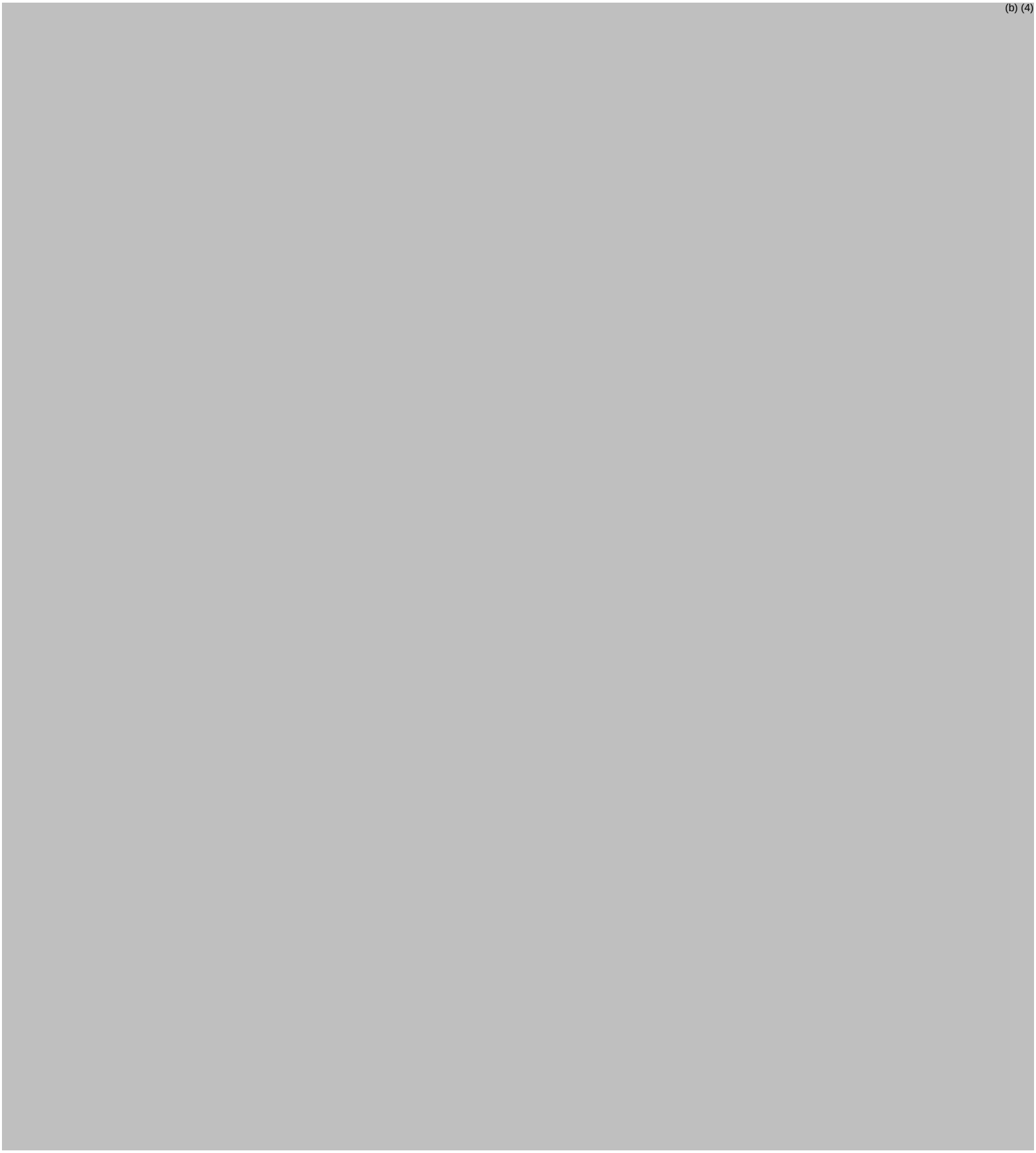
A thorough labeling review was conducted by Michelle Jackson, PhD, ODEIV/DNDP (Team Leader: Franscisco Martinez-Murillo, PhD, ODEIV/DNDP).[23] Based on the recommendations from Dr Jackson's review, several information requests (17 Novemeber 2017, and 19 March, 8 June, 21 September, 28 Septemenber, and 22 October 2018) were sent to the Sponsor during the current review cycle. In response, the Sponsor submitted font and format specifications on 1 December 2017 and revised labeling on 30 March, 15 June, 27 September and 3 October 2018. A review of these responses was performed by Hana Mujahid, PhD, DNDP in an Addendum Labeling Review.[24]

The proposed labeling in the submission of 20 October 2017 included color draft labeling copies of the principal display panel (PDP) and Drug Facts labeling for the immediate container (2-count) and outer container (24-count carton). On 21 November 2017, an information request was sent to the Sponsor requesting

[22] Proprietary Name Review; Division of Medication Error Prevention and Analysis (DMEPA); NDA 207964; 18 January 2018
[23] Labeling Review for ReadyPrep™ CHG 2% Chlorhexidine Gluconate Cloth *Draft Labeling*; NDA 207964; 16 March 2018.
[24] NDA 207964 Addendum Labeling Review for ReadyPrep CHG 2% Chlorhexidine Gluconate Cloth.

submission of full annotated specifications (e.g., bolding, font/type size of text, headings, barlines, hairlines, bullets, etc.) for the Drug Facts labeling. The Sponsor provided this information on 1 December 2017 (see **Figure 5** below). Dr. Jackson conducted a review of the submitted annotated labeling from 1 December 2017 and identified numerous labeling deficiencies regarding bolding, font/type size of text, headings, and bullets. The specific findings are detailed in her review. Based on her findings, Dr. Jackson recommended a Complete Response.

(b) (4)



(b) (4)

Dr. Jackson identified the following required and recommended changes for the labeling deficiencies:

Required Changes

Principal Display Panel for Immediate Container and Outer Container (24-Count Carton)

1. Revise the pharmacological category from (b) (4) to read: "PATIENT PREOPERATIVE SKIN PREPARATION". Additionally, bold and increase the size of the pharmacological category to be the same size as the established name or at least half the size of the most prominent display of the tradename (ReadyPrep™ CHG) in accordance with 21 CFR 201.61(c).

2. Revise the established name of the drug from (b) (4) to "2% CHLORHEXIDINE GLUCONATE* CLOTH" for labeling consistency across over-the-counter chlorhexidine gluconate drug products.

3. Revise the (b) (4) to appear as: "*EQUIVALENT TO 500 MG CHLORHEXIDINE GLUCONATE PER CLOTH".

4. Relocate the sterility statement "NON-STERILE" to directly follow the pharmacological category (Patient Preoperative Skin Preparation) on the PDP and anywhere else in the

labeling the pharmacological category appears. Present the sterility statement "NON-STERILE" in bold font and in the same font size as the pharmacological category.

5. Relocate the established name of the drug (2% CHLORHEXIDINE GLUCONATE* CLOTH) to directly follow the proprietary name (ReadyPrep™ CHG), and to be subsequently followed by the pharmacological category (PATIENT PREOPERATIVE SKIN PREPARATION) per 21 CFR 201.61. The sterility statement "**NON-STERILE**" should follow the pharmacological category, followed by the "*EQUIVALENT TO 500 MG CHLORHEXIDINE GLUCONATE PER CLOTH" statement for labeling consistency across over-the-counter chlorhexidine gluconate drug products.

6. Revise the declaration of the net quantity of contents statement on the PDP to be in boldface type per 21 CFR 201.62(g).

7. The outer carton appears to have alternate principal display panels (a second principal display panel in a different side of the package), and information presented in one panel seems to be missing from the other one, e.g., statements such as: "Non-sterile", "Single use only", "For external use only", "Fragrance free", and "Rinse free". Revise where packages bear alternate principal display panels to ensure that information required to be placed on the principal display panel is duplicated on each additional principal display panel, in accordance with 21 CFR 201.60. Furthermore, per 21 CFR 201.62(d), the declaration of net quantity of contents shall be located on the principal display panel of the label, and with respect to packages bearing alternate principal display panels it shall be duplicated on each principal display panel. Suggested placement for the net quantity of contents on the alternate principal display panel is above the perforated area (opening) on the lower third of the panel. If this placement is used for the net quantity of contents statement, removal of the perforated label should not affect the visibility or constitution of the statement.

Outside Drug Facts for Outer Container (24-Count Carton)

8. Revise the pharmacological category from (b) (4) to read: "PATIENT PREOPERATIVE SKIN PREPARATION" on the top and side panel of the outer container. Add the sterility statement "**NON-STERILE**" to directly follow the pharmacological category. Revise the side panel of the outer container to be consistent with the statements on the principal display panel.

Outside Drug Facts for Outer Container (24-Count Carton) and Immediate Container

9. Ensure that the expiration date is present on the outer container (24-count carton) and immediate container label in accordance with 21 CFR 201.17. Indicate the location where you intend to display the expiration date for placement only.

Outer Container (24-Count Carton) and Immediate Container Drug Facts

10. Remove (b) (4) following the "***Active ingredient***" subheading per 21 CFR 201.66.

11. Reformat the bulleted statements under "***Uses***", "**Do not use**", "**Allergy alert:**", "***Directions***", and "***Other information***" so that the end of one bulleted statement is

separated from the beginning of the next bulleted statement by at least two square "ems" (i.e., two squares of the size of the letter "M") and the complete additional bulleted statement(s) does not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under the heading should be vertically aligned with the bulleted statements appearing on the previous line, in accordance with 21 CFR 201.66(d)(4).

12. Remove the "**Do not use**" subheading and bulleted statements from under the "**For external use only**" warning and place them after the "**Allergy Alert:**" section of the Drug Facts. The "**For external use only**" statement should be in bold type directly under the "***Warnings***" heading in accordance with 21 CFR 201.66(c)(5)(i). In addition, place a hairline preceding the "**Allergy alert:**" subheading that follows the "**For external use only**" warning.

13. Reformat the "***Allergy alert***" warning subheading by inserting a colon after the "t" to appear as: "**Allergy alert:**" under the Drug Facts labeling "***Warnings***" heading, as required under 21 CFR 201.66(c)(5)(ii)(B) and (d)(1) and decrease the font size to be consistent with the font size used for other subheadings in the Drug Facts labeling.

14. Include a comma between the words "sensitization" and "or" and revise the first letter of the word "Irritation" from upper case to lower case, under the "**Stop use and ask a doctor if**" statement, so that it reads: "**Stop use and ask a doctor if** irritation, sensitization, or allergic reaction occurs. These may be signs of a serious condition." for consistency across chlorhexidine gluconate drug products labeling.

15. Move the "**To open package**" section to follow the "■ After package has been opened, discard any unused cloths" statement under the "***Directions***" subheading. Followed by the remainder of the bulleted statements under the "***Directions***" subheading.

16. Revise the subheading "***To open package***" to be unitalicized, per 21 CFR 201.66(d)(3) and decrease the font size to be consistent with the font size used for other subheadings in the Drug Facts labeling.

Outer Container Drug Facts

17. Revise "***Other Information***" to read: "***Other information***" by changing the first letter in "***Information***" to lower case, in accordance with 21 CFR 201.66(c)(8).

Immediate Container Drug Facts

18. Revise the title "***Drug Facts Continued***" to read: "***Drug Facts*** (continued)" per 21 CFR 201.66(c)(1).

Recommended Changes

Principal Display Panel for Outer Container (24-Count Carton)

19. Add the statement "DO NOT MICROWAVE" to the PDP of the outer container to be consistent with the statements on the immediate container PDP.

Principal Display Panel for Immediate Container and Outer Container (24-Count Carton)

20. Revise the placement of the following statements on the PDP by risk importance: "SINGLE USE ONLY", "FOR EXTERNAL USE ONLY", "DO NOT MICROWAVE", "FRAGRANCE FREE", and "RINSE FREE".

Outer Container (24-Count Carton) and Immediate Container Drug Facts

21. Revise the first letter of each bulleted statement under the "***Uses***", "**To open package**", "**Dry surgical sites** (such as abdomen or arm", "**Moist surgical sites** (such as inguinal fold), "***Inactive ingredients***", "***Directions***", and "***Other information***" from upper to lower case.

22. Revise the bulleted statement under the subheading "**Do not use**" from "■ on patients with known allergies to chlorhexidine gluconate or any other ingredients in this product" to read: "■ on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product" for consistency across all chlorhexidine gluconate topical antiseptic drug products.

23. Revise the bulleted statement under the subheading "**Do not use**" from "■ on open wounds or as a general skin cleanser" to read: "■ on open skin wounds or as a general skin cleanser".

24. Revise the order and format of the bulleted statements under the heading "***Directions***" to read: "■ use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns. ■ do not microwave ■ product and packaging are not sterile. Follow your hospital policy for skin preparation with nonsterile products. ■ use first cloth to prepare the skin area indicated for a moist or dry site, making certain to keep the second cloth where it will not be contaminated. Use second cloth to prepare larger areas. ■ discard each cloth after a single use ■ after package has been opened, discard any unused cloths". A period is used after each sentence only if a single bulleted statement contains two or more sentences.

25. Revise the bulleted statement "■ Avoid excess heat above 40°C (104°F)" to read: "■ avoid excessive heat above 40°C (104°F)" under the heading ***"Other information"***.

26. Revise the first letter of each inactive ingredient from upper to lower case under the "***Inactive ingredient***" heading.

Immediate Container Drug Facts

27. Revise the font size for the statements "Chlorhexidine gluconate 2% solution", dot leaders, and "Antiseptic" under the "***Active ingredient***" and "***Purpose***" headings, to be consistent with the format specifications used for other statements in the Drug Facts labeling.

Outer Container (24-Count Carton) Drug Facts

28. Revise the font size for the "***Active ingredient***", "***Purpose***" and "***Uses***" headings, bulleted text under the "***Uses***" heading, and the statements "Chlorhexidine gluconate 2% solution", dot leaders, and "Antiseptic" under the "***Active ingredient***" and "***Purpose***" headings to be consistent with the font specifications used for the other headings, statements, and bulleted text used in the Drug Facts labeling.

Addendum Labeling Review

An Addendum Labeling Review was completed by Hana Mujahid, PhD, DNDP. [25]In her review, Dr. Mujahid described the Information Requests and the communications from the Sponsor to address the above issues. The reader is referred to her review for a detailed description. Dr. Mujahid concluded that the Sponsor has addressed all outstanding information requests related to the PDPs, Drug Facts, and issues described above in the revised proposed labeling. Dr. Mujahid concluded that the revised proposed labeling submitted on 3 October 2018 is acceptable.

Dr. Mujahid also noted that during the review cycle, two additional issues were identified:

1) The statement, (b) (4) was not acceptable. Therefore, on 21 September 2018, an information request was sent to the Sponsor requesting that (b) (4) (b) (4)

[25] NDA 207964 Addendum Labeling Review for ReadyPrep CHG; October 2018.

(b) (4)

In response to FDA's request from 21 September and clarification on 24 September 2018, the Sponsor revised the statement to read: "Demonstrates continued antimicrobial activity for up to 6 hours after application" anywhere that the statement appeared in the revised proposed labeling submitted on September 27, 2018 and any subsequent submissions.

2) Upon further review of the labeling, it was noted that the "**Do not use**" section could be further revised to add emphasis and improve clarity. On October 22, 2018, FDA requested the Sponsor revise the third bulleted statement under the "**Do not use**" subheading "on open skin wounds or as a general skin cleanser" into two separate bulleted statements so that the third bulleted statement in the "**Do not use**" section reads: ▪ on open skin wounds ▪ as a general skin cleanser". FDA also noted under the "**Inactive ingredients**" heading the inactive ingredient "USP purified water" could be revised for clarity to read: "purified water USP". FDA provided the Sponsor with further clarification on October 22, 2018.

In conclusion, Dr. Mujahid recommended that an Approval letter be issued to the Sponsor for the submitted ReadyPrep CHG immediate and outer container labeling for NDA 207964 and request final printed labeling identical to the labeling submitted on 3 October 2018.

13 Postmarketing Recommendations

None.

14 Recommended Comments to the Applicant

None. Communcications with the Sponsor have adequately addressed issues as described in **Section 12** above.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FRANCIS E BECKER
10/30/2018