CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 207964
Priority or Standard	Standard
Submit Date(s)	20 October 2017
PDUFA Goal Date	20 November 2018
Division/Office	DNDP
Reviewer Name(s)	Martha Lenhart, MD, PhD
Established/Proper Name	2% Chlorhexidine gluconate
(Proposed) Trade Name	ReadyPrep CHG[1]
Applicant	Medline Industries
Dosage Form(s)	Cloth with solution
Applicant Proposed Dosing Regimen(s)	500 mg CHG per single cloth application Dosing instructions are surface area and skin moisture level related: one cloth for 5x5 inches of dry skin cleansing, one cloth for 2x5 inches of moist skin cleansing
Applicant Proposed Indication(s)/Population(s)	Preoperative skin preparation
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Preoperative skin preparation Use with care in premature infants or infants under 2 months of age

[1] Proposed proprietary name, ReadyPrep CHG, noted conditionally acceptable in DEMPA Review 23 Jan 2018. The name "ReadyPrep CHG" is used in this review to represent Medline's proposed 2% CHG cloth product.

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Glossary

AE	adverse event
AR	adverse reaction
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research
CHG	chlorhexidine gluconate
CFR	Code of Federal Regulations
CFU	colony forming units
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
CSS	clinical summary of safety
DAWN	Drug Abuse Warning Network
DDDP	Division of Dermatology and Dental Products
DNDP	Division of Nonprescription Products
DSC	Drug Safety Communication
eCTD	electronic common technical document
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	good clinical practice
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
MO	Medical Officer
NDA	new drug application
OSI	Office of Scientific Investigation
OTC	over-the-counter
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PSUR	periodic safety update report
RTF	refuse to file
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SSI	surgical site infection
TBM	to be marketed
WHO	World Health Organization
WRO	written response only

1. Executive Summary

1.1. Product Introduction

ReadyPrep CHG is composed of a 2% chlorhexidine gluconate (CHG) solution on single fiber, polyester cloth in a two-cloth per pack configuration for use as a topical antimicrobial agent indicated for preoperative skin preparation. A single impregnated cloth delivers (b) (4) 500 mg CHG when applied in a 3-minute vigorous rub followed by a 1-minute dry time at the therapeutic site of action. Anatomic location and moisture level of the skin determine directed surface area coverage of each ReadyPrep CHG cloth.

The active product ingredient, CHG, binds to skin and mucosal tissues. CHG demonstrates broad-spectrum activity against Gram-positive and Gram-negative bacteria, facultative anaerobes, aerobes, and yeast as a biguanide biocide targeting the bacterial cell wall at low concentrations and the cytoplasmic membrane at higher concentrations.[2] The antibacterial activity of CHG relies on its positive charge to bind to stratum corneum. Negatively charged ingredients in lotions and creams may inactivate antibacterial actions of CHG.

CHG is available in the U.S. in aqueous or alcohol formulations and dosage forms such as solution, cloth, sponge and swab. Multiple preoperative skin preparations products exist, approved through the NDA process or marketed via the monograph system. Table 2 summarizes currently marketed over-the-counter (OTC) preoperative skin preparations in the U.S.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Results of two pivotal Phase 3 studies and three pilot studies underpin Sponsor evidence of effectiveness for ReadyPrep CHG. Results of these clinical studies with a 70% responder rate at 10 minutes, and persistence of efficacy at 6 hours at abdomen and groin treatment sites, are augmented by two in vitro studies of effectiveness against a broad range of Gram-positive and Gram-negative bacteria, and yeast. A subsequent and third in vitro study, pharmacodynamic bridge, indicates comparable antimicrobial efficacy between the initial product formulation and the final to-be-marketed (TBM) formulation of ReadyPrep CHG.

Refer to the microbiology and statistical reviews for an expanded discussion of effectiveness.

[2] Leikin, J.B. (2008). "Chlorhexidine Gluconate", *Poisoning and Toxicology Handbook* (4th ed.), Informa, pp. 183–84. https://universalflowuniversity.com/Books/Medicine/Biochemistry/Poisoning%20and%20Toxicology%20Handbook%20-%20Leikin.pdf

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

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.[3] A 2016 Surgical Site Infection Guidelines from the American College of Surgeons and Surgical Infection Society, state 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.[4] Prevention of SSI is increasingly important as the number of surgical procedures performed in the U.S. continues to rise. Prevention of SSIs is a critical focus in patient care.

Clinical and in vitro study efficacy of CHG provides the basis of its use as an active ingredient in preoperative skin preparations. Use of CHG-based cloth for preoperative skin preparation provides an approach to preempting potential postoperative infections. Sponsor formulated CHG augments existing aqueous 2% CHG products, and its excipients may inhibit *Burkholderia cepacia* contamination.

Clinical efficacy of ReadyPrep CHG is established in two pivotal Phase 3 studies and three pilot studies achieving the required 70% responder at 10 minutes, with persistence of efficacy at 6 hours for both abdomen and groin treatment sites.[4] In vitro studies demonstrate its effectiveness against a broad range of Gram-positive and Gram-negative bacteria, facultative anaerobes, aerobes, and yeast.

The combined single, therapeutic application and multiple, challenge study applications of ReadyPrep CHG resulted in <1% of subjects (26 of 1931 treated) with adverse events. AEs were considered mild skin reactions and consistent with known CHG adverse events. A Sponsor-conducted pharmacokinetic study of 12 adult subjects across 24 hours resulted in no detectable systemic CHG after a single topical application of ReadyPrep CHG.

The active antiseptic ingredient of ReadyPrep CHG has been marketed for many years and the safety profile is well known. AEs associated with CHG and its use as an antiseptic are most commonly identified as skin reactions. Chemical burns in preterm infants, hypersensitivity, and anaphylaxis have been reported and are addressed through monitoring and label warnings.

ReadyPrep CHG demonstrated rapid and persistent reduction of skin flora, equivalent efficacy of initial and TBM formulations, minimal adverse events, and negligible active ingredient absorption. Given the efficacy results achieved and minimal safety risks identified in Sponsor studies, ReadyPrep CHG offers a beneficial, effective treatment option for preoperative skin preparation.

[3] Berríos-Torres, S.I. (2017). Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection. J*AMA Surg.* 152(8):784-791. doi:10.1001/jamasurg. https://www.cdc.gov/infectioncontrol/guidelines/ssi/index.html

[4] Ban, K.A. (2016). 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

Table 1: Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Prevention of SSI is increasingly important as the number of surgical procedures performed in the United States continues to rise[3] • Surgical site infections (SSI) are the most common hospital-acquired infections[4] • Estimated annual incidence of SSIs in U.S. ranges 160K-300K; annual cost of 3.5B-10B and increased length of hospitalization by 9.7 days [4]	Prevention of SSIs is a critical focus in patient care.
Current Treatment Options	• Multiple CHG preoperative skin preparations are currently marketed • Two 2% CHG products exist – one cloth and one solution	Clinical and in vitro study efficacy of CHG provides the basis of its use as an active ingredient in preoperative skin preparations.
Benefit	• Preoperative preparation with antimicrobial efficacy; demonstrated topical antimicrobial effect • Augments existing aqueous 2% CHG cloth and solution products • Product excipients may prevent contamination with *Burkholderia cepacia (B. cepacia)* • <1% of study subjects demonstrated AEs following therapeutic application; AEs were considered mild	Use of CHG-based cloth for preoperative skin preparation provides an approach to preempting potential postoperative infections.
Risk and Risk Management	• CHG adverse reactions: Skin sensitivity, Hypersensitivity/anaphylaxis that results in life threatening reaction or death Management: monitoring, labeling, safety communications • CHG bacterial contamination: *B. cepacia* may cause serious infection[5,6] Management: monitoring, CMC processes	Adverse events associated with CHG and its use as an antiseptic are most commonly identified as skin reactions. Hypersensitivity and anaphylaxis have been reported and are addressed through monitoring and label warnings.

[5] https://www.fda.gov/safety/recalls/ucm517547.htm

[6] Chang, C.Y. (2012). Microbial Stowaways in Topical Antiseptic Products. (2012). http://www3.med.unipmn.it/papers/2012/NEJM/2012-12-06_nejm/nejmp1212680.pdf

1.4. Patient Experience Data

Clinical studies for this product began in 2013. No patient experience data was collected.

X	Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

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.[3] 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.[4] Prevention of SSI is increasingly important as the number of surgical procedures performed in the U.S. continues to rise. Prevention of SSIs is a critical focus in patient care.

2.2. Analysis of Current Treatment Options

Preoperative skin preparation products marketed in the U.S. include chlorhexidine, hexachlorophene and iodine formulations. Table 2 lists approved OTC products with an indication of preoperative skin preparation. Dyna-Hex 2% solution and 2% CHG cloth (Sage) represent the two products most similar to the Sponsor proposed product, ReadyPrep 2% CHG cloth.

Table 2: Current OTC Preoperative Skin 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	3.15% CHG, 70% IPA

(all previously Chlorascrub)	
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, (b) (4),
HEX= Hexachlorophene
Source: Constructed from FDA Orange Book
https://www.pharmacompass.com/fda-orange-book/chlorhexidine-gluconate

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Patient preoperative skin preparations are approved through the NDA process or marketed via the monograph system. Although not proposed as a monograph product, this 505(b)(2) NDA submission follows requirements outlined in the 1994 proposed Tentative Final Monograph (TFM) for OTC antiseptic drug products.[7] NDA 207964 also includes studies consistent with the May 2015, TFM amendment proposing additional safety data to support the safety of antiseptic active ingredients derived from in vitro data characterizing the active ingredient antimicrobial properties and *in vivo* clinical studies meeting specified criteria of log reductions in bacterial counts. [8]

At the time of NDA 207964 submission, ReadyPrep CHG is not approved for use in the U.S. or internationally. Studies conducted under IND 107899 support NDA 207964.

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory Background

1) Meeting Requests

[7] FDA (1994). Tentative Final Monograph for OTC Health-Care Antiseptic Drug Products; Proposed Rule. 21 CFR Parts 333 and 369. https://www.gpo.gov/fdsys/pkg/FR-1994-06-17/html/94-14503.htm
[8] Federal Register, Vol. 80, No. 84, Friday, May 01, 2015, Department of Health and Human Services, FDA. 21 CFR Part 310. Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record. https://www.gpo.gov/fdsys/pkg/FR-2015-05-01/pdf/2015-10174.pdf

Table 3: Meeting Requests

Meeting Type	Meeting Date
Pre-IND	13 Dec 2011
Pre-IND	19 Sep 2012
Type B Pre-IND	5 Feb 2013 (TCon)
Type C Guidance	6 May 2013
Type A Refuse to File	23 May 2016
Advise Request	29 June 2016
Type C	6 Dec 2016 (WRO)
Type C	3 Mar 2017 (WRO)

Source: Augmented Introduction, Mod 2.2, Table 5, pg 7

(b) (4)

- Feb 2013 Meeting Minutes
  - Pilot scale process to manufacture cloth appears acceptable
  - Commercial scale process appears acceptable

(b) (4)

3) Submission NDA 207964
   - February 9, 2016

4) Refusal to File (RTF)
   - April 8, 2016

FDA RTF issues:

(b) (4)

  - Clinical Study Reports do not contain subgroup analysis
  - Application does not contain appropriate patent certification
- May 23, 2016 – Meeting to discuss RTF
- June 29, 2016 – General advice request

(b) (4)

- Included clinical study safety and efficacy findings by gender, age, and ethnic subgroups

5) Filing NDA 207964
   - Dec 2017

   Updates to earlier 2016 RTF submission
   - Sponsor relying on efficacy studies of initial formulation using an in vitro time-kill study as bridge between formulations
   - Sponsor reviewed AE databases from FAERS, WHO, and DAWN
   - Sponsor noted *B. cepacia* complex infection among ten most commonly reported AEs for chlorhexidine topical administration
   - Sponsor included waiver proposal for phototoxicity and photosensitivity human dermal safety studies

Reviewer comment
FDA agreed that it is reasonable to request a waiver for the phototoxicity and photoallergy studies for this product in the NDA submission. Whether the waiver will be granted is a review issue that will be considered during the NDA review period (6 Mar 2017 WRO). DDDP notes long history of CHG use, negative in vitro studies, and operative settings to be considered in the waiver determination.

Statistics and Microbiology Reviewers will address efficacy criteria and study limitations.

Summary of Issues and Actions

Table 4 summarizes key NDA issues described in the April 2016 RTF letter and subsequent and Sponsor actions.

Table 4: Summary of Issues and Actions

Issue	Action Taken
(b) (4)	Medline has (b) (4) (b) (4) As agreed upon with the Agency at the Type C meetings, Medline has conducted an in vitro comparability of the two formulations (b) (4) (b) (4) to establish the bridge between the new formulation to the formulation that was used to conduct the pivotal clinical studies, sensitization/irritation study, and antimicrobial resistance study.
The application is incomplete because Clinical Study Reports in Module 5 of the eCTD do not contain a section on subgroup analysis.	As discussed with the Agency at the Type A meeting, Medline has conducted the specified subgroup analyses for studies R13-051, R13-052, R13-053, and R15-029. The subgroup analyses (for Study R13-053 and Study R15-029) are discussed in the relevant sections of this NDA.
The application does not contain an appropriate patent certification as required under 21 CFR 314.50(i).	Medline is not including literature references referring to patented listed drugs and will not be relying on the FDA's findings of safety and/or effectiveness for any listed drugs.

Source: Adapted from Introduction, Mod 2.2, Table 6, pgs 8-10 (continued on next page)

You have not formally submitted a waiver request for waiving the needed in vivo bioavailability/bioequivalence (BA/BE) study.	Medline will not rely on the FDA's findings of safety and/or effectiveness for any listed drugs. The negligible systemic bioavailability of CHG from ReadyPrep CHG is supported by the Sponsor's Phase 1 study and information from published studies (Section 2.7.1).
Provide raw plate count data for the following studies: • Study R14-013 • Study R14-012 • Study R13-053 • Study R15-029	Medline has provided this information in this submission (Section 5.3.5.1 and 5.3.5.4).
If you intend to propose a waiver for the phototoxicity and photosensitivity human dermal safety studies, request such a waiver and identify the basis for your request eg, absoption spectra.	As agreed upon with the Agency at the Type C meetings, phototoxicity and photoallergy studies are not required. A formal request for a waiver is provided in Section 1.12.13.
The application does not provide safety information from a complete set of postmarketing databases.	As agreed upon with the Agency, appropriate searches of postmarketing databases were conducted and the results are included and discussed in the Integrated Summary of Safety.
Regarding missing data: • Define an intent-to-treat (ITT) analysis population to include all randomized patients meeting the screening day and treatment day criteria (i.e., 1.3 x 10^3 CFU/cm^2 per abdominal site (left or right) and 1.0 x 10^5 CFU/cm^2 per groin site (left or right). Include all ITT subjects in the primary analyses.	The primary analyses have been conducted on the population of all randomized patients meeting the screening and treatment day criteria per body site.
• Describe strategies used in the study to help with retention and minimize missing values. Missing data cannot be excluded or replaced later with other subjects (as done in the study report) as it can seriously impact the ITT principle and interpretation of the study results. Conduct sensitivity analyses for testing robustness of the evidence to assumptions on the missing values.	There were no missing data due to exclusion; therefore, there were no replacement data. In the efficacy studies, baseline samples were collected for each of four possible body sites (left or right for the abdomen or groin) on both the screening and treatment days. Based on these baseline samples, a subject could meet inclusion criteria for none, some, or all of the body sites. Therefore, if a subject only meets inclusion criteria on the groin and not the abdomen, a separate subject will be used for the abdomen in order to fulfill the targeted enrollment for all body sites.
Regarding blinding: • Describe the measures to prevent unblinding. • Describe the procedures used to ensure maintenance of overall study blinding and whether data monitoring personnel had access to unblended data.	Unblinding in Study R13-053 is discussed in the Integrated Summary of Efficacy. The Sponsor has conducted a post-hoc analysis of the data before and after unblinding and determined that there was no effect on the study findings.
Due to concerns over study integrity, Medline has removed efficacy data from Study R13-052 from the integrated summary of efficacy as well as all related efficacy summary tables, datasets and, define files.	The removal of Study R13-052 efficacy data was agreed upon with the Agency. The study report is included in the NDA submission, and the safety data from the study is presented and discussed in the appropriate NDA sections.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable. The Sponsor reports no international marketing of the proposed product.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An Office of Scientific Investigations (OSI) request was submitted for due diligence given that 50% of pivotal efficacy/safety study data was derived from a foreign study site (Study R15-029). Additionally, the DNDP Statistics team requested detailed documentation of procedures used to ensure data quality at the various stages of the study (including data entry and data analysis) and documentation of errors. This circumstance resulted in a major amendment and extension of the PDUFA deadline for 90 days.

The main deficiencies identified during the OSI audit were:

- 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 bacterial counts

OSI concluded (audit filed 27 Aug 2018) that although GCP violations were observed during the inspection of the clinical investigator that they were unlikely to substantially influence the determination of efficacy and safety of the product. The final compliance classification for the inspection is Voluntary Action Indicated (VAI).

The Microbiology and Statistics Reviewers will evaluate Sponsor data and OSI findings for potential impact on efficacy.

4.2. Product Quality

The chemistry manufacturing and controls (CMC) review is deferred to the CMC Reviewer.

4.3. Clinical Microbiology

The Sponsor is relying on pivotal clinical studies and in vitro studies to support the antimicrobial effectiveness of ReadyPrep CHG.

Refer to the Microbiology Reviewer assessment for a discussion of studies supporting efficacy including in vitro studies R14-012 (antibiotic cross-resistance), R14-013 (time-kill), and R17-004 (time-kill, bridging).

4.4. Nonclinical Pharmacology/Toxicology

To support the nonclinical safety of ReadyPrep CHG, the Sponsor is relying on:

- primary pharmacodynamic studies, including studies to demonstrate the antimicrobial properties of the ReadyPrep CHG formulation, to evaluate the potential for the development of antimicrobial resistance or antibiotic cross-resistance in bacterial populations exposed to the ReadyPrep CHG formulation, and to bridge between initial and final ReadyPrep CHG formulations. (R17-023 and R17-004)
- FDA's findings of nonclinical safety for Hibiclens (NDA 017768; approved 17 Sept1976)
- nonclinical data from published literature, including pharmacology, pharmacokinetic, and toxicology information

Review of the nonclinical safety of ReadyPrep is deferred to the Nonclinical Reviewer.

4.5. Clinical Pharmacology

To support the clinical pharmacologic aspects of ReadyPrep CHG, the Sponsor is relying on:

- single dose PK study (R17-023) to assess systemic exposure of CHG from ReadyPrep CHG
- published literature evidence of systemic CHG exposure

Refer to the discussion by the Clinical Pharmacology Reviewer for additional content and clinical relevance of Sponsor provided literature.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 5 summarizes Sponsor conducted clinical studies supporting efficacy and safety of ReadyPrep CHG.

Table 5: Summary of Clinical Studies

Study Number	Info	Study Design	Study & Control DDRR	Txmt Duration	Evaluation Time Point	Study Site	Subjects	Subjects with AE
R13-053 Pivotal Phase 3	E, S	R, B, C V+A	TP/V 3m x 1 DH2 2m x 2	8 h	I, 10m, 6h,8h	US-V	347	0
R15-029 Pivotal Phase 3	E, S	R, P-C, C	TP/V 3m x 1 DH2 2m x 2	8 h	I, 10m, 6h,8h	R	340	0
R13-052	S	R, B, C V+A	TP/V 3m x 1 DH2 2m x 2	8 h	I, 10m, 6h,8h	US-M	879	23
R13-042 Pilot	E, S	R, P-C, C	TP 1, 2 or 3m x 1 DH2 2m x 2	8 h	I, 10m, 6h,8h	US-V	27	0
R14-015 Pilot	E, S	R, P-C, C	TP DH2 2m x 2 1 or 2m x 1	8 h	I, 10m, 6h,8h	US-M	33	0
R15-028 Pilot	E, S	R, P-C, C	TP 3m x 1 DH2 2m x 2	8 h	I, 10m, 6h,8h	R	14	0
R16-034*	S	C, open-label	TP 3m x 1	3 m	Pre/post txmt	US-V	30	0
R17-023*	PK, S	R, 3-P, 3-S, crossover	TP 3m x 1	24 h	Pre, 4,8,24h post txmt	US-ND	12	3
R13-051 Challenge Sensitization	S	R, B, C V+A	TP/V, DH2: occlusive patch 24h x 24d	21 d	Daily and post final patch removal	US-M	39	10
R13-051 Challenge Irritation	S	R, B, C V+A	TP/V, DH2: Induction and challenge	37 d	Daily Challenge: 30m, 24, 48 and 72h post patch removal	US-M	210	36

E= efficacy; S=safety; PK=pharmacokinetic; R= randomized; B=blinded; C=controlled; V=vehicle; A=active; TP=test product; DH2=Dyna-Hex2; I=immediate; m=minutes; h=hours; US-ND=North Dakota (Algorithme Pharma); US-M=Montana (BioScience); US-V=Virginia (MicroBioTest); R=Romania (EVIC Romania)
*Indicates studies conducted with the modified, final product formulation. All other studies used the initial formulation (b) (4)
(b) (4)
Source: Adapted from Integrated Summary of Safety, Mod 5.3.5.3, Table 1, pg 7

Reviewer comment
Study R13-052 was initially designated as a pivotal safety and efficacy design. This study was

later modified to support product safety only as agreed to with FDA (Type A Meeting Minutes, 21 June 2016). All efficacy and safety data for this study are included in the NDA package. The Sponsor discusses R13-052 as safety only study in Module 5 and identifies it as the study reporting the most adverse events with 23 of 879 subjects experiencing 25 adverse events. See the MO review of safety (Section 8 of this review).

5.2. Review Strategy

The overall approach to this review is as follows:

- Summarize Sponsor submission and refer to the efficacy review by DNDP's Microbiology Reviewer and efficacy analyses provided by the DNDP Statistical Reviewer.
- Review safety data from all studies, excluding challenge studies reviewed by Division of Dermatology and Dental Products' (DDDP) MO.
- Summarize Sponsor submission and refer to the safety review of challenge studies performed by the DDDP MO.
- Evaluate adverse events associated with safety study endpoints.
- Assess postmarketing data and medical literature references provided by Sponsor.

The following NDA submissions are included in the DNDP MO safety review:

SDN 37, 09/28/2018 Non-clinical /Response to IR
SDN 36, 09/27/2018 Labeling/Container-Carton Draft
SDN 31, 05/30/2018 Clinical /Response to IR
SDN 30, 03/30/2018 Multiple Categories/Clinical Information Amendment
SDN 26, 02/16/2018 Clinical/Safety Update/Literature References
SDN 25, 01/26/2018 Multiple Categories/ISE
SDN 16, 10/20/2017 Multiple Categories/NDA resubmission
SDN 13, 11/01/2016 Meeting/Comparability Study SDN 7, 04/01/2016 Clinical /Response to IR/Clinical Study Reports/ISS
SDN 1, 02/09/2016 Multiple Categories/NDA original submission

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Clinical Inspection Summary 08/27/2018
Meeting Minutes 06/21/2016
RTF Letter 04/08/2016

6. Review of Relevant Trials Used to Support Efficacy

6.1. Trials Used to Support Efficacy

Five Sponsor submitted clinical efficacy studies include:
R13-053: Pivotal, Phase 3

R 15-029: Pivotal, Phase 3
R13-042: Pilot
R14-015: Pilot
R15-028: Pilot

Pivotal Clinical Efficacy Study R13-053 was a randomized, paired-comparisons study design where each subject received two of the three study treatments (ReadyPrep CHG cloth, placebo solution cloth, or Dyna-Hex 2 2% CHG [positive control]) to assess antimicrobial efficacy. The primary efficacy endpoint was the $\log_{10}$ reduction of skin flora at the abdominal and groin sites at 10 minutes following application of the product relative to the baseline $\log_{10}$ counts. Secondary efficacy evaluations were the $\log_{10}$ differences of skin flora at the abdominal and groin sites at 6 hours and 8 hours following application of the test materials relative to the baseline $\log_{10}$ counts. The primary hypothesis was that the ReadyPrep CHG cloth should achieve a 2 $\log_{10}$ per cm^2 reduction of skin flora at the abdominal site and a 3 $\log_{10}$ per cm^2 reduction on the groin site.

Balanced randomization:

- Treatment balance. Each subject received two different treatments, one on right side of body and one on left. Treatment combinations: ReadyPrep CHG and placebo solution; ReadyPrep CHG and Dyna-Hex; placebo solution and Dyna-Hex 2
- Left/right balance. Equal left and right sides treatments
- Site/sample time balance. Each groin and abdomen sample site divided into four areas and each sampled once (one at baseline, one at 10 minutes, one at 6 hours, and one at 8 hours).

Treatment administration:

- ReadyPrep CHG: A single cloth from a 2-cloth pack was used per test site. Product was applied topically by vigorously scrubbing in a back and forth motion for three minutes over a 5” x 5” area on the abdomen or a 2” x 5” area on the groin, and the skin was allowed to air-dry for one minute.
- Placebo solution cloth: A single cloth from a 2-cloth pack was used per test site. Product was applied topically by vigorously scrubbing in a back and forth motion for three minutes over a 5” x 5” area on the abdomen or a 2” x 5” area on the groin, and the skin was allowed to air-dry for one minute.
- Dyna-Hex 2 – 10 mL (5 mL x 2) was used per test site. 5 mL product dispensed from a 4 fluid ounce bottle onto a sterile gauze pad was applied for two minutes over a 5” x 5” area on the abdomen or a 2” x 5” are on the groin, and the area was wiped with a sterile towel or sterile gauze. The procedure was repeated with an additional 5 mL product dispensed onto a fresh sterile gauze pad.

Product application and bacterial sample collections were not blinded. The study personnel performing the bacterial enumerations were blinded. As defined by the study protocols, bacterial count data from subjects that failed to exhibit "Treatment 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) were not analyzed. Additional subjects were used to reach targeted analysis numbers.

Inclusion Criteria:

- healthy males and females at least 16 years or older (subjects under 18 years of age require written custodial consent) with clear skin within 6 inches of test sites
- willingness to follow pre-study instructions
- met screening day baseline CFU counts at abdominal and groin sites

Exclusion Criteria:
Topical or systemic antimicrobial exposure within 14 days prior to the screening day; a variety of chemical exposures associated with pools, skin treatments and household products; and history of sensitivity to adhesives or CHG. Subjects with diabetes, skin allergies, and those pregnant or nursing were also excluded.

Statistical Analysis of Efficacy Results

Results were reported as colony forming units (CFU) per plate. An estimated CFU per square centimeter for the sampled area was then calculated as:

(average CFU per plate) × (dilution factor) × (6 mL) / (3.8 cm^2)

The base-10 logarithms of these values were taken and the differences in the $\log_{10}$ CFU/cm^2 between baseline and 10 minutes, baseline and 6-hours, and baseline and 8-hours were calculated. A subject was considered a responder for the groin if the $\log_{10}$ CFU reduction at 10 minutes for the groin was at least three. A subject was considered a responder for the abdomen if the $\log_{10}$ CFU reduction at 10 minutes for the abdomen was at least two. All calculations were made using SAS 8.2.

Primary endpoint objectives at 10 minutes were:

- Lower bound of a 95% confidence interval for responder rate of the ReadyPrep CHG is ≥ 70%
- Lower bound of a 95% confidence interval for responder rate of active control is ≥ 70%
- Both test product and active control are superior to the vehicle control

In secondary efficacy analysis, at the 6 and 8-hour time points, both the test product and the active control should maintain skin flora counts less than the baseline with the appropriate log reduction.

Subject Disposition

Subjects who met the minimum baseline inclusion criteria on the screening and treatment day of the study on both sides of the body (groin and abdomen) were considered evaluable for efficacy for that region. All treated subjects were considered evaluable for safety. Four hundred eighty-nine (489) subjects consented to the study, and screening samples collected from 458 subjects. Only subjects with qualifying screening counts of at least 1.3×10^3 CFU/cm^2 per abdominal site and 1.0×10^5 CFU/cm^2 per groin site were treated in the study.

Per study protocol, subjects (N = 347) were treated prior to baseline bacterial enumeration, and samples from subjects that did not exhibit "Treatment Day baseline" counts of at least 1.3×10^3 CFU/cm^2 per abdominal site and 1.0×10^5 CFU/cm^2 per groin site were not analyzed. Three hundred twenty-five (325) subjects qualified met baseline criteria for further analysis.

Primary Efficacy Results

The lower bounds of the confidence intervals for the abdomen and groin at 10-minutes post-treatment were 88.16% and 79.32%, respectively. The responder rates were 100% for abdomen and groin at 6 and 8-hours post-treatment. Sponsor reported results for ReadyPrep CHG appear to have met the required primary efficacy targets for both body areas at all studied time points (70% responder rate at 10 minutes and a 100% responder rate at 6 and 8 hours).

Secondary Efficacy Results

Sponsor submitted data appears to demonstrate that ReadyPrep CHG is more effective at 10 minutes for both body sites than the placebo cloth and Dyna-Hex 2. Using $\log_{10}$ CFU reductions, ReadyPrep CHG also appears significantly more effective at 6 and 8-hours for both body areas than the placebo cloth and Dyna-Hex 2.

Pivotal Clinical Efficacy Study R15-029

Similar to Study R13-053, this was a randomized, paired-comparisons study design with each subject receiving two out of the three study treatments (ReadyPrep CHG cloth, placebo solution cloth, or Dyna-Hex 2 – 2% CHG [positive control]). The study evaluated the $\log_{10}$ reduction of skin flora at abdominal and groin sites at 10 minutes following application of the study treatment relative to baseline $\log_{10}$ counts. The secondary efficacy measures were the $\log_{10}$ differences of skin flora at the abdominal and groin sites at 6 and 8-hours post-treatment relative to the baseline $\log_{10}$ counts.

Randomization and treatment administration mirror R13-053.

Inclusion Criteria:

- healthy males and females 18 years or older with clear skin within 6 inches of test sites

- willingness to follow pre-study instructions
- met screening day baseline CFU counts at abdominal and groin sites

Exclusion Criteria:
Topical or systemic antimicrobial exposure within 14 days prior to the screening day; a variety of chemical exposures associated with pools, skin treatments and household products; and history of sensitivity to adhesives or CHG. Subjects with diabetes, skin allergies, and those pregnant or nursing were also excluded.

Statistical Analysis of Efficacy Results

Results were calculated and reported similar to R13-053. The Sponsor states all calculations used the SAS/STAT statistical analysis program.

Subject Disposition

Subjects who met the minimum baseline inclusion criteria on the Screening and Treatment Day of the study on both sides of the body (groin and abdomen) were considered evaluable for efficacy for that region. All treated subjects were considered evaluable for safety. Four hundred, eighty-six (486) subjects consented to the study, and screening samples were collected from 461 subjects. Per study protocol, subjects (N = 344) were treated prior to baseline bacterial enumeration, and samples from subjects that did not exhibit "Treatment Day baseline" counts of at least 1.3×10^3 CFU/cm^2 per abdominal site and 1.0×10^5 CFU/cm^2 per groin site were not analyzed. Three hundred twenty-five (323) subjects met baseline criteria for further analysis of the abdominal and groin or individual sites.

Overall, 320 subjects were treated on both abdomen and groin.

Reviewer comment
The final subject number for R15-029 may change following the assessment by OSI, and evaluation by Microbiology and Statistics Reviewers.

Primary and Secondary Efficacy Results

Initial Sponsor submitted data appear to indicate effectiveness of ReadyPrep CHG. An analysis of updated subject results is deferred to the Microbiology and Statistics Reviewers.

Persistence of Effect

ReadyPrep CHG appears to have achieved 6-hour persistence in two pivotal studies (R13-053 and R15-029) as defined by persistent reduction in normal flora below elevated levels identified at baseline.

Due to the acute use nature of the product as a preoperative preparation, no tolerance effects were expected or evaluated.

Additional Analyses Conducted on the Individual Trial

Additional analyses included an 8-hour efficacy assessment. Refer to the Microbiologist Reviewer and Labeling comments regarding significance of this additional 2-hour study time.

Compliance with Good Clinical Practices

R13-053 researchers state that this study was conducted according to applicable E6 ICH Guideline for Good Clinical Practices (GCPs) and the Standard Operating Procedures of MicroBioTest.

R15-029 researchers state that this study was conducted according to applicable Good Clinical Practices (GCPs), including 45 CFR 160 and 164, 21 CFR 50, 56, 330 and Tentative Final Monograph for Healthcare Antiseptic Drug Products, ICH E6, the Study Protocol and any Protocol Amendments and the Standard Operating Procedures of Evic Romania/ S.C. BIO HIGH TECH S.R.L.

Financial Disclosure

Financial Disclosure Forms submitted for nine clinical studies indicate no apparent conflict of interest. See Appendix 13.2

Protocol Violations/Deviations

R13-053: eight protocol deviations reported with five incorrect product used, applied or recorded and three in which pregnancy tests not performed on day of testing.

R15-029: refer to the OSI report and Statistics Reviewer comments.

Data Quality and Integrity

Refer to the OSI report and comments by the Microbiology and Statistics Reviewers.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The Sponsor is relying on findings of two pivotal Phase 3 studies (Study R13-053 and Study R15-029) and support of three pilot studies (Study R13-042, Study R14-015, and Study R15-028) for efficacy. All studies were conducted as randomized, placebo-controlled (Sponsor placebo solution cloth), active-controlled (Dyna-Hex 2), paired-comparisons studies. The primary objective of these studies was measurement of the antimicrobial effectiveness of ReadyPrep CHG as agreed to by the FDA and meeting a 6-hour efficacy criterion. All Sponsor submitted pivotal and pilot efficacy studies were conducted up to 8-hours following a single application of treatment product. Reported results include subgroup demographic breakouts.

The primary analysis for pivotal efficacy studies depended on the proportion of subjects meeting a "responder" definition. A responder was defined as having a 3-log reduction from baseline on the groin and a 2-log reduction on the abdomen at 10 minutes and for whom the skin flora at 6 hours post-application had not returned to baseline. To demonstrate efficacy, both ReadyPrep CHG and the active control were required to meet all the following three criteria:

1) Lower bound of confidence interval (CI) for the responder rate of test product ≥ 70%;
2) Lower bound of 95% CI for the responder rate of active control ≥ 70%; and
3) Superiority of both test product and active control to vehicle or negative control

Efficacy studies were conducted with an initial ReadyPrep CHG formulation (b) (4) An in vitro time-kill study (R17-004) appears to demonstrate comparable antimicrobial efficacy of the two ReadyPrep CHG formulations. The Sponsor is relying on efficacy studies conducted with the old formulation and the pharmacodynamic bridge of R17-004 to support the TBM ReadyPrep CHG formulation.
For further discussion, refer to the Microbiology and Statistics reviews for efficacy assessments.

7.1.1. Primary Endpoints

Efficacy endpoints rely on responder rate and bacterial count reductions. The primary efficacy endpoint was the $\log_{10}$ reduction of skin flora at the abdominal and groin sites at 10-minutes following application of ReadyPrep CHG relative to the baseline $\log_{10}$ counts.

Refer to the Microbiology Reviewer comments for a full discussion of efficacy endpoints.

7.1.2. Secondary and Other Endpoints

Secondary efficacy evaluations were the $\log_{10}$ differences of skin flora at the abdominal and groin sites at 6-hours and 8-hours following application of the study materials relative to the baseline $\log_{10}$ counts.

Refer to the Microbiology Reviewer comments for a full discussion of efficacy endpoints.

7.1.3. Subpopulations

The Sponsor tabulated study-based demographics that included age (Table 6), gender (Table 7) and ethnicity (Table 8) breakouts.

Refer to the Microbiology and Statistical Reviewer assessments of subpopulation efficacy and to Section 8 for MO safety review.

Table 6: Treated Subjects Age Distribution

Age Category (Years)	Pivotal Studies		Pilot Studies			Combined
	R13-053	R15-029	R13-042	R14-015	R15-028	
<18	12 (1.9%)	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)	**13 (1.7%)**
18-40	218 (62.8%)	80 (23.5%)	19 (55.9%)	13 (39.4%)	1 (7.1%)	**331 (43.1%)**
41-64	99 (28.5%)	234 (68.8%)	12 (35.3%)	17 (51.5%)	11 (78.6%)	**373 (48.6%)**
65-74	16 (4.6%)	26 (7.6%)	2 (5.9%)	3 (9.1%)	2 (14.3%)	**49 (6.4%)**
>74	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**2 (0.3%)**
Total	**347**	**340**	**34**	**33**	**14**	**768**

Source: Summary of Clinical Efficacy, Mod 2.7.3, Table 27

Table 7: Treated Subjects Gender Distribution

Sex	Pivotal Studies		Pilot Studies			Combined
	R13-053	R15-029	R13-042	R14-015	R15-028	
Male	208 (59.9%)	158 (46.5%)	16 (47.1%)	21 (63.6%)	3 (21.4%)	**406 (52.9%)**
Female	139 (40.1%)	182 (53.5%)	18 (52.9%)	12 (36.4%)	11 (78.6%)	**362 (47.1%)**
Total	**347**	**340**	**34**	**33**	**14**	**768**

Source: Summary of Clinical Efficacy, Mod 2.7.3, Table 28

Table 8: Treated Subjects Ethnicity Distribution

Race	Pivotal Studies		Pilot Studies			Combined
	R13-053	R15-029	R13-042	R14-015	R15-028	
Caucasian	139 (40.0%)	340 (100%)	10 (29.4%)	30 (90.9%)	14 (100%)	**533 (69.4%)**
African-American	65 (18.7%)	0 (0%)	2 (5.9%)	0 (0%)	0 (0%)	**67 (8.7%)**
Hispanic/Latino	45 (13.0%)	0 (0%)	4 (11.8%)	1 (3%)	0 (0%)	**50 (6.5%)**
Native American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**
Asian	88 (25.4%)	0 (0%)	18 (52.9%)	1 (3%)	0 (0%)	**107 (13.9%)**
Other	10 (2.9%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	**11 (1.4%)**
Total	**347**	**340**	**34**	**33**	**14**	**768**

Source: Summary of Clinical Efficacy, Mod 2.7.3, Table 26, pg 22

Reviewer comment
Pilot Study R13-042 indicates 34 subjects treated in efficacy subgroup table however, a similar table for the safety evaluation (Summary of Clinical Safety, Mod 2.7.4, Table 4,) includes only 27 treated subjects of 34 enrolled as shown in Table 10 and 11 of the MO safety review. The clinical study report from MicroBioTest (17 April 2014), Section 5.2 "treated" number appears to be the number of enrolled subjects. Seven subjects failed a screening baseline. So, 34 subjects were enrolled, 27 treated, and 24 passed treatment baselines. This variance does not appear to impact efficacy or safety analyses.

Dose and Dose-Response

Application and dosing instructions of ReadyPrep CHG were determined by pilot clinical studies (R13-042, R15-028, and R14-015) and from in vitro studies of antimicrobial activity (R14-012

and R14-013). Evaluation of application times occurred at 1, 2, and 3 minutes. Pivotal clinical studies show reduction of skin microbes following a 3-minute application time (for one cloth) over a 2 x 5 inch wet area (groin, Figure 1) or a 5 x 5 inch dry area (abdominal, Figure 2). A Sponsor conducted skin coverage and drying time study (R16-034) demonstrated that the mean dose of CHG applied from a single cloth was 3.66 g and the mean dose per area was 0.0081 g/cm^2.

Figure 1: Groin sites

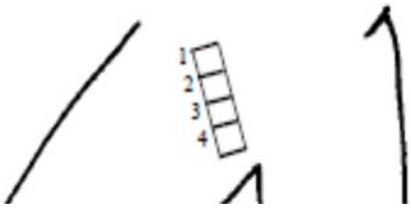
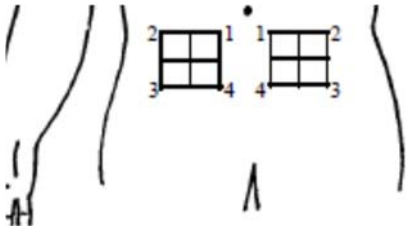


Figure 2: Abdominal sites



7.2. Integrated Assessment of Effectiveness

The presented data appear to demonstrate efficacy of ReadyPrep CHG cloth in all clinical pivotal and pilot studies as well as in vitro assessments. The Sponsor conducted subgroup analyses of efficacy data to address a deficiency identified in the Refusal to File letter (8 April 2016). Results suggest no difference in efficacy across age, gender, and ethnicity but are limited by study demographics. Study R15-029 with Caucasian adult only enrollment and Study R13-053 with ReadyPrep CHG treatments in only 9 of 19 pediatric subjects aged 16-17 years preclude extensive analysis. Overall, there was no significant difference in efficacy results between the pivotal study conducted in the U.S. and the pivotal study conducted in Romania.

Refer to the Microbiology and Statistics Reviewer comments for expanded efficacy evaluations.

8. Review of Safety

8.1. Safety Review Approach

The review evaluates safety study data, postmarketing data, and published literature submitted by the Sponsor. Safety issues associated with chlorhexidine containing drugs are generally related to skin irritation, circumstances of use, hypersensitivity reactions, and fire risk (dependent on alcohol content). The review assesses occurrence of known, common adverse reactions associated with chlorhexidine containing products, evidence of anaphylaxis, and subpopulation unique safety issues. For a review of challenge study safety data, refer to the evaluation provided by the Division of Dermatology and Dental Products (DDDP).

The following eight safety study submissions are included in the review:

- R13-053: Pivotal, Phase 3
- R15-029: Pivotal, Phase 3
- R13-052: Safety
- R13-042: Pilot
- R14-015: Pilot
- R15-028: Pilot
- R16-034: Skin coverage
- R17-023: PK

8.1.1. Overall Exposure

Application of preoperative skin preparations is considered acute rather than chronic use. The Sponsor provided safety analyses for two application regimens defined as "therapeutic application" or single application and "multiple applications" or challenge application.
The Sponsor conducted eight therapeutic application and one multiple application, with irritation and sensitization phases, studies. Overall, nine clinical studies treated 1931 subjects with ReadyPrep CHG. One thousand six hundred eighty-two (1682) therapeutic application subjects were evaluated for safety up to 8 hours after use. Two hundred forty-nine subjects (249) were exposed to multiple applications of ReadyPrep CHG over the course of a 21-day treatment period as part of the challenge study's irritation and sensitization phases.

(b) (4)

Study R17-004 bridged initial and TBM ReadyPrep CHG formulations. Study R17-023 (pharmacokinetics) and Study R16-034 (skin coverage) used the TBM ReadyPrep CHG. Table 9 summarizes subject exposure to ReadyPrep CHG.

Table 9: Summary of Subject Exposure to ReadyPrep CHG

Application Regimen Duration	Number of Subjects Receiving a Mean Daily Dose (2% CHG)				
	Pilot/Pivotal Studies	Non-Pivotal Safety Study	Sensitization/ Irritation Studies	Total (any dose)	Percent of Total
Therapeutic Application (Non-efficacy)	NA	42	NA	42	2%
Therapeutic Application 8 Hours	761	879	NA	1640	85%
Multiple Application 21 Days	NA	NA	210/39	249	13%
	Total			1931	100%

Source: Summary of Clinical Safety, Mod 2.7.4, Table 2, pg 10

[9] DARRTS, Meeting Minutes, 7 December 2016

8.1.2. Relevant characteristics of the safety population:

Demographics of study subjects

Table 10 depicts a study-based, age distribution of treated subjects. Most subjects were aged between 18-40 years (56%) and 41-64 years (37%). Pediatric subjects (16-17 years old) represented less than two percent (>2%) and geriatrics (>65 years of age) represented slightly more than five percent (5.3%) of subjects. More than 80% of the subjects receiving a single application or multiple applications of ReadyPrep CHG were in a combined age range of 18-64 years.

Table 10: Study-based Subject 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.

Source: Summary of Clinical Safety, Mod 2.7.4, Table 5, pg 10

Table 11: Study-based Subject 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.

Summary of Clinical Safety, Mod 2.7.4, Table 4, pg 10

Table 12 summarizes demographic characteristics of the therapeutic (single) ReadyPrep CHG application, non-challenge safety study subjects.

Table 12: Summary of Demographic Characteristics for Therapeutic Application Studies (excludes R13-051)

Demographic Parameters	# Subjects (N)	# Subjects/1682 as % of total (n)
Sex		
Male	1139	61.7
Female	792	38.3
Age Group		
16-17 years	26	1.5
18-40 years	937	55.7
41-64 years	630	37.5
65 - 74 years	76	4.5
≥ 74 years	13	0.8
Ethnicity		
Caucasian	1330	79.2
African American	95	5.6
Hispanic	62	3.7
Asian	128	7.6
Native American	30	1.8
Other[1]	37	2.2
Region		
United States	1328	79
Romania	354	21

N=cumulative number of subjects in safety studies excluding challenge studies; n= cumulative percentage of subjects in safety studies not including challenge studies.
Source: Constructed by consolidation of Sponsor data

Categorization of Adverse Events

The Sponsor used Medical Dictionary for Regulatory Activities (MedDRA®) version 16.1 to record AEs. This version existed in 2013 at the initiation of Sponsor studies.

8.1.3. Adequacy of the safety database:

Sponsor study characteristics and findings framed the safety assessment:

- Size and adequacy
  - Eight studies; total 1682 subjects

    - Additional 249 subjects enrolled in challenge (irritation and sensitization) studies assessed by DDDP Reviewer
- Exposure to the appropriate dose
    - Single cloth each site (abdomen, groin)
    - Single, therapeutic dosing consistent with intent for acute treatment regimen
    - Multiple dosing for irritation and sensitization assessed by DDDP Reviewer
- Duration of treatment
    - Acute, intent as preoperative skin preparation
    - Label directions: 3-minute rub, 1-minute drying time
- Patient demographics
    - Table 12 summary
    - Characteristics with reference to the U.S. target population
    - Romanian study population explained to be consistent in terms of geographic variances and skin flora to U.S. study site participants

Reviewer comment
Sponsor submitted content is adequate. Although limited in terms of pediatric and ethnic enrollment, study subject demographics are generally in-line with anticipated patient populations exposed to preoperative skin preparation products. A 2017, National Health Statistic Report reviewing characteristics of 48.3 million surgical and nonsurgical procedures were performed during 28.6 million ambulatory surgery visits to hospitals and ambulatory surgery centers combined in the U.S. during 2010. For both males and females, 39% of procedures were performed on those aged 45–64. [10] *This percentage is similar to Sponsor study subjects.*

Limited enrollment of an ethnically diverse study population was notable in the 100% Caucasian study (R15-029). The Sponsor explained that this Romanian study population was consistent in terms of geographic variances and skin flora to U.S. study site participants. Study results mirrored those of the pivotal U.S. study.

Safety study recruitment was bounded by the youngest age of 16 years and had no older age limit. Five studies recruited only 18 and older. Despite limited pediatric subjects in Sponsor conducted studies, the potential for adverse events in the pediatric subpopulation is addressed by current CHG product label warnings that highlight potential risk for the neonatal group.

This reviewer recommends consideration of annual reporting with subgroup analyses to augment identification of relevant subgroup specific adverse events.

[10] HHS CDC National Center of Health Statistics Report 28 Feb 2017
https://www.cdc.gov/nchs/data/nhsr/nhsr102.pdf

8.2. Adequacy of Applicant's Clinical Safety Assessments

8.2.1. Issues Regarding Data Integrity and Submission Quality

See OSI comments in audit findings filed 27 Aug 2018 for study R15-029.

8.2.2. Categorization of Adverse Events

In the pivotal safety studies, an adverse event was defined as "any undesirable clinical occurrence in a subject whether or not it was considered to be drug related." Adverse events were graded as mild, moderate, or severe according to the following definitions:

- Mild: Causing no limitation of usual activities; the subject may experience slight discomfort.
- Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort.
- Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.[11]

Serious adverse events were defined as events that were fatal or life-threatening, permanently or significantly disabling/incapacitating, requiring inpatient hospitalization or prolongation of existing hospitalization, or resulting in a congenital anomaly/birth defect.

The investigator was responsible for identifying adverse events occurring on the treatment day. Adverse events could also be reported later by the subject. Skin irritation rated as 3 was considered a reportable adverse event and required removal from study. Table 13 outlines the scoring scale for skin conditions following the therapeutic application regimen in studies R13-053, R15-029, R13-052, R13-042, R14-015, and R15-028. Table 14 shows an expanded scale used in R16-034, the skin coverage study.

Table 13: 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.

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 6, pg 14-15

[11] Clinical Study Reports, Mod 5.3.1.1, Protocol section 7.2

Table 14: Scoring Scale for Skin Conditions in the Skin Coverage Study

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	

Source: Clinical Study Reports (R16-34), Mod 5.3.5.4, Appendix 16.1.2

8.2.3. Routine Clinical Tests

Using the rationale that CHG is not systemically available when applied to intact skin (the proposed indication) and supported by no detectable CHG levels of ReadyPrep CHG in PK Study R17-023, no routine clinical testing for effects of CHG exposure was performed.

The Sponsor's approach to other clinical testing included:

- urine pregnancy testing in the safety challenge studies at screening and at the final visit
- vital sign measurement only in the safety challenge studies
- clinical laboratory evaluations in the PK study (R17-023)
- physical exams not performed other than skin inspection

Reviewer comment
Sponsor rationale for limited routine testing in studies of ReadyPrep CHG is consistent with science supporting marketed CHG products and study protocols.

8.2.4. Deaths

None reported.

8.2.5. Serious Adverse Events

None reported.

8.2.6. Dropouts and/or Discontinuations Due to Adverse Effects

The Sponsor states no discontinuations occurred in studies with single, therapeutic application of ReadyPrep CHG. Dropouts and a protocol modification occurred during the challenge studies. Refer to the review by DDDP for expanded comments.

8.2.7. Significant Adverse Events

None reported for ReadyPrep CHG.

8.2.8. Treatment Emergent Adverse Events and Adverse Reactions

A FDA Drug Safety Communication (DSC) published in February 2017 warned that an increasing number of rare but serious allergic reactions had been reported with skin antiseptic products containing chlorhexidine gluconate. Fifty-two cases of anaphylaxis were identified in the FAERS database, medical literature, and National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance database. Two of these allergic reactions resulted in death. No severe allergic, anaphylactic reactions occurred in Sponsor-conducted studies. A warning for this risk is included in the Drug Facts label for ReadyPrep CHG.

8.2.9. Immunogenicity

Refer to the DDDP review of challenge studies for discussion of immunogenicity.

8.3. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues identified.

8.4. Safety Analyses by Demographic Subgroups

Pediatric Use
Four clinical studies obtained safety information in a pediatric population of 16-17 year old subjects. These included one pilot (R13-042), one non-pivotal (R13-052) and one pivotal (R13-053) study, and both the irritation and sensitization challenge (R13-051) studies were open to enrollment for the pediatric population.

In the therapeutic application group (single application), no pediatric subjects experienced an adverse event following a single application of ReadyPrep CHG cloth. Two mild adverse events occurred in the pediatric population following multiple applications in the sensitization study. No severe or serious adverse events were observed in 35 pediatric subjects (16-17 years of age) treated with ReadyPrep CHG.

Geriatric Use
No serious or severe adverse events were observed in 103 geriatric subjects treated with ReadyPrep CHG. One geriatric subject (Subject (b) (6) Study R13-052) experienced dizziness following a single application of both ReadyPrep CHG cloth and Dyna-Hex 2. This adverse event was considered mild in severity, assessed as unrelated to the treatments, and resolved with recumbence.

Demographic Subgroup Summary

There is no apparent statistical evidence of adverse events occurring at different frequencies by age, gender, or ethnicity for the therapeutic applications. Table 15, Table 16, and Table 17 highlight subgroup related adverse events in Study R13-052.

Table 15: Incidence of Adverse Events by Age

Age Category	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 Application[c]						
<18	13 (01%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)
18-40	577 (66%)	17 (03%)	12 (02%)	5 (01%)	4 (01%)	2 (00%)
41-64	252 (29%)	5 (02%)	4 (02%)	2 (01%)	0 (00%)	1 (00%)
65-74	27 (03%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)
>74	10 (01%)	1 (10%)	1 (10%)	1 (10%)	0 (00%)	0 (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.
[d] One subject had an AE related to two different test substances; for the purposes of this table, the AE was attributed to both test substances.
[e] Two subjects each had one AE related to two different test substances; for the purposes of this table, the AEs were attributed to both test substances.

Source: Clinical Study Reports, Mod 5.3.5.1, R13-052 Addendum, Table 3, pg 3

Table 16: Incidence of Adverse Events by Gender

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.

Source: Clinical Study Reports, Mod 5.3.5.1, R13-052 Addendum, Table 1, pg 1

Table 17: Incidence of Adverse Events by Ethnicity

Race	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 Application[c]						
African American	20 (02%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)
Asian	11 (01%)	1 (09%)	1 (09%)	1 (09%)	0 (00%)	0 (00%)
Caucasian	785 (89%)	20 (03%)	14 (02%)	7 (01%)	4 (01%)	3 (00%)
Hispanic	12 (01%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)	0 (00%)
Native American	29 (03%)	1 (03%)	1 (03%)	0 (00%)	0 (00%)	0 (00%)
Other	22 (02%)	1 (05%)	1 (05%)	0 (00%)	0 (00%)	0 (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.

Source: Clinical Study Reports, Mod 5.3.5.1, R13-052 Addendum, Table 2, pg 2

8.5. Specific Safety Studies/Clinical Trials

Principal measures of safety included skin irritation scores and incidence of adverse events for two application regimens titled “therapeutic” and “multiple.”

1. Therapeutic Application (single application) targeted the safety evaluation to intended use of the ReadyPrep CHG as a preoperative surgical preparation product.
   - The instructions for use on the labeling of the ReadyPrep CHG cloth indicate vigorous scrubbing of the target area (approximately 5 x 5 inches) for 3 minutes.
   - Three 3 pilot, 1 safety, and 2 pivotal studies evaluated this single application technique of ReadyPrep CHG cloth for sustained antimicrobial activity on the skin for up to 8 hours.
   - A 2% CHG active comparator (Dyna-Hex 2) and a Vehicle cloth (b) (4) were also evaluated in a single application regimen for up to 8 hours. As Dyna-Hex 2 is a solution, a 2 x 2 inch sterile gauze pad was used in its application.
   - Treatments were applied to the groin and abdominal test areas according to a randomized schedule. Up to two different treatments (ReadyPrep CHG, Vehicle cloth, or Dyna-Hex 2) were applied on the same subject during testing.
   - The same therapeutic application regimen (3-minute vigorous scrubbing) was used in the skin coverage study (R16-034) and the PK study (R17-023).
   - In the PK study control arm, the skin area was cleaned as in the treatment arms, but no application was performed.
   - In the skin coverage study, there was no control treatment arm and the test product was applied to a 7 x 10 inch area. The antimicrobial efficacy of ReadyPrep CHG was not evaluated in these studies.
2. Multiple Applications (challenge studies) used repeated patch applications of ReadyPrep CHG solution to characterize the potential irritation and sensitization of the test product over a 21-day period.
   - Both studies were conducted under the same protocol (R13-051).
   - The irritation study enrolled 39 subjects and the sensitization study enrolled 210 subjects.
   - In the Irritation study, all subjects received ReadyPrep CHG, Dyna-Hex 2, 0.1% Sodium Lauryl Sulfate (SLS, positive control), Vehicle (b) (4) and Saline (negative control) on occlusive skin patches daily on their back.
   - In general, the method required application of occlusive patches 20 times over a period of 3 weeks (21 days), during which the skin was evaluated for reactions daily.

Safety Results

Eight clinical studies evaluated the safety of a single, therapeutic application, and a challenge study, consisting of irritation and sensitization phases, evaluated multiple applications of ReadyPrep CHG. In six of eight studies involving a single therapeutic application, no adverse events were reported; no adverse events reported in subjects of pilot studies (R13-042, R14-015, R15-028), the skin coverage study (R16-034), and the two pivotal safety and efficacy studies (R13-053 and R15-029).

Both pivotal studies, R13-053 and R15-029, with a combined 687 subjects, had no AEs. In PK Study R17-023, three subjects reported five adverse events; one of the subjects reported two application site reactions of pain and pruritus following the groin site application of CHG. The Sponsor states single application associated adverse events occurred in Safety Study R13-052, in which 23 of 879 subjects reported 25 adverse events. Overall, the Sponsor reports that non-challenge studies resulted in 17 subjects reporting adverse events after treatment with ReadyPrep CHG, nine subjects reporting adverse events with Dyna-Hex 2, and four reporting adverse events with the vehicle cloth.[12] The most common adverse events reported for all treatments related to skin and subcutaneous tissue disorders such as pruritus, irritation, and rash and general disorders and pain at the administration site. Table 18 lists study-based, test-product associated incidence of adverse events.

Reviewer comment
Tables 15-17, 18 and 19 list varying numbers of subjects reporting Dyna-Hex2 reactions. The reported number ranges 7-9 subjects. Sponsor provided details do not clarify a distinction for this reporting. Given 879 subjects in Study R13-052 and the calculated incidence of AEs that includes all subjects from all single, therapeutic application studies (N=1640), this variance does not appear to alter the safety results for ReadyPrep CHG.

[12] Summary of Clinical Safety, Mod 2.7.4.2.1.2, pg 17

Table 18: Incidence of Adverse Events

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%)

Source: Overview of Safety, Mod 2.5.5, Table 5, pg 10

The non-pivotal safety study, R13-052, involving a single therapeuti application, reported adverse events in 3% of subjects. Adverse events included dermal skin reactions such as redness, rash, and pain with none serious, significant, or unexpected. According to the Sponsor, all adverse events resolved satisfactorily, and the skin irritation observed consisted of expected reactions observed 10 minutes following scrubbing the sites and subsided in severity at subsequent sample times. Table 19 summarizes adverse events associated with Study R13-052 and Table 20 summarizes subject case reports primarily for Study R13-052.

Table 19: Summary of Adverse Events for 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.

Source: Summary of Clinical Safety, Mod 2.7.4.2.1.2, Table 8, pg 18

Table 20: Summary of Subject Case Reports for Non-Challenge Studies

Subject #	Treatments Applied	Time on Product(s) (Days)[a]	Reported Event	Serious	Severity	Un-Expected	With-drawn	Sex	Ethnicity	Age	Related to Treatment [b]
Therapeutic Application (Non-efficacy)											
(b) (6)	Control treatment	30 minutes	Sore throat	No	Mild	Yes	No	M	C	21	None
	Control treatment	30 minutes	Congestion	No	Mild	Yes	No	M	C	21	None
	ReadyPrep cloth	10 minutes	Itching at application site	No	Mild	Yes	No	F	C	21	Possible
	ReadyPrep cloth	10 minutes	Burning at application site	No	Mild	Yes	No	F	C	21	Possible
	ReadyPrep cloth	11 hours	Headache	No	Mild	Yes	No	F	N	28	None
	ic Application										
	ReadyPrep cloth	6 hours	Stinging	No	Mild	No	No	M	N	54	Possible
	ReadyPrep cloth; Dyna-Hex 2	6 hours	Dizzy	No	Mild	No	No	M	C	81	None
	ReadyPrep cloth; ReadyPrep vehicle	10 minutes	Dizzy/nausea/disorientation	No	Mild	No	No	F	C	25	Unknown
	ReadyPrep cloth; ReadyPrep vehicle	Immediate	Itchy	No	Mild	No	No	M	C	30	Possible
	ReadyPrep vehicle; Dyna-Hex 2	8 hours	Rash/irritation at test site(s)	No	Mild	No	No	M	C	27	Probable
	ReadyPrep cloth	6 hours	Itchy	No	Mild	No	No	F	O	24	Possible
	ReadyPrep cloth; Dyna-Hex 2	6 hours	tape pull/tenderness	No	Mild	No	No	M	C	61	Possible
	ReadyPrep cloth	6 hours	Burning	No	Mild	No	No	F	C	62	Possible
	ReadyPrep cloth; Dyna-Hex 2	6 hours	Stinging	No	Mild	Yes[c]	No	F	C	48	Possible
	ReadyPrep cloth	6 hours	Soreness	No	Mild	No	No	M	C	34	None
	Skin markers before product application	N/A	Rash/irritation at test site(s)	No	Mild	No	Yes[a]	M	C	19	None
	ReadyPrep cloth; Dyna-Hex 2	6 hours	Itchy	No	Mild	No	No	F	A	19	Possible
	ReadyPrep cloth; Dyna-Hex 2	7 minutes	Itchy	No	Mild	No	No	M	C	18	Possible
	ReadyPrep cloth	6 hours	Itchy	No	Mild	No	No	M	C	23	Possible
	ReadyPrep cloth	10 minutes	Itchy	No	Mild	No	No	F	C	25	Possible
	ReadyPrep cloth; Dyna-Hex 2	6 hours	Car Accident	No	Mild	Yes[c]	No	M	C	19	None
	ReadyPrep cloth	<6 hours	Itchy	No	Mild	No	No	F	C	19	Possible
	ReadyPrep vehicle	<8 hours	Abrasion	No	Mild	No	No	M	C	18	None
	Dyna-Hex 2	8 hours	Itchy	No	Mild	No	No	F	C	36	Possible
	ReadyPrep cloth	6 hours	Itchy	No	Mild	No	No	M	C	20	Definite
	Product not yet applied	N/A	Hairline fracture of ankle	No	Moderate	No	No	F	C	20	None
	Product not yet applied	N/A	Hairline fracture of ankle	No	Moderate	No	No	M	C	59	None
	ReadyPrep cloth	6 hours	Itchy	No	Mild	No[d]	No	F	C	31	Possible

Source: SDN 1, Initial NDA submission, legacy Clinical Study Report, R13-052, Pivotal Part2

Table 20 lists subjects (b) (6) from study R13-052. Subject (b) (6) reported involvement in a minor car accident. He had no health complaints before or after product application and the car accident. Dizziness in subjects (b) (6) and (b) (6) resolved spontaneously with recumbence and did not recur.

Reviewer comment
Case narratives for Study R 13-052 are consistent with Sponsor attribution of treatment related AEs. The Sponsor states since no SAEs were reported and no subject discontinued from studies R13-053, R15-029, R13-042, R14-015, R15-028, R16-34, and R17-023, no narratives were submitted for review.[13]

[13] Integrated Summary of Safety, Mod 5.3.5.3, pg 42-43

Multiple applications, challenge studies, markedly increased the adverse events reported to 17%-26% for CHG products. Use of Dyna-Hex2 in these studies resulted in dropouts due to skin irritation scores of 6-7 (refer to DDDP review for discussion of scoring and study results). The Sponsor notes that the IRB mandated removal of Dyna-Hex2 testing on remaining subjects. Neither ReadyPrep CHG nor the positive control were reported to induce similar high levels of dermal response. Refer to the review by DDDP for expanded commentary on challenge test results.

Overall, Sponsor data indicate a <1% incidence of adverse reactions at the treatment site in 1931 treated subjects inclusive of challenge study subjects. No deaths or serious adverse events occurred in any of the clinical studies. No intrinsic or extrinsic factors appeared to affect the safety of ReadyPrep CHG.

Reviewer comment
Adverse events noted in Sponsor studies are consistent with the known safety profile for CHG products and were among the 10 most commonly identified in FAERS. The safety profile for ReadyPrep CHG in Sponsor conducted studies is within the expected safety profile of topical drug products containing 2% CHG.

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

Not performed.

8.6.2. Human Reproduction and Pregnancy

Pregnancy was an exclusion criterion. Negligible absorption occurs through intact skin.

8.6.3. Pediatrics and Assessment of Effects on Growth

Not addressed.

8.6.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Chlorhexidine is not generally associated with abuse. Overdose is unlikely given negligible absorption through intact skin and single use indication of the proposed product. Overexposure that may occur in neonates and adverse events associated with application to specific anatomic locations is addressed in labeling.

8.7. Safety in the Postmarket Setting

ReadyPrep CHG is not marketed in the U.S. or internationally.

Sponsor submitted postmarket support of CHG safety includes database and published literature searches:

- 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

8.7.1. Adverse Events Identified in Postmarket Experiences

FAERS

From the FAERS database, adverse events associated with topical CHG administration and 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. Five of the deaths were reported in patients exposed to topical or cutaneous administration of CHG as listed below.

-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 female (age unspecified). She was administered topical chlorhexidine. Death was reported due to chemical injury.

-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. [14]

Table 21 lists the ten most commonly reported adverse events for topical CHG administration.

[14] Integrated Summary of Safety, Mod 5.3.5.3, pgs 49-50

Table 21: Ten Most Commonly Reported Adverse Events for Topical Chlorhexidine

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)

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 23, pg 48

Reviewer comment
These FAERS findings do not alter the known safety profile for CHG. The FDA DSC published in February 2017 warned that an increasing number of rare but serious allergic reactions had been reported with skin antiseptic products containing chlorhexidine gluconate. A warning for this risk is included in the Drug Facts label for ReadyPrep CHG. No severe allergic or anaphylactic reactions occurred in Sponsor-conducted studies.

Table 22 illustrates no increasing or decreasing trends in adverse events reported between 2009 and 2016. Adverse events were reported most often in Europe and North America, with 135 events each. Fifty-nine (59) adverse events did not have age information specified. For those patients with age information available, ages ranged from under 1 year to 92 years of age. FAERS reports show a slight female predominance in occurrence of adverse events (49.7 vs 39.9%).

Table 22: Year of Adverse Event Reporting for Chlorhexidine

Year reported	Number of patients
2009 (Q1-Q4)	37
2010 (Q1-Q4)	27
2011 (Q1-Q4)	45
2012 (Q1-Q4)	44
2013 (Q1-Q4)	42
2014 (Q1-Q4)	35
2015 (Q1-Q4)	39
2016 (Q1)	37
Total	**308**

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 25, pg 50

WHO VigiAcess
The Sponsor searched the WHO VigiAcess database for Hibiclens and ChloraPrep reported adverse events and summary statistical information. A total of 9837 events representing 4743 records were reported for Hibiclens and 1710 events representing 603 records were reported for ChloraPrep. For Hibiclens, adverse events reported in ≥2% of events of 9837 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%). Table 23 lists the ten most commonly reported adverse events for Hibiclens.

Table 23: Ten Most Commonly Reported Adverse Events for Hibiclens

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)

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 30, pg 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%). Table 24 lists the ten most commonly reported adverse events for ChloraPrep.

Table 24: Ten Most Commonly Reported Adverse Events for ChloraPrep

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)

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 31, pg 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.[15]

[15] Integrated Summary of Safety, Mod 5.3.5.3, pg 53

Table 25: Gender Distribution of Adverse Events for Chlorhexidine Products

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)**

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 34, pg 54

Overall, adverse events reported by WHO were similar to FAERS, with the most common events related to allergy or hypersensitivity and a gender distribution showing a higher percentage of AE reports related to females.

DAWN

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.

DATABASE SEARCH SUMMARY

Postmarket database searches of CHG products provided valuable information though had limitations. Incomplete data was best interpreted along-side safety information derived from multiple database sources. 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.

Reviewer comment

The adverse events reported in the searched databases are consistent with the known safety profile of CHG and no new trends or patterns were identified, however, further assessment of gender related adverse event occurrence may be warranted.

LITERATURE

The Sponsor conducted a PubMed search for published literature supporting the safety of CHG. 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.

The 120-safety update identified an additional 13 publications of CHG clinical studies. In the prospective studies, CHG was used for surgical skin preparation, full-body bathing, and surgical site irrigation. No notable adverse events were reported in studies of 5525 adults. Seven studies with 5095 adult subjects enrolled had mean age 59.0 years with a range of 17 -87. There were 3268 males (64.1%) and 1827 females (35.9%). Four studies reported no AEs and five did not discuss AEs. No published reports specific to elderly populations were identified.

Two of the 13 publications identified in the 120-day safety update noted adverse events in neonates.[16] [17]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.[18] Reference, Section 12.1 lists Sponsor submitted literature summaries.

Reviewer comment
The Sponsor complied with FDA Advice letter responses of September 2016 by providing summaries and discussions of database and medical literature searches. Recommended analyses by seriousness, gender, and age groups: less than 6 months, 6 months to less than 18 years, 18 years to less than 65, and 65 years and older were reported by the Sponsor to be limited by database content. Subgroup analysis is provided within noted limitations.

Information from the Sponsor provided safety literature search does not alter the known safety profile of CHG.

8.7.2. Expectations on Safety in the Postmarket Setting

The safety of CHG-based preoperative skin preparation products is generally well known. No new safety concerns are expected with the Sponsor product.

8.7.3. Additional Safety Issues From Other Disciplines

Refer to the analysis by the DDDP Reviewer for additional safety comments.

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[16] Kieran, E.A. (2018). 2% Chlorhexidine-70% Isopropyl Alcohol versus 10% Povidone-iodine for Insertion Site Cleaning Before Central Line Insertion in Preterm Infants: A Randomised Trial. Arch Dis Child Fetal Neonatal Ed. https://fn.bmj.com/content/103/2/F101.long
[17] Neri, I. (2017). Chlorhexidine-Induced Chemical Burns in Very Low Birth Weight Infants. J Pediatr *191*, 262-265.e2. https://www.sciencedirect.com/science/article/pii/S0022347617310569?via%3Dihub
[18] DARRTS SDN 26,120-day Safety Update, Mod 1.11.3, 16 Feb 2018

8.8. Integrated Assessment of Safety

Seven of nine Sponsor conducted clinical safety studies used an initial ReadyPrep CHG formulation (b) (4) These studies reported few AEs. Two pivotal safety studies reported no AEs in 687 subjects. Overall, safety studies reported < 1% AEs in 1931 subjects; none were serious or severe. No anaphylactic reactions occurred.

No oldest age limit and a youngest age of 16 years bounded safety study recruitment. Five of eight studies recruited adults only. Two mild AEs occurred in the pediatric population following multiple applications in the sensitization study. No severe or serious AEs were observed in 35 pediatric subjects treated with ReadyPrep CHG. No serious or severe AEs were observed in 103 geriatric subjects treated with ReadyPrep CHG. One geriatric subject experienced dizziness in a non-pivotal study.

Sponsor conducted studies show female subject enrollment at half that of males and with an incidence of female reported adverse events at 4% (8 subjects or 3% ReadyPrep CHG related); twice that of males. Gender distribution in the WHO database search demonstrated a similar, higher percentage of AE reports related to females.
Clinical study subjects were predominately Caucasian (89%) with one all Caucasian pivotal study. The Sponsor explained that this Romanian study population was consistent in terms of geographic variances and skin flora to U.S. study site participants and study results mirrored the pivotal U.S. study. Analysis of ethnicity related AEs was limited in this demographic.

Postmarket database searches identified AEs consistent with known chlorhexidine reactions. 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. In the 120-day update, the Sponsor's updated FAERS database search of 2017 Q1 through 2017 Q3, noted serious AE reports with CHG products as the primary suspect drug in 120 primary case IDs that included three anaphylactic reactions and two resultant deaths attributed to topical CHG administration. This is in addition to the five deaths identified in the FAERS database search conducted for the seven-year period, 2009 Q1 through 2016 Q4. A total of seven deaths are attributed to topical CHG use across eight years of FAERS data.

Publication reported side effects of CHG in 15 clinical trials enrolling 3699 subjects included tingling, irritation, macular erythema, maculopapular erythema, dermatitis, skin rash, and mild redness. Seven of the publications stated no adverse events were observed. The 120-day safety report included an additional 13 publications. No notable AEs were reported in 5525 adults. However, AEs were observed in neonates in two published reports with three of 148 CHG-treated neonates exhibiting skin reactions, and in one report of case studies, five premature infants sustained chemical burns with one resultant death. [16] [17]

Reviewer comment
AEs identified in published studies of premature infants are addressed with labeling stating "Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." The Clinical Pharmacology Reviewer noted CHG absorption in a published study of 12 pediatric subjects undergoing daily bathing; four of 12 had detectable blood levels of CHG.[19]

The article describes drawing samples from a central line or using residual blood from other blood draws. It does not describe which scenario existed for the four positive samples; one positive result in 4 of 12 subjects and no repeated detection in any subject regardless of timeframe. Leading to the possibility that timing of bath to replacement of a central line and blood draw or timing of potential single stick blood draw to bath may have resulted in specimen contamination. The article concludes that there was no evidence of CHG accumulation in the bloodstream of children (as young as 3 months) from daily CHG bathing.[19] *The results of this study add to the body of knowledge for CHG but are not conclusive in terms of defining an acute relationship of CHG bathing and CHG absorption in children. The use of CHG for bathing represents an area for further study to discern absorption and clinical relevance in children.*

Sponsor conducted studies and literature searches did not report anaphylaxis as an AE in any of the studies while two deaths associated with topical CHG anaphylaxis were identified in 2017 FAERS reporting. Sponsor studies and database search results indicate a potentially increased incidence of AEs in females exposed to CHG. These two areas, female predominance and anaphylaxis, may merit additional monitoring.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Nonprescription Drug Labeling

The proposed product label is comparable to similar CHG, preoperative skin preparation products. It addresses using care in neonates, includes an allergy alert, and "do not use" for lumbar puncture or meningeal contact, on open wounds or as a general skin cleanser.

[19] Lee, A. (2011). Blood concentrations of chlorhexidine in hospitalized children undergoing daily chlorhexidine bathing. Infection control and hospital epidemiology 32, 395-397

Draft Labeling[20]

(b) (4)

[20] DARRTS, Label Update 27 Sep 2018

(b) (4)

Reviewer comment

Directions following "to open package" may pose a safety issue. This section states "to keep the second cloth where it will not be contaminated" unless read through to the last bulleted direction in a continuation column, it is possible that the second cloth will be saved for later use and introduce pre-opened product as a potentially contaminated skin prep. Recommend input of Labeling Reviewer on label comprehension.

Risk Evaluation and Mitigation Strategies

Not applicable for an OTC product.

11. Postmarketing Requirements and Commitments

Not applicable for an OTC product.

Reviewer comment
Although PMRs and PMCs are not typically required of OTC products, this reviewer recommends

consideration of CHG hypersensitivity and anaphylaxis focused literature searches in conjunction with annual reports to provide ongoing monitoring of known, perhaps increasing numbers of adverse events.[21] Additionally, educational outreach to healthcare providers may enhance recognition and management of rare but life-threatening reactions to CHG.

[21] Abdallah, C. (2015). Perioperative chlorhexidine allergy: Is it serious?
J Anaesthesiol Clin Pharmacol. Apr-Jun;31(2):152-4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4411825/

12. Appendices

12.1. References/ Sponsor Submitted Literature for Safety

Source[a]	Drug(s), Dose, Route	Study Design	Number of Subjects	Duration of Treatment	Safety Results
(Park et al., 2017) (South Korea)	4% CHG (Hexiclean Brush, Firson) before srugery and painted with aqueous solution of 2% CHG (α-Hexidin, Firson)	Randomized, controlled,	267	Single use	No significant adverse events occurred from antiseptic administration.
(Swan et al., 2016) (US)	Bathing with 2% CHG (Bactoshield, STERIS) in warm tap water	Single-cnter, pragmatic, randomized	161	28 days every other day	The incidence of adverse skin occurrences was 18.6%. Of these occurrences, 13% were perceived as possibly related to bathing and 0% were probably related to bathing. There were 16 Grade 1 reactions, 26 Grade 2 reactions, and 1 Grade 3 reaction. However, a blinded reviewer determined that the Grade 3 (severe) reaction was due to an allergic reaction to a systemic penicillin antibiotic and was not related to full-body bathing.
(Edmiston et al., 2015) (US)	118 mL 4% CHG shower (Clorox Healthcare 4% CHG Skin Cleaning Kit, the Clorox Company)	Randomized	120	2 or 3 showers	Three participants (5.0%) in the 2-shower group and 2 (3.3%) in the 3-shower group reported slight tingling and irritation on the torso following application but did not view this as a significant event requiring notification of the principal investigator or study coordinator.
(Srinivas et al., 2015) (India)	0.5% CHG in 70% isopropyl alcohol	Randomized, controlled	158	Painted around incision site 3 times	No AE observed during the study.
(Tangsathapompong et al., 2014) (Thailand)	2% CHG in 70% alcohol	Controlled, cluster-randomized	315	Not specified	No adverse skin reactions were noted. However, the authors acknowledge that they excluded preterm newborns, who may frequently have irritation from skin antiseptics.
(Hsieh et al., 2014) (Taiwan)	4% CHG washcloth for pre-operative scrubbing (hepatectomy) (Antigerm, Panion & BF Biotech)	Randomized, controlled, double-blind	50	Single use (3 minutes)	No adverse events (such as pruritus, erythema, or chemical burn) were manifested relative to the agents/solutions used for skin antisepsis.
(David et al., 2014) (US)	Bathing with CHG-soaked, pre-packaged disposable washcloths (dose not specified) (Sage Products)	Randomized, controlled	Not specified	3 times a week for 6 months	No severe reactions to CHG among subjects. The adverse effects of CHG were similar to what was previously reported (not detailed).
(Bajaj et al., 2014) (US)	20, 40, 60, 80, or 100% of 2% CHG diluted in saline (BactoSheild, STERIS Corp)	Randomized, controlled	110	One or two 2 minute scrubs	No subjects experienced an adverse reaction to the CHG preparation.
(Yamamoto et al., 2014) (Japan)	1% CHG in 79% ethanol	Randomized, controlled	47	Not specified	No serious or adverse reactions were observed throughout the study.
(Nuntnarumit and Sangsuksawang, 2013) (Thailand)	Bathing with 1% aqueous CHG	Randomized, controlled	Not specified	Not specified	No skin erythema, burn, or contact dermatitis was observed, nor were any systemic adverse effects noticed.
(Milstone et al., 2013) (US)	Bathing with 2% CHG cloth (Sage Products)	Unmasked, cluster-randomized, controlled, two-period crossover	1515	Daily baths for >2 days	There were no SAEs. Skin reactions were reported in 43 patients receiving CHG baths, but only 12 of these 43 reactions were related to CHG bathing. Reactions included faint macular erythema (6), maculopapular erythema (5), and dermatitis (1). The crude incidence of CHG-related skin reactions was 1.12 per 1000 days exposed. Of the 1547 total patients, 39 withdrew from treatment, although it is not known whether these patients were receiving CHG or control baths at the time of AE unless specified. This was due to skin irritation from CHG (12), skin irritation due to underlying condition (1), no reason (8), did not like smell or feel (3), allergic reaction (2), did not tolerate bathing procedure (2), concern about chemical exposure (1), and preferred to use a lotion not compatible with CHG (1).
(Schlett et al.,	2% CHG full body wipes (Sage	Cluster-	781	3 times a	About 6% reported changes (irritation or burning,

2012) (US)	Products)	randomized, controlled		week for 6 weeks	itching, redness, or rash), but did not distinguish between CHG and control groups.
(Montecalvo et al., 2012) (US)	2% CHG cloths (Sage Products); Use 1 package of 6 clothes with 1 cloth each for the following anatomic areas: neck/shoulders and chest, both arms and hands, abdomen/groin/perineum, right leg/foot, left leg/foot, and back and buttocks. More than 1 package was used if needed.	Multicenter, 3-phase	Not specified	Single use	Chlorhexidine bathing was well tolerated. Few adverse events were observed. Chlorhexidine bathing was discontinued in 3 patients because of skin rash and restarted in 2 of the 3 patients without an AE. The third patients also had thrombocytopenia that resolved with the discontinuation of multiple medications and chlorhexidine.
(Olson et al., 2012) (US)	1% CHG in 61% ethyl alcohol (3M Avagard Surgical and Healthcare Personnel Hand Antiseptic with Moisturizer)	Randomized, controlled	25	Applied 12 times over 5 days	No AE were recorded during the study. The product was well-tolerated by the study population.
(Arvaniti et al., 2012) (Greece)	CHG sponge (Biopatch; Antimicrobial Dressing; Johnson & Johnson Wound Management)	Multicenter, randomized, controlled	150	Median duration 7 days	No patients developed severe contact dermatitis, whereas mild local redness was observed in one patient and it resolved after dressing removal.

AE = adverse event; CHG = chlorhexidine gluconate; PICC = peripherally inserted central catheter; SAE = serious adverse event;

Source: Integrated Summary of Safety, Mod 5.3.5.3, Table 40 pg 60-62

Identification of Literature Source	Dose of CHG	Summary of Study Design	Primary Safety Results
(Frisch et al., 2017) US	Skin preparation: 2% CHG (Chloraprep) Irrigation: 0.05% CHG (Irrisept); periodic	Retrospective review of consecutive total knee or hip arthroplasty surgical patients	• No statistical difference in infection rates was observed between patients that did or did not receive surgical site CHG irrigation. • All patients were exposed to CHG through pre-surgery skin preparation. No safety concerns were discussed.
(Ghobrial et al., 2018) US	Skin preparation: 2% CHG (Chloraprep)	Prospective study of consecutive adult neurosurgical spine patients at two hospitals	• No significant difference in surgical site infection rates was observed between patients prepared with 2% CHG and 7.5% PI solution. • No other safety concerns were discussed.
(Huang et al., 2017)	Skin preparation: 2% CHG	Meta-analysis of studies comparing the use of CHG and PI for skin preparation prior to cesarean section	• No significant difference in surgical site infection rates was detected between patients prepared with CHG and PI ($p = 0.07$). • One of six studies reported a low rate of adverse events, with no significant difference between groups. One of six studies reported no significant skin or allergic reactions in either group.
(Kieran et al., 2017) Ireland	Skin preparation: 2% CHG (Chloraprep)	Randomized controlled trial in neonates undergoing placement of central venous catheters	• No significant difference in catheter-related bloodstream infection rates was observed between neonates prepared with 2% CHG and 10% PI solution. • In the CHG treatment arm, 3/148 neonates (2%) had skin reactions. All cases occurred in infants <28 weeks of gestational age and resolved without treatment. The incidence rate was not statistically different compared to the PI treatment arm ($p = 0.677$). • In the CHG treatment arm, 17/148 (11.5%) neonates exhibited confirmed late onset sepsis and 13/148 (8.7%) neonates had suspected sepsis; the incidence rates were not statistically different compared to the PI treatment arm ($p = 0.249$ and $p = 0.835$, respectively). • Abnormal thyroid function was observed in 12 infants in the PI treatment arm; no cases were observed in the CHG treatment arm ($p < 0.001$).

Identification of Literature Source	Dose of CHG	Summary of Study Design	Primary Safety Results
(Makhni et al., 2018) US	Skin preparation: 2% CHG cloth (Styrker)	Prospective study of at-home, preoperative skin preparation	• Adverse events were not reported in this study. • One subject withdrew prior to treatment due to awareness of an allergy to *an unspecified ingredient in CHG wipes.*
(Neri et al., 2017) Italy	Skin preparation: 0.5 – 2% CHG	Case studies of very low birth weight, preterm neonates	• Five (5) infants suffered chemical burns within the first 2 days of life, caused by the use of 0.5 – 2% aqueous or alcohol CHG solutions before the insertion of intravascular devices. • One of the 5 infants (24-week gestational age; 602 g) died 17 days after disinfection at the site of umbilical catheter infection with 2% CHG aqueous solution. Comorbidities included respiratory distress syndrome, sepsis, and pulmonary hypertension. • Four of the 5 patients' (23 – 29 weeks gestational age) skin injuries epithelialized within 3 weeks. Two patients developed hypertrophic scars that were improved by silicone dressings. These 4 patients were discharged.
(Patrick et al., 2017) UK	Skin preparation: 2% CHG (Chloraprep), following 10% PI	Randomized, controlled, parallel-group trial in patients undergoing spinal surgery	• Levels of bacteria were significantly lower in the group treated with both PI and CHG compared to the group treated with PI alone ($p = 0.009$). • No other safety concerns as a result of treatment were discussed. One patient was excluded prior to the study due to unspecified sensitivity to skin antiseptic.
(Pérez-Garza et al., 2017) Mexico	Hand washing: CHG dose not specified (Hibiclens)	Prospective study of hand washing to remove *Escherichia coli* and *Enterococcus faecalis* in agricultural environments	• CHG soap effectively removed from hands contaminated with *E. coli* or *E. faecalis* at 10^3 and 10^6 CFU/g. • *E. coli* and *E. faecalis* grew in the CHG hand washing rinsate over the study period (20 hr). • No adverse events were discussed.

Identification of Literature Source	Dose of CHG	Summary of Study Design	Primary Safety Results
(Ruiz et al., 2017) Spain	Daily bathing: 2% CHG wipes (ClinellWash Cloths)	Prospective study of patients on mechanical ventilation or colonized by MDROs	• After introduction of CHG wipes, the incidence of patients colonized by MDROs significantly decreased over 11 months of treatment ($p = 0.027$). No changes were observed in the surgical critical care unit where CHG wipes were not used ($p = 0.725$). • No treated patients had moderate or severe skin reactions after CHG application during the period of intervention (11 months).
(Ryder and Duley, 2017) US	Skin preparation: 2% CHG (Chloraprep)	Drug-drug interaction study on healthy volunteer subjects' abdomens	• Gum mastic liquid adhesive and liquid adhesive remover did not affect the antiseptic effectiveness (based on microbial reductions from baseline) of CHG. • No adverse events occurred. Subjects were observed for erythema, edema, itching, maceration, contact dermatitis, allergic reaction, and skin damage.
(Sharpe et al., 2017) US	NA	Survey (Neonatal PICC1) of neonatal nurses or nurse practitioners	• Of 83 respondents, 41 (49.4%) reported using CHG to disinfect patients' skin prior to PICC insertion. • The survey did not assess for adverse events related to CHG administration.
(Velázquez-Meza et al., 2017) Mexico	Daily bathing: 2% CHG wipes (Clorhexi-Wipes)	Prospective study of the effect of CHG whole-body washing on MRSA presence in ICUs	• Over a 6-month intervention period, CHG bathing significantly reduced the frequency of MRSA isolates ($p = 0.003$). • CHG bathing did not affect biofilm production of the MRSA isolates ($p = 0.168$). • Adverse events were not reported in this study.
(Yasuda et al., 2017) Japan	Skin preparation: 0.5% CHG (b) (4) (b) (4) and 1.0% CHG (Hexizac AL Solution 1%)	Randomized, controlled, open-label, parallel study in adult patients undergoing central catheter insertions	• Catheter colonization was significantly decreased in the 0.5% CHG and 1.0% CHG groups compared to the PI treatment group ($p = 0.04$ and $p = 0.04$, respectively). No significant differences were observed across treatment groups for catheter-related bloodstream infection rates. • No systemic or local adverse events were observed in any of the treatment groups.

Source: DARRTS, 120-day Safety Update, Mod 5.4 Literature Update, 16 Feb 2018

12.2. Financial Disclosure

The Sponsor submitted an FDA form 3454 certifying no financial arrangements were made with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Sponsor also certified that each listed clinical investigator was required to disclose a proprietary interest in this product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b) did not disclose any

such interests. And certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Investigators of nine covered clinical studies indicate nothing to disclose.

Covered Clinical Study: R13-051

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

Covered Clinical Study: R13-052

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

Covered Clinical Study: R14-015

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

0

Covered Clinical Study: R13-042

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 21		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

Covered Clinical Study: R13-053

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 23		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

Covered Clinical Study: R15-028 and R15-029

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

0

Covered Clinical Study: R16-034

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

Covered Clinical Study: R17-023

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

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/

MARTHA K LENHART
11/06/2018

FRANCIS E BECKER
11/06/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: 10/22/2018

From: Carol Langley, MD, MPH, Medical Officer, DDDP

Through: Kendall Marcus, MD, Division Director, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP

To: Terri Michele, MD, Division Director, DNDP

CC: Frank Becker, MD, Clinical Team Leader, DNDP
Martha Lenhart, MD, PhD, Medical Officer, DNDP
Barbara Gould, CPMS, DDDP
Tisha Washington, RPM Staff, DDDP

Re: DDDP Consult # 1890: DNDP NDA 207964 resubmission: Please review dermal safety studies from dermatology perspective.

Materials Reviewed:

- 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: applicant's waiver request, two Agency information requests (IRs), and applicant responses to IRs

Conclusion:

The study submitted was adequate in design and conduct for evaluation of irritation and contact sensitization potential of the test product, ReadyPrep CHG, a 2% chlorhexidine gluconate (CHG) cloth. The study results indicate that significant irritation occurred with the test product; however, contact sensitization was not observed during this study.

This reviewer makes note of the following issues:

- Although this study evaluated an earlier formulation of the test product, [redacted], we agree with prior responses from the Agency that additional testing is not required at this point.
- The Agency 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.
- As noted in the Background section below, 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. We agree 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."
- The applicant submitted a Request for Waiver of Requirement for Phototoxicity and Photoallergenicity Studies. Following Agency guidance and recommendations, the applicant demonstrated that CHG in the test product absorbs light between [redacted] and [redacted] nm, and documented that the molar extinction coefficient (MEC) exceeds the ICH S10 threshold. However, 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.

Background:

Chlorhexidine gluconate is an established antimicrobial and antiseptic agent. Medline Industries, Inc. (the Sponsor) has submitted a New Drug Application (NDA) for ReadyPrep CHG, a 2% chlorhexidine gluconate (CHG) cloth. The product is designed as a single use, topical antimicrobial agent for preoperative skin cleansing treatment to reduce bacterial bioburden that contributes to surgical site infections. The solution is designed to dry on the skin and not be washed off. The applicant submitted results of dermal safety studies, specifically cumulative irritation and sensitization, in support of their application. The review of these studies is presented below. The sponsor has also submitted a request for a waiver for additional dermal safety studies (phototoxicity and photoallergenicity).

Of note, the initial studies conducted by the sponsor, including the R13-051 irritation/sensitization study, involved a slightly different formulation, [redacted] The sponsor did not perform irritation/sensitization testing on the final to-be-marketed formulation, based on communications between FDA and the sponsor in March 2017 in which FDA agreed that irritation/sensitization testing of the final formulation would not be required.

It is also worth noting that topical chlorhexidine gluconate products have been associated with hypersensitivity reactions, anaphylaxis and a number of deaths (see FDA Drug Safety Communication, dated Feb 2, 2017; also documented by sponsor in their 120-day Safety Update, dated Feb 16, 2018). CHG has also been associated with chemical burns and skin irritation in neonates, including at least one death. The sponsor's 120-day Safety Update did not identify any new safety signals. Per the sponsor and the DNDP team, appropriate language is included in the proposed labeling of ReadyPrep CHG to address these issues.

Review

1. Evaluation of Irritation and Sensitization Potential - Study R13-051

Principal Investigator: John Pullman, M.D.
BioScience Laboratories, Inc., Butte, Montana

Study Title: A randomized and observer-blinded study to evaluate the cumulative irritation and contact sensitizing potential of one finished test product

Study population: Study involved healthy subjects at least 16 years of age.

- 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.

Study design: This was a Phase 1, single center, double-blind, randomized, vehicle and reference-controlled study. Study conducted 8/08/14 - 10/18/14; study completed 3/25/15

Study procedures:

Test products:

- Medline 2% Chlorhexidine Gluconate Cloth (Test Product)
- Medline Cloth [redacted] (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:
A sufficient number of healthy subjects at least 16 years of age were recruited into the study to ensure thirty (30) subjects, including both males and females, completed the Cumulative Irritation Evaluation. Following the standard approach to evaluating cumulative irritation, [redacted] (b) (4) with filter paper discs were used to apply approximately 0.02 mL of the Test Product, Vehicle, Reference Product, the

Negative Control material, and the Positive Control material to 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. All skin sites were evaluated visually by a trained evaluator prior to each patch application and following the final patch removal.

Sensitization Evaluation:
A sufficient number of healthy subjects at least 16 years of age were admitted into the study to ensure that at least 200 subjects completed the study. Thirty-three (33) of these Subjects also completed the Cumulative Irritation Evaluation component of the study. The sensitization study consisted of three phases: Induction, Rest, and Challenge Phases.

Induction Phase: Following the standard approach to assessing sensitization, (b) (4) (b) (4) tape with filter paper discs were used to apply approximately 0.02 mL of the Test Product, Vehicle Product, Reference Product, and the Negative Control material. The Positive Control sites for the subjects that participated in the Cumulative Irritation Evaluation were not evaluated during this phase. 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.

Skin sites were evaluated following each patch removal by a blinded evaluator, with the scores serving to evaluate the product's skin irritation potential. If a subject developed an irritation score of 3 or greater during the Induction Phase with any product, the next application of that material was moved to an adjacent, unused site. If an irritation score of 3 or greater occurred at the new site with that same product, no further induction applications of the material responsible were made going forward. However, subjects that had a reaction to the product were patched with that material at an unused site during the Challenge Phase of the study. The irritation data from the new site was not used in the evaluations for the Induction Phase, and the final score from the original site was carried forward at each subsequent daily evaluation.

Rest Phase: The Induction Phase was followed by a 2-week Rest Phase during which no products or patches were applied.

Challenge Phase: 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.

Dermal Response Evaluations for Irritation and Sensitization Evaluations

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

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.

Safety monitoring
Subject safety was monitored by careful evaluations of test sites for adverse reactions. Adverse reactions were fully documented, reported as Adverse Events, and followed to resolution

Reference Product Discontinuation
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.

Adverse Events:
Forty-six Adverse Events occurred during the course of the study. All Adverse Events were mild in severity and non-serious in nature. The events were documented appropriately and resolved satisfactorily.

Ten subjects experienced Adverse Events during the Irritation Evaluation. Two Adverse Events were related to both the Test Product and the Reference Product. One event was related to the Reference Product only and one event was related to the Positive Control

only. No Adverse Events were related to the Vehicle or Negative Control. Three Adverse Events were not related to test material application. One Adverse Event had an unknown relationship to test material application, one had a possible relationship to test material application, and one had a probable relationship to test material application.

Thirty-six subjects experienced Adverse Events during the Sensitization Evaluation. One Adverse Event was related to both the Test Product and the Reference Product. Twelve events were related to the Reference Product only and three events were related to the Test Product only. No Adverse Events were related to the Vehicle, Positive Control, or Negative Control. Eighteen Adverse Events were not related to test material application. Three Adverse Events had an unknown relationship to test material application and one had a possible relationship to test material application.

Study results:

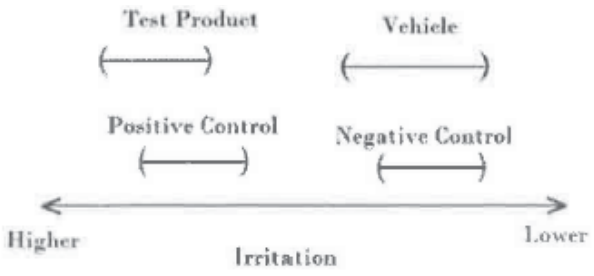
Irritation:
The table below shows results of the Cumulative Irritation Evaluation for each product tested, including minimum, maximum and mean values for the Daily Dermal Response Score, summarizing results for the 21 day duration of the study across all 33 subjects. The table also shows the Total Cumulative Irritation Score for each product. Dermal response scores for the Cumulative Irritation Evaluation are presented in Appendix 1.

Cumulative Irritation Evaluation – Results

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

Statistical Conclusions for the Cumulative Irritation Evaluation

There were differences among the products using the four contrasts. The Test Product was different from the Vehicle and the Negative Control. The Vehicle and Negative Control were the same. The Test Product and the Positive Control were the same.



Test Product = Positive Control > Vehicle = Negative Control

Sensitization:

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.

The Vehicle Product [redacted] (b) (4) was not a skin sensitizing agent. The Vehicle Product did demonstrate some irritancy following patch removal. All observed irritancy decreased in degree of severity over the 72-hour period following patch removal.

The Negative Control Product (0.9% Physiological Saline, USP) was not a skin sensitizing agent, as expected. The Negative Control Product did demonstrate some irritancy following patch removal. All observed irritancy decreased in degree of severity over the 72-hour period following patch removal.

Conclusions:

Cumulative Irritation Evaluation
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 [redacted] (b) (4) and the Negative Control (0.9% Physiological Saline, USP). The Vehicle produced an equivalent low level of irritation when compared to the Negative Control.

Sensitization Evaluation:
Sensitization was not observed with any of the products tested.

Reviewer's comments:
This study was adequate in design and conduct for evaluation of irritation and contact sensitization potential of the test product. The study results indicate that significant

irritation occurred with the test product; however, contact sensitization was not observed during this study.

This reviewer makes note of the following issues:

- Although this study evaluated an earlier formulation of the test product, including two excipients not in the final to-be-marketed product, we agree with prior responses from the Agency that additional testing is not required at this point.
- The Agency 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.
- As noted in the Background section above, 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.
    - We agree 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." Selected relevant language from draft labeling is below, in italics:

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.*

2. Request for Waiver of Requirement for Phototoxicity and Photoallergenicity Studies

The applicant's NDA Resubmission, received October 20, 2017, included a Request for Waiver of Requirement for Phototoxicity and Photoallergenicity Studies (Section 1.12.13).

In the "NDA 207964 Filing Communication – No Filing Review Issues Identified" letter dated 21 December 2017, the Agency 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)."

At different times, the applicant submitted apparently contradictory statements regarding whether the test product, 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 Dec 6, 2016 and NDA Resubmission, Section 1.12.13, Request for Waiver of Requirement for Phototoxicity and Photoallergenicity Studies, received Oct 20, 2017), the applicant 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 applicant's response to the Agency's information request on this issue, dated June 8, 2018, the applicant 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 (b) (4) exceeded the ICH S10 threshold."

Given contradictory responses from the applicant about whether the test product absorbs light between 290 and 700 nm, another IR was sent to applicant on Oct 17, 2018 asking for clarification. The applicant responded on Oct 22, 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). In fact, these data demonstrate that there is low absorption in the (b) (4) nm range. This misinterpretation is the cause of the discrepancy in reported absorption spectrum data."

Figure 1 below shows the UV absorption spectrum for CHG in the test product, as documented in the original and revised waiver request, showing absorption of UV/visible light between (b) (4) and (b) (4) nm:

Figure 1: UV Absorption Spectrum of Chlorhexidine in ReadyPrep CHG

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 applicant 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 applicant, this suggests low potential for phototoxicity.

Reviewer's comments:
The applicant has provided clarification that CHG in the test product, ReadyPrep, CHG, does absorb light between (b) (4) and (b) (4) nm, and that the molar extinction coefficient (MEC) for the product exceeds the ICH S10 threshold. The applicant has also conducted in vitro phototoxicity testing of their product, and states that in vitro data from the 3T3 Neutral Red Uptake assay suggests that CHG does not exhibit phototoxic potential. However, there are concerns about how well this in vitro testing correlates with in vivo clinical response. In general, the Agency has not accepted a negative result from this in vitro test as adequate, in and of itself, to support a waiver.

However, the Agency recognizes 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; as noted by the applicant, it is unlikely that significant light exposure would occur, aside from the lighting in the surgical suite. Given these factors, the Agency supports granting the applicant's request for a waiver of phototoxicity and photoallergenicity studies.

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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/

CAROL L LANGLEY
10/25/2018

SNEZANA TRAJKOVIC
10/25/2018