CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 20, 2018
From	Theresa M. Michele, MD Director, Division of Nonprescription Drug Products
Subject	Division Director Summary Review
NDA/BLA #	207964
Applicant Name	Medline Industries, Inc.
Date of Submission	October 20, 2017
PDUFA Goal Date	November 20, 2018 (3 month clock extension due to major amendment)
Proprietary Name / Established (USAN) Name	ReadyPrep CHG
Dosage Forms / Route of Administration / Strength	Cloth/topical/2% (equivalent to 500 mg chlorhexidine gluconate per cloth)
Proposed Indication(s)	Patient Preoperative Skin Preparation (adults and pediatric patients ≥ 2 months of age) • Helps reduce bacteria that potentially can cause skin infection • For preparation of the skin prior to surgery
Proposed Dosing Regimen(s)	Dry surgical sites (such as abdomen or arm) • Use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Moist surgical sites (such as inguinal fold) • Use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub back and forth for 3 minutes, completely wetting treatment area, then discard. Allow to dry for one (1) minute. Do not rinse.
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review--DNDP	Martha Lenhart/Francis Becker
Medical Officer Review--DDDP	Carol Langley/Snezana Trajkovic
Statistical Review	Elande Baro/Rima Izem
Pharmacology Toxicology Review	Charlie Thompson/Jane Sohn
Clinical Pharmacology Review	Kunyi Wu/Seong Jang
CMC Review/OBP Review	Friedrich Burnett/Elise Luong/Tarun Mehta/Denise Miller/Teshara Bouie/Paul Purdue/Carl Lee/Swapan De
Clinical Microbiology Review	Michelle Jackson/Francisco Martinez-Murillo
IDS Labeling Review	Hana Mujahid/Michelle Jackson/Francisco Martinez-Murillo
Clinical Inspections	Sharon Gerson/Susan Thompson
CDTL Review	Francis Becker
OSE/DMEPA	Grace Jones/Chi-Ming Tu
DSI	Sharon Gershon/Susan Thompson
RPM DNDP/CPMS	Celia Peacock/Dan Brum
Regulatory	Jagjit Grewal

CDTL=Cross-Discipline Team Leader DDDP=Division of Dermatology and Dental Products
DMEPA=Division of Medication Error Prevention and Analysis
DNDP=Division of Nonprescription Drug Products DSI=Division of Scientific Investigations
IDS=Interdisciplinary Scientist OBP=Office of Biotechnology Products
OND=Office of New Drugs OSE= Office of Surveillance and Epidemiology
RPM=Regulatory Project Manager CPMS=Chief of Project Management Staff

1 INTRODUCTION

Medline Industries, Inc. (Medline) submitted this 505(b)(2) new drug application seeking approval for direct to OTC chlorhexidine gluconate 2% cloth (proposed trade name ReadyPrep™ CHG) as a patient preoperative skin preparation for preparation of the skin prior to surgery and to help reduce bacteria that potentially can cause skin infection. This indication is well-established in the OTC space for both NDA and monograph products, and the language is consistent with other approved OTC patient preoperative skin preparation products. The product is composed of a 2% CHG solution (equivalent to 500 mg CHG per cloth) on a single fiber, polyester cloth in a two-cloth per pack configuration. In their 505(b)(2) application, Medline is relying on Hibiclens 4% topical CHG solution (NDA 17768, approved 1976) to support the nonclinical safety of their product.

The clinical development program for this application included three pilot and two pivotal clinical simulation studies to evaluate safety and efficacy, one PK study to evaluate absorption, one clinical safety study to evaluate cumulative irritation and contact sensitization, and one clinical study to assess skin coverage. This review serves as a summary review for the application.

2 BACKGROUND

2.1 Patient preoperative skin preparations

A variety of patient preoperative skin preparation products are available OTC for use prior to surgery. The patient preoperative skin preparation indication was established under the OTC drug monograph for healthcare antiseptics (21 CFR 310). Most recently, FDA's preliminary findings regarding the ingredients and criteria for safety and effectiveness were established in a final monograph in December 2017 (82 FR 60474). Products containing CHG, such as the Medline proposed product, do not fall under the monograph and must be submitted as NDAs. NDA drugs include a variety of CHG/IPA products, as well as those containing CHG/alcohol, CHG alone, and iodine/IPA. Products available under the OTC drug monograph include a number of different ingredients, including alcohol (ethyl alcohol), benzalkonium chloride, benzethonium chloride, iodine, and IPA. There is one other CHG cloth currently marketed for the same indication (Sage Products, NDA 21,699; originally approved in 2005).

In 2013, FDA issued a drug safety communication (DSC) to alert healthcare professionals that although antiseptic products have inherent antimicrobial activity, OTC patient preoperative and preinjection skin antiseptics that are not manufactured as sterile drug products may become contaminated with bacteria during manufacture or use. The DSC was based on reports linking outbreaks of infection to antiseptic preoperative and pre-injection products contaminated with microorganisms. FDA asked manufacturers of these antiseptic products to revise labeling to indicate whether the product is sterile or non-sterile and ensure that products are packaged in single-use containers, i.e. containers that hold only enough product for one patient application. Medline has not proposed the current product to be sterile.

2.2 Relevant Regulatory History

The proposed CHG product was developed under IND 107,899, initially submitted in December 2013. FDA met with Medline in two early phase meetings to discuss the development program and endpoints for the clinical simulation efficacy studies, but the sponsor did not request a pre-NDA meeting.

Medline submitted an initial application in February 2016, which received a refuse to file (RTF) action because the application failed to address the safety of novel excipients, there were no subgroup analyses for the clinical trials, and the application lacked appropriate patent certification. Following the RTF, three additional meetings were granted to discuss resolution of the RTF deficiencies as well as a number of review issues outlined in the RTF letter. In the current review cycle, Medline submitted a revised clinical study report addressing unreported protocol deviations found during FDA inspection of the pivotal clinical study site. This revised study report qualified as a major amendment, extending the review clock by 3 months.

3 CHEMISTRY, MANUFACTURING, AND CONTROLS

The Medline CHG cloth is a 2% CHG solution (equivalent to 500 mg CHG per cloth) on a single fiber, polyester cloth in a two-cloth per pack configuration. Each individual cloth measures 9 x 10.5 inches, with a liquid application of (b) (4) g per cloth. The formulation has a

[redacted] The product is non-sterile.

Manufacturing quality reviews were performed for the drug substance, drug product, process, microbiology, facilities inspections, and environmental assessment. Reviews demonstrated that quality aspects of the application were acceptable and the facilities inspections were likewise found acceptable. Based on stability data, the product is granted a 24-month shelf life when stored at 25°C/60% relative humidity.

4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The sponsor is relying on FDA's findings for Hibiclens to support the non-clinical safety of CHG and submitted no nonclinical studies as part of this application. The nonclinical team determined that the dose and duration for the Hibiclens product supports the proposed dose and duration of the CHG cloth. This reliance was changed late in the review cycle from reliance on the literature. To address the non-clinical deficiency resulting in a refusal to file after the initial submission, the sponsor removed [redacted] To bridge to the previous formulation, which is what was tested in the clinical trials, Medline performed an in vitro time-kill study, which demonstrated no change in efficacy [redacted]. The current formulation contains no novel excipients and no impurities requiring qualification.

5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The sponsor submitted a single dose pharmacokinetic study in 12 adult healthy volunteers to evaluate the absorption of CHG. The study was a 3-way crossover study, evaluating Medline CHG cloth on an abdominal site (5x5 inches), Medline CHG cloth on groin site (5x2 inches), and one control treatment with no application in each subject. The area covered is consistent with the instructions for use of the product. CHG was not detectable in any blood samples in the study (limit of assay quantitation 200 pg/mL). This is consistent with the literature demonstrating extremely limited absorption of CHG from intact skin in adults.

In addition, Medline submitted a literature search which included available study data in pediatrics. There was one study in preterm neonates (one extremity exposed prior to PICC line insertion), one in term and preterm infants aged 0 to 3 months (daily baths), and one in children aged 3 months to 18 years (daily baths). All three studies demonstrated absorption, the greatest of which was in preterm neonates. The clinical significance of this absorption is unknown, and it is difficult to extrapolate these results from daily baths to the labeled single dose use of the Medline CHG cloth.

The Medline CHG cloth is labeled for use down to age 2 months, with the following warning "use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." This age range and warning language is standard for all CHG products, and the sponsor is also relying on FDA's findings of safety and efficacy for Hibiclens 4% CHG, which has similar labeling. These data are acceptable to support approval.

6 CLINICAL MICROBIOLOGY

As part of the efficacy assessment of Medline CHG cloth, Medline submitted two modified time kill studies, one of which compared versions of the formulation (b) (4) In addition, the application included an antimicrobial resistance study and a neutralization validation study. Because CHG is a well-known antimicrobial agent with broad spectrum activity, FDA accepts a modified in vitro testing scheme with a limited number of organisms using a time-kill approach rather than requiring a full battery of organisms and minimum inhibitory concentration (MIC) testing as well. In both studies, Medline CHG cloth formulation demonstrated greater than a 3 $\log_{10}$ reduction killing effect in 6 minutes and 10 minutes for most organisms tested both at full strength and half strength, and there was no difference between versions of the formulation (b) (4) The resistance study did not show trends towards increased resistance over time with serial passage through increasing concentrations of the antiseptic, nor was there any evidence of cross resistance to various antibiotics after incubation with sublethal concentrations of the antiseptic. These results are acceptable for approval.

7 CLINICAL AND STATISTICAL EFFICACY

Medline submitted two pivotal clinical simulation efficacy trials to support their application: R13-053: MicroBioTest Laboratories; and R15-029: Evic Romania. There was one additional pivotal study which was terminated prematurely at a third laboratory due to low enrollment rates and concerns related to blinding and missing data. This study is included in the safety analysis only.

Both pivotal studies were randomized within subject, active and vehicle controlled, single-center studies in healthy volunteers. Study R13-053 included only adults aged 18 and older, while study R15-029 included adults and adolescents aged 16 and 17. Although the design was open label, study staff performing bacterial counts and statistical analyses were blinded to treatment. Subjects meeting inclusion criteria underwent a 2 day run in period during which bathing was prohibited, followed by baseline bacterial sampling from two abdominal and two groin sites. Subjects with baseline counts of $\geq 1.3 \times 10^3$ per cm^2 bilaterally on the abdominal region and $\geq 1.0 \times 10^5$ per cm^2 bilaterally on the inguinal region were eligible for entry into the treatment phase for study. On treatment day, subjects had two different surgical prep solutions placed on each of the four sites, followed by bacterial sampling at 10 minutes, 6 hours, and 8 hours post-prep. Each study included three arms: Medline 2% CHG cloth, Medline vehicle cloth (negative control), and Dyna-Hex 2 solution (active control).

Outcome measures for the studies were based on criteria established in the FDA 1994 Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products (59 FR 31402) for preoperative antiseptics. The primary endpoint for each site (abdomen and groin) was the responder rate at 10 minutes with a secondary endpoint of the responder rate at 6 hours and statistical superiority to the vehicle. Consistent with efficacy criteria established in the monograph and for other NDA products relying upon clinical simulation studies, antimicrobial efficacy is based on an absolute responder rate and absolute reduction in bacterial counts rather than demonstrating a statistically significant improvement over placebo. Clinical simulation studies are a surrogate endpoint for a reduction in surgical site infections, although we do not have definitive dose response data clearly linking a

particular level of magnitude of bacterial reduction in simulation studies to the level of reduction in surgical site infections. Recent data do, however, demonstrate a reduction in surgical site infections compared to an active control with use of a CHG/IPA preoperative preparation[1], all of which were approved based on absolute log reduction criteria.

A predefined "win" was based on achieving a lower bound of the 95% confidence interval of percent responders that was greater than or equal to 70%. On the abdomen, a responder was defined as a subject with a 2 $\log_{10}$ per cm^2 bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. On the groin, a responder was a subject with a 3 $\log_{10}$ per cm^2 bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. Of note, the criteria defining the analysis under the OTC drug monograph was recently modified in a new final rule published in December 2017 (and included in public deferral letters in January 2017). For the purposes of this NDA, FDA agreed to accept predefined 70% responder criteria at a 10 minute time point given that the studies were designed and initiated prior to publication of the final rule. The updated analysis applies the use of non-inferiority of test product to active control by a margin of 0.5 and superiority of test product to negative control by a margin of 1.2 $\log_{10}$ for patient preoperative skin preparation. Rather than using only a change from baseline, each criterion uses the average treatment effect, an estimated difference of the effect of two treatments correcting for baseline count. These new criteria were provided to the sponsor in a written response only meeting on March 3, 2017.

The Medline CHG cloth met the prespecified 70% responder rate (lower bound of the 90% confidence interval) at 10 minutes for both the abdomen and groin site in both pivotal studies. Further the Medline cloth was statistically superior (based on average treatment effects) to both Dyna-Hex 2 and vehicle cloth. See Table 1. Post-hoc sensitivity analyses performed by the FDA statistical team demonstrated that protocol violations observed in Study R15-053 did not affect the overall conclusions of the trial.

The CHG cloth also demonstrated the expected 100% responder rates for both body regions demonstrating that bacterial counts do not increase above baseline at 6 hours. Interestingly, the vehicle control also performed nearly this well, with 98% (abdomen) and 100% (groin) responder rates in Study R13-053, and 96% (abdomen) and 100% (groin) in Study R15-029. In addition, the sponsor also measured an 8 hour timepoint, which was not considered a primary or secondary outcome of the trials.

Dyna-Hex 2 did not meet the prespecified 70% responder rate in both studies at the groin and in one study at the abdomen, which theoretically raises questions regarding the validity of study conduct. However, the active control met criteria for the abdomen in one study and was close to meeting criteria for the groin and the abdomen in the other study. Therefore, I concur with the conclusions of the clinical, clinical microbiology, and statistical team that efficacy was adequately demonstrated.

[1] Tuuli MG, Liu J, Stout MJ, et al. A randomized trial comparing skin antiseptic agents at cesarean delivery. New Engl J Med 2016; 374:647-55.

Table 1: Results of Medline CHG cloth pivotal efficacy studies

		Study R13-053		Study R15-029	
		Estimate	95% CI	Estimate	95% CI
Abdomen					
Responder Rate	Medline Cloth	93% (235/252)	(89%, 96%)	81% (194/241)	(75%, 85%)
	DynaHex 2	85% (216/254)	(80%, 89%)	72% (181/253)	(66%, 77%)
	Vehicle	50% (24/48)	(35%, 65%)	50% (25/50)	(36%, 65%)
ATE* Difference	Medline Cloth—DynaHex 2	-0.26	(-0.39, -0.13)	-0.34	(-0.52, -0.16)
	Vehicle—Medline Cloth	1.22	(0.99, 1.46)	0.81	(0.50, 1.12)
	Vehicle—DynaHex 2	0.97	(0.74, 1.20)	0.47	(0.17, 0.78)
Groin					
Responder Rate	Medline Cloth	86% (218/254)	(81%, 90%)	85% (213/252)	(79%, 89%)
	DynaHex 2	65% (162/249)	(59%, 71%)	73% (189/259)	(67%, 78%)
	Vehicle	25% (12/48)	(14%, 40%)	56% (29/52)	(41%, 70%)
ATE* Difference	Medline Cloth—DynaHex 2	-0.60	(-0.80, -0.41)	-0.90	(-1.12, -0.68)
	Vehicle—Medline Cloth	1.80	(1.45, 2.14)	0.94	(0.55, 1.33)
	Vehicle—DynaHex 2	1.19	(0.85, 1.54)	0.04	(-0.35, 0.42)

*ATE=difference between 2 treatments in estimated mean log bacterial counts at 10 minutes; estimated by linear regression of log-bacterial counts at 10 minutes on treatment and baseline log-bacterial counts, in each body region.

Table from FDA statistical review by Dr. Elande Baro

Medline requested a specific labeling statement of (b) (4)

(b) (4)

8 SAFETY

For this NDA, Medline conducted one specific dermal safety trials to evaluate cumulative irritation/sensitization. In addition, safety data are also available from two pivotal clinical

simulation safety and efficacy trials, three pilot clinical simulation safety and efficacy trials, one pharmacokinetic bioavailability study, one skin coverage and drying time study, and one additional controlled efficacy study which is not being relied upon for efficacy results due to study conduct issues at the site. Of these, only the skin coverage and the PK study used the to-be-marketed formulation. Overall, there were 1931 unique subjects exposed to Medline CHG cloth as part of this development program. Because the to-be-marketed formulation is identical to the formulation tested in most of the studies (b) (4) it is acceptable to use the safety data from trials with previous formulation, as the to-be-marketed formulation would not be expected to raise new safety issues.

In addition, the sponsor submitted post-marketing data for CHG, including FAERS database, WHO Vigibase, Drug Abuse Warning Network, and published medical literature. Review of these data were consistent with the known adverse event profile of CHG, as captured in class labeling. The major serious adverse event observed was anaphylaxis, with several deaths reported in the FAERS database. This serious adverse event was recently labeled for all CHG products[2], and this product carries the required class labeling.

8.1 Safety in clinical trials

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

Dermal safety

The cumulative irritation/sensitization study was a single-site, open label, randomized study in 194 subjects comparing CHG cloth to vehicle control, DynaHex® (active control), 0.1% sodium lauryl sulfate (positive control), and 0.9% saline (negative control). Trial design included a 21 day induction period, followed by a rest phase and rechallenge. As expected, the CHG products demonstrated mild irritation potential consistent with the known profile of CHG, the negative control showed no irritation, and the positive control was consistent with CHG. No sensitization potential was observed.

The sponsor submitted a request for a waiver of phototoxicity and photoallergenicity studies, including an in vitro 3T3 neutral red update assay which demonstrated a low potential for phototoxicity. Typically, in vitro data would be insufficient to grant a waiver of these tests, but given the long-marketing history of CHG products and the indication as a preoperative antiseptic, the clinical review team from the Division of Dermatology and Dental Products determined that the chance of phototoxicity is low. I concur with this assessment.

8.2 Consumer studies

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

[2] https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm540654 htm

the sponsor provided adequate justification that a human factors study was not necessary to assess correct device use of this combination product.

9 ADVISORY COMMITTEE MEETING

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

10 PEDIATRICS

Other CHG products are approved for use in adults and children of all ages, with the following precaution for use in children younger than two months of age, “Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.” In addition, the literature reviewed demonstrates that CHG can be absorbed in children, particularly premature infants, who may have an immature skin barrier. While the original application for Hibiclens did include juvenile toxicology studies, neurologic outcomes in those studies were not investigated to current standards, which is expected given that Hibiclens was approved more than 40 years ago. Further, limitations of the literature data regarding absorption make it difficult to determine the risk when Medline CHG cloth is used in this population. Because other topical antiseptic options have particular known safety risks (e.g. hypothyroidism with iodine containing compounds), CHG remains a reasonable alternative when used cautiously. The indication for this product is for single use as a preoperative skin preparation, not for daily bathing. Labeling will include a specific contraindication, "Do not use as a general skin cleanser.”

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

11 OTHER RELEVANT REGULATORY ISSUES

11.1 OSI Audits

OSI site inspections were conducted at one clinical investigator site in Romania performing efficacy testing (pivotal study ER 15/150). The final compliance classification of this site was Voluntary Action Indicated (VAI) due to a number of Good Clinical Practice violations that after evaluation were determined to be unlikely to substantially impact the validity of the data from the study. Most of the violations were due to transcription errors, scrub times/sampling times that were outside of the protocol-specified window, and screen failures due to baseline bacterial counts that were included in the trial. A sensitivity analysis performed on the data excluding subjects with protocol violations and discrepancies did not change the overall efficacy of the study, and the violations did not affect subject safety or safety analyses.

11.2 Financial Disclosure

The sponsor certified that there were no substantial financial disclosures to report for any of the covered studies.

11.3 Environmental Assessment

A categorical exclusion was granted for this application.

12 LABELING

12.1 Proprietary name

The proposed proprietary name, ReadyPrep™ CHG, was deemed acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

12.2 Consumer labeling

Medline submitted a carton label holding 24 packs and a container label (each with 2 cloths) for ReadyPrep CHG. Both the carton label and the container label include Drug Facts Labeling.

Labeling reviews were completed by DMEPA and DNDP labeling reviewers, who recommended a number of changes to the proposed label for consistency between the consistency with class labeling and requirements based on OTC labeling regulations. The final DFL will include various class safety labeling statements, as follows: a prominent statement on the principal display panel that the product is non-sterile; an allergy alert; contraindications for use for lumbar puncture or in contact with the meninges, on open skin wounds, and as a general skin cleanser; and directions to use with care in premature infants or infants under 2 months of age. There are also warnings on the principal display panel that the product is for single use only and not to microwave. As noted previously, a (b) (4) claim (b) (4) was not supported based on the submitted data.

13 DECISION/ACTION/BENEFIT RISK ASSESSMENT

13.1 Regulatory action

Medline has submitted adequate data to support approval of CHG cloth for OTC use as a patient preoperative skin preparation antiseptic. As such, the action for this application will be Approval.

13.2 Risk Benefit Assessment

The overall risk-benefit assessment support OTC approval of Medline CHG cloth as a patient preoperative skin preparation for the Uses “for preparation of the skin prior to surgery and helps reduce bacteria that potentially can cause skin infection.” This will be the second CHG cloth product available on the OTC market as a patient preoperative skin preparation antiseptic.

In terms of efficacy, the pivotal studies replicated efficacy findings for the primary endpoint of a 70% responder rate for both the abdominal and inguinal region, with responders being defined as a 2 $\log_{10}$ per cm^2 bacterial reduction compared to baseline at 10 minutes for the abdominal region, and as a 3 $\log_{10}$ per cm^2 bacterial reduction compared to baseline at 10 minutes for the inguinal region. The clinical simulation study designs were acceptable for demonstration of efficacy for a patient preoperative skin preparation antiseptic.

In terms of clinical safety of Medline CHG cloth, the safety database is adequate for approval, with adverse events primarily related to skin irritation. This is a known effect of CHG products. The effect was as expected in the dermal safety irritation study, suggesting that the proposed formulation does not lead to a product that is substantially more irritating than other products in this category. Review of available post-marketing history of CHG revealed only the known risk of rare cases of anaphylaxis; the product will carry the recently updated allergy alert class labeling.

The two potential safety issues of concern for this product in particular are systemic absorption in infants younger than 2 months and off label use for bathing in an attempt to reduce hospital acquired infections. The two concerns are somewhat related, as there are a number of studies in the literature reporting such use, both in adults and children, and the cloth presentation may predispose to use of this product for bathing, which would be expected to increase absorption. Literature data demonstrating systemic absorption in children and young infants are concerning. Because this application did not trigger PREA, further pediatric absorption studies were not required, and it is difficult to assess risk in this population given the limitations of the available data. However, because alternatives in this population are limited and the product is intended for single use, I believe that the benefits of having another product option on the market outweigh potential risks. To mitigate this risk, the product will carry required class labeling to use with caution in infants less than 2 months of age as well as a contraindication for use as a general skin cleanser.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

13.4. Recommendation for other Postmarketing Requirements and Commitments

None.

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/

THERESA M MICHELE
11/20/2018