CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

OTHER REVIEW(S)

Addendum Labeling Review for ReadyPrep™ CHG 2% Chlorhexidine Gluconate Cloth *Draft Labeling*

SUBMISSION DATES:	October 20, 2017; December 1, 2017; March 30, 2018; June 15, 2018; September 27, 2018; October 3, 2018; October 25, 2018; and October 30, 2018
NDA/SUBMISSION TYPE:	207964 (Original)
ACTIVE INGREDIENT:	Chlorhexidine gluconate, 2%
DOSAGE FORM:	Cloth
SPONSOR:	Medline Industries, Inc. One Medline Place Mundelein, IL 60060 Bill Parthun Director, Research and Development bparthun@medline.com (847) 643-3839
REVIEWER:	Hana Mujahid, PhD, ODEIV/DNDP
TEAM LEADER:	Francisco Martínez-Murillo, PhD, ODEIV/DNDP
PROJECT MANAGER:	Celia Peacock, RDN, MPH, ODEIV/DNDP

I. BACKGROUND

This review is an addendum to Michelle Jackson's and my review dated March 16, 2018. Briefly, on February 9, 2016, the Sponsor submitted NDA 207964 ReadyPrep™ CHG patient preoperative skin preparation as an original new NDA. On April 8, 2016, the FDA issued a refuse to file letter to this application on the grounds of insufficient information provided, including failing to address [redacted] (b) (4), lack of subgroup analysis section in the clinical study reports, and missing the required patent specifications or statements, and other minor concerns. On October 20, 2017, the Sponsor resubmitted NDA 207964 in response to the Agency's April 8, 2016, refuse to file letter. ReadyPrep™ CHG is composed of a 2%

chlorhexidine gluconate solution (equivalent to 500 mg chlorhexidine gluconate per cloth) on single fiber, polyester cloth (9 in x 10.5 in) in a two-cloth per pack configuration and is for single use only. The indication for this product is patient preoperative skin preparation. Please refer to the March 16, 2018 review for the inital assessement of this submission and complete background information.

In response to FDA's information requests dated November 17, 2017, March 19, June 8, September 21, September 28, and October 22, 2018, the Sponsor submitted font and format specifications on December 1, 2017 and revised labeling on March 30, June 15, September 27, October 3, October 25, and October 30, 2018, and addressed any outstanding labeling requests. This addendum reviews the information requests issued by the Agency and the Sponsor's responses. A list of the submitted proposed labeling and submission dates is presented below. This addendum also includes the conclusions of the label and labeling review performed by DMEPA from a medication error perspective (see section II.B below). Following, is our clinical microbiology review and recommendations on the labeling included in the submission, for additional review and recommendations of the submission, refer to other disciplines reviews and assessements.

Submitted Labeling for NDA 207964 (Original)	
	Dates
ReadyPrep™ CHG 2- count immediate container ReadyPrep™ CHG outer container (24-count carton)	October 20, 2017 March 30, 2018 June 15, 2018 September 27, 2018 October 3, 2018 October 25, 2018 October 30, 2018

II. REVIEWER'S COMMENTS

A. Review of Response to FDA's March 19, June 8, September 21, September 28, and October 22, 2018 Information Requests

Information requests were sent to the Sponsor on March 19, June 8, September 21, September 28, and October 22, 2018. The Sponsor responded with revised draft labeling on March 30, June 15, September 27, October 3, October 25, and October 30, 2018. Below is the review.

a. Principal Display Panel for Immediate and Outer Container

The following summary for the request for information for the principal display panel (see complete information request from March 19, 2018 in DARRTS) applies to both, the immediate and outer container unless otherwise specified. Any subsequent communications related to the March 19, 2018 information request for the PDP are described in the reviewer's comments below.

1) Revise the pharmacological category from (b) (4) to read: "PATIENT PREOPERATIVE SKIN PREPARATION". Additionally, bold and increase the size of the pharmacological category to be the same size as the established name or at least half the size of the most prominent display of the tradename (ReadyPrep™ CHG), in accordance with 21 CFR 201.61(c).
2) Revise the established name of the drug from (b) (4) to read: "2% CHLORHEXIDINE GLUCONATE* CLOTH".
3) Revise the (b) (4) to appear as: "*EQUIVALENT TO 500 MG CHLORHEXIDINE GLUCONATE PER CLOTH".
4) Relocate the sterility statement "NON-STERILE" to directly follow the pharmacological category (Patient Preoperative Skin Preparation) on the PDP and anywhere else in the labeling the pharmacological category appears. Present the sterility statement "NON-STERILE" in bold font and in the same font size as the pharmacological category.
5) Relocate the established name of the drug (2% CHLORHEXIDINE GLUCONATE* CLOTH) to directly follow the proprietary name (ReadyPrep™ CHG), and to be subsequently followed by the pharmacological category (PATIENT PREOPERATIVE SKIN PREPARATION), per 21 CFR 201.61. The sterility statement "**NON-STERILE**" should follow the pharmacological category, followed by the "*EQUIVALENT TO 500 MG CHLORHEXIDINE GLUCONATE PER CLOTH" statement for labeling consistency across over-the-counter chlorhexidine gluconate drug products.
6) Revise the declaration of the net quantity of contents statement on the PDP to be in boldface type, per 21 CFR 201.62(g).
7) Revise where packages bear alternate principal display panels to ensure that information required to be placed on the principal display panel is duplicated on each additional principal display panel, in accordance with 21 CFR 201.60. Furthermore, per 21 CFR 201.62(d), the declaration of net quantity of contents shall be located on the principal display panel of the label, and with respect to packages bearing alternate principal display panels it shall be duplicated on each principal display panel.
8) Revise the placement of the following statements on the PDP by risk importance: "SINGLE USE ONLY", "FOR EXTERNAL USE ONLY", "DO NOT MICROWAVE", "FRAGRANCE FREE", and "RINSE FREE".
9) Add the statement "DO NOT MICROWAVE" to the PDP of the outer container to be consistent with the statements on the immediate container PDP.

Reviewer's comments: *In response to the Agency's request from March 19, 2018, the Sponsor revised the content, format, and position of the statement of identity (per II.A.a.1, 2, 5, and 7), chlorhexidine gluconate equivalency (per II.A.a.3), "**NON-STERILE**" (per II.A.a.4), and net quantity of contents statements on the principal display panel (PDP) (per II.A.a.6) and any alternate PDPs (per II.A.a.7) of the immediate and outer container in the revised proposed labeling submitted on March 30, 2018. The Sponsor did include the "DO NOT MICROWAVE" statement on the outer container PDP (per II.A.a.9) in its March 30, 2018 revised proposed*

labeling but did not revise the placement of this and remaining statements in II.A.a.8 by risk importance. This was a recommended change and not required by regulation.

As stated above, the Sponsor included the net quantity of contents statement on the alternate PDP of the outer container (per II.A.a.7) in its March 30, 2018 revised proposed labeling submission. However, in doing so, the position of the statement of identity and other statements on the alternate PDP of the outer container required further revisions. On June 8, 2018 (see complete information request in DARRTS), we provided the Sponsor with a clarifying recommendation to relocate the pharmacological category to directly follow the established name, then the sterility statement, followed by the chlorhexidine gluconate equivalency statement. In response to the Agency's request from June 8, 2018, the Sponsor submitted revised proposed labeling on June 15, 2018 addressing this recommendation.

Upon further review of the proposed labeling we noted the statement (b) (4) *in the PDPs was not acceptable.* (b) (4)

(b) (4)

In response to our information request from September 21, 2018, the Sponsor requested further clarification on September 21, 2018 via email communication (see below).

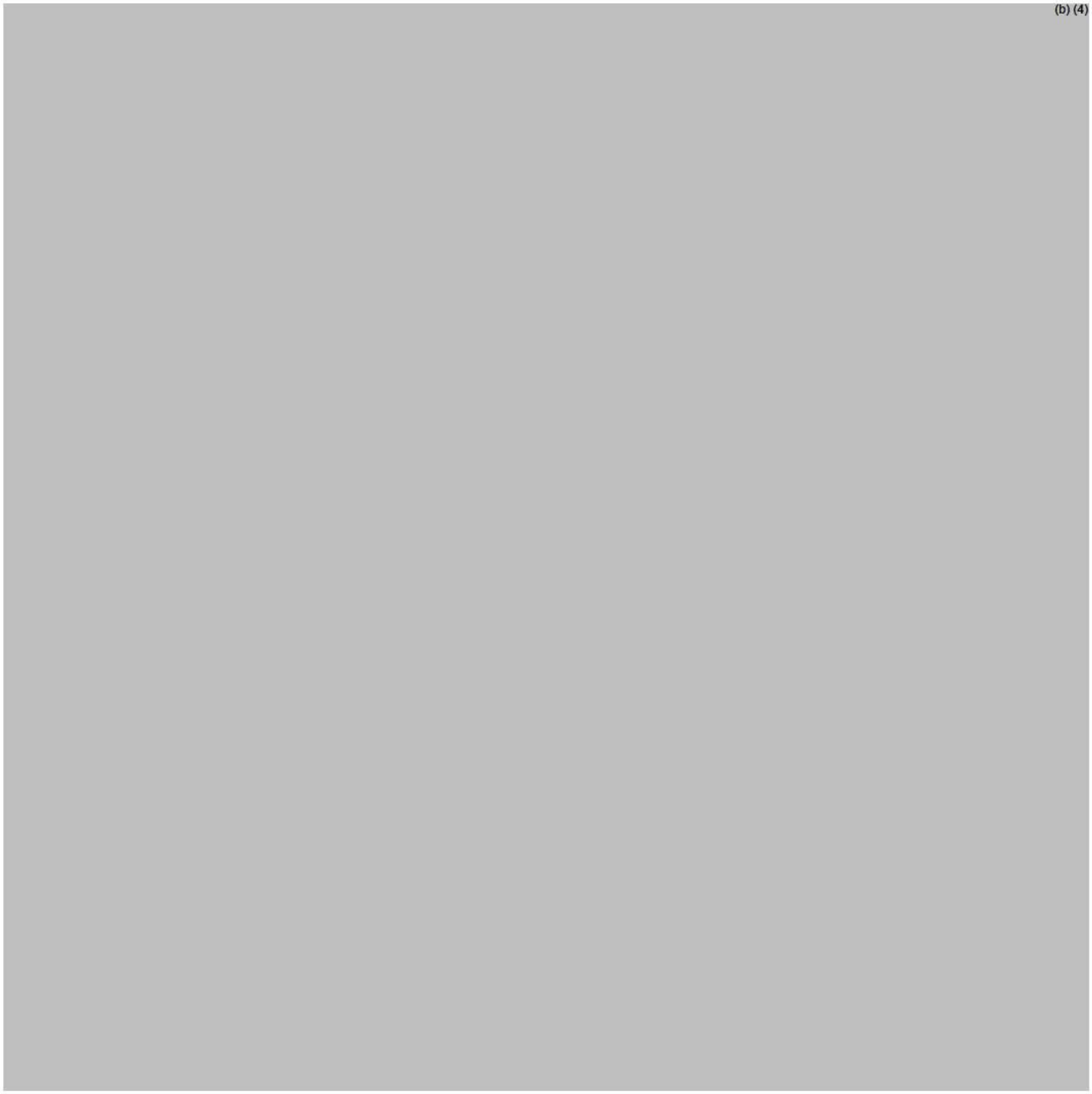
(b) (4)

On September 24, 2018, we provided the Sponsor with clarification via email communication (b) (4)

(b) (4)

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

The Sponsor has addressed all outstanding information requests related to the PDPs in the revised proposed labeling submitted on October 30, 2018 and it is acceptable.


(b) (4)

(b) (4)

[redacted]

b. Outside Drug Facts for Immediate and Outer container

On March 19, 2018 (see complete information request in DARRTS), we requested the Sponsor indicate the location of the expiration date (for placement only) on the outer and immediate container per 21 CFR 201.17. Also, we requested to revise the pharmacological category and add the sterility statement to the top and side panel of the outer container, and to revise the side panel to be consistent with the statements on the PDP.

Reviewer's comments: *In response to the Agency's request from March 19, 2018, the Sponsor indicated in its March 30, 2018 revised labeling that for the outer container the expiration date*

will be imprinted at time of manufacture beside the barcode, outside and below the Drug Facts (see section II.B for applicable comments). For the immediate container, the expiration date will be jet coded onto the side outside and below the Drug Facts at the time of manufacture (see section II.B for applicable comments). And revised the pharmacological category and added the sterility statement to the top and side panel of the outer container. Also, the side panel was revised to be consistent with the statements on the PDP in the revised proposed labeling submitted on March 30, 2018 and any subsequent submissions.

In the revised proposed labeling submitted on June 15, 2018 , we noted the Sponsor inadvertently omitted the barcode for the outer container. We conveyed this to the Sponsor on September 21, 2018 (see complete information request in DARRTS). In response to the Agency's request from September 21, the revised proposed labeling submitted on September 27, 2018 for the outer container (as well as any subsequent submissions) includes the barcode.

The Sponsor has addressed all outstanding information requests for outside the Drug Facts in the revised proposed labeling submitted on October 30, 2018 and it is acceptable.

(b) (4)

(b) (4)

[redacted]

c. Drug Facts for Immediate and Outer container

The following summary for the request for information for the Drug Facts labeling (see complete March 19, 2018 information request in DARRTS) applies to both the immediate and outer container unless otherwise specified. Any subsequent communications related to the March 19, 2018 information request for the Drug Facts labeling are described and summarized in the reviewer's comments below.

1) Remove (b) (4) following the *"**Active ingredient**"* subheading per 21 CFR 201.66.
2) Reformat the bulleted statements under "***Uses***", "**Do not use**", "**Allergy alert:**", "***Directions***", and "***Other information***" per 21 CFR 201.66(d)(4).
3) Remove the *"***Do not use***"* subheading and bulleted statements from under the *"***For external use only***"* warning and place them after the *"***Allergy Alert:***"* section of the Drug Facts. The "**For external use only**" statement should be in bold type directly under the "***Warnings***" heading in accordance with 21 CFR 201.66(c)(5)(i). In addition, place a hairline preceding the "**Allergy alert:**" subheading that follows the "**For external use only**" warning.
4) Reformat the "***Allergy alert***" warning subheading by inserting a colon after the "t" to appear as: "**Allergy alert:**" under the Drug Facts labeling "***Warnings***" heading, as required under 21 CFR 201.66(c)(5)(ii)(B) and (d)(1) and decrease the font size to be consistent with the font size used for other subheadings in the Drug Facts labeling.
5) Include a comma between the words "sensitization" and "or" and revise the first letter of the word "Irritation" from upper case to lower case, under the "**Stop use and ask a doctor if**" statement.
6) Move the "**To open package**" section to follow the "■ After package has been opened, discard any unused cloths" statement under the "***Directions***" subheading. Followed by the remainder of the bulleted statements under the "***Directions***" subheading.
7) Revise the subheading *"**To open package**"* to be unitalicized, per 21 CFR 201.66(d)(3), and decrease the font size to be consistent with the font size used for other subheadings in the Drug Facts labeling.
8) Revise the first letter of each bulleted statement under the "***Uses***", "**To open package**", *"***Dry surgical sites*** (such as abdomen or arm", "**Moist surgical sites** (such as inguinal

fold), "***Inactive ingredients***", "***Directions***", and "***Other information***" from upper to lower case.

9) Revise the bulleted statement under the subheading "**Do not use**" from "■ on patients with known allergies to chlorhexidine gluconate or any other ingredients in this product" to read: "■ on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product" for consistency across all chlorhexidine gluconate topical antiseptic drug products.
10) Revise the bulleted statement under the subheading "**Do not use**" from "■ on open wounds or as a general skin cleanser" to read: "■ on open skin wounds or as a general skin cleanser".
11) Revise the order and format of the bulleted statements under the heading "***Directions***" to read: "■ use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns. ■ do not microwave ■ product and packaging are not sterile. Follow your hospital policy for skin preparation with non-sterile products. ■ use first cloth to prepare the skin area indicated for a moist or dry site, making certain to keep the second cloth where it will not be contaminated. Use second cloth to prepare larger areas. ■ discard each cloth after a single use ■ after package has been opened, discard any unused cloths". A period is used after each sentence only if a single bulleted statement contains two or more sentences.
12) Revise the bulleted statement "■ Avoid excess heat above 40°C (104°F)" to read: "■ avoid excessive heat above 40°C (104°F)" under the heading ***"Other information"***.
13) Revise the first letter of each inactive ingredient from upper to lower case under the "***Inactive ingredients***" heading.
14) For the immediate container, revise the title "***Drug Facts Continued***" to read: "***Drug Facts*** (continued)*",* per 21 CFR 201.66(c)(1).
15) For the immediate container, revise the font size for the statements "Chlorhexidine gluconate 2% solution", dot leaders, and "Antiseptic" under the "***Active ingredient***" and "***Purpose***" headings, to be consistent with the format specifications used for other statements in the Drug Facts labeling.
16) For the outer container, revise "***Other Information***" to read: "***Other information***" by changing the first letter in "***Information***" to lower case, in accordance with 21 CFR 201.66(c)(8).
17) For the outer container, revise the font size for the "***Active ingredient***", "***Purpose***" and "***Uses***" headings, bulleted text under the "***Uses***" heading, and the statements "Chlorhexidine gluconate 2% solution", dot leaders, and "Antiseptic" under the "***Active ingredient***" and "***Purpose***" headings to be consistent with the font specifications used for the other headings, statements, and bulleted text used in the Drug Facts labeling.

Reviewer's comments: *In response to the Agency's request from March 19, 2018, the Sponsor revised the "**Active ingredient**" subheading (per II.A.c.1) and reformatted the "**Allergy alert:**" (per II.A.c.4) and "**To open package**" (per II.A.c.7) text. The bulleted statements under the "**Uses**", "**Do not use**", "**Allergy alert:**", and "**Directions**" have also been reformatted (per II.A.c.2). The order of the "**Do not use**", "**For external use only**" and "**Allergy alert:**" sections was revised (per II.A.c.3). A hairline preceding the "**Allergy alert:**" was added and the format of the "**For external use only**" warning has been revised to be in bold type (per II.A.c.3). The order and format of the subsections and bulleted statements under the "**Directions**"(per*

*II.A.c.11) have been revised, as well as the format of the "**Other information**" (per II.A.c.12), and "**Inactive ingredients**" (per II.A.c.13) sections. The statements under the "**Stop use and ask a doctor if**" (per II.A.c.5) and "**Do not use**" (per II.A.c.9 and 10) sections were also revised per the Agency's request. Furthermore, the first letter of each bulleted statement under the "**Uses**", "**To open package**", "**Dry surgical sites** (such as abdomen or arm"), "**Moist surgical sites** (such as inguinal fold), "**Inactive ingredients**", "**Directions**", and "**Other information**" was revised from upper to lower case (per II.A.c.8). The "**Drug Facts** (continued)" title has been revised (per II.A.c.14) in the immediate container and "**Other information**" heading has been revised (per II.A.c.16) in the outer container. These requested changes (II.A.c.1 through 14 and 16) have been addressed in the revised proposed labeling submitted on March 30, 2018, and any subsequent submissions. It appears the Sponsor did not revise the font size for the "**Active ingredient**" and "**Purpose**" headings and the statements under these headings ("Chlorhexidine gluconate 2% solution", dot leaders, and "Antiseptic) for the immediate and outer container (II.A.c.15 and 17), however this was a recommended change and not required by regulation. In revising the bulleted statements under the "**Uses**" heading (II.A.c.2) in the immediate container labeling, the Sponsor inadvertently omitted an indentation for the second line in the first bulleted statement . We provided clarification to the Sponsor for this on June 8, 2018 (see complete information request in DARRTS). The Sponsor addressed this recommendation in its June 15, 2018 revised proposed labeling, and any subsequent submissions.*

*Upon further review of the "**Directions**" section (revised per II.A.c.11), we noted the sequence of the subsections and bulleted statements could be revised to improve clarity and reduce redundancy for the directions for use. On September 21, 2018 (see complete information request in DARRTS), we provided the Sponsor with a recommendation to revise the "**Directions**" section so that the generally applicable statements appeared firstly, followed by how to open the package, then by directions for use on dry and moist surgical sites, and lastly by the directions for discarding any used or unused clothes, with the word "discard" in bold face type.*

*In response to the Agency's request from September 21, 2018, the Sponsor revised the "**Directions**" section in the revised proposed labeling submitted on September 27, 2018. However, for the outer container, the bulleted statement "▪ after package has been opened, discard any unused cloth" present at the bottom of the section, was replicated inadvertently as the fourth bulleted statement. Furthermore, the visual graphic used to signal continuation of the Drug Facts was placed contiguous to the bulleted text in the immediate container Drug Facts labeling, rather than on the bottom right hand corner of the Drug Facts box. Also, for the immediate container Drug Facts labeling, the Sponsor inadvertently omitted the word "a" before the word "single" in the ninth bulleted statement. For both the immediate and outer container, the Sponsor inadvertently omitted a dash between the words "non" and "sterile" in the third bulleted statement under the "**Directions**" heading. In addition, we noted that the first bulleted statement under the "**Do not use**" subheading revised per the Agency's request from March 19, 2018 (II.A.c.9) required further revision from "on patients with known allergies to…" to read: "on patients allergic to…". We provided the Sponsor with further clarification on September 28, 2018 to address these deficiencies (see complete information request in DARRTS). The Sponsor submitted revised proposed labeling on October 3, 2018 addressing these changes.*

*Upon further review of the labeling, we noted the "**Do not use**" section could be further revised to add emphasis and improve clarity. On October 22, 2018, we requested the Sponsor revise the third bulleted statement under the "**Do not use**" subheading "on open skin wounds or as a general skin cleanser" into two separate bulleted statements so that the third bulleted statement in the "**Do not use**" section reads: ▪ on open skin wounds ▪ as a general skin cleanser". We also noted under the "**Inactive ingredients**" heading the inactive ingredient "USP purified water" could be revised for clarity to read: "purified water USP". We provided the Sponsor with further clarification on October 22, 2018. The Sponsor submitted revised labeling on October 25, 2018 addressing these deficiencies. However, the Sponsor inadvertently omitted the barlines and hairlines in and around the Drug Facts for the outer carton in the revised proposed labeling. We requested clarification from the Sponsor regarding these changes in the proposed labeling for the outer carton via email on October 25, 2018. In response, the Sponsor clarified that this was a "technical glitch" and that the bar lines and hairlines should be in the proposed labeling for the outer carton, as they were previously, to separate the headings and subsections. On October 30, 2018, the Sponsor submitted revised proposed labeling addressing this deficiency. The Sponsor has addressed all outstanding information requests in the revised proposed labeling submitted on October 30, 2018 and it is acceptable.*

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B. Division of Medication and Error Prevention and Analysis' (DMEPA) Label and Labeling Review

DMEPA completed the review of the proposed name, ReadyPrep™ CHG and concluded that this name is conditionally acceptable (see DMEPA review from January 18, 2018 in DARRTS). DMEPA will conduct another review once all the deficiencies are addressed and the submission is ready for approval.

On June 15, 2018, DMEPA uploaded a Label and Labeling Review in DARRTS evaluating the proposed labeling for the immediate and outer container for areas of vulnerability that could lead to medication errors. DMEPA concluded that a human factors validation study is not needed for this product and provided a recommendation to the Division of Nonprescription Drug Products for the format of the expiration date for the proposed product to increase clarity and promote safe use. Specifically, DMEPA offered the following recommendation for the Division:

> Consider using an appropriate format for the expiration date to minimize confusion and reduce the risk for deteriorated drug medication errors. We recommend using a format such as MMMYYYY (e.g., JAN2019) or MMMDDYYYY (e.g., JAN312019).

Reviewer's comments: *We provided the Sponsor DMEPA's recommendation on September 21, 2018 (see complete information request in DARRTS). The Sponsor did not specify whether it would use this format in its labeling in its September 27, 2018 submission.*

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted ReadyPrep™ CHG immediate and outer container labeling for NDA 207964 and request final printed labeling identical to the labeling submitted on October 30, 2018:

- ReadyPrep™ CHG immediate container (2-count)
- ReadyPrep™ CHG outer container (24-count carton)

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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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/

HANA MUJAHID
10/31/2018

FRANCISCO MARTINEZ-MURILLO
10/31/2018

Clinical Inspection Summary

Date	August 27, 2018
From	Sharon Gershon, Pharm.D, Susan Thompson, M.D., Team Leader, Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Theresa Michele, DNDP Division Director Steve Osborne, Team Leader DNDP Martha Lenhart, Clinical Reviewer, DNDP Celia Peacock, Regulatory Project Manager ODE IV/Division of Non-Prescription Drug Products
NDA #	NDA 207964
Applicant	Medline Industries
Drug	ReadyPrep (chlorhexidine gluconate cloth 2%)
NME	No
Therapeutic Classification	Priority
Proposed Indication	Preparation of the patient's skin prior to surgery or injection
Consultation Request Date	December 18, 2017
Summary Goal Date	September 20, 2018
Action Goal Date	November 20, 2018
PDUFA Date	November 20, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

One foreign clinical investigator (CI) site (Dr. Rozalia Olsavszky, Romania) was inspected for NDA 207964. Protocol No. R15-029/ ER15/050 was audited: "Assessment of the antimicrobial efficacy of Medline 2% CHG cloth preoperative skin preparation." Although GCP violations were observed during the inspection of the clinical investigator, Dr. Rozalia Olsavszky, they are unlikely to substantially impact the determination of efficacy and safety of the product. The final compliance classification for the inspection is Voluntary Action Indicated (VAI).

The data from the CI site submitted by the sponsor in support of the pending application are acceptable, and the study was conducted adequately to support approval.

BACKGROUND

The sponsor seeks approval of Ready Prep CHG (Chlorhexidine Gluconate 2% Cloth) as an Over-the-Counter (OTC) topical pre-surgical skin preparation to reduce microorganisms on treated skin.

The following protocol was conducted in support of efficacy:

Protocol ER15/050 or Medline Protocol R15-029: Assessment of the antimicrobial efficacy of Medline 2% CHG cloth preoperative skin preparation.

This was a randomized, paired-comparisons design where each subject received two out of the three treatments: Medline 2% CHG cloth, Medline placebo solution cloth, or Dyna-Hex 2 – 2% CHG (positive control).

For each groin and abdomen region, 248 evaluations for each active treatment and 48 evaluations for the placebo control were required. Due to baseline failures and replacements, the actual number of subjects treated with at least one product was 340.

The main criteria for inclusion were healthy males or females at least 18 years of age with skin within 6 inches of the test regions that were free of tattoos, dermatoses, abrasions, cuts, lesions, or other skin disorders, and with no dermatological conditions or known history of sensitivity to natural rubber latex, adhesive skin products, or CHG. Each test product remained on the treatment area for 8 hours (±30 min). Post-treatment microbial samples were collected at 10-minutes (±30 sec), 6-hours (±30 min), and 8 hours (±30 min). Post application timing began upon completion of the treatment material application, including drying time. Microbial samples were collected using a scrub cup technique.

The primary measure of antimicrobial efficacy was the $\log_{10}$ reduction of skin flora at the abdominal and groin sites relative to Treatment Day baseline counts at 10-minutes following application of the product. The active products were to achieve a 2 $\log_{10}$ per cm^2 reduction at the abdominal site and a 3 $\log_{10}$ per cm^2 reduction at the groin site.

The secondary measure of antimicrobial efficacy was the $\log_{10}$ difference relative to the Treatment Day baseline $\log_{10}$ counts of skin flora at the abdominal and groin sites at 6-hours and 8-hours following application of test product. The skin flora $\log_{10}$ counts were not to exceed the Treatment Day baseline $\log_{10}$ counts.

Results were reported as Colony Forming Units (CFU) per plate. Each sample was plated in triplicate so there were three CFU values reported per sample.

The principal measures of safety were the recording of skin irritation scores and the incidence of adverse events reported during the study. Each test product remained on the treatment area for 10 minutes (± 30 seconds). Post-treatment samples were taken at 30 seconds (± 5 sec) and 10-minutes (± 30 sec).

Rationale for Site Selection: An inspection of Dr. Olsavszky was conducted in (b) (4) The review division (DNDP) requested a re-inspection of Dr. Olsavszky's site for NDA 207964 because these were two very different types of studies using different methods and with different outcome measures. (b) (4) The Medline 2% CHG Cloth study (NDA 207964) assessed bacterial log reductions at different pivotal time points that were important for approval. Very few sites conduct these types of studies, and since the site in Romania is likely to conduct more types of these studies in the future, the review division wishes to understand and clarify study conduct practices at this site.

II. RESULTS (by site):

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

Key to Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. **Rozalia Olsavszky, MD**
   Bucharest, Romania

This inspection covered the authority and administration of the clinical study, the study protocol and amendments, Institutional Review Board (IRB) submissions and approvals, subject selection criteria and informed consent, source data and case report forms, financial disclosure forms, electronic records and signatures, Investigational Product (IP) controls, adverse event reporting and monitoring activities.

The study screened 386 subjects. A total of 117 were screen failures, and 29 subjects were withdrawn. Due to baseline failures and replacements, the actual number of subjects treated with at least one product was 340.

The ORA investigator conducted a comprehensive case history review for 38 subjects in the study. The site's source documents were reviewed and compared with the data listings. There was no evidence of under-reporting of adverse events at the site. There were no deaths and no Serious Adverse Events (SAEs). Documentation showed that the site's study staff was adequately trained on the conduct of the study.

After this inspection, an exit interview was held with Dr. Olsavszky. No Form FDA-483, Inspectional Observations, was issued. Items were discussed with Dr. Olsavzky and site management. They concurred with all deficiencies and agreed to a corrective action plan. Although no Form FDA-483 was issued after the inspection, OSI judged that the deficiencies

noted and discussed are considered regulatory violations, and OSI has classified the inspection as VAI. The main deficiencies 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.

Record review disclosed that the first subject was screened and signed informed consent on (b) (6) the first subject received the test article on (b) (6) and the last follow-up for any study subject was (b) (6)

The laboratory for this study was in the basement of the inspected facility. The ORA investigator visited the lab and observed a mock demonstration of the Investigational Product (IP) application, the capture of source data, the specimen sampling, the disposition of the sample, and the laboratory procedures related to the sample analyses. No significant deficiencies were noted while observing these demonstrations.

The CI's level of compliance with the study protocol was evaluated and, overall, protocol compliance was adequate, aside from issues noted above. Some deviations were noted that were not documented in the study file and reported to the sponsor.

IND Safety Reports, unanticipated problems involving risk to human subjects, and protocol deviation reports were submitted to the IRB as required. All other documents requiring IRB review and approval including protocol amendments, and Informed Consent Document (ICD) revisions were also submitted to and approved by the IRB prior to being implemented by the CI.

A total of 100% of the subjects' Informed Consent Documents (ICD) were reviewed, and all were signed prior to enrollment in the study. The appropriate IRB approved version of the ICD was used for all subjects.

The site maintained a study folder for each subject enrolled. Each study folder included the paper source records, the subject's medical history, the subject's signed ICD, subject study visits, and laboratory results. The ORA investigator conducted a review that included protocol adherence, number of subjects enrolled, randomization, required evaluations, documentation practices, protocol deviations, adverse events, drug administration and accountability, adherence to inclusion/exclusion criteria, contraindicated medications, informed consent procedures, and record maintenance. The CI's raw data was organized, legible, and in good condition. The initials/signatures of appropriately delegated personnel were in the source records depicting their participation in the various aspects of the trial.

A review of the Investigational Product (IP) accountability records was performed. Access to the IP was limited to the CI, Sub-Investigators, and study coordinators. Review disclosed that all investigational products were dispensed by the appropriate personnel. The IP was accounted for and discrepancies were properly documented

A comprehensive review for 38 subjects was performed. Data in the subjects' source records was compared with the data recorded in the CRFs. Data reviewed included primary efficacy endpoints, inclusion and exclusion, adverse events, concomitant medications, and protocol deviations.

The ORA investigator reviewed source records for 73 subjects for sample application (scrub) times and microbial sampling times and found discrepancies between source records and data listings. He also found that for many subjects the scrub times and the sample collection times fell outside the protocol specified timeframes (out of window; OOW). To better understand these discrepancies, the ORA investigator created an Excel spreadsheet of the data for these subjects. The site's explanation for the discrepancies was because the site transferred data from the source records and Case Report Forms to an Excel spreadsheet as an intermediate step and transcription errors occurred in the process. It was the data from the Excel spreadsheet with noted transcription errors that was submitted to the sponsor. The sponsor then submitted this data to the FDA. The ORA field investigator noted that the site reported most discrepancies as protocol deviations to the sponsor.

The following regulatory violations were identified:

1. Failure to following the investigational plan.

   a. The protocol required that the Medline products, 2% CHG cloth, and placebo cloth be scrubbed for three minutes over each treatment area. For Dyna-Hex 2 (positive control) the protocol required the product be applied for two minutes over each treatment area, and then the procedure to be repeated with additional test product.

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

   Reviewer Comments: This isolated finding is unlikely to have a significant impact on the efficacy evaluation.

   b. The protocol required that each test product remain on the treatment area for 8 hours (±30 min). Post-treatment microbial samples were to be collected at 10-minutes (±30 sec), 6-hours (±30 min), and 8 hours (±30 min).

   For 73 of 340 records reviewed, the field investigator identified subjects whose 10-minute (±30 seconds) sample collection time fell outside this window.

Reviewer Comments: The OOW range was 15 seconds to two minutes, and is unlikely to have a significant impact on the efficacy outcome. The site reported these deviations to the sponsor.

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

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

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

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

2. Failure to maintain accurate records.

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

Reviewer Comments: Most of these discrepancies were reported to the NDA as protocol violations. The discrepancies were minor and transcription errors that happened when the site transferred data from source records to an Excel spreadsheet. These errors are unlikely to impact the integrity of the data.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
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/s/

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08/27/2018

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08/27/2018

KASSA AYALEW
08/27/2018

HUMAN FACTORS, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 13, 2018
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 207964
Product Name and Strength:	ReadyPrep CHG (Chlorhexidine Gluconate) Topical Cloth, 2%
Product Type:	Single-Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	Medline Industries, Inc.
FDA Received Date:	March 30, 2018
OSE RCM #:	2017-2514
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA review process for ReadyPrep CHG, we reviewed the proposed container label and carton labeling for areas of vulnerability that could lead to medication errors.

The application received a Refuse to File (RF) letter on April 8, 2016. The Applicant resubmitted their application on October 20, 2017.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant noted on the proposed ReadyPrep CHG container label and carton labeling submitted on March 30, 2018 that the expiration date would be imprinted at the time of manufacturer. However, they did not provide the exact format of the expiration date. Therefore, we provide recommendations on the presentation of the expiration date for container label and carton labeling.

On March 19, 2018, we requested the Applicant provide a comprehensive risk analysis and justification for not performing a human factors (HF) study for this proposed combination

product.[a] On March 30, 2018, the Applicant submitted their response.[b] Although the Applicant did not provide a comprehensive use-related risk analysis, they provided their justification for not performing HF studies.

As a preoperative skin preparation product, this proposed chlorhexidine gluconate cloth combination product would be used in hospital surgical room environments by healthcare professional (HCP) end users, and use of the proposed product involves tearing the container packaging at the labeled notch to open, and then using the cloth to cleanse the surgical site. The risks associated with use of this product are well understood and we have not identified any additional or unique considerations that would warrant the need for additional data at this time. Therefore, we determined that a HF study is not necessary at this time.

4 CONCLUSION & RECOMMENDATIONS

We conclude that (1) a human factors validation study is not needed for this product, and (2) the format of the expiration date for the proposed product may be improved to increase clarity and promote safe use of the proposed product.

4.1 RECOMMENDATIONS FOR THE DIVISION

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

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

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ReadyPrep CHG received on March 30, 2018 from Medline Industries, Inc.

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

	area, then discard. Allow area to dry for one (1) minute. Do not rinse. • Moist surgical sites (such as inguinal fold): use one cloth to cleanse each 65 cm² area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to dry for one (1) minute. Do not rinse.
How Supplied	2-count immediate container 24-count carton
Storage	• Store product flat • Store between 20-25°C (68-77°F) • Avoid excessive heat above 40°C (104°F)
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 14, 2018, we searched DMEPA's previous reviews using the terms, ReadyPrep CHG. Our search identified 2 previous Proprietary Name reviews.[c,d] We have not reviewed the container label and carton labeling for ReadyPrep CHG.

[c] Jones G. Proprietary Name Review for ReadyPrep CHG IND 107899. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 FEB 06. RCM No.: 2014-39498.

[d] Jones G. Proprietary Name Review for ReadyPrep CHG NDA 207964. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 17. RCM No.: 2017-18589074.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following ReadyPrep CHG labels and labeling submitted by Medline Industries, Inc.

- Container label received on March 30, 2018
- Carton labeling received on March 30, 2018

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

GRACE JONES
06/13/2018

CHI-MING TU
06/13/2018

QUYNHNHU T NGUYEN
06/13/2018

DANIELLE M HARRIS
06/15/2018

Labeling Review for ReadyPrep™ CHG 2% Chlorhexidine Gluconate Cloth *Draft Labeling*

SUBMISSION DATE:	October 20 and December 1, 2017
NDA/SUBMISSION TYPE:	207964 (Original)
ACTIVE INGREDIENTS:	2% chlorhexidine gluconate (CHG)
DOSAGE FORM:	Cloth
SPONSOR:	Medline Industries, Inc. One Medline Place Mundelein, IL 60060 Bill Parthun Director, Research and Development bparthun@medline.com (847) 643-3839
REVIEWER:	Michelle Jackson, PhD, ODEIV/DNDP
TEAM LEADER:	Francisco Martínez-Murillo, PhD, ODEIV/DNDP
PROJECT MANAGER:	Celia Peacock, RDN, MPH, ODEIV/DNDP

I. BACKGROUND

On February 9, 2016, the Sponsor submitted NDA 207964 ReadyPrep™ CHG patient preoperative skin preparation as an original new NDA. On April 8, 2016, the FDA issued a refusal to file letter to this application on the grounds of insufficient information provided, including failing to address (b) (4) lack of subgroup analysis section in the clinical study reports, and missing the required patent specifications or statements, and other minor concerns. On October 20, 2017, the Sponsor resubmitted NDA 207964 in response to the Agency's April 8, 2016, refusal to file letter. ReadyPrep™ CHG is composed of a 2% chlorhexidine gluconate solution (equivalent to 500 mg chlorhexidine gluconate per cloth) on single fiber, polyester cloth (9 in x 10.5 in) in the two-cloth per pack configuration and is for single use only. The indication for this product is patient preoperative skin preparation. The

proposed labeling submitted in the submission included color draft labeling copies of the principal display panel (PDP) and Drug Facts labeling for the immediate container (2-count) and outer container (24-count carton).

On November 21, 2017, an information request sent via email to the Sponsor requested submission of full annotated specifications (e.g., bolding, font/type size of text, headings, barlines, hairlines, bullets, etc.) for the Drug Facts labeling. The Sponsor responded on December 1, 2017, with submission of full annotated specifications for the Drug Facts labeling. This review describes the microbiology reviewer's findings and recommendations on the Sponsor's submission from December 1, 2017. See the list of submitted labeling in the table below.

Submitted Labeling, October 20, 2017	**Representative of Following SKUs**
2-count immediate container	NA
Outer container (24-count carton)	NA
(b) (4)	NA
Submitted Labeling, December 1, 2017	**Representative of Following SKUs**
2-count immediate container annotated label	NA
Outer container (24-count carton) annotated label	NA
(b) (4)	

II. REVIEWER'S COMMENTS

A. ReadyPrep™ CHG Outer Container (24-Count Carton)

i. Labeling Outside Drug Facts

a. Principal Display Panel (PDP)

(b) (4)

1. Proprietary Name

The proprietary name ReadyPrep CHG™ for chlorhexidine gluconate cloth, 2% was initially submitted under IND 107899 on October 7, 2014. DMEPA found the name, ReadyPrep™ CHG, conditionally acceptable on February 6, 2015, under IND 107899 (refer to February 6, 2015 review in DARRTS under IND 107899). The Sponsor submitted NDA 207964 on February 9, 2016 and consequently, requested review of the proposed proprietary name, ReadyPrep™ CHG, on February 23, 2016. However, the Agency found the application incomplete to allow for a substantive review, and on April 8, 2016, the application received a Refuse to File (RTF) letter. On October 20, 2017, the Sponsor resubmitted NDA 207964 and requested review of the proposed proprietary name on October 26, 2017. DMEPA has completed the review of the proposed name, ReadyPrep™ CHG, and has concluded that this name is conditionally acceptable (see DMEPA review from January 18, 2018 in DARRTS).

Reviewer's comments: *The Division of Medication Error Prevention and Analysis (DMEPA) has completed a review of the proposed proprietary name, ReadyPrep™ CHG, and has concluded that this name is conditionally acceptable. If any of the proposed product characteristics as stated in the October 20, 2017 and October 26, 2017 submissions is altered prior to approval of the marketing application, the name must be resubmitted for review. DMEPA will conduct another review once all the deficiencies are addressed and the submission is ready for approval.*

2. Statement of Identity

Within the statement of identity, the Sponsor's submission presents the established name below the pharmacological category, which is presented after the proprietary name. The Sponsor proposes the following pharmacological category: (b) (4) portrayed in a small font, relative to the established name. And, proposes the following established name of the drug: "Chlorhexidine Gluconate 2%".

Reviewer's comments: *For the over-the-counter (OTC) principal display panel (PDP), 21 CFR 201.61 requires that the statement of identity, consisting of the established name of the drug followed by a statement of the pharmacological category, follow the proprietary name, and requires that it be presented in bold face type on the PDP and the font "be in a size reasonably related to the most prominent printed matter". The order of placement of the established name of the drug and general pharmacological category on the PDP will need to be revised per 21 CFR 201.61; the proprietary name (ReadyPrep™ CHG), should be followed by the established name of the drug (2% Chlorhexidine Gluconate* Cloth), and subsequently followed by the pharmacological category (Patient Preoperative Skin Preparation). For consistency across over-the-counter chlorhexidine gluconate drug products, the proposed established name of the drug "Chlorhexidine Gluconate 2%" should be revised to read "2% Chlorhexidine Gluconate* Cloth" or "(Chlorhexidine gluconate, 2%)* Cloth" (see teleconference minutes for NDA 21669 from April 19, 2005 in DARRTS).*

The proposed pharmacological category (b) (4) *is not acceptable, and should be revised to read: "Patient Preoperative Skin Preparation", for labeling consistency across over-the-counter chlorhexidine gluconate drug products (see teleconference minutes for NDA 21669 from April 19, 2005 in DARRTS) and in accordance to the June 17, 1994, tentative final monograph (TFM) for OTC Healthcare Antiseptic Drug Products (59 FR 31402, at 31443). The pharmacological category will also need to be bolded and in a size reasonably related to the most prominent printed matter on the PDP, in this case, the proprietary name; i.e., it needs to be at least half the size of the tradename (ReadyPrep™ CHG), in accordance with 21 CFR 201.61(c).*

3. The Sponsor presents the statement: (b) (4) under the established name of the drug.

   Reviewer's comments: *The proposed statement* (b) (4) (b) (4) (b) (4) *so that it reads "*EQUIVALENT TO 500 MG CHLORHEXIDINE GLUCONATE PER CLOTH". The asterisked statement should not be placed after the established name of the drug product, but should instead appear after the sterility statement "NON-STERILE" on the PDP (See section II.A.i.a.9 for applicable comments and labeling review for NDA 21669/S-019 from March 19, 2014 in DARRTS).*

4. The statement "Provides rapid bactericidal action against a broad spectrum of microorganisms" is included on the PDP.

   Reviewer's comments*: This statement is consistent with the labeling claims on other approved products in this drug product category and is acceptable. However, the appropriateness of this claim will also be addressed in the microbiology efficacy review and will need to be demonstrated by in vitro and clinical data.*

5. The statement "Significantly reduces the number of microorganisms on intact skin" is included on the PDP.

   Reviewer's comments*: This statement is consistent with the labeling claims on other approved products in this drug product category and is acceptable. However, the appropriateness of this claim will also be addressed in the microbiology efficacy review and will need to be demonstrated by in vitro and clinical data.*

6. The statement "Demonstrates continued antimicrobial activity for up to (b) (4) hours after application" is included on the PDP.

***Reviewer's comments**: This statement is acceptable. The appropriateness of this claim was demonstrated by clinical data and is addressed in the microbiology efficacy review.*

7. The NDC number "NDC: 53329-XXX-XX" is located on the upper right corner of the PDP.

   ***Reviewer's comments**: The NDC number conforms with 21 CFR 207.33. The location of the NDC number on the PDP is acceptable.*

8. The Medline logo has been included on the upper left hand corner of the PDP.

   ***Reviewer's comment:** This is acceptable.*

9. The statement "NON-STERILE" is included on the lower third of the PDP.

   Background: On November 14, 2013, FDA sent a CBE supplement request letter to Sponsors requesting labeling changes for topical antiseptic drug products indicated for patient preoperative skin preparation. FDA determined that a class labeling change was warranted for patient preoperative skin preparation based on our review of safety information. We performed a review of safety issues pertaining to contaminated topical antiseptic products, and, to help reduce the risk of contamination and subsequent infections, the FDA requested class labeling changes for topical antiseptic drug products indicated for patient preoperative skin preparation as follows:

   - Revise product labels to indicate the sterility or non-sterility of the drug product.
   - Secondary packaging (lidding) single use applicators that are sterilized in an enclosed package should also include a sterility statement regarding the status of the applicator. The sterility statement will inform the healthcare professionals of the sterilization status (sterile or non-sterile) of the applicator so that healthcare professionals can decide whether the product may be introduced into a sterile field. This statement should be no longer than the "Non-Sterile Solution" or "Sterile Solution" statement on the PDP.
   - An applicator that is sterilized should include the following sterility statement: "Applicator is sterile if package is intact." This statement should immediately follow the solution sterility statement, which should be at least equally prominent as the applicator statement in terms of font size and other formatting.

   ***Reviewer's comments**: The placement and format of the statement "NON-STERILE" on the lower third of the PDP is not consistent with class labeling safety changes requested in 2013 (see CBE Supplement Request Letter for NDA 21669 from November 17, 2013 in DARRTS) and is not acceptable. The sterility statement "**NON-STERILE**" should be placed after the pharmacological category (Patient Preoperative Skin Preparation) on the PDP and anywhere else in the labeling the pharmacological category appears. The sterility statement should be in bold font and in the same font size as the pharmacological category.*

10. The Sponsor presents the statements: “FRAGRANCE FREE”, “RINSE FREE”, “SINGLE USE ONLY.”, and “FOR EXTERNAL USE ONLY.” on the lower third of the PDP.

    Reviewer’s comment: *These statements should be reordered and presented by risk importance on the PDP as the following: “SINGLE USE ONLY”, “FOR EXTERNAL USE ONLY”, “FRAGRANCE FREE”, and “RINSE FREE”. See also section II.A.i.a.11 for applicable comments.*

11. The statement “DO NOT MICROWAVE” is not included on the lower third of the PDP of the outer container.

    Reviewer’s comment: *The statement “DO NOT MICROWAVE” is presented on the immediate container PDP. For labeling consistency across over-the-counter chlorhexidine gluconate drug products, the statement “DO NOT MICROWAVE” should also be included on the outer container PDP. The placement of the statement “DO NOT MICROWAVE” on the PDP should be after the statement “FOR EXTERNAL USE ONLY” and before the “FRAGRANCE FREE” statement. The statements should be ordered by risk importance on the PDP as the following: “SINGLE USE ONLY”, “FOR EXTERNAL USE ONLY”, “DO NOT MICROWAVE”, “FRAGRANCE FREE”, and “RINSE FREE” See also section II.A.i.a.10 for applicable comments.*

12. The reference catalog number REF MSC095CHG is located on the lower right corner of the PDP.

    Reviewer’s comment: *This is acceptable.*

13. The net quantity of contents statement “**24** PACKS OF 2 CLOTHS” is partially in boldface type and located on the lower third portion of the PDP.

    Reviewer’s comments: *The net contents declaration is not in accordance with 21 CFR 201.62. The statement should appear in boldface type per 21 CFR 201.62(g).*

14. The size of the cloth “9x10.5 in (22.9 x 26.7 cm)” has been included on the lower third of the PDP beside the declaration of the net quantity of contents statement.

    Reviewer’s comment: *This is acceptable.*

15. The statement “DISPOSABLE CLOTHS” has been included on the lower third of the PDP under the statement describing the size of the cloths.

    Reviewer’s comments: *This is acceptable. This statement is currently included on other patient preoperative skin preparation approved products with a cloth dosage form.*

b. Alternate Principal Display Panel

The Sponsor proposes an alternate principal display panel for a panel that arguably could serve as the frontal display panel for the packaging. This alternate PDP shows missing information from that described under the PDP section above (see section II.A.i.a.). Particularly, statements such as "NON-STERILE", "SINGLE USE ONLY", "FOR EXTERNAL USE ONLY", "FRAGRANCE FREE", and "RINSE FREE" and the declaration of the net quantity of contents is not included in this alternate PDP.

Reviewer's comments: *This alternate, different principal display panel is not acceptable. Per 21 CFR 201.60, where packages bear alternate principal display panels, all information required to be placed on the principal display panel shall be duplicated on each principal display panel. Furthermore, per 21 CFR 201.62(d) and (e), the declaration of the net quantity of contents shall be placed within the bottom 30% of the area of the PDP, and with respect to packages bearing alternate principal panels it shall be duplicated on each principal display panel.*

Suggested placement for the declaration of the net quantity of contents on the alternate principal display panel is below the claim "Demonstrates continued antimicrobial activity for up to (b) (4) *hours after application" and above the perforated area on the lower third of the alternate PDP. The Sponsor should ensure that removal of the perforated label does not affect the visibility or constitution of the net quantity statement. See also sections II.A.i.a.1-15 for applicable comments.*

(b) (4)

Reviewer's comments: *The top panel of the outer container contains the proposed proprietary name and pharmacological category. For consistency with the principal display panel, it is recommended that the pharmacological category be revised from* (b) (4) *o read: "PATIENT PREOPERATIVE SKIN PREPARATION". The sterility statement "**NON-STERILE**" should be added below the pharmacological category. The sterility statement should be in bold font and be the same font size as the pharmacological category. See section II.A.i.a.2 and 9 for applicable comments.*

(b) (4)

Reviewer's comments: *The side panel of the outer container contains the same format and statements present on the PDP of the immediate container (section II.B.i.a.). The Sponsor should revise the side panel of the outer container to be consistent with the statements on the principal display panel and alternate principal*

display panel on the 24-count carton and immediate container. See sections II.A.i.a.1-15 for applicable comments.

3. Logos and Statements Outside of the *Drug Facts* Labeling on the Side Panel

(b) (4)

Reviewer's comments: *This is acceptable. Logos and statements are consistent with other patient preoperative skin preparation approved products with a cloth dosage form.*

4. Contact information for Medline Industries, Inc.

(b) (4)

Reviewer's comment: *This is acceptable.*

5. Barcode

(b) (4)

Reviewer's comments: *This is acceptable. The barcode is in accordance with 21 CFR 201.25(c).*

6. Expiration Date

Reviewer's comments: *The expiration date location has not been included on the outer container (24-count carton). This is not acceptable. The Sponsor should include the location of the expiration date on the outer container (24-count carton) and immediate container label in accordance with 21 CFR 201.17.*

ii. Drug Facts Labeling 24-Count Carton (Outer Container)

a. ***Active ingredient***

(b) (4)

(b) (4)

Reviewer's comments: *This is not acceptable.* (b) (4) (b) (4) *should be deleted.*

b. ***Uses***

The Sponsor proposes the following for the "***Uses***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *This is not acceptable. The bulleted statements under "**Uses**" should be revised so that the end of one bulleted statement be separated from the beginning of the next bulleted statement by at least two square "ems" (i.e., two squares of the size of the letter "M") and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line, per 21 CFR 201.66(d)(4). Additionally, the first letter of each bulleted statement under the "**Uses**" subheading should be changed from upper to lower case.*

c. ***Warnings***

1. **For external use only**

The "**For external use only**" statement is placed directly below the "***Warnings***" heading, preceding the "**Do not use**" subsection in the *Drug Facts* labeling:

(b) (4)

Reviewer's comment: *This is not acceptable. Per 21 CFR 201.66(d)(8), the "***For external use only***" section should be set off using a barline. This statement should precede the "***Allergy alert:***" section in the Drug Facts labeling.*

2. **Do not use**

The "**Do not use**" subheading and bulleted statements are placed under the "**For external use only**" statement in the *Drug Facts* labeling.

Reviewer's comments: *This is not acceptable. The "***Do not use***" subheading and bulleted statements will need to be removed from under the "***For external use only***" statement and placed after the "***Allergy Alert:***" section of the Drug Facts labeling. Additionally, the bulleted statements under "***Do not use***" should be revised so that the end of one bulleted statement is separated from the beginning of the next bulleted statement by at least two square "ems" (i.e., two squares of the size of the letter "M") and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line, per 21 CFR 201.66(d)(4). Furthermore, for consistency across approved chlorhexidine gluconate drug products, under the "***Do not use***" subheading, the bulleted statement: "▪ on patients with known allergies to chlorhexidine gluconate or any other ingredients in this product" should be revised to read: "▪ on patients with known allergies to chlorhexidine gluconate or any other ingredient in this product", and the bulleted statement: "▪ on open wounds or as a general skin cleanser" should be revised to read: "▪ on open skin wounds or as a general skin cleanser".*

3. **Allergy alert:**

The "**Allergy alert:**" section is placed under the "**Uses**" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *This is not acceptable. The "***Allergy alert:***" section will need to be removed from under the "***Uses***" section and placed under the "***Warnings***" subheading following the "***For external use only***" statement per 21 CFR 201.66(c)(5)(i)(B). Additionally, the subheading "***Allergy Alert***" should be revised to read: "***Allergy alert:***" per 21 CFR 201.66(c)(5)(ii)(B) and (d)(1), and the font size should be reduced to be consistent with the font size used for other subheadings in the Drug Facts labeling. The statements "This product may cause a severe allergic reaction. Symptoms may include:" should not be bolded, as specified in the FDA CBE Supplement Request letter dated February 2, 2017 (see CBE*

Supplement Request Letter for NDA 21669 from February 2, 2017 in DARRTS). The bulleted statements "■ shock ■ facial swelling ■ hives ■ rash" should be revised so that the end of one bulleted statement be separated from the beginning of the next bulleted statement by at least two square "ems" (i.e., two squares of the size of the letter "M") and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line, per 21 CFR 201.66(d)(4).

4. **When using this product**

The Sponsor proposes the following for the "**When using this product**" subsection in the *Drug Facts* labeling:

(b) (4)

Reviewer's comment: *This is consistent with Drug Facts labeling across OTC chlorhexidine gluconate drug products and is acceptable.*

5. **Stop use and ask a doctor if**

The Sponsor proposes the following for the "**Stop use and ask a doctor if**" subsection in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments*: This is not acceptable. As specified in the FDA CBE Supplement Request letter dated February 2, 2017 (see CBE Supplement Request Letter for NDA 21669 from February 2, 2017 in DARRTS), and for consistency across chlorhexidine gluconate drug products labeling, a comma should be included between the words "sensitization" and "or" and the word "Irritation" should be in lower case, under the "***Stop use and ask a doctor if***" statement, so that it reads:*
"**Stop use and ask a doctor if** irritation, sensitization, or allergic reaction occurs. These may be signs of a serious condition."

6. **Keep out of reach of children**

The Sponsor proposes the following for the "**Keep out of reach of children.**" subsection in the *Drug Facts* labeling:

(b) (4)

Reviewer's comment: *The "***Keep out of reach of children.***" section is in conformance with 21 CFR 201.66 and 21 CFR 330.1(g). This is acceptable.*

d. ***Directions***

The "***Directions***" section is placed under the "**To open package**" subsection in the *Drug Facts* labeling. The Sponsor proposes the following for the "***Directions***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *This is not acceptable. The order and format of the bulleted statements under the heading "**Directions**" should be revised to read: ■ use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns. ■ do not microwave ■ product and packaging are not sterile. Follow your hospital policy for skin preparation with non-sterile products. ■ use first cloth to prepare the skin area indicated for a moist or dry site, making certain to keep the second cloth where it will not be contaminated. Use second cloth to prepare larger areas. ■ discard each cloth after a single use ■ after package has been opened, discard any unused cloths" These statements should be followed by the subheading "***To open package***" and its bulleted statements.*

1. **To open package**

The "**To open package**" subsection is placed below the "**Keep out of reach of children.**" subsection, and above the "***Directions***" section in the *Drug Facts* labeling. The Sponsor proposes the following for the "**To open package**" subsection in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments*: This is not acceptable. The bulleted text under the subheading "**To open package**" should be relocated in the Drug Facts to follow the "■ after package has been opened, discard any unused cloths" statement under the "**Directions**" subheading. The subheading "***To open package***" should be in bold type and not be italicized, per 201.66(d)(3), and the font size should be reduced to be consistent with the other subheadings: "***Dry surgical sites*** (such as abdomen or

arm)*" and "***Moist surgical sites** (such as inguinal fold)*", under the "**Directions**" header. Additionally, the first letter of each bulleted statement under the "***To open package**" subheading section should be changed from upper to lower case.*

2. **Dry surgical sites (such as abdomen or arm)**

The Sponsor proposes the following for the "**Dry surgical sites** (such as abdomen or arm)" subsection under the "***Directions***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *The statements in the directions for "***Dry surgical sites** (such as abdomen or arm)*" are acceptable. However, the first letter of the bulleted statement under the "***Dry surgical sites** (such as abdomen or arm)*" subheading section should be changed from upper to lower case.*

3. **Moist surgical sites (such as inguinal fold)**

The Sponsor proposes the following for the "**Moist surgical sites** (such as inguinal fold)" subsection under the "**Dry surgical sites** (such as abdomen or arm)" subsection in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *The statements in the directions for "Moist surgical sites (such as inguinal fold)" are acceptable. However, the first letter of the bulleted statement under the "***Moist surgical sites** (such as inguinal fold)*" subheading section should be changed from upper to lower case.*

e. ***Other information***

The Sponsor proposes the following for the "***Other Information***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *This is not acceptable. The header "**Other Information**" will need to be revised to read: "**Other information**", per 21 CFR 201.66. The bulleted statement "■ Avoid excess heat above 40°C (104°F)" should be revised to*

*read: "■ avoid excessive heat above 40°C (104°F)". Additionally, each bulleted statement should be separated from the beginning of the next bulleted statement by at least two square "ems" (i.e., two squares of the size of the letter "M") and the complete additional bulleted statement(s) shall not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line, per 21 CFR 201.66(d)(4). The first letter of each bulleted statement under the "**Other information**" heading should be changed from upper to lower case.*

f. ***Inactive ingredients***

The Sponsor proposes the following for the "***Inactive ingredients***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *This is not acceptable. The first letter of each inactive ingredient should be changed from upper to lower case.*

iii. Format Specifications

a. The font specifications for the "**Allergy alert:**" and "**To open package**" subheadings are not in conformance with 21 CFR 201.66.

Reviewer's comments: *The font size for the "***Allergy alert:***" and "***To open package***" subheadings will need to be decreased to be consistent with font sizes used for other subheadings in the Drug Facts labeling. In addition, the font size for the "**Active ingredient**", "**Purpose**" and "**Uses**" headings, bulleted text under the "**Uses**" heading, and the statements "Chlorhexidine gluconate 2% solution", dot leaders, and "Antiseptic" under the "**Active ingredient**" and "**Purpose**" headings should be revised to be consistent with font specifications for the other headings, subheadings, statements, and bulleted text used in the Drug Facts labeling.*

B. ReadyPrep™ Immediate Container Packaging

i. Labeling Outside Drug Facts

a. Principal Display Panel (PDP)

Reviewer's comments: *The format and placement of the statement of identity, "***NON-STERILE***" statement, and additional proposed statements on the PDP is not acceptable. See sections II.A.i.a.1-15 for applicable comments.*

b. Outside of Drug Facts - Outside Principal Display Panel

1. Logos and statements outside of Drug Facts.

Reviewer's comments: *This is acceptable. An additional statement "Non-Sterile." has been added to the immediate container, which is not present on the outer*

container (24-count carton) outside the Drug Facts. See section II.A.i.c.3 for applicable comments.

2. Contact information for Medline

(b) (4)

Reviewer's comment: *This is acceptable.*

3. Barcode

(b) (4)

Reviewer's comments: *This is acceptable. See section II.A.i.c.5 for applicable comments.*

4. Expiration date

Reviewer's comments: *The expiration date location is not defined. This is not acceptable. See section II.A.i.c.6 for applicable comments.*

ii. Drug Facts Labeling (Immediate Container)

a. ***Active ingredient***

(b) (4)

(b) (4)

Reviewer's comments: *This is not acceptable. See section II.A.ii.a for applicable comments.*

b. ***Uses***

The Sponsor proposes the following for the "***Uses***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *The formatting of the bulleted statements under the "**Uses**" heading is not acceptable. See section II.A.ii.b for applicable comments.*

c. ***Warnings***

1. **For external use only**

The "**For external use only**" statement is directly below the "***Warnings***" heading, preceding the "**Do not use**" subsection in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *This placement and formatting is not acceptable. See section II.A.ii.c.1 for applicable comments.*

2. **Do not use**

The "**Do not use**" subheading and bulleted statements are placed under the "**For external use only**" statement in the *Drug Facts* labeling.

Reviewer's comments: *This is not acceptable. See section II.A.ii.c.2 for applicable comments.*

3. **Allergy alert:**

The "**Allergy alert:**" section is under the "***Uses***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *The placement and formatting of the "***Allergy alert:***" subheading and bulleted statements is not acceptable. See section II.A.ii.c.3 for applicable comments.*

4. **When using this product**

The Sponsor proposes the following for the "**When using this product**" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comment: *This is consistent with Drug Facts labeling across OTC chlorhexidine gluconate drug products and is acceptable.*

5. **Stop use and ask a doctor if**

The Sponsor proposes the following for the "**Stop use and ask a doctor if**" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *The Sponsor's proposed "***Stop use and ask a doctor if***" section is not consistent with other chlorhexidine gluconate drug products labeling and is not acceptable. See section II.A.ii.c.5 for applicable comments.*

6. **Keep out of reach of children**

The Sponsor proposes the following for the "**Keep out of reach of children.**" subsection:

(b) (4)

Reviewer's comment: *The "***Keep out of reach of children.***" section is in conformance with 21 CFR 201.66 and 21 CFR 330.1(g). This is acceptable.*

d. ***Directions***

The Sponsor proposes the following for the "***Directions***" section in the *Drug Facts* labeling:

Reviewer's comments: *The order and format of the bulleted statements under the heading "***Directions***" in the Drug Facts labeling is not acceptable. See section II.A.ii.d for applicable comments.*

1. **To open package**

The "**To open package**" subsection follows the "**Keep out of reach of children.**" subsection and precedes the "***Directions***" section in the *Drug Facts* labeling.

Reviewer's comments: *The format, content and placement of the subheading "***To open package***" is not acceptable. See section II.A.ii.d.1 for applicable comments.*

2. **Dry surgical sites (such as abdomen or arm)**

The Sponsor proposes the following for the "**Dry surgical sites** (such as abdomen or arm)" subsection under the "***Directions***" section in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *The statements to be included in the directions for "***Dry surgical sites** (such as abdomen or arm)*" are acceptable. However, the first letter of the bulleted statement under the "***Dry surgical sites** (such as abdomen or arm)*" subheading section should be changed from upper to lower case. See section II.A.ii.d.2 for applicable comments.*

3. **Moist surgical sites** (such as inguinal fold)

The Sponsor proposes the following for the "**Moist surgical sites** (such as inguinal fold)" subsection under the "***Directions***" heading in the *Drug Facts* labeling.

(b) (4)

Reviewer's comment: *The statements to be included in the directions for "***Moist surgical sites** (such as inguinal fold)*" are acceptable. However, the first letter of the bulleted statement under the "***Moist surgical sites** (such as inguinal fold)*" subheading section should be changed from upper to lower case. See section II.A.ii.d.3 for applicable comments.*

e. ***Drug Facts*** **(continued)**

The Sponsor proposes the following for the "***Drug Facts*** (continued)" heading in the *Drug Facts* labeling:

(b) (4)

Reviewer's comments: *This is not acceptable. The title will need to be revised from "**Drug Facts** Continued" to read: "**Drug Facts** (continued)" per 21 CFR 201.66(c)(1).*

f. ***Other information***

The Sponsor proposes the following for the "***Other information***" section of the *Drug Facts* labeling:

Reviewer's comments: *The formatting and content of the bulleted statements is not acceptable. See section II.A.ii.e for applicable comments.*

g. ***Inactive ingredients***

The first letter of each inactive ingredient is in upper case under the "***Inactive ingredients***" section in the *Drug Facts* labeling:

Reviewer's comments: *This is not acceptable. See section II.A.ii.f for applicable comments.*

iii. Format Specifications

a. The font specifications for the "**Allergy alert:**" and "**To open package**" subheadings are not in conformance with 21 CFR 201.66.

Reviewer's comments: *The font size for the "**Allergy alert:**" and "**To open package**" subheadings need to be decreased to be consistent with the font size used for other subheadings in the Drug Facts labeling. The font size for the statements "Chlorhexidine gluconate 2% solution", dot leaders, and "Antiseptic" under the "**Active ingredient**" and "**Purpose**" headers should be revised to be consistent with the format specifications used for other statements in the Drug Facts.*

III. RECOMMENDATIONS

We currently recommend a COMPLETE RESPONSE to the Sponsor with the following labeling deficiencies:

Required Changes

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

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

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

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

4. Relocate the sterility statement "NON-STERILE" to directly follow the pharmacological category (Patient Preoperative Skin Preparation) on the PDP and anywhere else in the labeling the pharmacological category appears. Present the sterility statement "NON-STERILE" in bold font and in the same font size as the pharmacological category.

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

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

7. The outer carton appears to have alternate principal display panels (a second principal display panel in a different side of the package), and information presented in one panel seems to be missing from the other one, e.g., statements such as: "Non-sterile", "Single use only", "For external use only", "Fragrance free", and "Rinse free". Revise where packages bear alternate principal display panels to ensure that information required to be placed on the principal display panel is duplicated on each additional principal display

panel, in accordance with 21 CFR 201.60. Furthermore, per 21 CFR 201.62(d), the declaration of net quantity of contents shall be located on the principal display panel of the label, and with respect to packages bearing alternate principal display panels it shall be duplicated on each principal display panel. Suggested placement for the net quantity of contents on the alternate principal display panel is above the perforated area (opening) on the lower third of the panel. If this placement is used for the net quantity of contents statement, removal of the perforated label should not affect the visibility or constitution of the statement.

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

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

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

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

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

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

11. Reformat the bulleted statements under "***Uses***", "**Do not use**", "**Allergy alert:**", "***Directions***", and "***Other information***" so that the end of one bulleted statement is separated from the beginning of the next bulleted statement by at least two square "ems" (i.e., two squares of the size of the letter "M") and the complete additional bulleted statement(s) does not continue to the next line of text. Additional bulleted statements appearing on each subsequent horizontal line of text under the heading should be vertically aligned with the bulleted statements appearing on the previous line, in accordance with 21 CFR 201.66(d)(4).

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

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

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

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

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

Outer Container Drug Facts

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

Immediate Container Drug Facts

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

Recommended Changes

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

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

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

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

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

21. Revise the first letter of each bulleted statement under the "***Uses***", "**To open package**", "**Dry surgical sites** (such as abdomen or arm", "**Moist surgical sites** (such as inguinal

fold), "***Inactive ingredients***", "***Directions***", and "***Other information***" from upper to lower case.

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

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

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

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

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

Immediate Container Drug Facts

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

Outer Container (24-Count Carton) Drug Facts

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

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHELLE M JACKSON
03/16/2018

FRANCISCO MARTINEZ-MURILLO
03/16/2018