CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 207964
Review # 1

Drug Name/Dosage Form	ReadyPrep CHG
Strength	Chlorhexidine gluconate 2% Cloth
Route of Administration	Topical
Rx / OTC Dispensed	OTC
Applicant	Medline Industries Inc., Mundelein, IL 60060
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	20-October-2017	ONDP/OPF/FR
Response to quality IR	16-January-2018	ONDP
Response to quality IR	23-February-2018	ONDP/OPF
Response to quality IR	22-March-2018	ONDP
Response to quality IR	10-July-2018	ONDP

Quality Review Team

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

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/16/2017	None
(b) (4)	III	(b) (4)		4	Adequate	N/A	None
(b) (4)	III	(b) (4)		1&4	Adequate	11/14/2016	None

C. [1] Action codes for DMF Table:
D. 1 – DMF Reviewed.
E. Other codes indicate why the DMF was not reviewed, as follows:
F. 2 –Type 1 DMF
G. 3 – Reviewed previously and no revision since last review
H. 4 – Sufficient information in application
I. 5 – Authority to reference not granted
J. 6 – DMF not available
K. 7 – Other (explain under "Comments")
L. [2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107899	2% CHG Cloth Preservative Skin Preparation

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Office of Surveillance	NA			

Table of Contents

Executive Summary (NDA-207964)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the resubmitted application the drug substance, drug product, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application (see attached reviews). The drug product is granted a 24-month shelf life when stored at 25ºC/60%RH.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments:

Current application (NDA-207964) was originally submitted to the Agency on 09 February 2016 but was not filed mainly due to clinical, non-clinical issues. While not related to "refuse to file" the letter dated 08 April 2016 included advice to address some CMC issues. The applicant resubmitted the application with the CMC response. All quality-related (drug substance, drug product, manufacturing process, microbiology and facility) issues are resolved during this review cycle.
Facility review with "acceptable recommendation" is completed on 05 October 2018.

A. Drug Product [ReadyPrep CHG] Quality Summary

1. **Strength: 2%** Chlorhexidine Gluconate Cloth

2. **Description/Commercial Image:**

ReadyPrep CHG is a non-sterile cloth dosage form which delivers 2% CHG topical solution to the site of administration. The product is packaged in a single-use, unit-dose presentation containing 2 clothes sealed in a (b) (4) pouch, which provides the equivalent to 500 mg of CHG per cloth.
The cloth substrate is white/off-white (b) (4) 100% polyester material and size of each individual cloth is 9 x 10.5 inches ((b) (4)). The liquid application to the cloth is intended to be (b) (4) g per cloth; therefore, the target fill for the liquid will be no less than (NLT) (b) (4) g per package (= (b) (4) g/cloth x 2 cloths). It is manufactured as a (b) (4) . It includes additional ingredients t (b) (4) It is formulated at a pH range (b) (4) , (b) (4) The finished product is packaged in a primary container closure system and is a (b) (4)

3. Summary of Product Design

The manufacturing process for ReadyPrep CHG occurs in (b) (4) (b) (4) (b) (4) The product consists of a prepackaged set of two (b) (4) disposable cloths (b) (4) containing CHG as the active ingredient.
Microbiological quality is tested in accordance with USP <61> and <62>, using acceptance criteria established according to the guidelines of USP <1111>. The proposed formulation used (b) (4)

List of Excipients:
Benzalkonium chloride, Dimethicone emulsion, Glycerin, Isopropyl alcohol, Propylene glycol and Purified water.

4. Process Selection (Unit Operations Summary)

The finished product manufacturing process is similar manufacturing process to NDA 21,669 which is also a Chlorhexidine Gluconate 2% Topical Cloth product. (b) (4) (b) (4)

The primary container closure system is a (b) (4) (b) (4)

6. Expiration Date & Storage Conditions

The drug product is granted a 24-month shelf life when stored at 25ºC/60%RH.
The storage statement will be written as "Store between 20ºC – 25ºC (68ºF - 77ºF); avoid excess heat above 40ºC (104ºF). This reflects the numerical value of the controlled room temperature [stored at 25ºC (77ºF) with excursions permitted to 15ºC-30ºC (59ºF-86ºF)].

7. List of co-packaged components: None

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	ReadyPrep CHG
Non Proprietary Name of the Drug Product	2% chlorhexidine gluconate Cloth
Non Proprietary Name of the Drug Substance	chlorhexidine gluconate
Proposed Indication(s) including Intended Patient Population	Patient preoperative skin preparation, for the preparation of the skin prior to surgery and to help reduce bacteria that can potentially cause skin infection
Duration of Treatment	Single use topical application:
Maximum Daily Dose	N/A
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I.
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: No
   - PK studies: Yes
   - IVIVC: No

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations

None

F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	3	2	12	Controlled with specifications
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on limited data provided.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Controlled with specifications.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Regarding Chemistry Manufacturing and Controls, the application may be approved.

Application Technical Lead Signature:

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Friedrich Burnett

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Donna Christner

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DRUG PRODUCT

Product Background: Chlorhexidine gluconate (CHG) is commonly used in antimicrobial applications. Chlorhexidine primarily acts by binding to the anionic surface of cells, disrupting membrane integrity and causing leakage and, eventually, coagulation of the cytosolic components that result in cell death (McDonnell and Russell, 1999). Medline has developed a 2% CHG product, ReadyPrep CHG, that includes a cloth dosage form of CHG intended for a topical route of administration.

The applicant relies on data from Sponsor-conducted studies and published literature to support approval of ReadyPrep CHG. Because the pharmacology and safety of CHG solutions for antimicrobial preoperative skin preparation are generally well understood, no safety pharmacology or toxicology studies were conducted to support the applicant's 505(b)(2) application.

NDA: 207964

Drug Product Name / Strength: 2% Chlorhexidine Gluconate/ (b) (4) 500 mg per cloth

Proposed Proprietary Name: ReadyPrep CHG (acceptable by the labelling review team as of 03/19/18)

Indication: Patient preoperative skin preparation

Route of Administration: Topical

Dosage Form: Saturated solution in a polyester cloth

Applicant Name: Medline Industries, Inc.

Reference Listed Drug: Hibichens (NDA 017768)

Review Summary: *The NDA contains sufficient CMC information and all CMC issues have been resolved adequately. Long-term (12 months) and 6 months accelerated condition stability data shows no detectable impurities/degradants. The proposed product ReadyPrep 2% CHG in polyester cloth is granted the proposed shelf-life of 2 years.*

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(b) (4)

[redacted]

Post-Approval Stability Protocol and Commitment

Medline commits that at least one commercial lot of ReadyPrep CHG per year will be enrolled in the post-approval stability program. The annual stability lot will be stored at the general case, long-term conditions defined by ICH Q1A at 25 °C ± 2° C/60% RH ± 5% RH. The product will be tested at 3, 6, 9, 12, 18, and 24 months to the specifications listed in Table 1.

Table 1: Post Approval Stability Commitment Specifications		
Test	Method	Stability Limits
Appearance	(b) (4) 00208	Two folded and stacked cloths, (b) (4) (b) (4)
Chlorhexidine Gluconate (CHG) Assay	00286	(b) (4)% ((b) (4)% of label claim)
Organic Specified Impurities: (b) (4)	00286	NMT[1] (b) (4)ppm
Organic Unspecified Individual Impurities	00286	NMT[2] (b) (4)%
Organic Impurities: Total Impurities	00286	NMT[2] (b) (4)%
pH	00003	(b) (4)
Container Weight	00167	Report Results
Antimicrobial Effectiveness Testing (AET)[3]	USP<51> (b) (4) 00110	Meet the requirements as per USP 51category 2 products: *"Not less than 2.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days for bacteria. No increase from the initial calculated count at 14 and 28 days for Yeast and Mold."*
Total Aerobic Plate Count	USP <61> / <62> (b) (4) 00081	NMT (b) (4)CFU/wipe
Yeast and Mold		NMT (b) (4)CFU/wipe
Gram Negative Organisms		Risk Assessment
Staphylococcus aureus		Absent
Bacillus cereus		Absent
Pseudomonas aeruginosa		Absent
Candida albicans		Absent

[1]NMT = not more than
[2]Per FDA's request will be added as a specification on future batches.
[3]Not performed at all time points; see discussion

Reviewer's Assessment: ADEQUATE.

R Regional Information

Environmental Analysis

Medline is requesting categorical exclusion with respect to chlorhexidine gluconate solution provided as 2% solution and intended for topical use, under 21 CFR 25.31(b) and 21 CFR 25.15(d). The estimated concentration of chlorhexidine gluconate solution at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The maximum yearly production of the active moiety of chlorhexidine gluconate solution, excluding any salt, complexes, or inactive components, during the first 5 years of post-approval production is estimated to be less than (b) (4) kg and would result in an estimated aquatic exposure significantly lower than the threshold of 1 ppb described

in the regulations. The request for categorical exclusion from the requirement to submit an environmental assessment is proposed and provided in Module 1.12.14.

Reviewer's Assessment: ADEQUATE.

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed action. (Refer to EA assessment from the EA reviewer.)

Methods Verification Package

None

Reviewer's Assessment: N/A.

There is no methods verification package in the NDA. The methods are based on compendial methods.

Comparability Protocols

None

Reviewer's Assessment: N/A.

There are no comparability protocols in the NDA.

Post-Approval Commitments

Covered in page-40.

Reviewer's Assessment: ADEQUATE.

See page-40, Post-Approval Stability Protocol and Commitment.

Lifecycle Management Considerations

Long-term stability studies as stated in the post-approval commitment.

Reviewer's Assessment: Continue long-term stability studies as stated in the post-approval commitment.

APPROVABILITY DEFICIENCIES: None

Primary Drug Product Reviewer Name and Date: Elise Luong, Ph.D.; 06/11/18.

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D., I concur with the reviewer's assessment; 06/11/18.

{For NDA only}

R Regional Information

1.14 Labeling

ReadyPrep CHG is an OTC product, the Office of Nonprescription Drug Product is responsible for labeling reviews to ensure compliance with OTC labeling requirements. ONDP reviews the CMC information for consistency with information provided in the NDA. The drug established name and CMC information in the provided labeling are accurate.

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Reviewer's Assessment: All parts presented on the labels are adequate from the drug product reviewer's perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

List of Deficiencies: None.

Primary Labeling Reviewer Name and Date: Elise Luong, Ph.D.; 06/11/18.

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D., I concur with the reviewer's assessment; 06/11/18.

Elise Luong

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Danae Christodoulou

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background: This product is a non-sterile surgical cloth to be used as a pre-surgical skin preparation. The cloth contains a 2% solution of chlorhexidine gluconate. This is proposed to be an over-the-counter product.

NDA: 207-964

Drug Product Name / Strength: ReadyPrep CHG (Chlorhexidine Gluconate) 2%

Route of Administration: topical

Applicant Name: Medline Industries

Manufacturing Site:
Medline Industries, Inc.
(ReadyCare Facility)
1710 S. Lakeside Drive
Waukegan IL 60085

FEI #: 3003983334

Method of Sterilization: NA, product is not sterile

Review Recommendation: Adequate

Review Summary: The product is a package containing two cloths saturated with 2% Chlorohexidine gluconate solution to be used as a body wipe prior to surgery. The review concentrated on the method suitability studies for the microbial limits release testing.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
20 October 2017	20 October 2017	N/A	23 October 2017

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks:
This NDA was originally submitted to the Agency on 09 February 2016 but was not filed. While the quality microbiology filing review did not have any filing issues, there was a request to supply the method suitability reports for the microbial limits release testing. This resubmission included those requested reports.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: NA

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance

Reviewer's Assessment: ***NA,*** review not required as drug substance is not sterile.

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – This is a polyester cloth saturated with a 2% Chlorhexidine Gluconate Topical Solution. The product is used to wipe/cleanse the skin prior to surgery.
- **Drug product composition** – The drug product is a 2% Chlorhexidine Gluconate solution impregnated onto a polyester cloth.
  The chlorhexidine Gluconate solution is as follows (copied from Table 1 in section 3.2.P.3.2

Table 1: Proposed Batch Formula – 2% Chlorhexidine Gluconate Topical Solution USP		
Component	**Quality Standard**	**Amount per batch, lb**
Purified Water	USP	(b) (4)
Drug Substance (b) (4)% Chlorhexidine Gluconate Solution, USP)	(b) (4)	
Glycerin	USP	
Propylene Glycol	USP	
(b) (4)% Dimethicone NF Emulsion	(b) (4)	
Isopropyl Alcohol	USP	
(b) (4)% Benzalkonium Chloride	NF	
Total Batch Size		

- **Description of container closure system** – The container closure system is a (b) (4) pouch. Each pouch contains two cloths.

Reviewer's Assessment: ***Adequate,*** the requisite information was provided.

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(b) (4)

The acceptance criteria were met.

Reviewer's Assessment: ***Adequate***
The method suitability for USP <62> used the correct selective media for the detection of the challenge organism but these selective medias will not be used in the routine testing; the routine testing will be using TSA. This is not an issue as the method suitability testing performed for USP <61> established the ability of the TSA media to support the growth of these specified organisms.
Note: The method suitability for USP <61> also was used to support testing for USP <51>. This is acceptable.

P.8 Stability

Long term storage is proposed to be (b) (4) °C for 24 months.

P. 8.1 Stability Summary and Conclusion

Microbial testing in the stability included
- TAMC NMT (b) (4) cfu/wipe
- TYMC NMT (b) (4) CFU/wipe
- Absence of *S. aureus, B. cereus, Ps. aeruginosa* and *C. albicans*

Antimicrobial Effectiveness testing per USP <51>: meets the requirement of a Category 2 product

Stability storage conditions are as follows
- Long term: 25C/60%RH
  - Microbial Limits: 0, 6, 9, 12, and 24 months
  - AET performed 0, 6, 12 and 24 months
- Accelerated: 40C/75%RH
  - Microbial Limits: monthly through 6 months
  - AET performed at 0 and 6 months

Reviewer's Assessment: ***Adequate,*** all microbiological testing to date met the acceptance criteria.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

At least one commercial lot of ReadyPrep CHG will be placed on stability under long term storage conditions. The testing time points are 3, 6, 9, 12, 18, and 24 months. The Microbial limits testing will be performed at each time point with the AET testing performed only at 0 and 24 months.

Reviewer's Assessment: ***Adequate***

P.8.3 Stability Data

Three batches were placed on stability

LOT 16GE0700, 16GE0701 and 16GE0702; all three manufactured in (b) (4)

Data through the 12 month time point was provided for each lot.

Reviewer's Note: Stability testing for three earlier batches were also provided. These lots were CHGPQ2, CHGPQ2, and CHGPQ4 and were manufactured in (b) (4) These were placed on stability and data through 12 months was provided. These three lots were not included in the sponsor's stability discussion.

Reviewer's Assessment: ***Adequate;*** all microbiological testing provided met the acceptance criteria. The lots will be testing through the 24 month time point.

R Regional Information

Executed Batch Records

Executed batch records for six stability batches were provided. Additionally, batch records for lots 966239, CHGSAM01, and 17BE0748 were also provided.

Reviewer's Assessment: ***Adequate***

List of Deficiencies: None

Primary Microbiology Reviewer Name: Denise Miller

OPQ/OPF/DMA/Branch II, Sr. Microbiologist

Secondary Reviewer Name: Bryan Riley Ph.D.

OPQ/OPF/DMA/Branch II, Acting Branch Chief

Denise Miller

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Bryan Riley

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