CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207964

REFUSAL TO FILE

Medline Industries, Inc.
Attention: Bill Parthun
Director, Research and Development
One Medline Place
Mundelein, IL 60060

Dear Mr. Parthun:

Please refer to your New Drug Application (NDA) dated and received February 9, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ReadyPrep (chlorhexidine gluconate cloth), 2%.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

The application is incomplete because it does not on its face contain information required under section 505(b) of FDCA and §314.50:

- The application fails to address the safety of (b) (4) (b) (4)

- The application is incomplete because Clinical Study Reports in module 5 of the eCTD (Electronic Common Technical Document) do not contain a section on subgroup analysis. Report the safety and efficacy findings by gender, age, and racial subgroups.

- The application does not contain an appropriate patent certification as required under 21 CFR 314.50(i). Per your emailed correspondence dated March 21, 2016, you acknowledge that the literature you intend to rely upon describes various listed drugs (NDA 017768 Hibiclens, NDA 020832 ChloraPrep, NDA 021074 Avagard, and NDA 021669 chlorhexidine gluconate cloth 2%), which is considered to be reliance on FDA's findings of safety and/or effectiveness for the listed drugs. Your submission of FDA form 3542a does not address the patent

certification or statement requirements for a 505(b)(2) application that relies for approval upon FDA's findings of safety and/or effectiveness for a listed drug(s) (see 21 CFR 314.50(i) and 21 CFR 314.54). FDA form 3542a is intended to provide patent information, as required per 21 CFR 314.53, for the drug that is subject of the new drug application (i.e., ReadyPrep (chlorhexidine gluconate cloth), 2%). Provide a revised Form FDA 356h specifying reliance on the listed drugs described in the literature that are the basis of your 505(b)(2) application. Provide an appropriate patent certification or statement with respect to any relevant patents that claim the listed drugs and that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug according to 21 CFR 314.54(a)(1)(vi).

While not related to our refusal to file this application, you should address the following issues if the application is resubmitted.

Chemistry, Manufacturing, and Controls

1. The method suitability study in support of the microbial limits testing per USP <61> was not found in the submission. (b) (4)

(b) (4)

2. You have not formally submitted a waiver request for waiving the needed in vivo bioavailability/bioequivalence (BA/BE) study. Per 21 CFR 320.21(a)(2), submit a formal request with your rationale and supportive information to justify the waiver for your drug product.

3. Provide detailed manufacturing process information for the 100% polyester cloth or refer to the appropriate Drug Master File (DMF).

4. Provide your acceptance criteria for the polyester cloth. Because the cloth will be saturated with the chlorhexidine gluconate (CHG) solution throughout the shelf-life of the product, address whether leachable/extractable studies have been conducted, and if so, provide the quantitative results for these studies.

5. Establish a limit for total impurities for the drug product and justify each specified and unspecified impurity. Your proposed regulatory limit for the (b) (4) impurity of not more than (NMT) (b) (4) ppm is reasonable; however, you did not set a regulatory limit for all other impurities (related substances and degradants).

6. Provide 18-month updated stability summaries and stability data generated for stability lot CHGPQ2, CHGPQ3, and CHGPQ4, including QC HPLC chromatograms (with all peaks labelled) for these lots.

7. Provide the Certificates of Analysis (COAs) for the drug substance batches used to manufacture the supporting drug product batches.

8. Provide the drug substance regulatory specifications.

9. Clarify what tests from the drug substance specifications are used for the incoming drug substance. If the test methods differ from the DMF or USP monograph, submit the analytical method and validation data.

Clinical Microbiology

1. Provide raw plate count data for the following studies:
   - Study R14-013: "Time-Kill Test Medline 2% CHG Solution"
   - Study R14-012: "Evaluation of Potential for Development of Antimicrobial Resistance"
   - Study R13-053: "Assessment of the Antimicrobial Efficacy of Medline 2% CHG Cloth Preoperative Skin Preparation"
   - Study R13-029: "Assessment of the Antimicrobial Efficacy of Medline 2% CHG Cloth Preoperative Skin Preparation"
   - Study R13-052: "Assessment of the Antimicrobial Efficacy of Medline 2% CHG Cloth Preoperative Skin Preparation"

2. Provide drying time and skin coverage studies for the Medline 2% CHG Cloth.

Clinical

1. If you intend to propose a waiver for the phototoxicity and photosensitivity human dermal safety studies, request such a waiver and identify the basis for your request e.g., absorption spectra.

2. The application does not provide safety information from a complete set of post-marketing databases. In general, we expect the Integrated Summary of Safety to contain an analysis of different sources of post-marketing safety data, which includes the applicant's own pharmacovigilance database, if applicable, and an assessment of safety reports from the FDA Adverse Events Reporting System (FAERS), World Health Organization (WHO) Vigibase, National Poison Data System (NPDS) from American Association of Poison Control, Drug Abuse Warning Network (DAWN), and medical literature. The literature must be in English or translated into English. We expect the review of the medical literature to summarize the literature with an overall conclusion to support the risk-benefit of the drug. If any of these are not to be provided, justify the reason for not doing so.

(b) (4)

Labeling

1. Submit the full annotated specifications (e.g., bolding, font/type size of text, headings, barlines, hairlines, bullets, etc.) for the *Drug Facts* labeling.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions call Celia Peacock, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

THERESA M MICHELE
04/08/2016