CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208288Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208288

COMPLETE RESPONSE

3M Health Care (Infection Prevention Division)
Attention: Dianne Gibbs
Regulatory Affairs Director, IPD Division
Building 275-5W-06
St. Paul, MD 55144-1000

Dear Ms. Gibbs:

Please refer to your New Drug Application (NDA) dated March 3, 2017, received March 3, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for SoluPrep™ (2% chlorhexidine gluconate and 70% isopropyl alcohol), solution.

We acknowledge receipt of your amendment dated March 3, 2017, which constituted a complete response to our May 6, 2016, action letter.

We also acknowledge receipt of your major amendment dated July 31, 2017, which was not reviewed for this action per your request on August 22, 2017, to withdraw the July 31 submission. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

NONCLINICAL

The proposed specifications of NMT (b) (4)% for the impurity, (b) (4), and NMT (b) (4)% for the impurity (b) (4) are above the qualification threshold per the ICH guidance for industry *Q3B(R2) Drug Product Impurities*. The dermal rabbit study (#16-014) submitted on March 3, 2017, does not include a sufficient tissue battery to assess systemic toxicity.

We also note that the doses administered in your rabbit dermal study do not appear to support your proposed impurity specifications for the 26 mL applicator, using the available data. This relies upon your proposed maximal use for the 26 mL applicator, the proposed impurity stability specifications, and conversion of the doses administered to animals to human equivalent doses. As an alternative to human equivalent doses, clinical pharmacokinetic data and animal

toxicokinetic data can be used to provide animal-to-human exposure margins. In addition, human pharmacokinetic from an adequate maximal use trial (MUsT) can demonstrate minimal systemic absorption of the impurities of concern. Absent these data, you have not provided adequate qualification data to support your proposed impurity specifications.

To resolve this deficiency, provide an adequate qualification study in a single animal species (e.g., a single extended dose study) or otherwise adequately address the systemic exposure to [redacted] (b) (4). As discussed during a teleconference on August 22, 2017, data from a Franz Cell assay does not supplant clinical pharmacokinetic data for informing the animal-to-human exposure margin, or demonstrating minimal absorption of the impurities of concern. In such cases the in vivo assessment of exposure (through a MUsT) is considered the definitive demonstration.

Alternatively, you can control the level of impurities to that of a relevant approved product using the total daily exposure resulting from four 26 mL applicators per day. This relies upon your proposed use for the 26 mL applicator, which results in higher estimated patient exposures than the anticipated use of the 10 mL applicator. If you choose this pathway, provide updated stability specifications consistent with your justification.

For a description of extended single dose studies, refer to ICH guidance for industry M3(R2) *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*. Briefly, one group of animals should be sacrificed on the day following dosing and an additional group on day 14 post-dose. Provide justification that your dosing regimen reflects the expected clinical use of your product. Specifically, ensure that the time and extent of application of your product in your animal studies is sufficient to address the anticipated maximal duration and extent of application in humans if your product is approved. To address systemic toxicity after dermal administration, assess a full battery of tissues. Animals may be dosed by the dermal route, with assessments for mortality, clinical signs, body weights, organ weights, food consumption, gross pathology, histopathology, and toxicokinetic parameters of the impurities after a single administration, with further evaluations conducted 2 weeks (14 days) later to assess delayed toxicity and/or recovery. In the absence of clinical pharmacokinetic data, ensure that the study addresses adequate exposure using body surface area conversion of doses, and a complete assessment of local and systemic effects. Provide justification for your study design in your submission.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

CHEMISTRY, MANUFACTURING AND CONTROLS

We acknowledge that you have accepted the Agency's recommendation for the drug product impurity levels and updated specifications (dated 21 August, 2017). Since the qualification of impurities is still inadequate, updated specifications for the drug product will remain as "tentative specifications".

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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
09/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208288

COMPLETE RESPONSE

3M Health Care (Infection Prevention Division)
Attention: Dianne Gibbs
Regulatory Affairs Director, IPD Division
3M Center
Building 275-5W-06
St. Paul, MN 55144-1000

Dear Ms. Gibbs:

Please refer to your New Drug Application (NDA) dated and received July 6, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for SoluPrep™ Film-Forming Sterile Surgical Solution (2% chlorhexidine gluconate and 70% isopropyl alcohol).

We also acknowledge receipt of your amendments dated April 21, 25, and 29, 2016, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. You have failed to demonstrate replicative efficacy in two pivotal clinical simulation studies, based on the previously agreed upon primary endpoints and statistical analyses. Study EM-05-012760 passed on all primary efficacy analyses; however, Study EM-05-013260 did not pass the ≥ 70% responder rate primary endpoint for the inguinal site. Thus, replicative efficacy was demonstrated for the abdominal site, but replicative efficacy was not demonstrated for the inguinal site. We have previously communicated to you (IND 076549, Advice/Information Request, April 17, 2015) that your proposed alternative primary efficacy analyses to be conducted in the event that the positive control fails to meet the 70% threshold are not acceptable.

   Conduct a repeat study of the inguinal region with adequate controls that meets the pre-specified primary endpoint.

2. The financial disclosure information provided in the NDA is not sufficient. Eleven of 20 subinvestigators listed on the revised 1572 for pivotal study EM-05-012760 are missing disclosure information. Also, one of the five subinvestigators is missing financial disclosure

information for study EM-05-013260. The guidance for industry (E6) Good Clinical Practice Guidance: Consolidated Guidance, section 8.2, (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf) indicates that this information should be documented before the trial starts formally. Financial arrangements between investigators and the sponsor can introduce bias in trial data that may be difficult to evaluate. In addition to the potential impact on efficacy outcome data, this is an issue of study conduct.

Describe your efforts to obtain financial disclosure both before and after the trial. Discuss the potential impact lack of financial disclosure may have on data integrity, especially efficacy data in the pivotal trials. Provide specific information regarding the role of each subinvestigator in the trials and whether that role had any involvement in determination or documentation of outcome data. In order to evaluate the possible impact on efficacy outcomes, identify how many subjects each subinvestigator had a role with during the trial. To the extent feasible for a single center trial, submit analyses dropping the subjects of all subinvestigators without financial disclosure per pivotal trial. Provide datasets for each pivotal trial that allow independent verification of the sensitivity analyses, (i.e. the subinvestigator is named for each subject by "usubjid" in efficacy datasets for each study). As a subinvestigator may have participated in more than one trial, for each trial in the NDA indicate whether there is missing subinvestigator information, list the missing subinvestigator(s), and provide a listing of all subinvestigators in the respective trial. For any additional clinical trials you conduct for this NDA, ensure that you collect financial disclosure information prior to start of the trial. You may also provide additional strategies you believe may evaluate this issue.

CLINICAL PHARMACOLOGY

You proposed to rely on literature to support the pharmacokinetics and absorption profile of your chlorhexidine/isopropyl alcohol product in humans. However, you provided inadequate literature references of human pharmacokinetic data evaluating isopropyl alcohol as a preoperative skin preparation and for the combination chlorhexidine/isopropyl alcohol.

You may rely on adequate literature for IPA and CHG/IPA to demonstrate absorption after use as a surgical skin preparation with a similar level of skin coverage to that proposed for the largest size product (26 mL), rely upon FDA's findings of safety for a listed drug(s), or conduct a maximal use pharmacokinetic study with the final, to-be-marketed formulation of your product.

NONCLINICAL

You failed to provide qualification data for two impurities, (b) (4), which exceed the allowed impurity threshold per ICH Q3B (R2) guidance (i.e., <1%) . We refer you to the meeting minutes from the teleconference held on January 12, 2016 between representatives of your company and the FDA.

Conduct qualification studies for [redacted] according to the qualification program as stated in ICH Q3B(R2) guidance *Impurities in New Drug Products*, which can be found at this link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf

PRODUCT QUALITY

Your proposed limits of [redacted]% for two related impurities, [redacted], exceed ICH Q3B (R2) limits (i.e., <1%) and are therefore unacceptable. Based on your quantitative stability data, [redacted] will reach 1.0% at [redacted] months, and [redacted] will exceed 1.0% at [redacted] months. These degradants continue to rise and accumulate in the drug product throughout the shelf-life. Even though you have proposed interim specifications for an interim shelf-life of [redacted] months, impurity [redacted] still exceeds the ICH limit of <1.0%. Therefore, at this time, no expiration date can be granted for this drug product.

To justify your proposed expiry dating, conduct qualification studies for [redacted]. Refer to Nonclinical Comments.

MICROBIOLOGY

1. The container closure integrity test (CCIT) validation data provided in the submission dated March 10, 2016 demonstrates that the proposed headspace oxygen analysis method has a detection rate of approximately 33% or less for defects that are 50 µm or larger in 10.5 mL drug product (DP) filled ampules. Moreover, you did not detect defects of any size in the 26 ml DP filled ampules. Further, the information presented indicates that your selected test method is only capable of detecting holes of 50 µm or greater, which, per the USP 1207.1 you previously provided, corresponds to an air leak rate of > 0.360 standard cc per second (sccs). Kirsch, et. al. (also referenced in the Parenteral Drug Association's Technical Report 27) demonstrated that a leakage rate that correlates with microbial ingress is approximately 10^{-5} sccs, which is considerably lower than what your results demonstrate. With the low detection rate demonstrated by positive controls, and without further information to correlate your proposed method with the potential for microbial ingress, the method that you propose is not acceptable as a CCIT method.

   Provide CCIT results from a validated testing method capable of detecting microbial ingress in order to demonstrate the integrity of the proposed container closure system (glass ampules) for the DP.

2. Provide CCIT results for the [redacted] pouch used to package the DP applicator. Provide a description of methods (and applicable validation information), a description of controls, and a summary of results.

3. Regarding [redacted] monitoring during production, the December 9, 2015 response (under section Q5) stated that [redacted]

[redacted]." Clarify if [redacted] for the 26.0 mL ampules is the same for the 10.5 mL ampule [redacted] during commercial production.

4. The information provided for the requalification (RQ) schedule for the [redacted] is acknowledged. However, [redacted] This is not acceptable, [redacted]

   Revise your SOP to provide a [redacted]

5. The December 9, 2015 submission stated that two samples from the 46 samples were tested for bioburden, [redacted] whereas the other 44 samples were taken from ampules that were placed in the stability program. Identify the source of each sample (lot numbers) and clarify if the 44 samples that were taken from the stability programs were [redacted].

6. In regard to the bioburden testing per [redacted] testing method STP00036, address the following concerns:
   a. Clarify the name of the microorganisms that are used as positive monitors for aerobic bacteria and fungi organisms.
   b. Clarify any additional rinsing steps (rinse fluid and volume) or neutralization buffers that are used to neutralize the antimicrobial activity of the DP against aerobic bacteria and fungi.
   c. Provide validation testing data to demonstrate that the STP00036 is capable or recovering aerobic

7. The information provided in the submission dated August 12, 2015 and November 6, 2015 included validation data for [redacted] lack clarity, and the report appears to contain discrepancies. Address the following points:
   a. The significance of the "[redacted] procedures described in protocol 201404182 is unclear; further, it is unclear if these were utilized in testing to support the conclusion that the method is validated.

b. The Phase 1 Validation report (745554.1) was performed according to protocol 201401236. A description of this method was not provided, and it is unclear how this relates to the proposed method intended for product testing ((b) (4) testing method #201404182).
c. Eight samples were utilized for Phase 2 testing (786924); however, results were only reported for three samples. No explanation was provided to indicate why the other five samples were discarded.

8. In regard to the sterility testing requirement for release of the DP, address the following concerns:
   a. The possibility of testing the (b) (4) instead of performing sterility testing for DP release that was discussed during the December 1, 2015 teleconference. As discussed, (b) (4) is dependent on the validation data for the testing method ((b) (4) testing method # 201404182) of the (b) (4). Revise the DP specifications to include a sterility testing method that has been fully validated.
   b. It was noted that the December 9, 2015 submission stated that "additional sterility testing will only be conducted as part of release only if (b) (4) Note that a backup method for sterility testing cannot be utilized for DP release in instances where the primary sterility testing method fails or in instances where an in-process control fails. This represents a testing-into-compliance process, and increases the chances of acceptance of false negative results. Clearly state the sterility testing method for the DP release, noting that inclusion of a backup testing method is not acceptable.

9. Your proposal to utilize CCIT in lieu of sterility testing for filled ampoules in the stability program is acceptable. Provide a stability specification which includes a validated CCIT method.

10. Incorporate a specification for sterility testing for the drug product applicator or CCIT for the (b) (4) pouch into the stability program.

PROPRIETARY NAME

Refer to our correspondence dated, October 19, 2015 which addresses the proposed proprietary name, SoluPrep™. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and

clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

CLINICAL

1. For all safety-related proposed labeling statements that are not directly supported by data from your conducted clinical studies, such as conditions of use, “Do Not Use”, pediatric use, and hypersensitivity/anaphylaxis, specify the literature articles that you are relying

upon to support each labeling statement. Provide an adequate summary of the relied upon literature. If you intend to rely upon "non-product specific literature" for such purposes, as stated in your application, you should ensure that the specified literature articles conform to your intent. Note that reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's findings of safety and/or effectiveness for the listed(s).

2. Discuss the drape adhesion study designs as related to real-world use.

3. Describe efforts to minimize or address bias in the small, open-label studies conducted by employees and used to support labeling (e.g., coverage and dry time studies).

4. Submit datasets that correspond to Listings 16.2.8.1 and 16.2.8.2 in the study report for study EM-05-013260 such that a comparison of adverse events with and without HEDTA can be verified.

5. The protocol for study EM-05-012680 submitted to the NDA on March 15, 2016 in amendment 23 does not appear to contain changes in dwell time noted on page 51/90 (adobe reader page number). Specify which pages of the protocol submitted in amendment 23 contain these changes.

6. Provide a dataset showing adverse events for study EM-05-012680 by unique subject id (column variable "usubjid").

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110 If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

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
05/06/2016