

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210872Orig1s000

OTHER REVIEW(S)

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**



Date	March 18, 2019
To	Teshara Bouie, Program Management OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMB
Requesting Division	OPQ/OPRO
From	Marc Neubauer CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Sarah Mollo, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRRID/GHDH
Subject	Consult for Submission # NDA 210872 ICCR #2018-03257 ICC#1800603
Recommendation	Device Constituents Parts of the Combination Product are Approvable

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-03257
ICC tracking # (Lead)	ICC1800603
Submission Number	NDA 210872
Sponsor	Zurex Pharma, Inc.
Drug/Biologic	Isopropyl alcohol, 70% v/v
Indications for Use	Patient preoperative skin preparation solution for use in presurgical settings as an antiseptic/antimicrobial agent to reduce bacteria that potentially can cause skin infection.
Device Constituent	Sterile applicator

Table 2. Review Team				
CDER/CBER Lead Review Division	OPQ/OPRO			
Submission RPM	Teshara Bouie, Program Management			
Lead Device Reviewer	Marc Neubauer			
The CDRH review is being managed under ICC #: ICC1800603				
Discipline Specific Consults	Reviewer Name	(Center/Office/Division/Branch)	CON#	Acceptable
Sterility	John Stansberry	(CDRH/ODE/DAGRID/INCB)	CON1828333	Yes
Biocompatibility	Jacqueline Gertz	(CDRH/ODE/DAGRID/GHDB)	CON196260	Yes

Table 3. Important Dates	
Final Lead Device Review Memo Due	3/20/109

2. PURPOSE/BACKGROUND

2.1. Scope

The CDER consult request states the following: “The Sponsor has included a number of nonclinical studies of device biocompatibility in the NDA. Please assign a reviewer.”

The goal of this review is to perform a device review on the sterile applicator including essential performance requirements, verification, stability, risk analysis, sterility, biocompatibility and finished product specifications.

2.2. Prior Interactions

N/A

2.3. Indications for Use

Combination Product	Indications for Use
Isopropyl alcohol, 70% v/v	Patient preoperative skin preparation solution for use in presurgical settings as an antiseptic/antimicrobial agent to reduce bacteria that potentially can cause skin infection.
Applicator	Delivery of the drug

3. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The following information was provided in Sequence # 001.2.3.P.7.

Container Closure System Overview

ZuraPrep™ solution is provided in a proprietary 10.5-mL applicator container closure system. The container closure system is comprised of

(b) (4)

(b) (4)

The suitability of all applicator components has been assessed in a biological risk assessment (*ZX-ZP-0087*), including nonclinical biocompatibility of the patient contacting foam sponge. The primary container has demonstrated compatibility with the drug product solution through successful performance of the 3 pilot lots on stability, as well as a chemical characterization evaluation, reference *section 3.2.P.2.4.* drug product with no unexplained degradation observed on stability.

(b) (4)

Primary Container Closure

Table 3.2.P.7-1 describes the primary container closure general characteristics including reference to applicable specifications and work instructions used in manufacture of the primary container components.

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5. DISCIPLINE SPECIFIC REVIEWS

5.1. Biocompatibility

Type/duration of contact

ZuraPrep components are classified as:

Contact type: Intact skin

Contact Duration: Limited (^{(b) (4)} hours)

Per ISO 10993 guidance – Attachment A:

The following endpoint assessments are recommended for a device with above identified contact type and contact duration:

- Cytotoxicity
- Sensitization
- Irritation or Intracutaneous reactivity

Note: The Handle would only intentionally contact the gloved hand of the user.

Material List

<u>Component</u>	<u>Material</u>	<u>Contact type</u>	<u>Endpoints (s)</u>
Foam	(b) (4)	Intact skin, limited	CSI

Test article(s)
ZuraPrep Applicator Foam Pad

All of the direct and indirect contacting components were used in the test article, and none of the non-contacting components were included. The test article was sterilized in the same manner as the final finished device. This is acceptable.

Reviewer's Comments

The biocompatibility tests could not be located in the original submission. See Agency Information Request #4, Question 2 in Section 8). The sponsor provided references.

The sponsor was asked to justify why the lonely testing required for biocompatibility was cytotoxicity, sensitization and irritation. See Agency Information Request #4, Question 2 in Section 8). Their response was adequate.

Cytotoxicity – Other methods

The test article, ZuraPrep™ Applicator Foam Pad, was evaluated to determine the potential for cytotoxicity. This study was conducted based on the requirements of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity. Triplicate wells were dosed with a 1 cm x 1 cm portion of the test article. Triplicate wells were dosed with a 1 cm length (0.25 inch outer diameter) portion of (b) (4) as a negative control. Triplicate wells were dosed with a 1 cm x 1 cm portion of (b) (4) as a positive control. Each was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating at 37°C in the presence of 5% CO₂ for 24-26 hours, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis.

The negative and positive control articles performed as expected, thereby confirming the suitability of the system test.

The test article (ZuraPrep™ Applicator Foam Pad) showed evidence of causing mild cell lysis or toxicity by producing a grade of 2 (reactivity – mild) for all three replicates tested after the 24-26 hour incubation period, thus meeting the requirements of the cytotoxicity test (i.e. all results for the test article less than or equal to grade 2 – mild reactivity). Additionally, it is noted that the 24-26 hour incubation period utilized in the testing is well beyond the intended patient contact time with the test article (limited use; less than 5 minutes patient contact time).

The scores obtained after 24-26 hours of incubation were as follows:

Table 6: Individual Scores

Articles	Zone of Lysis Beyond Article (mm)	Grade	Reactivity	
Test Article: (ZuraPrep™ Applicator Foam Pad)	(1)	0	2*	Mild
	(2)	0	2*	Mild
	(3)	0	2*	Mild
Negative Control: (b) (4)	(1)	0	0	None
	(2)	0	0	None
	(3)	0	0	None
Positive Control: (b) (4)	(1)	6	3*	Moderate
	(2)	7	3*	Moderate
	(3)	6	3*	Moderate

*Complete cell lysis was observed under the article.

Note: (1), (2), and (3) denote replicates.

Reviewer's comments:

The Agarose method was used to evaluate Cytotoxicity. Per 10993-5 section 8.4.1.1 this test method is not appropriate for leachables that cannot diffuse through the agar layer or that may react with agar. The use of agar diffusion assay for the assessment of cytotoxicity shall be justified.

Sensitization – Other methods

The test article, ZuraPrep™ Applicator Foam Pad, was evaluated for the potential to elicit delayed dermal contact sensitization in the guinea pig. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization.

The test article was occlusively patched to the intact skin of ten animals for 6 hours (± 30 minutes), three times a week, over a 3 week period. The control article was similarly patched to five animals. Following a 2-week recovery period, the ten test and five control animals were occlusively patched with the test article and the control article. All sites were observed for evidence of dermal reactions at 24 and 48 hours after patch removal.

The test article, ZuraPrep™ Applicator Foam Pad, showed no evidence of causing delayed dermal contact sensitization in the guinea pig. Dermal reaction scores at 24 and 48 hours post challenge with the test article were 0 (No visible change) for all control and test animals included in the study.

Reviewer's comments:

This is not the type of guinea pig test that we would traditionally expect to see. The results of the testing were comparable to the negative control. A proper induction phase was not conducted. Based on the information provided, it's not clear that this protocol would ever produce a reaction, even if the material was a sensitizer. A positive control was not included. However, based on the low risk and short contact duration of the device, we will not ask for repeated testing.

Irritation – Other methods

The test article, ZuraPrep™ Applicator Foam Pad, was evaluated for primary skin irritation in rabbits. This study was conducted in accordance with the guidelines of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. Two 25 mm x 25 mm sections of both the test article and control article were topically applied to the skin of each of three rabbits and left in place for a minimum of 23 hours and a maximum of 24 hours. The sites were graded for erythema and edema at 1, 24, 48 and 72 hours after removal of the single sample application.

There was no erythema and no edema observed on the skin of the animals treated with the ZuraPrep™ Applicator Foam Pad (test article) throughout the study duration. The Primary Irritation Index for the test article was calculated to be 0.0. The irritation response of the ZuraPrep™ Applicator Foam Pad was categorized as negligible.

Reviewer's comments:

This was endpoint was evaluated in a reasonably appropriate way. The results were similar to negative control.

5.2. Sterility



Consultant's Comments:

The sterilization information provided by the sponsor appears adequate and acceptable. [redacted] (b) (4)
[redacted] and the results met the acceptance
criteria. [redacted] (b) (4) See

Agency Information Request #3, Question 1 in Section 8)

The sponsor provided a description of the packaging for the device but the sponsor did not include seal strength testing. See Agency Information Request #2, Question 2 in Section 8).

The sponsor provided a shelf life testing using samples that were real time aged and samples that were subjected to accelerated aging. At the 24-month time point, all tested samples passed visual inspection and real time aging.

6. RISK ANALYSIS AND COMPLIANCE

The sponsor provided a biological risk assessment document and a sterility assessment. Due to the low risk of the device and since there is no dosing, we did not ask for a general risk assessment. Their essential performance requirements are adequately defined and verified through the device's shelf-life of twenty-four months.

Zurex will comply with cGMPs, 21 CFR parts 210 and 211. Additionally, as per 21 CFR 4.4(b)(1) following compliance with cGMPs, to demonstrate compliance with both sets of regulations, we provide a *partial SOP index* from the drug product manufacturer [REDACTED] (b) (4) and the applicable site-specific SOP's regarding management controls, purchasing controls, and CAPA.

- *SOP CO-020*, Medical Device Quality System Requirements – Management Responsibility
- *SOP PR-001*, Purchasing Operation
- *SOP CO-1141*, Corrective and Preventive Actions and Effectiveness Review

Reviewer's Comments

The sponsor's risk analysis and compliance approach is acceptable for a device with this level of risk. See Agency Information Request #3, Question 2 in Section 8 for their discussion on their approach for complying to the CFR regulations.

(b) (4)

ICC#1800603

NDA 210872, Isopropyl Alcohol, 70%, Applicator
Zurex Pharma, Inc.

(b) (4)

8. INTERACTIVE REVIEW

Agency Information Request #1 (sent on 08/13/2018) – Adequate

It appears you have not provided your [REDACTED] ^{(b) (4)} protocol and report for the applicator (device). Provide the date when you will provide this information.

Sponsor Response (received on 08/13/2018)

We acknowledge receipt of your request below. Please note that the [REDACTED] ^{(b) (4)} report is included in the NDA submission (SN 0001) under 32r-reg-info, file named tcp-16-037-bioburden. We acknowledge that the report exhibits (which contain the protocol) are not included and will remedy this via an informational amendment. For ease of review the protocol (exhibit 2 to the report) has been included.

Please confirm this is an adequate initial written response via email or if you require a formal submission with the exhibits via Thursday?

Reviewer Comments

The sponsor provided their (b) (4) protocols and reports. We have adequate information to begin primary review.

Agency Information Request #2 (sent on 10/14/2018) - Inadequate

1) In your submission, you did not identify and define any essential performance requirements (EPRs). For example, your device will require an activation force in order to use the device. Please define an activation force in Newtons, provide any other EPRs you have identified and defined, and provide the testing that verifies your device can meet these EPRs.

Zurex response:

The essential performance requirements for the plastic applicator packaging components are defined by each packaging component's quality specification in place at the component manufacturer and referenced in *section 3.2.P.7*. The "activation force" is addressed (b) (4)

Each packaging system component is inspected and released at receipt by the drug product manufacturer, (b) (4) per applicable master packaging component specification in place based on the component drawings. To follow is a listing of the critical attributes of the packaging components and the related performance characteristic tested by the component supplier (b) (4)

(b) (4)

(b) (4)



Reviewer Comments

The sponsor provided adequate essential performance requirements. Another IR request was sent to the sponsor requesting that they provide stability data demonstrating the EPRs are maintained throughout the shelf-life of the product.

- 2) In your submission, you provided package integrity testing that included visual inspection and dye penetration testing. However, it is unclear if you performed seal integrity testing or seal strength testing for your packaging. The seal integrity testing will ensure that your device packaging can maintain sterility of the subject device. Please provide a summary of the seal integrity testing performed on your device packaging.

Zurex response:

The sterile barrier system used for the 10.5-mL single-use applicator

(b) (4)



ICC#1800603

NDA 210872, Isopropyl Alcohol, 70%, Applicator

Zurex Pharma, Inc.

(b) (4). Table 2 below presents a summary of the sterile barrier system seal integrity testing performed at both the sterile barrier system supplier and the drug product manufacturer.



Reviewer Comments

The sponsor's response is acceptable because the package integrity testing summary appears adequate and acceptable. This deficiency is resolved

Agency Information Request #3 (sent on 10/29/2018) - Adequate

- 1) The pyrogenicity status of your device is unclear. Pyrogenicity testing is used to help protect patient from the risk of febrile reaction due to gram negative bacterial endotoxins or other sources of pyrogens. (b) (4)
(b) (4) please provide complete study reports for:
- a. Bacterial endotoxin test using LAL method per ANSI/AAMI ST72:2002 Bacterial endotoxins-Test methodologies, routine monitoring, and alternatives to batch testing and USP 24<161> for endotoxin evaluation. USP 24<161> suggests 3-10 samples evaluation for LAL), and
 - b. Material mediated pyrogenicity test using rabbit model per ISO 10993, Biological evaluation of medical devices, Part 11 Tests for systemic toxicity. For endotoxin limits and related requirements, you are recommended to follow FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers” June 2012 at the link <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf>.” (b) (4)
(b) (4)

Zurex response:

The drug product single-use applicator (b) (4)
(b) (4) Current USP 41 <161> is applicable to devices labeled sterile and nonpyrogenic that have contact directly or indirectly with the cardiovascular system, lymphatic system, or cerebrospinal fluid. Please note that for the preoperative use indication we seek, the drug product will be labeled for external use only, is applied only to intact skin, has limited contact (less than 2 minutes), and does not come in contact with any bodily fluids nor would it be implanted into the body. Therefore, the single-use applicator does not meet any of the conditions that would require endotoxin evaluation or pyrogenic testing. Accordingly, no pyrogen testing is planned to be conducted with this product.

Zurex has developed the applicator/components following current USP <661> - plastic packaging materials and their materials of construction as reflected in the container closure sections of pending NDA 210827. The suitability of all applicator components has been assessed in a biological risk assessment (ZX-ZP-0087), including nonclinical biocompatibility of the patient contacting foam sponge.

Reviewer Comments

The sponsor’s response is acceptable because (b) (4) the device is for external use only. This deficiency is resolved.

- 2) You have not stated how you will ensure compliance of the device QS (21 CFR Part 820) regulations that pertain to your combination product. State which of the approaches under 21 CFR 4.4(b) you plan to take for ensuring compliance to the device QS regulations. Demonstrate you are complying by providing an index of your standard operating procedures (SOPs) and providing the SOPs associated with management controls, design controls, purchasing controls and CAPA.

Zurex response:

As discussed above, we have approached the development of this product from the perspective of a drug product. For the components within our drug product, we will comply with 21 CFR parts 210 and 211. (b) (4)

(b) (4) we would view the applicator/container closure system to be equivalent to a liquid medication dispenser, a Class 1 device that is exempt from design controls.

As stated above, Zurex will comply with cGMPs, 21 CFR parts 210 and 211. Additionally, as per 21 CFR 4.4(b)(1) following compliance with cGMPs, to demonstrate compliance with both sets of regulations, we provide a *partial SOP*

index from the drug product manufacturer [REDACTED] (b)(4) and the applicable site-specific SOP's regarding management controls, purchasing controls, and CAPA.

- *SOP CO-020*, Medical Device Quality System Requirements – Management Responsibility
- *SOP PR-001*, Purchasing Operation
- *SOP CO-1141*, Corrective and Preventive Actions and Effectiveness Review

Reviewer Comments

The sponsor provided their strategy for complying with GMP regulations and provided adequate 21 CFR 820 procedures.

Agency Information Request #4 (sent on 02/06/2019) - Adequate

1. In your response dated 11/20/2018, for Deficiency #1, you identified an essential performance requirement for activation force [REDACTED] (b)(4) and state the testing is done by the component manufacturer. Although this testing can be done by the component manufacturer, essential performance requirements should go through stability testing and ensure essential performance requirements can be maintained throughout the device's shelf-life. Please test activation force (opening force) and any other device essential performance requirements using your 2-year aged devices from your real-time stability studies and provide the protocol and report for our review. Alternatively, if you do not have 2-year aged samples, please provide accelerated aging protocol and test reports that demonstrated the essential performance requirements are met over the labeled shelf-life of the device.

Reviewer Comments

The sponsor provided stability testing on two-year aged samples. All samples met the acceptance criteria. Their response is adequate.

2. In your document, Report ZX-ZP-0087; Biological risk assessment for ZuraPrepZ 10.5 mL Single-Use Applicator, you state in Page 6, Section 5, that the ZuraPrep Applicator should be evaluated for cytotoxicity, sensitization, irritation, acute systemic toxicity and material mediated pyrogenicity. In Appendix B, you provide the results of these tests for the foam part of your device which is the only direct contact component. Address the following deficiencies:
 - a. Appendix B does not include the acute systemic toxicity and material mediated pyrogenicity test reports and protocols. Provide the test reports and protocols for acute systemic toxicity and material mediated pyrogenicity.
 - b. We could not locate the test protocols and reports for your cytotoxicity, sensitization, irritation testing. Information such as you extracted your samples is missing in Appendix B. Provide your test protocols and reports for your cytotoxicity, sensitization, irritation testing and ensure it includes all relevant test parameters required in the ISO 10993 standard.

Zurex response:

The table referenced above indicates potential tests that could be necessary depending on the outcome/risk assessment. This is described in the paragraphs directly following the table listing in Section 5. Please note that for the preoperative use indication we seek, neither tests were deemed necessary or conducted. We reference the risk assessment provided and more recently the Zurex response to Question 3 in a prior information request for pyrogenicity information provided via SN0008 on 11/20/2018.

The protocol and reports for the three studies are included in NDA 210872, SN0001, module 4/42/423/4237/42377 as study numbers ZX-ZP-00063 (cytotoxicity), ZX-ZP-0064 (sensitization), and ZX-ZP-0065 (irritation).

Reviewer Comments

For Part A, the sponsor provided an appropriate justification for why cytotoxicity, sensitization, irritation testing are the only tests required for device components that have limited contact time with skin only. The sponsor provided the location of the test protocol and reports in the original submission for Part B. Their response is adequate.

Agency Information Request #5 (sent on 02/06/2019) - Adequate

1. You have selected to use the Agar overlay method to address the cytotoxicity endpoint. Per ISO 10993-5 section 8.4.1.1, This test method is not appropriate for leachables that cannot diffuse through the agar layer or that may react with agar. Provide a justification for the use of the agar assay. Specifically, please comment on the ability of the expected leachables and manufacturing residuals to pass through the agar and reach the cells.

Zurex response:

The agarose mixture used was prepared with equal amounts of 2% agarose and 2X MEM supplemented with 10 % fetal bovine serum and neutral red. This medium is suitable for extraction of both polar and nonpolar constituents. The mixture with 2X MEM would equate to a final agarose content of approximately 1% which would make the agarose layer sufficiently porous for the cytotoxicity screening of the drug product applicator (b)(4) foam pad. This model was indicative of suitable biocompatibility prior to proceeding with testing in humans. Further, in order to prevent dehydration of the agarose (due to the absorptive nature of the foam), the test article was hydrated with 1X MEM supplemented with 5% fetal bovine serum for approximately 24 hours at 37°C prior to application to the test system (agarose layer).

ISO 10993-5 and other ISO standards have been used throughout development as guidance in the evaluation of our drug product applicator with the cytotoxicity test representing one aspect of a battery of biocompatibility screening tests that were performed prior to initiation of the two large-scale clinical simulation studies. While the ISO test methodologies were followed, it is important to reiterate that the intended use of our applicator is to dispense a single dose of the drug product (70% isopropyl alcohol) to intact skin with a limited contact time (2 minutes) in a controlled healthcare environment. The time that the foam pad contacts the same skin cells is a fraction of the total application time indicated per labeling of 2 minutes due to the continuous back and forth application motion over the intended coverage area. For cytotoxicity testing, based on the intended use of the applicator, no ISO methodology listed in the standard (ISO 10993-5) is specifically applicable or strictly specified. In consideration of the suggested methods, 1) there are limitations with the direct contact method due to the physical characteristics of our test article and 2) the extraction method has been known to be prone to variable/inconsistent results. Therefore, the agarose study was considered to be the best model for screening of our applicator, especially considering that it has contact with intact skin.

For the agarose study conducted, the use of a positive control validated that preparation of our test system was suitable for our test purposes, i.e. allowing known inhibitory leachables/extractables to diffuse appropriately. Further, it should be noted that any conclusions about the biological safety of the applicator were not based solely on the results of the cytotoxicity study. Study ZX-ZP-0063 was used in the development program, in conjunction with the animal sensitization and irritation studies, to provide sufficient support allowing advancement to the clinical simulation trials. The extractable profile of the (b)(4) foam presented in Zurex study ZX-ZP-0080 also used ISO standards as guidance and overestimates the potential exposure due to the exaggerated design (extraction for 24 hours at 50°C). The extractables observed were assessed per Biological Risk Assessment Report ZX-ZP-0087 and concluded to appropriately meet the requirements to be considered safe for use in application of the drug product solution to intact skin with limited contact time.

Reviewer Comments

Their response is acceptable. They have adequately addressed this deficiency.

2. Your test article received a cytotoxicity grade of 2 for all three replicates. While this does meet the requirements outlined in 10993-5, we do not expect to see a grade of 2 for (b) (4) foam products. An increased score could suggest the presence of manufacturing residuals on the foam. Please provide a justification for the acceptability of a cytotoxicity grade of 2 for a (b) (4) foam.

Zurex response:

Please refer to the above response to item 1. As discussed in the above Zurex response, cytotoxicity has been used as one in a battery of tests along the development path of the drug product container closure system. ISO standards have been used throughout the development process as guidance. While a mild cytotoxic response was observed, this can be attributed to the exaggerated study design and not indicative of the overall performance of the product according to the intended use. Controlled clinical testing in addition to the biological risk assessment performed (ZX-ZP-0087) have not highlighted any safety concerns, mitigating the risk posed by any potential extractables/leachables from the (b) (4) foam pad.

The cytotoxicity study results are determined by the technician's measurement of a zone of inhibition in millimeters (mm). A response under the test article with no zone of inhibition extending out from the test article is considered mildly reactive, grade 2 (passing). The contact time employed, using the standard as guidance, was 24 hours at 37°C. This extended contact time of the test article with supplemented media is the most likely contributor to the results observed. The absence of any measurable zone (even 1 mm vs the 6-7 mm observed in the positive control) beyond the test article across the three replicates provides ample evidence that the cytotoxic response is more related to study design than leachable/extractable agents.

Please note that the drug product solution will be dispensed at the point of use by a healthcare professional. The time the solution contacts the foam pad will be approximately equal to the time used to apply the drug product to the patient. The time the foam pad contacts the patient will be approximately 2 minutes or less and will be applied in a back and forth continual motion over the prescribed coverage area. The cytotoxicity results, while mildly reactive, were suitable to support further clinical use and development of the (b) (4) foam pad. Additional biocompatibility testing performed showed no evidence of a safety concern and has been discussed and presented in the Biological Risk Assessment Report ZX-ZP-0087. The irritation study performed in rabbits and the sensitization study performed in guinea pigs showed no positive response. Therefore, the applicator progressed to clinical simulation testing. The cytotoxicity study needs to be considered within the limitations of the test design (exaggerated) versus intended use, as discussed above, and in the context of the other biocompatibility results presented and discussed in ZX-ZP-0087. It should also be noted that 1) the irritation study used exaggerated exposure conditions (direct contact with skin for ~24 hours) and 2) the sensitization study used exaggerated conditions (direct contact with skin for ~6 hours/day, three times/week, for 3 weeks); even with these exaggerated exposures, no in vivo responses were observed. In totality, the risk associated with this material, extensively used across multiple medical applications, for its intended use is negligible.

Clinical experience with the (b) (4) foam pad (applicator with drug product solution) is considerable through completion of two independent pivotal efficacy trials in which safety was assessed. The applicator, including the exact (b) (4) foam pad, was used in drug product application of 1-2 different test areas (abdomen and inguinal areas, 1 applicator per site) per person in over 1400 subjects (n= 1126 for the drug product and n=306 for the vehicle application) resulting in only 8 total treatment emergent AE's across the two products applied, none attributed to the (b) (4) foam pad.

Reviewer Comments

Their response is acceptable. They have adequately addressed this deficiency.

ICC#1800603

NDA 210872, Isopropyl Alcohol, 70%, Applicator

Zurex Pharma, Inc.

9. OUTSTANDING DEFICIENCIES

No outstanding deficiencies.

10.RECOMMENDATION

Device Constituents Parts of the Combination Product are Approvable

11.APPENDIX

- 1) Sterility Consult
- 2) Biocompatibility Consult



Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

CON1828333 (ICC1800603)
Consult Review

Date: December 5, 2018
To: Marc Neubauer
From: CDR John Stansberry, INCB, DAGRID/ODE
Through: CAPT Elizabeth Claverie, Branch Chief, INCB, DAGRID/

Background:

The sponsor Zurex Pharma, Inc has submitted a NDA (NDA210872) for an applicator (ZuraPrep) which contains (Isopropyl alcohol 70%). According to the sponsor, this application relies on the Agency's previous findings of safety for the reference listed drug, ChloroPrep® (2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol), marketed by Becton Dickinson and Co., under NDA 020832. ZuraPrep and ChloroPrep both contain 70% v/v isopropyl alcohol at the same concentration, have the same dosage form, route of administration, and indication. The outside of the subject device is sterile (b) (4) and the single use device (SUD) (b) (4)

Recommendation:

No additional information is required. Sterility/shelf-life data and test reports for the subject device in ICC1800603 are adequate and acceptable.

Purpose:

Review of the sterility/shelf-life data and test reports for the subject device in ICC1800603.

Indications for Use:

Patient preoperative skin preparation solution for use in presurgical settings as an antiseptic/antimicrobial agent to reduce bacteria that potentially can cause skin infection

Device Description:

ZuraPrep solution is a nonsterile, blue, isopropyl alcohol based topical antiseptic/antimicrobial solution containing a combination of excipient ingredients, which have demonstrated a broad safety profile and most of which are generally recognized as safe for multiple administration routes, including dermal.

The components, their function, and quality are provided in Table 3.2.P.1-1.

Component	Amount (per unit)	Type of Ingredient	Function	Reference to Quality Standards
Isopropyl alcohol, (b) (4)	70% (v/v)	Active ingredient	Antiseptic (b) (4)	USP
Citric acid (b) (4)	(b) (4)	Excipient	(b) (4)	USP
(b) (4)	(b) (4)	Excipient	(b) (4)	USP
Methylparaben	(b) (4)	Excipient	(b) (4)	NF
Propylparaben	(b) (4)	Excipient	(b) (4)	NF
Methylene blue (b) (4)	(b) (4)	Excipient	(b) (4)	USP
Purified water	(b) (4)	Excipient	(b) (4)	USP
NF = National Formulary; USP = United States Pharmacopeia (b) (4)				

Isopropyl alcohol has clearly demonstrated antimicrobial effectiveness both individually and in the drug product formulation. While all excipients, excluding purified water, show some subtherapeutic antimicrobial activity alone or in combination as the vehicle, they do not achieve the therapeutic bacterial log reduction requirements across a broad microbial spectrum that is considered effective in both in vitro and in vivo efficacy models. Each excipient's primary function in the drug product formulation is as described above in Table 3.2.P.1-1.

ZuraPrep solution is packaged into a single use 10.5-mL applicator container closure system comprised (b) (4)

(b) (4)

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The sponsor used the real time aging and accelerated/heat-aging method demonstrate that the packaging will maintain a sterile barrier. The shelf-life for the finished device is one (2) years from date of manufacture. After real time and accelerated aging, sample were evaluated by visual inspection and dye penetration. All tested samples passed visual inspection and dye penetration testing.

Long Term Stability: 25°C ± 2°C / 60% RH ± 5% RH			Test Interval (Months)						
Test Name	Test Method	Specification	0	3	6	9	12	18	24
Container									
Container Appearance	Visual	No visual evidence of deterioration	X	X	X	X	X	X	X
Sterile Barrier Seal Integrity Dye Penetration	ASTM F1929 Method B	Pass						X**	X
Solution									
Description	Visual	Cobalt blue, clear solution	X	X	X	X	X	X	X
pH	QI-020	(b) (4)	X	X	X	X	X	X	X
Isopropyl Alcohol (% v/v)	SOP-TM-0002	(b) (4) %	X	X	X	X	X	X	X
Total Impurities	(b) (4)	NMT (b) (4) %							
Related Substances	SOP-TM-0005	NMT % NMT %	X	X	X	X	X	X	X
(b) (4) Citric Acid	SOP-TM-0001	(b) (4) mg/mL	X	X	X	X	X	X	X
Propylparaben	SOP-TM-0003	mg/mL	X	X	X	X	X	X	X
Methylparaben	SOP-TM-0003	mg/mL	X	X	X	X	X	X	X
Methylene Blue (%)	SOP-TM-0003	(b) (4) %	X	X	X	X	X	X	X
Report RRT (b) (4) %)		For Info Only							
Related Substances Specified Identified - (b) (4)		NMT (b) (4) %							
Specified Unidentified Impurity (RRT (b) (4) Report all ≥ (b) (4) %)	SOP-TM-0004	NMT %	X	X	X	X	X	X	X
Any Other Unknown (Report all ≥ (b) (4) %)		NMT %							
Total Impurities	SOP-TM-0004	NMT (b) (4) %	X	X	X	X	X	X	X
Total Aerobic Microbial Count (TAMC)	USP* <61>	NMT (b) (4) cfu/g	X				X		X
Total Yeasts & Molds (TYMC)	USP* <61>	NMT (b) (4) fu/g	X				X		X
Microbial Limits									
Pseudomonas aeruginosa	USP* <62>	Absence	X				X		X
Staphylococcus aureus		Absence							

* USP reference is for USP Current
** Implemented with specification Form-S0007 v03 update.

Reviewer's Comments: The sponsor provided a shelf life testing using samples that were real time aged and samples that were subjected to accelerated aging. At the 24-month time point, all tested samples passed visual inspection and real time aging.

APPEARS THIS WAY ON ORIGINAL

List of Deficiencies

1. The pyrogenicity status of your device is unclear. Pyrogenicity testing is used to help protect patient from the risk of febrile reaction due to gram negative bacterial endotoxins or other sources of pyrogens. (b) (4)

please provide complete study reports for:

a. Bacterial endotoxin test using LAL method per ANSI/AAMI ST72:2002 Bacterial endotoxins-Test methodologies, routine monitoring, and alternatives to batch testing and USP 24<161> for endotoxin evaluation. USP 24<161> suggests 3-10 samples evaluation for LAL), and

b. Material mediated pyrogenicity test using rabbit model per ISO 10993, Biological evaluation of medical devices, Part 11 Tests for systemic toxicity. For endotoxin limits and related requirements, you are recommended to follow FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers” June 2012 at the link <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf>. (b) (4)

Sponsor comment:

The drug product single-use applicator (b) (4)

Current USP 41 <161> is applicable to devices labeled sterile and nonpyrogenic that have contact directly or indirectly with the cardiovascular system, lymphatic system, or cerebrospinal fluid. Please note that for the preoperative use indication we seek, the drug product will be labeled for external use only, is applied only to intact skin, has limited contact (less than 2 minutes), and does not come in contact with any bodily fluids nor would it be implanted into the body. Therefore, the single-use applicator does not meet any of the conditions that would require endotoxin evaluation or pyrogenic testing. Accordingly, no pyrogen testing is planned to be conducted with this product. Zurex has developed the applicator/components following current USP <661> - plastic packaging materials and their materials of construction as reflected in the container closure sections of pending NDA 210827. The suitability of all applicator components has been assessed in a biological risk assessment (ZX-ZP-0087), including nonclinical biocompatibility of the patient contacting foam sponge.

Reviewer comment:

The sponsor's response is acceptable because (b) (4)
the device is for external use only. This deficiency is resolved.

2. In your submission, you provided package integrity testing that included visual inspection and dye penetration testing. However, it is unclear if you performed seal integrity testing or seal strength testing for your packaging. The seal integrity testing will ensure that your device packaging can maintain sterility of the subject device. Please provide a summary of the seal integrity testing performed on your device packaging include real time aged or accelerated aged samples.

Sponsor comment:

The sterile barrier system used for the 10.5-mL single-use applicator

(b) (4)

Table 2 below presents a summary of the sterile barrier system seal integrity testing performed at both the sterile barrier system supplier and the drug product manufacturer.

(b) (4)

Reviewer comment:

The sponsor's response is acceptable because the package integrity testing summary appears adequate and acceptable. This deficiency is resolved.

John Stansberry, PhD

Reviewer

CAPT Elizabeth Claverie-Williams, MS

Branch Chief



Memorandum: Biocompatibility Consult

To: Marc Neubauer, Lead Reviewer, CDRH/DAGID/GHDB
From: Jacqueline Gertz, Biomedical Engineer, CDRH/DAGID/GHDB
Date: March 8, 2019
Subject: NDA 210872
Device: Zuraprep applicator
Sponsor: Zurex Pharma

Summary Recommendation:

- No additional biocompatibility questions required.

Of note: quotes from the Sponsor are written in *italics*, comments to be directed to the Sponsor are in **bold**.

I. Scope of Consult Request

- Biocompatibility review of patient-contacting components

II. Information Reviewed

- Biocompatibility Section

III. Background

On the fly consult for non-traditional CSI test methods

IV. Indications for Use

Isopropyl alcohol, 70% v/v: Patient preoperative skin preparation solution for use in presurgical settings as an antiseptic/antimicrobial agent to reduce bacteria that potentially can cause skin infection.

V. Device Description

ZuraPrep™ solution is provided in a proprietary 10.5-mL applicator container closure system. The container closure system is comprised

(b) (4)

(b) (4)

VI. Biocompatibility Summary

Type/duration of contact

ZuraPrep components are classified as:

Contact type: Intact skin

Contact Duration: Limited ((b) (4) hours)

Per ISO 10993 guidance – Attachment A:

The following endpoint assessments are recommended for a device with above identified contact type and contact duration:

- Cytotoxicity
- Sensitization
- Irritation or Intracutaneous reactivity

Note: The Handle would only intentionally contact the gloved hand of the user.

Material List

<u>Component</u>	<u>Material</u>	<u>Contact type</u>	<u>Endpoints (s)</u>
Foam	(b) (4)	Intact skin, limited	CSI

Test article(s)

ZuraPrep Applicator Foam Pad

All of the direct and indirect contacting components were used in the test article, and none of the non-contacting components were included. The test article was sterilized in the same manner as the final finished device. This is acceptable.

Cytotoxicity – Other methods

The test article, ZuraPrep™ Applicator Foam Pad, was evaluated to determine the potential for cytotoxicity. This study was conducted based on the requirements of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity. Triplicate wells were dosed with a 1 cm x 1 cm portion of the test article. Triplicate wells were dosed with a 1 cm length (0.25 inch outer diameter) portion of (b)(4) as a negative control. Triplicate wells were dosed with a 1 cm x 1 cm portion of (b)(4) as a positive control. Each was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating at 37°C in the presence of 5% CO₂ for 24-26 hours, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis.

The negative and positive control articles performed as expected, thereby confirming the suitability of the system test.

The test article (ZuraPrep™ Applicator Foam Pad) showed evidence of causing mild cell lysis or toxicity by producing a grade of 2 (reactivity – mild) for all three replicates tested after the 24-26 hour incubation period, thus meeting the requirements of the cytotoxicity test (i.e. all results for the test article less than or equal to grade 2 – mild reactivity). Additionally, it is noted that the 24-26 hour incubation period utilized in the testing is well beyond the intended patient contact time with the test article (limited use; less than 5 minutes patient contact time).

The scores obtained after 24-26 hours of incubation were as follows:

Table 6: Individual Scores

Articles	Zone of Lysis Beyond Article (mm)	Grade	Reactivity	
Test Article: (ZuraPrep™ Applicator Foam Pad)	(1)	0	2*	Mild
	(2)	0	2*	Mild
	(3)	0	2*	Mild
Negative Control: (b)(4)	(1)	0	0	None
	(2)	0	0	None
	(3)	0	0	None
Positive Control: (b)(4)	(1)	6	3*	Moderate
	(2)	7	3*	Moderate
	(3)	6	3*	Moderate

*Complete cell lysis was observed under the article.

Note: (1), (2), and (3) denote replicates.

Reviewer's comments:

The Agarose method was used to evaluate Cytotoxicity. Per 10993-5 section 8.4.1.1 this test method is not appropriate for leachables that cannot diffuse through the agar layer or that may react with agar. The use of agar diffusion assay for the assessment of cytotoxicity shall be justified.

Deficiency: You have selected to use the Agar overlay method to address the cytotoxicity endpoint. Per ISO 10993-5 section 8.4.1.1, This test method is not appropriate for leachables that cannot diffuse through the agar layer or that may react with agar. Provide a justification for the use of the agar assay. Specifically, please comment on the ability of the expected leachables and manufacturing residuals to pass through the agar and reach the cells.

Sponsor's response: The agarose mixture used was prepared with equal amounts of 2% agarose and 2X MEM supplemented with 10 % fetal bovine serum and neutral red. This medium is suitable for extraction of both polar and nonpolar constituents. The mixture with 2X MEM would equate to a final agarose content of approximately 1% which would make the agarose layer sufficiently porous for the cytotoxicity screening of the drug product applicator (b)(4) foam pad. This model was indicative of suitable biocompatibility prior to proceeding with testing in humans. Further, in order to prevent dehydration of the agarose (due to the absorptive nature of the foam), the test article was hydrated with 1X MEM supplemented with 5% fetal bovine serum for approximately 24 hours at 37°C prior to application to the test system (agarose layer).

ISO 10993-5 and other ISO standards have been used throughout development as guidance in the evaluation of our drug product applicator with the cytotoxicity test representing one aspect of a battery of biocompatibility screening tests that were performed prior to initiation of the two large-scale clinical simulation studies. While the ISO test methodologies were followed, it is important to reiterate that the intended use of our applicator is to dispense a single dose of the drug product (70% isopropyl alcohol) to intact skin with a limited contact time (2 minutes) in a controlled healthcare environment. The time that the foam pad contacts the same skin cells is a fraction of the total application time indicated per labeling of 2 minutes due to the continuous back and forth application motion over the intended coverage area. For cytotoxicity testing, based on the intended use of the applicator, no ISO methodology listed in the standard (ISO 10993-5) is specifically applicable or strictly specified. In consideration of the suggested methods, 1) there are limitations with the direct contact method due to the physical characteristics of our test article and 2) the extraction method has been known to be prone to variable/inconsistent results. Therefore, the agarose study was considered to be the best model for screening of our applicator, especially considering that it has contact with intact skin.

For the agarose study conducted, the use of a positive control validated that preparation of our test system was suitable for our test purposes, i.e. allowing known inhibitory leachables/extractables to diffuse appropriately. Further, it should be noted that any conclusions about the biological safety of the applicator were not based solely on the results of the cytotoxicity study. Study ZX-ZP-0063 was used in the development program, in conjunction with the animal sensitization and irritation studies, to provide sufficient support allowing advancement to the clinical simulation trials. The extractable profile of the (b)(4) foam presented in Zurex study ZX-ZP-0080 also used ISO standards as guidance and overestimates the potential exposure due to the exaggerated design (extraction for 24 hours at 50°C). The extractables observed were assessed per Biological Risk Assessment Report ZX-ZP-0087 and concluded to appropriately meet the requirements to be considered safe for use in application of the drug product solution to intact skin with limited contact time.

Reviewer's comments: this is acceptable.

Deficiency: Your test article received a cytotoxicity grade of 2 for all three replicates. While this does meet the requirements outlined in 10993-5, we do not expect to see a grade of 2 for (b)(4) foam products. An increased score could suggest the presence of manufacturing residuals on the foam. Please provide a justification for the acceptability of a cytotoxicity grade of 2 for a (b)(4) foam.

Sponsor's response: Please refer to the above response to item 1. As discussed in the above Zurex response, cytotoxicity has been used as one in a battery of tests along the development path of the drug product container closure system. ISO standards have been used throughout the development process as guidance. While a mild cytotoxic response was observed, this can be attributed to the exaggerated study design and not indicative of the overall performance of the product according to the intended use. Controlled clinical testing in addition to the biological risk assessment performed (ZX-ZP-0087) have not highlighted any safety concerns, mitigating the risk posed by any potential extractables/leachables from the (b)(4) foam pad.

The cytotoxicity study results are determined by the technician's measurement of a zone of inhibition in millimeters (mm). A response under the test article with no zone of inhibition extending out from the test article is considered mildly reactive, grade 2 (passing). The contact time employed, using the standard as guidance, was 24 hours at 37°C. This extended contact time of the test article with supplemented media is the most likely contributor to the results observed. The absence of any measurable zone (even 1 mm vs the 6-7 mm observed in the positive control) beyond the test article across the three replicates provides ample evidence that the cytotoxic response is more related to study design than leachable/extractable agents.

Please note that the drug product solution will be dispensed at the point of use by a healthcare professional. The time the solution contacts the foam pad will be approximately equal to the time used to apply the drug product to the patient. The time the foam pad contacts the patient will be approximately 2 minutes or less and will be applied in a back and forth continual motion over the prescribed coverage area. The cytotoxicity results, while mildly reactive, were suitable to support further clinical use and development of the (b)(4) foam pad. Additional biocompatibility testing performed showed no evidence of a safety concern and has been discussed and presented in the Biological Risk Assessment Report ZX-ZP-0087. The irritation study performed in rabbits and the sensitization study performed in guinea pigs showed no positive response. Therefore, the applicator progressed to clinical simulation testing. The cytotoxicity study needs to be considered within the limitations of the test design (exaggerated) versus intended use, as discussed above, and in the context of the other biocompatibility results presented and discussed in ZX-ZP-0087. It should also be noted that 1) the irritation study used exaggerated exposure conditions (direct contact with skin for ~24 hours) and 2) the sensitization study used exaggerated conditions (direct contact with skin for ~6 hours/day, three times/week, for 3 weeks); even with these exaggerated exposures, no in vivo responses were observed. In totality, the risk associated with this material, extensively used across multiple medical applications, for its intended use is negligible.

Clinical experience with the (b)(4) foam pad (applicator with drug product solution) is considerable through completion of two independent pivotal efficacy trials in which safety was assessed. The applicator, including the exact (b)(4) foam pad, was used in drug product application of 1-2 different test areas (abdomen and inguinal areas, 1 applicator per site) per person in over 1400 subjects (n= 1126 for the drug product and n=306 for the vehicle application) resulting in only 8 total treatment emergent AE's across the two products applied, none attributed to the (b)(4) foam pad.

Reviewer's comments: this is acceptable.

Sensitization – Other methods

The test article, ZuraPrepTM Applicator Foam Pad, was evaluated for the potential to elicit delayed dermal contact sensitization in the guinea pig. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization.

The test article was occlusively patched to the intact skin of ten animals for 6 hours (±30 minutes), three times a week, over a 3 week period. The control article was similarly patched to five animals. Following a 2-week recovery period, the ten test and five control animals were occlusively patched with the test article and the control article. All sites were observed for evidence of dermal reactions at 24 and 48 hours after patch removal.

The test article, ZuraPrepTM Applicator Foam Pad, showed no evidence of causing delayed dermal contact sensitization in the guinea pig. Dermal reaction scores at 24 and 48 hours post challenge with the test article were 0 (No visible change) for all control and test animals included in the study.

Reviewer's comments:

This is not the type of guinea pig test that we would traditionally expect to see.

The results of the testing were comparable to the negative control. A proper induction phase was not conducted. Based on the information provided, it's not clear that this protocol would ever produce a reaction, even if the material was a sensitizer. A positive control was not included.

However, based on the low risk and short contact duration of the device, we will not ask for repeated testing.

Irritation – Other methods

The test article, ZuraPrepTM Applicator Foam Pad, was evaluated for primary skin irritation in rabbits. This study was conducted in accordance with the guidelines of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. Two 25 mm x 25 mm sections of both the test article and control article were topically applied to the skin of each of three rabbits and left in place for a minimum of 23 hours and a maximum of 24 hours. The sites were graded for erythema and edema at 1, 24, 48 and 72 hours after removal of the single sample application.

There was no erythema and no edema observed on the skin of the animals treated with the ZuraPrepTM Applicator Foam Pad (test article) throughout the study duration. The Primary Irritation Index for the test article was calculated to be 0.0. The irritation response of the ZuraPrepTM Applicator Foam Pad was categorized as negligible.

Reviewer's comments:

This endpoint was evaluated in a reasonably appropriate way. The results were similar to negative control.

VII. Detailed Recommendations

Deficiencies for the Sponsor sent on 3/8/2019

1. You have selected to use the Agar overlay method to address the cytotoxicity endpoint. Per ISO 10993-5 section 8.4.1.1, This test method is not appropriate for leachables that cannot diffuse through the agar layer or that may react with agar. Provide a justification for the use of the agar assay.

Biocompatibility Review Memorandum – (continued)

Specifically, please comment on the ability of the expected leachables and manufacturing residuals to pass through the agar and reach the cells.

2. Your test article received a cytotoxicity grade of 2 for all three replicates. While this does meet the requirements outlined in 10993-5, we do not expect to see a grade of 2 for (b)(4) foam products. An increased score could suggest the presence of manufacturing residuals on the foam. Please provide a justification for the acceptability of a cytotoxicity grade of 2 for a (b)(4) foam.

The Sponsor responded to the deficiencies on 3/12/2019. All deficiencies have been resolved. See review memo sections above for Sponsor’s responses and review of these responses.

Digital Signature Concurrence Table	
Consultant Reviewer	

Drafted: 11/6/2018 (JGertz)

Revised: 11/7/2018 (JGertz, JJohnson, SMollo, JGoode); 11/13/2018 (JGertz, JLGoode); 11/27/2018 (JGertz, JLGoode), 11/30/2018 (JGertz)

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/

SHERRY A STEWART
05/01/2019 03:56:09 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: April 9, 2019
Requesting Office or Division: Division of Nonprescription Drug Products (DNNDP)
Application Type and Number: NDA 210872
Product Name and Strength: ZuraGard (Isopropyl Alcohol) Solution, 70%
Applicant/Sponsor Name: Zurex Pharma
FDA Received Date: April 8, 2019
OSE RCM #: 2018-1487-1
DMEPA Safety Evaluator: Grace P. Jones, PharmD, BCPS
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Division of Nonprescription Drug Products (DNBP) requested that we review the revised container label and carton labeling for ZuraGard (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling for ZuraGard are acceptable from a medication error perspective. We have no further recommendations at this time.

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^a Jones G. Human Factors, Label, and Labeling Review for ZuraGard (NDA 210872). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 18. RCM No.: 2018-1487.

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/

GRACE JONES
04/09/2019 11:16:04 AM

CHI-MING TU
04/09/2019 11:55:06 AM

Labeling Review for ZuraGard™ Isopropyl Alcohol (70% v/v) Solution *Draft Labeling*

SUBMISSION DATES: June 29, 2018; October 24, 2018; December 6, 2018;
February 15, 2019; March 27, 2019; April 8, 2019

NDA/SUBMISSION TYPE: 210872 (Original)

ACTIVE INGREDIENT: Isopropyl alcohol (70% v/v)

DOSAGE FORM: Solution

SPONSOR: Zurex Pharma, Inc.
2113 Eagle Drive
Middleton, WI 53562

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Executive Vice President, Regulatory Affairs and Quality
Assurance Operations
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REVIEWER: Hana Mujahid, PhD, ODEIV/DNDP

TEAM LEADER: Francisco Martínez-Murillo, PhD, ODEIV/DNDP

PROJECT MANAGER: Sherry Stewart, PharmD, ODEIV/DNDP

I. BACKGROUND

On June 29, 2018, the Sponsor submitted NDA 210872 ZuraPrep™ Solution (isopropyl alcohol, 70% v/v) as an original new NDA. ZuraPrep™ is composed of an isopropyl alcohol (70% v/v) non-sterile solution supplied in a single use 10.5 mL sterile applicator with a sponge tip. (b) (4) as a patient preoperative skin preparation solution for use in presurgical settings as an antiseptic/antimicrobial agent to reduce the bacteria that potentially can cause skin infection. This application relies on the Agency's previous finding of safety for the reference listed drug, ChloroPrep One-Step (isopropyl alcohol, 70% v/v and chlorhexidine gluconate, 2% w/v), under NDA 020832. The Sponsor submitted proposed labeling including

color draft copies of the principal display panel (PDP) and Drug Facts labeling for the 10.5 mL applicator (immediate container), 10.5 mL applicator secondary packaging (applicator (b) (4)), and the outer carton. A proposed package insert (target product information or consumer information leaflet) for the 25-count outer carton containing the Drug Facts labeling is also included.

On September 7, 2018, a 74-day filing letter 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, along with requests for additional information covering Statistics, Clinical Pharmacology, Regulatory, and Chemistry, Manufacturing, and Controls disciplines (see September 7, 2018 filing letter in DARRTS, under NDA 210872). The Sponsor responded on October 24, 2018 with submission of full annotated specifications for the Drug Facts labeling for the 25-count outer carton package insert.

On September 26, 2018, a Proprietary Name Denied letter was sent to the Sponsor for its proposed name “ZuraPrep™” (see section II.A.i.a.1 for applicable comments). On December 6, 2018, the Sponsor submitted a new proprietary name request for review with a new proposed name, “ZuraGard™”, along with labeling for the 25-count outer carton and 10.5 mL applicator (b) (4) incorporating this new proposed name. We requested the Sponsor submit draft labeling and font and format specifications for the proposed container closure (refer to February 1, 2019 information request in DARRTS). On February 15, 2019, the Sponsor submitted draft labeling and font and format specifications with the proposed proprietary name “ZuraGard” for the 10.5 mL applicator, applicator (b) (4) (secondary packaging), outer carton, and package insert. In response to FDA’s information requests dated March 13, 2019, March 21, 2019, and April 4, 2019, the Sponsor submitted revised labeling and font and format specifications on March 27, 2019 and April 8, 2019 and addressed any outstanding labeling requests.

This review describes the recommendations on the Sponsor’s submission from February 15, 2019 and March 27, 2019, the information requests (labeling advice letter and addendums) issued by the Agency on March 13, March 21, and April 4, 2019, and the Sponsor’s responses and revised labeling submitted on March 27, 2019 and April 8, 2019. This review also includes the conclusions of the label and labeling review performed by DMEPA from a medication error perspective (see section II.E below). A list of the submitted proposed labeling and submission dates is presented below, followed by a detailed review of the labeling.

Submitted Labeling, February 15, 2019, March 27, 2019, and April 8, 2019
10.5 mL applicator
10.5 mL applicator secondary packaging (applicator (b) (4))
10.5 mL applicator 25-count outer carton
10.5 mL applicator package insert for 25-count outer carton

II. REVIEWER'S COMMENTS

A. ZuraGard™ Outer Container (25-Count Outer Carton)

i. Labeling Outside Drug Facts

a. Principal Display Panel (PDP)

(b) (4)

1. Proprietary Name

The proprietary name ZuraPrep™ for isopropyl alcohol solution, 70% v/v was submitted for review on June 29, 2018 under NDA 210872. On September 26, 2018, the Division of Medication Errors Prevention and Analysis (DMEPA) concluded that the proposed proprietary name, ZuraPrep™, is unacceptable for the following reasons (refer to September 26, 2018 proprietary name review and Proprietary Name Denied letter in DARRTS):

(b) (4)

(b) (4)

Subsequent to receiving a Proprietary Name Denied letter, on December 6, 2018, the Sponsor submitted a new proposed name, “ZuraGard”, and requested a proprietary name review. DMEPA acknowledged receipt of correspondence on December 18, 2018 and completed its review on March 1, 2019, concluding that the proposed proprietary name, ZuraGard, is acceptable (refer to March 1, 2019 proprietary name review and March 5, 2019 Proprietary Name Granted letter in DARRTS).

Reviewer’s comments: DMEPA has reviewed the proposed proprietary name, ZuraGardTM, to determine if there are any areas of vulnerability that could lead to medication error. On March 1, 2019, DMEPA completed its review and found the proposed proprietary name “ZuraGard” acceptable. Furthermore, DMEPA provided the Sponsor with comments regarding best practices in developing proprietary names

(b) (4)

This practice can result in creating multiple similar proprietary names, which might increase the risk of confusion among the products, especially when the products are stored alphabetically in distributor or pharmacy locations or when products are ordered from alphabetized lists (refer to March 1, 2019 proprietary name review and March 5, 2019 Proprietary Name Granted letter in DARRTS).

2. Descriptor

The descriptor “**Surgical Solution**” was placed directly below the trade name in the February 15, 2019 proposed labeling. We compare to other OTC antiseptic drug products with the pharmacological category of patient preoperative skin preparation labeled with descriptors. Approved product examples include “DuraPrep”, under NDA 021586, labeled with the descriptor “Surgical Solution”; “Scrub-Stat”, under NDA 019258, labeled with the descriptor “Antiseptic Foam Forming Solution”; and

most recently “SoluPrep”, under NDA 208288, labeled with the descriptor “Film-Forming Sterile Surgical Solution”.

Reviewer’s comments: *As we have consistently allowed the use of a descriptor following the tradename in similar products (i.e., DuraPrep and SoluPrep), this review found the descriptor “Surgical Solution” acceptable in the proposed labeling submitted on February 15, 2019 (refer to March 13, 2019 labeling advice letter in DARRTS). However, considering the recommendations received from DMEPA at the March 18, 2019 wrap-up meeting for this NDA regarding its concerns with the descriptor “Surgical Solution” potentially being mistaken as the dosage form, we recommended the Sponsor remove the statement “Surgical Solution” from after the trade name and add the dosage form “Solution” to the established name (see March 21, 2019 addendum to the March 13, 2019 advice letter in DARRTS). And, suggested the descriptor be relocated prior to the statement “For head, neck, and small prep areas” (see section II.A.i.a.3 and 6 and II.E for applicable comments).*

In accordance with the Agency’s request and as specified in 21 CFR 201.61, the Sponsor has changed the placement of the descriptor “Surgical Solution” on the PDP in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission and it is acceptable.

3. Statement of Identity

Within the statement of identity, the Sponsor’s submission from February 15, 2019 presents the pharmacological category below the established name, which is presented after the descriptor “Surgical Solution”. The Sponsor proposes the pharmacological category, “Patient Preoperative Skin Preparation”, portrayed in a small font relative to the established name. And, proposes the following established name of the drug: “70% v/v isopropyl alcohol (b) (4)”.

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, follows 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 placement order of the established name and general pharmacological category on the PDP requires revision per 21 CFR 201.61 (see section II.A.i.a.2 for applicable comments). The proprietary name (ZuraGard™), must be followed by the established name of the drug, and subsequently followed by the pharmacological category (Patient Preoperative Skin Preparation). The proposed established name of the drug “70% v/v isopropyl alcohol (b) (4)” should be revised to read “Isopropyl Alcohol, 70% v/v Solution” or “Isopropyl Alcohol (70% v/v) Solution” by including the dosage form and removing (b) (4) (see section II.A.i.a.2 and II.E for applicable comments).*

The proposed pharmacological category “Patient Preoperative Skin Preparation” in the proposed labeling submitted on February 15, 2019 is acceptable and in accordance to the June 17, 1994 tentative final monograph (TFM) for OTC Healthcare Antiseptic Drug Products (59 FR 31402, at 31443). However, the font of the pharmacological category requires bolding and revision to 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 (ZuraGard™), in accordance with 21 CFR 201.61(c). See mock representation below (from March 21, 2019 addendum to March 13, 2019 labeling advice letter in DARRTS):

Single Use

ZuraGard™

**Isopropyl Alcohol (70% v/v) Solution
Patient Preoperative Skin Preparation**

Non-sterile Solution

Applicator is sterile if package is intact

Surgical Solution

For head, neck, and small prep areas

BLUE

10.5 mL APPLICATORS

On March 13 and March 21, 2019, we requested the Sponsor revise the format and placement of the statement of identity as described above (refer to March 21, 2019 addendum to the March 13, 2019 advice letter in DARRTS). In accordance with the Agency’s request from March 21, 2019, and as specified in 21 CFR 201.61, the Sponsor has corrected the placement and format of the statement of identity on the PDP in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission and it is acceptable.

4. The Sponsor has included a blue banner with the statement “BLUE” in white font to indicate the color of the surgical preparation solution. The statement “BLUE” is located under the pharmacological category, followed by the statement “10.5 mL APPLICATORS” in the proposed labeling submitted on February 15, 2019.

Reviewer’s comments: *The proposed statement “BLUE” indicates the color of the surgical preparation solution. The statement should not be placed after the pharmacological category of the drug product, but instead appear after the sterility statements “Non-Sterile Solution” and “Applicator is sterile if package is intact” on the PDP (see section II.A.i.a.5 for applicable comments and refer to CBE supplement request letter to sponsors for NDA 021669 from November 14, 2013 in DARRTS). The size of the “BLUE” statement should be consistent with the size of the statement “10.5 mL APPLICATORS”.*

On March 13 and March 21, 2019, we requested the Sponsor revise the size of the “BLUE” statement to be consistent with the size of the statement “10.5 mL APPLICATORS” and relocate it to after the “For head, neck, and small prep areas” statement (see section II.A.i.a.2 and 3). In accordance with the Agency’s request from March 13 and March 21, 2019, the Sponsor has revised the placement and format of the “BLUE” statement in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission and it is acceptable.

On April 4, 2019, we requested the Sponsor revise the statement “10.5 mL APPLICATOR” to read: “0.36 fl oz (10.5 mL) APPLICATOR” by adding the net quantity in fluid ounces, per 21 CFR 201.62, to the outer carton, package insert, and secondary packaging (applicator (b)(4)) labeling (refer to April 4, 2019 information request in DARRTS). On April 5, 2019, the Sponsor asked via email communication if this statement (“10.5 mL APPLICATOR”) could remain as is on the outer carton, since its labeling already contains the net quantity in fluid ounces in the lower third of the PDP. We responded via email communication on April 5, 2019 that this was acceptable (see sections II.B.i.a and II.D.a for applicable comments).

5. The sterility statements “Non-sterile Solution” and “Applicator is sterile if package is intact” are included on the PDP following the “10.5 mL APPLICATORS” statement in the proposed labeling submitted on February 15, 2019.

Background: On November 14, 2013, FDA sent a CBE supplement request letter to Sponsors requesting class 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 (b)(4) 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 statements "Non-sterile Solution" and "Applicator is sterile if package is intact" on the PDP is not consistent with class labeling safety changes requested in 2013 in the proposed labeling submitted on February 15, 2019 (refer to November 17, 2013 CBE Supplement Request Letter for NDA 021669 in DARRTS) and is not acceptable. The sterility statement "Non-sterile Solution" should be placed after the pharmacological category (Patient Preoperative Skin Preparation) on the PDP and anywhere else in the labeling where the pharmacological category appears. The statement "Non-sterile Solution" should be followed by the statement "Applicator is sterile if package is intact". Both sterility statements should be in bold font and in the same font size as the pharmacological category. (b) (4)

On March 21, 2019, (b) (4)

In accordance with the Agency's request, the Sponsor has revised the placement and format of these statements on the PDP and anywhere else they appear in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

6. We recommend the statement "For head, neck, and small prep areas" be included on the PDP following the descriptor "Surgical Solution".

Reviewer's comments: In the proposed labeling for this product the maximal treatment area for one applicator (10.5 mL) is approximately 8.4 in. x 8.4 in. (457 cm²). Applicators of this size (10.5 mL) and relative treatment area are not intended to be used in excess to cover larger prep areas. To circumvent use on larger prep areas, we recommend the statement "For head, neck, and small prep areas" be included on the PDP following the statement "Surgical Solution". The inclusion and placement of this statement in the proposed labeling is consistent with labels on other recently approved 10.5 mL and 6 mL applicators in this drug product category (refer to August 8, 2018 approval letter and labeling for NDA 208288 (SoluPrepTM) and June 8, 2015 approval letter and labeling for NDA 021586/S-005 (DuraPrepTM) in DARRTS and see section II.A.i.a.2 for applicable comments).

On March 21, 2019, we requested the Sponsor add the statement "For head, neck, and small prep areas" below the statement "Surgical Solution" (refer to March 21, 2019 addendum to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency's request, the Sponsor has added the statement in the specified location in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

7. The NDC number "NDC #####-###-##" placeholder is located on the upper right corner of the PDP.

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

8. The statement "Single Use" is included on the upper third portion of the PDP followed by the proposed proprietary name "ZuraGard".

Reviewer's comments: The inclusion of the statement "Single Use" in the proposed labeling is consistent with class labeling safety changes requested in 2013 (see section II.A.i.a.5 for applicable comments). Inclusion of this statement will reduce the risk of infections from extrinsic contamination of these products by repeated use of non-sterile containers once opened. It is acceptable.

9. The net quantity of contents statement "25 applicators" followed by "0.36 fl. oz. (10.5 mL) each" is in unbolded font and located on the upper left hand corner of the PDP.

Reviewer's comments: The net contents declaration is not in accordance with 21 CFR 201.62. The "0.36 fl. oz. (10.5 mL) each" statement must be revised to read: "**0.36 fl oz (10.5 mL) each**" by removing the periods after "fl" and "oz" per 21 CFR 201.62(i)(1). The statement must appear in boldface type and on the lower third portion of the PDP per 21 CFR 201.62(e) and (g).

On March 13, 2019, we requested the Sponsor revise and relocate the content and format of the net quantity of contents statement on the PDP as described above (refer to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency's request, the Sponsor has revised the net quantity of contents statement on the PDP in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission and it is acceptable.

10. The proposed labeling includes the risk statements "**WARNING. FLAMMABLE. KEEP AWAY FROM FIRE OR FLAME.**" on the lower third portion of the PDP.

Reviewer's comments: Alcohol-based topical antiseptic products are associated with an increased incidence of surgical suite fires (see section II.A.ii.c.1 for applicable comments). The use of these warning statements on the PDP improves visibility and prominence of information relevant to the risk management of the product under the "Warnings" in the Drug Facts labeling. The inclusion of these statements on the PDP is acceptable.

11. The statements "Store between 15-30°C (59-86°F)" and "Avoid freezing and excessive heat above 40°C (104°F)" are included on the lower third portion of the PDP.

Reviewer's comments: These statements inform the user about the proper storage conditions of this product and are acceptable. These statements are also included in the Drug Facts labeling under the "Other information" heading.

On March 18, 2019, the Chemistry, Manufacturing, and Controls (CMC) reviewer, Dr. Elise Luong, provided her quality assessment review to the labeling team with the following recommendation (refer to February 25, 2019 review in PANORAMA):

“The labeling should be revised to state the standard storage language: “Store at 20 to 25°C (68 to 77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].”

On March 21, 2019, the labeling team had an internal discussion with the CMC team leader, Danae Christodoulou, regarding this recommendation. The labeling team explained the proposed labeling already includes the language “Store between 15-30°C (59-86°F)” and asked whether this was adequate and supported by the stability data provided by the Sponsor. The CMC team leader agreed that the language already present in the proposed labeling was appropriate for an OTC product and supported by stability data, and therefore acceptable and not in need of revision. Therefore, the presence and content of these statements in the proposed labeling is acceptable as is, without change.

12. A graphic image of the product applicator is included in the center position of the PDP.

***Reviewer’s comments:** This is acceptable.*

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 in the proposed labeling submitted on February 15, 2019. This alternate PDP includes similar information as described under the PDP section above (see section II.A.i.a). Particularly, additional statements such as “Professional Use Only”, (b) (4)

[REDACTED] The net quantity of contents and storage statements (see section II.A.i.a.9 and 11 for applicable comments) are not included in this alternate PDP.



Reviewer’s comments: This alternate, different principal display panel in the proposed labeling submitted on February 15, 2019 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 (b) (4)

*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 through 12** for applicable comments.*

*On March 13 and March 21, 2019, we requested the Sponsor revise the format and placement of the statement of identity, sterility statements, descriptor, applicator description as described in sections **II.A.i.a.1 through 12** for the PDP and add the net quantity of contents statement as described above (see March 21, 2019 addendum to the March 13, 2019 advice letter in DARRTS). In accordance with the Agency's request from March 21, 2019, the Sponsor has revised the placement and format of the statement of identity and added the net quantity of contents statement on the alternate PDP in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable. The Sponsor has also added the statements "Store between 15-30°C (59-86°F)", "Avoid freezing and excessive heat above 40°C (104°F)", and the NDC number to the alternate PDP in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.*

(b) (4)

c. Outside of Drug Facts - Outside of Principal Display Panel

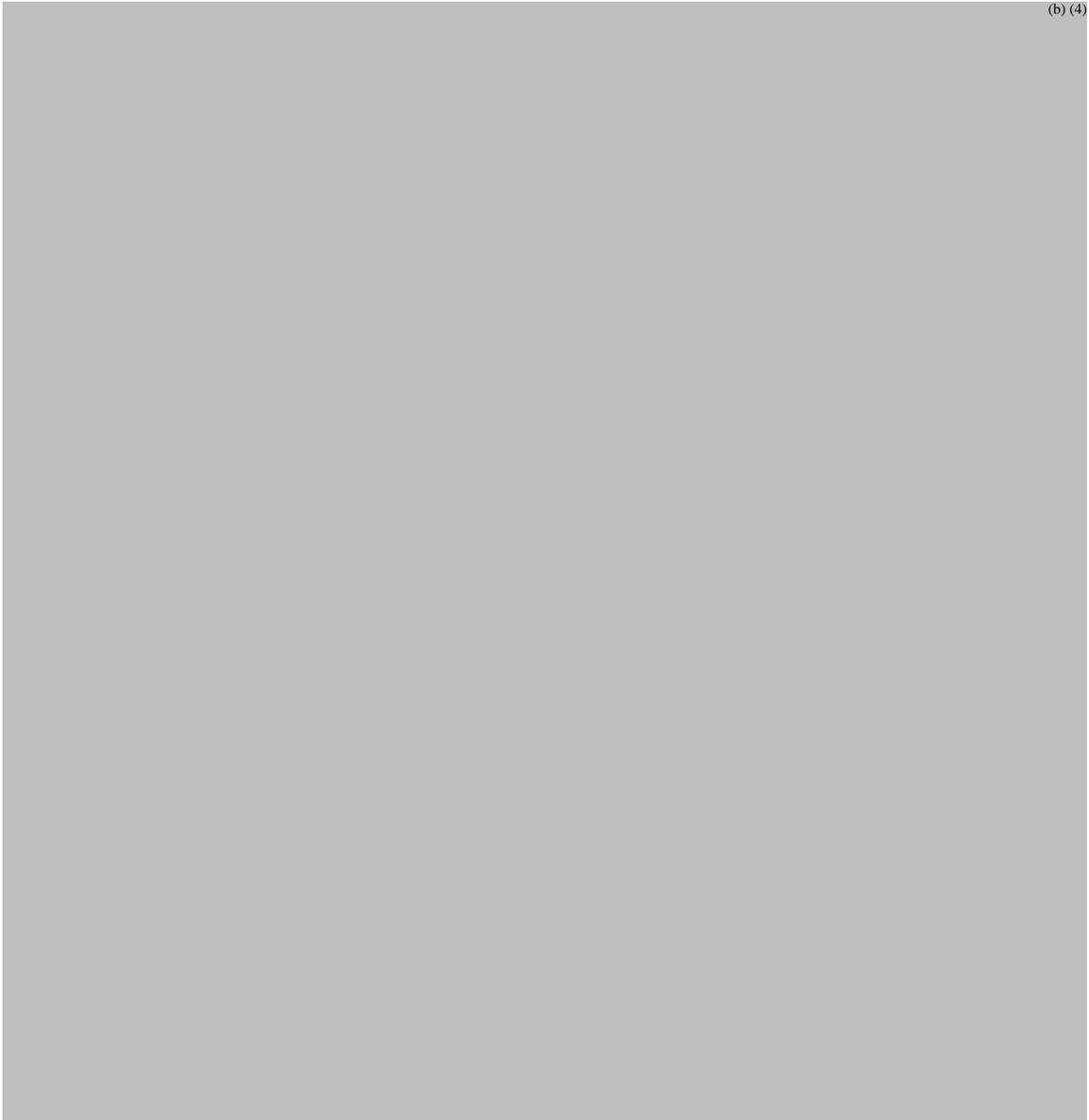
1. Proposed Top Panel of Outer Container (25-count carton)



Reviewer's comments: *The top panel of the outer container in the proposed labeling submitted on February 15, 2019, contains the proposed proprietary name, statement of identity, sterility statements, and applicator description. For consistency with the principal display panel, it is recommended that these statements be revised as described in sections **II.A.i.a.1 through 6 and 8**.*

*On March 13 and March 21, 2019, we requested the Sponsor revise the top panel as described in sections **II.A.i.a.1 through 6 and 8** (see March 13, 2019 labeling advice letter and March 21, 2019 addendum in DARRTS). In accordance with the Agency's request, the Sponsor has revised the top panel in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.*

2. Proposed Side Panel of the Outer Container (25-count carton)



Reviewer's comments: *The side panel of the outer container in the proposed labeling submitted on February 15, 2019, contains the same statements and statements' format present on the PDP and alternate PDP of the outer container (see section **II.A.i.a and b** for applicable comments). In addition to the statements on the PDP and alternate PDP, the side panel also contains the "Manufactured for" statement with the place of business and additional information per 21 CFR 201.1(i) and it is acceptable. However, the Sponsor should avoid the use of white font on the light blue background, as it does not provide enough contrast. 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 25-count carton. See sections **II.A.i.a.1 through 12 and II.A.i.b** for applicable comments.*

*On March 13 and March 21, 2019, we requested the Sponsor revise the side panel as described in sections **II.A.i.a.1 through 12 and II.A.i.b** (see March 13, 2019 and March 21, 2019 advice letters in DARRTS). In accordance with the Agency's request, the Sponsor has revised the format, content, and order of the statements on the side panel in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable. Furthermore, the Sponsor has added the expiration date (for placement only) in accordance with the Agency's March 13, 2019 request (per 21 CFR 201.17) and in the format recommended in our March 21, 2019 advice letter, and it is acceptable (see section **II.E** for applicable comments).*

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



Boxed Flammability Warning

FDA has allowed the use of pictograms to improve visibility and prominence, and to decrease the incidence of fires in the operating room. FDA is concerned about reports of burns that have been connected with the use of products containing alcohol. In the labeling review for DuraPrep Surgical Solution (refer to September 15, 2006 discipline

review for NDA 021586 in DARRTS), FDA allowed the use of the “no pooling” pictogram. The “no pooling” pictogram used in this proposed labeling is consistent with the pictogram used in the approved labeling for SoluPrep™ (NDA 208288) and DuraPrep™ (NDA 021586). The flammability pictogram in the proposed labeling is consistent with the pictogram used in the approved labeling for ChloroPrep™ (NDA 020832), DuraPrep™ (NDA 021586), and SoluPrep™ (NDA 208288). See section II.A.ii.c.1 for a detailed description regarding the flammability warning.

***Reviewer’s comments:** As specified in the FDA CBE-30 Supplement Request letter dated August 4, 2009 (refer to CBE-30 Supplement Request Letter for NDA 020832 from August 4, 2009 in DARRTS), and for consistency across chlorhexidine gluconate and isopropyl alcohol drug products labeling, the second bulleted statement in the boxed flammability warning in the proposed labeling submitted on February 15, 2019, “avoid getting solution into hairy areas. Hair may take up to 1 hour to dry. **Wet hair is flammable.**” should be revised to read: “avoid getting solution into hairy areas. **Wet hair is flammable.** Hair may take up to 1 hour to dry.” by changing the order of the second and third sentence in the bulleted statement. The remaining bulleted statements in the boxed flammability warning are consistent with the class labeling change from 2009. See section II.A.ii.c.1 for a detailed description regarding the flammability warning.*

On May 13, 2019, we requested the Sponsor revise the statement as described above (refer to May 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency’s request, the Sponsor has revised the second bulleted statement in the boxed flammability warning in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

4. The proposed side panel includes the tradename, statement of identity, sterility statements, applicator description, NDC number, (b) (4) statement outside and above the **Drug Facts** box and boxed flammability warning.

(b) (4)

Reviewer's comments: *The side panel of the outer container in the proposed labeling submitted on February 15, 2019 contains the same format and statements present on the PDP and alternate PDP of the immediate container. The Sponsor should revise the side panel of the outer container to be consistent with the statements on the PDP and alternate PDP on the 25-count carton. See sections II.A.i.a.1-12 and II.A.i.b for applicable comments.*

On March 13 and March 21, 2019, we requested the Sponsor revise the statements in the side panel as described in sections II.A.i.a.1-12 and II.A.i.b. In accordance with the Agency's request, the Sponsor has amended the format, content, and order of the statements in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable. Furthermore, in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, [REDACTED] (b) (4) and this is acceptable.

5. The barcode with a "for placement/position only (FPO)" description is located outside and below the **Drug Facts** box on the side panel in the proposed labeling submitted on February 15, 2019 and the revised proposed labeling submitted on March 27, 2019 and April 8, 2019.



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 (25-count carton) in the proposed labeling submitted on February 15, 2019. This is not acceptable. The Sponsor must include the location of the expiration date (for placement only) on the outer container (25-count carton) and the immediate container labels in accordance with 21 CFR 201.17 (see also section II.E for applicable comments). On March 13, 2019, we requested the Sponsor ensure the expiration date is present on the outer container (25-count carton) and we provided the recommended format on March 21, 2019 (see March 13, 2019 and March 21, 2019 labeling advice letters in DARRTS). In accordance*

with the Agency's requests, the Sponsor has added the expiration date on the side panel (for placement only) in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable (see section **II.A.c.2** for applicable comments).

On April 4, 2019, we requested the Sponsor confirm that the expiration date will also be present on the applicator (b) (4) (secondary packaging) as this location is more convenient for the end user to note (refer to April 4, 2019 information request in DARRTS and see section **II.E** for applicable comments). In the Sponsor's April 8, 2019 revised labeling submission, the Sponsor confirmed that the expiration date and lot number will be displayed on the applicator (b) (4) in the same format as the carton. This is acceptable.

ii. Drug Facts Labeling 25-Count Carton (Outer Container)

a. Active ingredient

The Sponsor proposes the following for the "**Active ingredient**" and "**Purpose**" sections of the Drug Facts labeling:



Reviewer's comments: Per 21 CFR 201.66(c)(2), the active ingredient heading is followed by the established name of the active ingredient and its quantity. In accordance with 21 CFR 201.66(c)(2), under the "**Active ingredient**" heading in the proposed labeling submitted on February 15, 2019 and any subsequent submission, the format and content of the established name, "Isopropyl alcohol", without the dosage form ("solution") is consistent with the USP monograph for isopropyl alcohol, per 21 CFR 201.66(c)(2), and its concentration format is consistent with the Drug Facts labeling of other OTC antiseptic drug products containing isopropyl alcohol (refer to August 8, 2018 approval letter for NDA 208288 (SoluPrepTM) and September 12, 2017 approval letter for NDA 020832/S-042 (ChloraPrepTM) in DARRTS). Under the "**Purpose**" heading, the purpose is stated as "Antiseptic", in accordance to the June 17, 1994, tentative final monograph (TFM) for OTC Healthcare Drug Products (59 FR 31402, at 31443). This is acceptable.

b. Use

The Sponsor proposes the following for the “*Use*” section in the Drug Facts labeling:



Reviewer’s comments: The “Use” section in the February 15, 2019 proposed labeling is not acceptable. There are multiple statements present under the “Use” heading. When there is more than one statement, each individual statement listed under the heading must be preceded by a bullet per 21 CFR 201.66(d)(4). In addition, the heading “Use” must be revised to read: “Uses” per 21 CFR 201.66(c)(4). Furthermore, the “Use” statements should be revised to read: “▪ for preparation of the skin prior to surgery ▪ helps reduce bacteria that potentially can cause skin infection”, in accordance to the June 17, 1994, tentative final monograph (TFM) for OTC Healthcare Drug Products (59 FR 31402, at 31443).

On March 13, 2019, we requested the Sponsor revise the “Use” heading and statements as described above (refer to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency’s request, the Sponsor has revised this section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable

c. Warnings

The Sponsor proposes the following, under the “*Warnings*” section in the Drug Facts labeling:

1. **“For external use only. Flammable, keep away from fire and flame. To reduce risk of fire, PREP CAREFULLY:” section:**

Background: On August 4, 2009, FDA sent a CBE-30 Supplement Request letter to sponsors requesting class labeling revisions for alcohol-based topical antiseptic products. FDA determined that a class labeling change was warranted for these products. The previous labeling had included warnings regarding flammability and the need for the product to be completely dry before the patient is either draped for surgery or an ignition source is used. The previous labeling had stated that drying takes a “minimum of 3 minutes on hairless skin.” and had warnings that the user

should avoid getting solution into the hair of the patient as [REDACTED] (b) (4)
[REDACTED] The length of time needed for hair to dry was not defined on the previous labeling.

The Agency's decision to include a more specific warning regarding the length of time required for the hair to dry was based on the following:

- The alcohol-based topical antiseptic products are associated with an increased incidence of surgical suite fires. Most of the documented fires are associated with the use of alcohol-based topical antiseptics in combination with electrocautery, electrosurgery, or laser surgery, particularly when the surgical site is not completely dry after the prep is applied.
- Hirsute areas are a particular risk factor. Recently completed studies show extended drying times when the products are used in hirsute areas.

In the class labeling action, FDA requested that the labeling be revised as follows:

- Revise the statement under the Drug Facts *Warnings* and the boxed flammability warning to read: "**To reduce risk of fire, PREP CAREFULLY:**"
- Revise the following bulleted statements under the subheading "**To reduce risk of fire, PREP CAREFULLY:**" to read:
 - "• avoid getting solution into hairy areas. **Wet hair is flammable.** Hair may take up to 1 hour to dry." The statement "**Wet hair is flammable**" should be bolded and in red print.
 - "• do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair)."
- Revise the bulleted statement under the *Directions* to read: "• avoid getting solution into hairy areas. **Wet hair is flammable.** Hair may take up to 1 hour to dry."

(b) (4)

Reviewer's comment: The “Warnings” section in the proposed labeling submitted on February 15, 2019 is not acceptable. For consistency across OTC alcohol-based topical antiseptic products, the subheading “**For external use only. Flammable, keep away from fire (b) (4) flame**” should be revised to read: “**For external use only. Flammable, keep away from fire or flame**” by changing the word (b) (4) to “or”. In addition, the first bulleted statement under the “Warnings” heading should be revised to read: “▪ solution contains alcohol and gives off **flammable vapors**” by changing the word “**vapor**” to read “**vapors**”.

As specified in the FDA CBE Supplement Request letter dated August 4, 2009 (refer to CBE Supplement Request Letter for NDA 020832 from August 4, 2009 in DARRTS) the second bulleted statement under the “Warnings” should be revised to read: “▪ avoid getting solution into hairy areas. **Wet hair is flammable. Hair may take up to 1 hour to dry.**” by removing the statement (b) (4) and adding the statement “Hair may take up to 1 hour to dry” and changing the order of the second and third sentence in the bulleted statement for consistency across OTC alcohol-based topical antiseptic products.

On March 13, 2019, we requested the Sponsor revise the “Warnings” section as described above (refer to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency’s request, the Sponsor has revised the “Warnings” section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

2. Do not use

The “Do not use” subheading and bulleted statements follow the “**For external use only. Flammable, keep away from fire and flame. To reduce risk of fire, PREP CAREFULLY:**” section in the Drug Facts labeling. The Sponsor proposes the following for the “Do not use” section:



Reviewer's comments: *The first bulleted statement under the “Do not use” subheading in the proposed labeling submitted on February 15, 2019 has been derived from the labeling originally approved for NDA 020832 (ChloroPrep™), the reference listed drug (RLD) for this current submission. The originally approved labeling for ChloroPrep included the statement “▪ on patients with known allergies to chlorhexidine gluconate (b) (4)”, as the second bulleted statement under the “Do not use” subheading in the Drug Facts labeling.*

On February 7, 2017, FDA sent a CBE Supplement Request letter to the Sponsor requesting labeling revisions. The Agency determined that a class labeling change was warranted for chlorhexidine gluconate (CHG) topical antiseptic drug products (refer to CBE Supplement Request Letter for NDA 020832 from February 2, 2017 in DARRTS). In order to reduce the incidence of anaphylactic reaction with CHG, and in the interest of clear and uniform labeling, the Agency requested that all CHG topical antiseptic product labels include the same specific language regarding this warning. Even labels that already address the allergy alert under the subheaders “Do not use” and “Stop use and ask a doctor if”. In accordance with this class labeling change, the bulleted statement under the “Do not use” subheading in ChloroPrep’s labeling was changed from “▪ on patients with known allergies to chlorhexidine gluconate (b) (4)” to read: “▪ on patients allergic to chlorhexidine gluconate or any other ingredient in this product”.

The inclusion of the statement “▪ on patients (b) (4) to isopropyl alcohol” in the proposed labeling is acceptable pending any review decisions from the clinical perspective. However, for consistency across OTC approved labeling for this drug product category, the first bulleted statement under the “Do not use” subheading should be revised to read: “▪ on patients allergic to isopropyl alcohol or any other ingredient in this product” by changing (b) (4) to read “allergic” and adding the statement “or any other ingredient in this product”.

Furthermore, for consistency across approved OTC approved labeling for this drug product category, under the “Do not use” subheading in the proposed labeling submitted on February 15, 2019, the second bulleted statement: “▪ for lumbar puncture or in contact with meninges” should be revised to read: “▪ for lumbar puncture or in contact with the meninges” by adding the word “the” before the word “meninges”.

On March 13, 2019, we requested the Sponsor revise the “Do not use” section as described above (refer to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency’s request, the Sponsor has amended the “Do not use” section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

3. When using this product

The Sponsor proposes the following, in the February 15, 2019 and any subsequent submission of proposed labeling, for the “When using this product” subsection in the Drug Facts labeling:

(b) (4)

Reviewer’s comment: *The original NDA clinical review of DuraPrep (NDA 021586) states in its executive summary that “DuraPrep solution should not be applied to the eyes, ears, or mucous membranes due to known associated toxicities with iodine and/or isopropyl alcohol use in these areas.” (refer to Dr. Jean M Mulinde’s Clinical Review, August 5, 2004 in DARRTS, under NDA 021586). Approved labeling for both DuraPrep (NDA 021586) and ChloroPrep (NDA 020832) include the warning: “When using this product keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a doctor.” Furthermore, the June 17, 1994, tentative final monograph (TFM) for OTC Healthcare Drug Products (59 FR 31402, at 31442) proposes the warning: “Do not use in the eyes” for patient preoperative skin preparations containing IPA (70-91.3%). And 21 CFR 369.21, requires the warning “For external use only. If taken internally serious gastric disturbances will result.” for alcohol rubbing compounds.*

Regarding alcohol-based topical antiseptics and ototoxicity, an animal study by Perez et al. found that 70% ethyl alcohol caused gross pathological changes to the middle ear space including erythema and edema; and in some animals edema of the external ear canal was so severe that testing of hearing was not possible (Perez et al., Laryngoscope, 110:1522-1527, 2000). A study in chinchillas testing several strengths of ethanol (0.1-100% pure ethanol) in the middle ear cavity concluded that there was evidence of ototoxicity for ethanol concentrations greater than 10% using cochlear microphonics (Morizona et al., Acta Otolaryngol, 92:33-40, 1981). Similarly, Ohashi et al. exposed guinea pigs to 400 ppm or 5500 ppm of isopropyl alcohol (IPA) for 24 successive hours and showed that IPA at the allowable level of 400 ppm had an acute effect on the mucociliary system of the middle ear mucosa (Ohashi et al., Journal of Applied Toxicology, Vol. 7(3):201-211, 1987). Recovery from damage occurred within

two weeks. At higher levels of exposure to IPA [REDACTED] (b) (4) moderate deterioration of the ciliary activity and severe damage of epithelial cells was observed and recovery within two weeks was not seen. A recent literature review article assessing the evidence regarding ototoxicity of surgical antiseptic preparations concluded that there is some evidence that iodine, chlorhexidine, hydrogen peroxide and alcohol based antiseptics have ototoxicity (Singh and Blakley, *J Otolaryngol Head Neck Surg.*, 47:18, 2018). This review determined that iodine based, non-alcoholic, non-detergent solutions may be the least ototoxic, but all should be used with caution. However, Singh and Blakley (2018) state that conclusive evidence for human ototoxicity from any solution is not strong.

We find that inclusion of this warning in ZuraGard™ is consistent with Drug Facts labeling across this OTC drug product category and is acceptable pending any additional review comments from the clinical perspective.

4. Stop use and ask a doctor if

The Sponsor proposes the following, in the February 15, 2019 and any subsequent submission of proposed labeling, for the “**Stop use and ask a doctor if**” subsection in the Drug Facts labeling:



Reviewer’s comments: This is consistent with Drug Facts labeling across this OTC drug product category and it is acceptable pending any additional review comments from the clinical perspective.

5. 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:



Reviewer's comments: The “**Keep out of reach of children.**” section is in conformance with 21 CFR 201.66 in the proposed labeling submitted on February 15, 2019. However, the statement “If swallowed, get medical help or contact Poison Control Center right away” must be revised to read: “If swallowed, get medical help or contact a Poison Control Center right away” by adding the word “a” before “Poison Control Center” per 21 CFR 330.1(g).

On March 13, 2019, we requested the Sponsor revise the “**Keep out of reach of children.**” section as described above (see March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency's request, the Sponsor has amended this section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

d. Directions

The “**Directions**” section is placed after the “**Warnings**” section in the Drug Facts labeling. The Sponsor proposes the following, in the February 15, 2019 proposed labeling, for the “**Directions**” section in the Drug Facts labeling:



Reviewer's comments: The first bulleted statement under the “**Directions**” section is derived from a class labeling change regarding use of CHG products in infants (refer to CBE Supplement Request Letter for NDA 020832 from October 21, 2011 in DARRTS). FDA determined that a class labeling change was warranted for CHG topical antiseptic drug products and requested the inclusion of a consistent warning regarding use of the CHG products in infants. This review was triggered by a 15-day MedWatch report describing a case of a chemical burn sustained by a neonate on whom a CHG-containing solution had been applied. FDA found 15 additional cases of severe irritation or chemical burns in FDA's Adverse Event Reporting System involving infants less than 3 months of age, after use of products containing only CHG or a combination of CHG and isopropyl alcohol.

In order to reduce the incidence of skin irritation and burns in infants, and in the interest of clear and uniform labeling, FDA requires that all CHG topical antiseptic product labels include this preventative language. Even labels that already state “Do not use in infants” should be revised so they will be consistent with all other CHG product labels. Therefore, the same labeling is required to be consistent across single ingredient CHG products and combination CHG/IPA products. FDA requested that the infant warning statement “▪ use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.” be placed as the first bulleted statement under the “Directions” in the Drug Facts labeling.

Likewise, use of topicals containing alcohol in infants (particularly under occlusive dressings) has been associated with development of measurable blood levels, local toxicity (irritancy, skin necrosis) and systemic toxicity (refer to Dr. Jean M Mulinde’s Clinical Review for DuraPrep, August 5, 2004 in DARRTS under NDA 021586). Furthermore, increased absorption may occur in infants less than 2 months of age (Mancini, A.J. Skin. Pediatrics 113 (4 Suppl):1114-1119, 2004). Use of topicals containing IPA in infants has also been associated with chemical burns (Schick et al., Pediatrics, 68(4):587-8, 1981; Weintraub et al., Pediatrics, 69(4):506, 1982; Brayer et al., Arch Pediatr, 11(8):932-5, 2004; Watkins and Keogh, J Paediatr Child Health, 28(4):306-8, 1992).

The inclusion of the infant warning statement in the proposed labeling is acceptable pending any review decisions from the clinical disciplines. However, for consistency across OTC approved labeling for this drug product category, this bulleted statement 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.” by adding the word “under” before the words “2 months”.

The sequence and content of the remaining bulleted statements under the “Directions” could be revised to improve clarity and for consistency across OTC approved labeling for this drug product category. Specifically, the generally applicable comments should appear first, followed by how to get the patient ready for the antiseptic solution, activating the applicator, the directions for use on dry and moist surgical sites, and lastly by the directions for drying times after applying the solution.

On March 18, 2019, the CMC reviewer, Dr. Elise Luong, provided her quality assessment review to the labeling team with the following recommendation (refer to February 25, 2019 review in PANORAMA):

“(2) The labeling should include a statement ‘Do not use when the sponge is already wet upon opening the package.’”

We agree that the statement recommended by the CMC reviewer provides important information regarding use of the product and should be included in the

generally applicable statements under the “**Follow all directions for use**” subsection under the “**Directions**” heading (statement is highlighted in green).

Therefore, the order, content, and format of the bulleted statements under the “**Directions**” heading need to be revised to read:

Follow all directions for use

- use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.
- do not use when the sponge is already wet upon opening the package
- discard the applicator after a single use along with any portion of the solution which is not required to cover the prepped area. It is not necessary to use the entire amount available.

Getting Patient Ready for Solution:

- use in well-ventilated area
- do not microwave or heat the solution applicator
- apply to clean, completely dry, residue-free, intact skin
- when hair removal is necessary, use a surgical clipper on the morning of the surgery. If a wet shave is used, thoroughly remove all soap residues.

Activating the Applicator:

- remove applicator from package; do not touch sponge
- hold the applicator with the sponge down. Depress the end cap/button to release the antiseptic, solution will flow into the sponge.

When Applying Solution:

- completely wet the treatment area with antiseptic
- **dry surgical sites** (such as abdomen or arm): use repeated back-and-forth strokes for 30 seconds
- **moist surgical sites** (such as inguinal fold): use repeated back-and-forth strokes for 2 minutes
- maximal treatment area for one applicator is approximately 8.4 in. x 8.4 in. (457 cm²)
- **do not allow solution to pool**; tuck prep towels to absorb solution, and then remove
- avoid getting solution into hairy areas. **Wet hair is flammable.** Hair may take up to 1 hour to dry.

After Applying Solution:

- to reduce the risk of fire, **wait until solution is completely dry** (minimum of 3 minutes on hairless skin; up to 1 hour in hair)

While Waiting for Solution to Completely Dry:

- do not drape or use ignition source (e.g., cautery, laser)
- check for pooled solution. Use sterile gauze to soak up pooled solution. Do not blot or wipe away because it may remove solution from skin.
- remove wet materials from prep area. Replace if necessary.

After Solution is Completely Dry:

- to reduce the risk of fire, begin draping and/or using cautery only after solution is completely dry and all wet materials are removed

- if incise drapes are used, apply directly to dry prep
- apply dressing following standard practices”

On March 13 and March 21, 2019, we requested the Sponsor revise the “Directions” section as described above (refer to March 13, 2019 and March 21, 2019 labeling advice letters in DARRTS). In accordance with the Agency’s requests, the Sponsor has amended the “Directions” section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

(b) (4)

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 acceptable. This section provides storage information and directions on how to remove the tint if desired. See section II.A.i.a.11 for applicable comments.

f. Inactive ingredients

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



Reviewer's comments: The "Inactive Ingredients" section in the February 15, 2019 proposed labeling is not acceptable. The "Inactive Ingredients" heading must be revised to read: "Inactive ingredients" by changing the first letter of "Ingredients" to lower case per 21 CFR 201.66(c)(8). The inactive ingredient "USP purified water" should be revised to read: "purified water USP" and the listing of the inactive ingredients be revised to maintain the alphabetical order per 21 CFR 201.66(c)(8).

On March 13, 2019, we requested the Sponsor revise the "Inactive ingredients" section and heading as described above (see March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency's request, the Sponsor has amended this section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

g. Questions?

The Sponsor proposes the following for the "**Questions?**" section of the Drug Facts labeling:



Reviewer's comments: The "Questions?" section includes a place holder for the telephone number of a source to answer questions about the product. The days of the week and times of the day when a person is available to respond to questions is also included per 21 CFR 201.66(c)(9). The Sponsor has also included a contact website. The "Questions?" section in the February 15, 2019 and any subsequent submission of proposed labeling is acceptable.

iii. Format Specifications

The font specifications for the outer container (25-count carton) are in accordance with 21 CFR 201.66.

Reviewer's comments: This is acceptable.

B. ZuraGard™ Applicator Secondary Packaging (Applicator (b) (4))

i. Principal Display Panel (PDP)

a. Labeling Outside and Above the Drug Facts

The February 15, 2019 proposed labeling includes the statement of identity, NDC number, sterility statements, applicator description, and flammability warnings outside and above the Drug Facts on the applicator secondary packaging (applicator (b) (4)).



Reviewer's comments: *The format, order, and placement of the statement of identity, sterility statements, and additional proposed statements on the PDP in the February 15, 2019 proposed labeling is not acceptable. See sections II.A.i.a.1-10 for applicable comments.*

On March 13, 2019 and March 21, 2019, we requested the Sponsor revise these statements as described in sections II.A.i.a.1-10 (see March 13, 2019 and March 21, 2019 advice letters in DARRTS). In accordance with the Agency's request, the Sponsor has amended the content, format, and order of the statements in the revised proposed labeling submitted on March 27, 2019 and it is acceptable. However, in doing so, the spacing between the statements in the statement of identity appears too small, as the letters in the statement between the lines are touching.

On April 4, 2019, we requested the Sponsor revise the spacing as described above and also requested the statement "10.5 mL APPLICATOR" be revised to read: "0.36 fl oz (10.5 mL) APPLICATOR" per 21 CFR 201.62 (refer to April 4, 2019 information request in DARRTS and see sections II.A.i.a.4 and II.D.a for applicable comments). On April 5, 2019, the Sponsor asked via email communication if the statement "10.5 mL (0.36 fl oz) APPLICATOR" would be acceptable, as medical technicians routinely refer to these applicators as the milliliter size and since their RLD labeling for ChloroPrep (NDA 020832), only identifies the net quantity by milliliters. On April 5, 2019, we responded via email communication that the alternative proposed was acceptable.

On April 8, 2019, the Sponsor submitted revised proposed labeling correcting the spacing within and around the statement of identity and added the net quantity in fluid ounces. This is acceptable.

(b) (4)



b. Labeling Outside and Below the Drug Facts

The labeling outside and below the Drug Facts contains the following statement:

(b) (4) in the proposed labeling submitted on February 15, 2019 and “S0010v05”, in the revised proposed labeling submitted on March 27, 2019 and April 8, 2019.



Reviewer’s comments: The statements (b) (4) “S0010v05” appear to be an internal code for the labeling. This is acceptable.

ii. Drug Facts Labeling**a. Active Ingredient**

Reviewer’s comments: The “Active ingredient” section in the proposed labeling from February 15, 2019 and revised proposed labeling from March 27, 2019 and

any subsequent submission, and it is acceptable. See section II.A.ii.a for applicable comments.

b. Use



Reviewer’s comments: This formatting and content of the “Use” statements is not acceptable in the proposed labeling submitted on February 15, 2019. See section II.A.ii.b for applicable comments. On March 13, 2019, we requested the Sponsor revise the “Use” section as described in section II.A.ii.b. In accordance with the Agency’s request, the Sponsor has revised the “Uses” heading and bulleted statements in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

c. Warnings

The “**For external use only. Flammable, keep away from fire (b) (4) flame. To reduce risk of fire, PREP CAREFULLY:**” section in the proposed labeling submitted on February 15, 2019 is not consistent across OTC alcohol-based topical antiseptic products. The thickness of the barline above the “**Do not use**” subheading is not consistent with the size of the remaining barlines in the **Warnings** section. The font of the “**Do not use**” subheading must not be italicized. See section II.A.ii.c.1-5 for applicable comments.



Reviewer's comments: The “Warnings” section of the Drug Facts labeling is not acceptable in the proposed labeling submitted on February 15, 2019. For consistency across OTC alcohol-based topical antiseptic products, the subheading “**For external use only. Flammable, keep away from fire** (b) (4) **flame**” should be revised to read: “**For external use only. Flammable, keep away from fire or flame**” by changing the word (b) (4) to “or”. In addition, the fourth bulleted statement under the “Warnings” heading should be revised to read: “▪ do not allow solution to pool” by changing the word (b) (4) to read “not”.

As specified in the FDA CBE Supplement Request letter dated August 4, 2009 (refer to CBE Supplement Request Letter for NDA 020832 from August 4, 2009 in DARRTS) the second bulleted statement under the “Warnings” should be revised to read: “▪ avoid getting solution into hairy areas. **Wet hair is flammable.** Hair may take up to 1 hour to dry.” by removing the statement (b) (4) and adding the statement “Hair may take up to 1 hour to dry.” and changing the order of the second and third sentence in the bulleted statement.

The subheading “**Do not use**” must be unitalicized, per 21 CFR 201.66(c)(5)(iii). The horizontal line above the “**Do not use**” subheading must be revised to be consistent with the size of the horizontal hairlines used to separate each of the subheadings in the remainder of the Drug Facts labeling, per 21 CFR 201.66(d)(8).

For consistency across OTC approved labeling for this drug product category, the first bulleted statement under the “**Do not use**” subheading should be revised to read: “▪ on patients allergic to isopropyl alcohol or any other ingredient in this product” by changing (b) (4) to read “allergic” and adding the statement “or any other ingredient in this product”.

Furthermore, for consistency across approved OTC approved labeling for this drug product category, under the “**Do not use**” subheading, the second bulleted statement: “▪ for lumbar puncture or in contact with meninges” should be revised to read: “▪ for lumbar puncture or in contact with the meninges” by adding the word “the” before the word “meninges”.

Also, the statement “If swallowed, get medical help or contact Poison Control Center right away” must be revised to read: “If swallowed, get medical help or contact a Poison Control Center right away”, by adding the word “a” before “Poison Control Center” per 21 CFR 330.1(g).

On March 13, 2019, we requested the Sponsor revise the “**Warnings**” section as described above (see March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency’s request, the Sponsor has amended the “**Warnings**” section in the revised proposed labeling submitted on March 27, 2019 and it is acceptable.

However, in the March 27, 2019 revised proposed labeling the Sponsor has inadvertently not bolded the following statements under the “**Warnings**” section:

- The words “*flammable vapors*” in the first bulleted statement and “*Wet hair is flammable.*” in the second bulleted statement under the “**Warnings**” heading are not in boldface type.

On April 4, 2019, we requested the Sponsor revise the statements as described above (refer to the April 4, 2019 information request in DARRTS). In accordance with the Agency’s request, the Sponsor has amended these statements in the revised proposed labeling submitted on April 8, 2019 and it is acceptable.

(b) (4)



d. *Directions*

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



Reviewer’s comments: The sequence and content of the bulleted statements under the “*Directions*” heading in the proposed labeling submitted February 15, 2019 could be revised to improve clarity and for consistency across OTC approved labeling for this drug product category. See section **II.A.ii.d** for applicable comments.

On March 13, 2019, we requested the Sponsor revise the “*Directions*” section as described in section **II.A.ii.d** (see March 13, 2019 and March 21, 2019 labeling

advice letters in DARRTS). In accordance with the Agency's requests, the Sponsor has revised the "**Directions**" section in the revised proposed labeling submitted on March 27, 2019 and it is acceptable.

However, the Sponsor has inadvertently not bolded the following statements in the "**Directions**" section:

- Under the "**When Applying Solution:**" subsection, the statements, "dry surgical sites", "moist surgical sites", "do not allow solution to pool", and "*Wet hair is flammable*" are not in boldface type.
- Under the "**After Applying Solution:**" subsection, the statement "..., *wait until solution is completely dry*" is not in boldface type.

On April 4, 2019, we requested the Sponsor revise the statements as described above (refer to the April 4, 2019 information request in DARRTS). In accordance with the Agency's request, the Sponsor has amended these statements in the revised proposed labeling submitted on April 8, 2019 and it is acceptable.



e. **Other information**

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



Reviewer's comments: The "Other information" section in the proposed labeling submitted on February 15, 2019 and revised proposed labeling submitted on March 27, 2019 and any subsequent submission, is acceptable. See section II.A.ii.e for applicable comments.

f. Inactive ingredients

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



Reviewer's comments: The "Inactive Ingredients" section in the proposed labeling submitted on February 15, 2019 is not acceptable. The "Inactive Ingredients" heading must be revised to read: "Inactive ingredients" by changing the first letter of "Ingredients" to lower case, per 21 CFR 201.66(c)(8). The inactive ingredient "USP purified water" should be revised to read: "purified water USP", and the listing of the inactive ingredients be revised to maintain the alphabetical order per 21 CFR 201.66(c)(8). See section II.A.ii.f for applicable comments.

On March 13, 2019, we requested the Sponsor revise the "Inactive ingredients" section as described above (see March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency's request, the Sponsor has amended this section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.

g. Questions?

The Sponsor proposes the following for the "**Questions?**" section of the Drug Facts labeling:

***Reviewer's comments:** The "Questions" section in the proposed labeling submitted on February 15, 2019 is not acceptable. A horizontal barline preceding the "Questions?" heading must be added per 21 CFR 201.66(d)(8). On March 13, 2019, we requested the Sponsor add this barline per 21 CFR 201.66(d)(8) (refer to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency's request, the Sponsor has added the barline above the "Questions?" section in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.*

iii. Format Specifications

The font specifications for the applicator secondary packaging (applicator (b) (4)) are in accordance with 21 CFR 201.66.

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

C. ZuraGard™ Applicator

The Sponsor proposes the following labeling for the 10.5 mL applicator:

(b) (4)

***Reviewer’s comments:** The applicator proposed labeling submitted on February 15, 2019 contains three of the four mandatory requirements (per 21 CFR 201.10(i)(B)) for small labels which include: the proprietary name of the drug; the established name; an identifying lot or control number; and the name of the distributor of the drug. The Sponsor should clarify where the identifying lot or control number will be placed on the labeling. The established name should be revised to read: “Isopropyl Alcohol (70% v/v) Solution” (see section **II.A.i.a.2 and II.E** for applicable comments). The statement “Surgical Solution” should be repositioned from after the trade name to follow the established name, followed by the statement “For head, neck, and small prep areas” (see section **II.A.i.a.2 and II.E** for applicable comments).*

*As specified in the FDA CBE Supplement Request letter dated August 4, 2009 (refer to CBE Supplement Request Letter for NDA 020832 from August 4, 2009 in DARRTS) the second bulleted statement under the “**Warnings**” should be revised to read: “▪ avoid getting solution into hairy areas. **Wet hair is flammable.** Hair may take up to 1 hour to dry.” by changing the order of the second and third sentence in the bulleted statement.*

On March 13, 2019 and March 21, 2019, we requested the Sponsor revise the applicator barrel label as described above (refer to March 13, 2019 and March 21, 2019 labeling advice letters in DARRTS). In accordance with the Agency’s request, the Sponsor has revised the applicator barrel label as recommended in the revised proposed labeling submitted on March 27, 2019. In addition, the Sponsor has added a placeholder for the expiration date in the format for small

labels recommended by DMEPA in the revised proposed labeling submitted on March 27, 2019 and it is acceptable (see section II.E for applicable comments).

D. ZuraGard™ Package Insert

The package insert will be placed within the outer carton. In the proposed labeling submitted on February 15, 2019, it is a (b) (4) insert which will be folded to (b) (4). One panel will contain the statement of identity, applicator information, sterility statements, flammability warnings, symbols, and distributor information. The second panel will contain the Drug Facts labeling. In the revised proposed labeling for the package insert submitted on March 27, 2019, it is a 6" x 8" insert, which will be folded horizontally to 6" x 2.67".

a. Labeling Outside the Drug Facts

The Sponsor proposes the following for the first panel of the package insert:



Reviewer's comments: The content and format of the statement of identity in the proposed labeling submitted on February 15, 2019 is not acceptable. The proposed established name of the drug "70% v/v isopropyl alcohol (b)(4)" should be revised to read "Isopropyl Alcohol, 70% v/v Solution" or "Isopropyl Alcohol (70% v/v) Solution" (see section **II.A.i.a.2** and **II.E** for applicable comments). The font of the pharmacological category ("Patient Preoperative Skin Preparation") will need to be bolded.

The proposed statement "BLUE" indicates the color of the surgical preparation solution. The statement should not be placed after the pharmacological category of the drug product, but instead appear after the sterility statements "Non-Sterile Solution" and "Applicator is sterile if package is intact" on the PDP (See section **II.A.i.a.1 through 10** for applicable comments and refer to CBE supplement request letter to Sponsors for NDA 021669 from November 14, 2013 in DARRTS). The size of the "BLUE" statement should be consistent with the size of the statement "10.5 mL APPLICATORS".

The placement and format of the statements "Non-sterile Solution" and "Applicator is sterile if package is intact" on the PDP is not consistent with class labeling safety changes requested in 2013 (refer to November 17, 2013 CBE Supplement Request Letter for NDA 021669 in DARRTS) and is not acceptable. The sterility statement "Non-sterile Solution" should be placed after the pharmacological category (Patient Preoperative Skin Preparation) on the PDP and anywhere else in the labeling where the pharmacological category appears. The statement "Non-sterile Solution" should be followed by the statement "Applicator is sterile if package is intact". Both sterility statements should be in bold font and in the same font size as the pharmacological category. The statement "Surgical Solution" should be removed from after the trade name and repositioned to follow the statement "Applicator is sterile if package is intact" (see section **II.A.i.a.2** and **II.E** for applicable comments). The statement "For head, neck, and small prep areas" should be included on the PDP following the statement "Surgical Solution" for consistency with labeling for applicators of this size (see section **II.A.i.a.2** and **II.E** for applicable comments).

As specified in the FDA CBE-30 Supplement Request letter dated August 4, 2009 (refer to CBE-30 Supplement Request Letter for NDA 020832 from August 4, 2009 in DARRTS), and for consistency across labeling for drug products in this category, the second bulleted statement in the boxed flammability warning "avoid getting solution into hairy areas. Hair may take up to 1 hour to dry. **Wet hair is flammable.**" should be revised to read: "avoid getting solution into hairy areas. **Wet hair is flammable.** Hair may take up to 1 hour to dry." by changing the order of the second and third sentence in the bulleted statement. The remaining bulleted statements in the boxed flammability warning are consistent with the class labeling change from 2009.

On March 13, 2019 and March 21, 2019, we requested the Sponsor revise the panel as described above (refer to March 13, 2019 and March 21, 2019 labeling advice letters in DARRTS). In accordance with the Agency's request, the Sponsor has amended this panel as recommended in the revised proposed labeling submitted on March 27, 2019 and it is acceptable.

*On April 4, 2019, we requested the Sponsor revise the statement "10.5 mL APPLICATOR" to read: "0.36 fl oz (10.5 mL) APPLICATOR" per 21 CFR 201.62 (refer to the April 4, 2019 information request in DARRTS and see sections **II.A.i.a.4** and **II.B.i.a** for applicable comments). On April 8, 2019, the Sponsor submitted revised proposed labeling adding the net quantity in fluid ounces. This is acceptable.*

(b) (4)



b. Drug Facts

The Sponsor proposes the following *Drug Facts* for the package insert:



Reviewer's comments: *The content of the "Use", "Warnings", and "Directions" sections in the proposed labeling submitted on February 15, 2019,*

*will need to be revised. Refer to section **II.A.ii.a through d** for applicable comments. The “**Inactive Ingredients**” heading will need to be revised to read: “**Inactive ingredients**”, refer to section **II.A.ii.f** for applicable comments. The indentation before the website in the “**Questions?**” section will need to be removed.*

*On May 13, 2019, we requested the Sponsor revise the Drug Facts labeling of the package insert as described in section **II.A.ii.a through d and f** and remove the indentation before the website in the “**Questions?**” section (refer to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency’s request, the Sponsor has amended the Drug Facts labeling of the package insert for the 25-count carton in the revised proposed labeling submitted on March 27, 2019 and any subsequent submission, and it is acceptable.*

iii. Format Specifications

The font specifications for the package insert for the 25-count outer carton are in accordance with 21 CFR 201.66.

***Reviewer’s comments:** This is acceptable*

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

DMEPA completed the review of the proposed name, ZuraGard™ and concluded that this name is acceptable (see section II.A.i.a.1 for applicable comments and March 1, 2019 proprietary name review and March 5, 2019 Proprietary Name Granted letter in DARRTS).

On March 18, 2019, 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 and conveyed concerns regarding the term “surgical solution” in the proposed labeling. Specifically, DMEPA offered the following recommendation for the Division:

1. “We defer to DNDP to determine if the term “surgical solution” or the term “solution” should be used to represent the dosage form throughout the container labels and carton labeling for this proposed product.
2. Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.”

Reviewer’s comments: *On March 21, 2019, we requested the Sponsor revise the proposed established name of the drug “70% v/v isopropyl alcohol (b)(4)” to read “Isopropyl Alcohol (70% v/v) Solution” by including the dosage form and removing (b)(4) in the Statement of Identity (refer to section II.A.i.a.2 and 3 for applicable comments). Furthermore, we requested the Sponsor remove the descriptor “Surgical Solution” after the proprietary name wherever it appears in the labeling and relocate it to follow the sterility statements (see March 21, 2019 addendum to March 13, 2019 labeling advice letter in DARRTS). On March 21, 2019, we also provided the Sponsor DMEPA’s recommendation regarding the expiration date (refer to March 21, 2019 addendum to March 13, 2019 labeling advice letter in DARRTS). In accordance with the Agency’s request, the Sponsor has revised the statement of identity wherever it appears in the proposed labeling submitted on March 27, 2019 and has included the expiration date (for placement only), in the format recommended by DMEPA, in the outer carton and applicator labeling.*

On April 4, 2019, we requested the Sponsor confirm that the expiration date will also be present on the applicator (b)(4) (secondary packaging) as this location is more convenient for the end user to note (refer to April 4, 2019 information request in DARRTS and see section II.A.i.c.6 for applicable comments). In the Sponsor's April 8, 2019 revised labeling submission, the Sponsor confirmed that the expiration date and lot number will be displayed on the applicator (b)(4) in the same format as the carton. This is acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the Sponsor for the submitted ZuraGard™ outer carton, secondary packaging (applicator (b)(4)), applicator (immediate container), and package insert labeling for NDA 210872 and request final printed labeling identical to the labeling submitted on April 8, 2019.

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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HANA MUJAHID
04/08/2019 04:06:49 PM

FRANCISCO MARTINEZ-MURILLO
04/08/2019 04:47:08 PM

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:	March 18, 2019
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 210872
Product Name and Strength:	ZuraGard (Isopropyl Alcohol) Solution, 70%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Over-the-Counter (OTC)
Applicant/Sponsor Name:	Zurex Pharma (Zurex)
FDA Received Date:	February 15, 2019
OSE RCM #:	2018-1487
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for ZuraGard (Isopropyl Alcohol) Solution, the Division of Nonprescription Drug Products (DNDP) requested that we review the proposed ZuraGard container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

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 FINDINGS AND RECOMMENDATIONS

Our review of the proposed container labels and carton labeling identified that in addition to the immediate container label and the carton labeling, Zurex is proposing a package insert for the carton and a secondary packaging applicator (b) (4) container label, which contains the same information that is provided in the DFL.

As a preoperative skin preparation product, this proposed isopropyl alcohol topical solution combination product would be used in hospital surgical room environments by healthcare professional (HCP) end users, and use of the proposed product involves opening and removing the single use applicator from the container packaging, and then pressing down on the cap end of the applicator sponge 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 human factors validation study is not necessary at this time.

Tables 2 and 3 below include the identified medication error issues with the submitted container labels and carton labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issue and Recommendation for DNDP			
	IDENTIFIED ISSUE	RATIONALE	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	We note that the dosage form is presented as “surgical solution” throughout the container labels and carton labeling.	We have not seen “surgical solution” as a dosage form.	We defer to DNDP to determine if the term “surgical solution” or the term “solution” should be used to represent the dosage form throughout the container labels and carton labeling for this proposed product.

Table 3. Identified Issue and Recommendation for Zurex Pharma (Entire table to be conveyed to the Applicant)			
	IDENTIFIED ISSUE	RATIONALE	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

4 CONCLUSION

Our evaluation of the proposed ZuraGard container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we provide our recommendations in Tables 2 and 3 for the Division and request that the Division conveys Table 3 in its entirety to Zurex Pharma so that the recommendation is implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for ZuraGard that Zurex Pharma submitted on February 15, 2019.

Table 4. Relevant Product Information for ZuraGard	
Initial Approval Date	N/A
Active Ingredient	Isopropyl alcohol
Indication	For the preparation of the (b) (4) skin prior to surgery. Helps (b) (4) reduce bacteria that potentially can cause skin infection.
Route of Administration	Topical
Dosage Form	Solution
Strength	70%
Dose and Frequency	<p>Drug Facts Label (DFL) <i>Directions:</i></p> <ul style="list-style-type: none"> • use with care in premature infants or infants 2 months of age. These products may cause irritation or chemical burns. • use in a well-ventilated area • maximal treatment area for one applicator is approximately 8.4 in. x 8.4 in. (457 cm²) • remove applicator from package; do not touch sponge • hold the applicator sponge down. Depress the end cap/button to release the antiseptic, solution will flow into the sponge • (b) (4) completely wet the treatment area • do not allow solution to pool; tuck prep towels to absorb solution, and then remove • dry surgical sites (such as abdomen or arm): use repeated back-forth strokes (b) (4) for (b) (4) 30 seconds • moist surgical sites (such as inguinal fold): use repeated back-forth strokes (b) (4) for (b) (4) 2 minutes • (b) (4) solution (b) (4) completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair). Do not blot or wipe away. • discard the applicator after single use along with any portion of the solution which is not required to cover the prep area. It is not necessary to use the entire amount available.

Table 4. Relevant Product Information for ZuraGard	
How Supplied	10.5 mL applicator 25-count carton (containing 10.5 mL applicators)
Storage	Store between 15-30°C (59-86°F) Avoid freezing and excessive heat above 40°C (104°F)
Container Closure	The solution is provided in a proprietary 10.5-mL applicator container closure system. The container closure system is comprised of (b) (4)  (b) (4)

^a Source: <\\cdsesub1\evsprod\nda210872\0001\m3\32-body-data\32p-drug-prod\zuraprep-solution\32p7-cont-closure-sys\container-closure-system.pdf>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 22, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, ZuraGard. Our search identified one proprietary name review for ZuraGard.^b We have not reviewed the container labels and carton labeling for ZuraGard.

^b Jones G. Proprietary Name Review for ZuraGard (NDA 210872). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 01. RCM No.: 2018-27767623.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following ZuraGard labels and labeling submitted by Zurex Pharma.

- Container label(s) received on February 15, 2019
- Carton labeling received on February 15, 2019

F.2 Label and Labeling Images

Container label(s)



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^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

GRACE JONES
03/18/2019 10:40:45 AM

CHI-MING TU
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: 9/19/2018

From: Melissa Reyes, MD, MPH, DTMH, Medical Officer, DDDP

Through: Kendall Marcus, MD, Division Director, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP

To: Theresa Michele, MD, Division Director, DNDP

CC: Francis Becker, MD, Clinical Team Leader, DNDP
Edward Chin, MD, Medical Officer, DNDP
Sherry Stewart, RPM, DNDP
Barbara Gould, CPMS, DDDP
Tisha Washington, RPM Staff, DDDP

Re: DDDP Consult #1946: New NDA containing phototoxicity and dermal sensitivity studies. Specifically, four dermal tolerability studies were conducted: Study ZX-ZP-0016 (phototoxicity study); Study ZX-ZP-0017 (cumulative irritation study); Study ZX-ZP-0018 (contact sensitization study); and Study ZX-ZP-0019 (photosensitization study). Please attend the all meetings and review these studies.

Materials Reviewed:

NDA 210872, study body reports for the following studies:

- Study ZX-ZP-0016 (phototoxicity study)
- Study ZX-ZP-0017 (cumulative irritation study)
- Study ZX-ZP-0018 (contact sensitization study)
- Study ZX-ZP-0019 (photosensitization study).

Conclusion:

Based on results of dermal safety studies submitted by the applicant, it is reasonable to conclude that ZuraPrep isopropyl alcohol 70% solution has the potential for irritation and sensitization, and thus should be adequately conveyed in labeling.

Based on the results of this study, it is reasonable to conclude that ZuraPrep™ does not have the potential for phototoxicity or photoallergenicity.

Background:

ZuraPrep (isopropyl alcohol, 70%) is a skin antiseptic/antimicrobial intended as a preoperative skin preparation solution to prevent and reduce the incidence of healthcare-associated infections occurring during surgical procedures.

The applicant submitted 4 dermal safety studies in support of their application. The review of each study is presented below.

Review

Evaluation of Irritation Potential

Study number: 130820-302.01

Protocol: ZX-ZP-0016

Principal investigator: Esther Campbell, BioScience Laboratories, Inc.

Study Title: A 21-day evaluation of the cumulative irritation potential of topically applied ZuraPrep and ZuraPrep without IPA in healthy adult volunteers

Conducted: 2/28/2014-12/23/2014

Date of Final Report: 12/23/2014, Date of amended Final Report: 1/15/2015

Study population: 30 healthy male and female subjects 18 years of age and older

Study design: This is randomized, single center, double blind, positive- and negative-controlled study.

Test products: 0.02 mL of test product applied via Finn Chambers on Scanpor® tape.

- ZuraPrep™
- ZuraPrep™ without isopropyl alcohol
- Chloraprep® (b) (4) tint (reference product with 2% chlorhexadine and 70% isopropyl alcohol)
- Sodium laurel sulfate, 0.1% (positive control)
- Saline, 0.9% (negative control)

Study procedures:

Test products were applied to the back of subjects using occlusive patches, daily for 21 days. After for 23 +/- 1 hours, the test products were removed. Ten minutes after test product removal, the application sites were evaluated for irritation reactions using scale below.

Scoring Scale:

TABLE I - SCORING SCALE FOR VISUAL EVALUATION OF SKIN CONDITION

SCORE	DESCRIPTION
0	no evidence of irritation
1	minimal erythema, barely perceptible
2	definite erythema, readily visible; minimal edema or minimal papular response
3*	erythema and papules
4*	definite edema
5*	erythema, edema, and papules
6†	vesicular eruption
7†	Strong reaction spreading beyond test site

* Product application on a site discontinued

† Adverse Event; subject discontinued from testing

Safety monitoring

No laboratory testing or vitals were taken during this study. Adverse events (AE) were reported during the conduct of this study. AEs were recorded and included the severity and relationship to drug. Application sites with an irritation score ≥ 3 that did not improve after 48 hours was considered an AE.

Study results:

The table below summarize the applicant's cumulative irritation study results by mean visual score of skin irritation of each test product (Table 2).

Table 2: Mean Visual Scores of Skin Irritation and Total Cumulative Irritation Score after Repeated Applications of Five Test Materials for 21 Consecutive Days

Evaluation	Test Material				
	Test Product #1 ZuraPrep™	Test Product #2 ZuraPrep™ without IPA	Reference Product Chlorazepate (b) (4) Tint	Positive Control 0.1% Sodium Lauryl Sulfate	Negative Control 0.9% Physiological Saline, USP
Baseline	0.00	0.00	0.00	0.00	0.00
Evaluation 1	0.00	0.00	0.00	0.00	0.00
Evaluation 2	0.06	0.00	0.18	0.06	0.03
Evaluation 3	0.53	0.35	0.53	0.12	0.06
Evaluation 4	0.79	0.47	0.88	0.38	0.06
Evaluation 5	1.03	1.00	1.50	0.65	0.32
Evaluation 6	1.50	1.35	2.44	0.79	0.44
Evaluation 7	2.62	2.35	3.00	1.09	0.91
Evaluation 8	3.03	2.65	3.18	1.24	0.71
Evaluation 9	2.79	2.32	3.09	1.12	0.59
Evaluation 10	2.47	2.24	3.09	1.97	0.56
Evaluation 11	2.88	2.59	3.27	2.12	1.09
Evaluation 12	2.79	2.50	3.21	1.77	0.44
Evaluation 13	3.03	2.59	3.27	1.94	0.29
Evaluation 14	3.06	2.74	3.29	2.06	0.24
Evaluation 15	3.12	2.74	3.29	2.21	0.32
Evaluation 16	3.09	2.79	3.32	2.21	0.38
Evaluation 17	2.94	2.68	3.32	2.62	0.94
Evaluation 18	3.09	2.68	3.38	2.71	1.06
Evaluation 19	3.27	2.97	3.35	2.65	0.24
Evaluation 20	3.27	2.94	3.32	2.74	0.27
Evaluation 21	3.27	3.03	3.38	2.68	0.24
Total Cumulative Irritation Score	1653	1461	1846	1125	312

NOTE: N = 34. All data collected from Subjects (b) (6) who withdrew from testing were not used in Table 2.

Utilizing the mean irritation score, ZuraPrep™ was more irritating than ZuraPrep™ without isopropyl alcohol and more irritating than positive control, while ZuraPrep™ and ZuraPrep™ without isopropyl alcohol were less irritating than the reference product. Based on the Berger and Bowman (1982) categorization of irritation based on total cumulative irritation score, ZuraPrep™, ZuraPrep™ without isopropyl alcohol, and the positive control are Level III, possibly mild in use.

The cumulative irritation study also analyzed the test products utilizing Friedman Analysis. The results of this statistical test are:

- ZuraPrep™, ZuraPrep™ without isopropyl alcohol, and positive control were less irritating than reference product.
- ZuraPrep™ was more irritating than ZuraPrep™ without isopropyl alcohol.
- ZuraPrep™ was more irritating than positive control.
- ZuraPrep™ without isopropyl alcohol was as irritating as positive control.

Safety: Four subjects experienced AEs during the study:

- Nausea (mild, product related, resolved)
- Sore throat and feeling “sniffly” (mild, product related, resolved)
- Tonsillitis (mild, product related, resolved, led to discontinuation)
- Light-headed (mild, product related, resolved)

Reviewer’s comments: This was a standalone cumulative irritation study that compared the irritation potential of ZuraPrep™, vehicle, reference product, positive control, and negative control. The reference product was included because it contained 70% isopropyl alcohol similar to test product, but also had the addition of 2% chlorhexadine. This study was adequate in design and conduct for evaluation of cumulative irritation potential of the test product. Overall, ZuraPrep™ was shown to have irritation potential under the study’s provocative conditions.

Evaluation of Sensitization Potential

Study number: 130821-303

Protocol: ZX-ZP-0018

Principal investigator: Margaret Butler, PhD, BioScience Laboratories, Inc.

Study title: A clinical evaluation of the contact sensitizing potential of topically applied ZuraPrep™ and ZuraPrep™ without IPA in health adult volunteer

Conducted: 2/28/2014-2/13/2015, Date of Final Report: 2/13/2015

Study population: 208 male and female healthy volunteers between 18 years of age and older

Study design: This was a single center double-blinded, randomized, controlled, within subject comparison study.

Test patches: 0.02 mL of test product applied via Finn Chambers on Scanpor® tape.

- ZuraPrep™
- ZuraPrep™ without isopropyl alcohol (vehicle)

- ChloroPrep® (b) (4) tint (reference product with 2% chlorhexadine and 70% isopropyl alcohol)
- Saline, 0.9% (negative control)

Study procedures: This study consisted of 3 phases: induction phase, rest phase, and challenge phase.

Induction phase: Test products were applied to the back of subjects using occlusive patches, three times weekly, for 3 weeks. Patches were left in place for 48 hours on weekdays and 72 hours on weekends. Application sites were evaluated 10 minutes after patch removal using the scale below.

Rest phase: On Day 22, patches were removed and the subjects entered a 14-day rest period during which no patch application was performed.

Challenge phase: After the rest period, the challenge phase consisted of a single 48-hour patch application on the naïve skin area. After 48 hours, patches were removed and evaluated at 30 minutes, 24 hours, 48 hours, and 72 hours after patch removal.

Scoring Scale: “Dermal Response” and “Other Effects” were evaluated using the following scales:

TABLE I - SCORING SCALE FOR VISUAL EVALUATION OF SKIN CONDITION

SCORE	DESCRIPTION
0	no evidence of irritation
1	minimal erythema, barely perceptible
2	definite erythema, readily visible; minimal edema or minimal papular response
3*	erythema and papules
4*	definite edema
5*	erythema, edema, and papules
6†	vesicular eruption
7†	Strong reaction spreading beyond test site

* Product application on a site discontinued

† Adverse Event; subject discontinued from testing

In addition, for each site with a “notable reaction,” a written description was included.

Safety monitoring: No laboratory testing or vitals were taken during this study. Adverse events (AE) were reported during the conduct of this study. AEs were recorded and included the severity and relationship to drug. Reactions not resolved at 72 hours after patch removal was tracked until resolved.

Study results:

The table below summarizes the reaction scores of subjects determined to have potential sensitization to ZuraPrep™ during the challenge phase.

Table 27. Potential Sensitization of ZuraPrep™

Subject	Visual Scores and Comments of Skin Irritation				Comment
	30 Minutes	24 Hours	48 Hours	72 Hours	
(b) (6)	0	0	1	Erythema only, on <50% site 2	Possible Sensitization, but Unlikely
	0	0	0	Erythema only, on <50% site 2	Possible Sensitization, but unlikely
	0	1	Erythema, minimal papules on 50% site 2	Erythema and scabbing 2	Possible Sensitization
	0	1	Erythema, minimal papules on 50% site 2	Erythema, minimal papules on <50% site 2	Possible Sensitization
	Erythema, minimal papules 2	Definite Erythema, minimal papules and scabbing 2	Definite Erythema and Papules 3	Definite Erythema, papules, edema, scabbing and crusting 5	Probable Sensitization

Subjects (b) (6) clearly presented a delayed response, albeit a very mild response. Sensitization is unlikely.

Subjects (b) (6) did not show a response until 24 hours and presented stronger reactions in addition to erythema. The distinction between irritation and sensitization was difficult in these two cases.

Overall, the study identified:

- Two subjects showed mild potential sensitization to ZuraPrep™
- Three subjects showed mild potential sensitization to reference product
- One subject showed sensitivity to ZuraPrep™ and reference product
- One subject showed potential sensitivity to reference product
- Two subjects showed mild potential sensitization to the negative control.

The applicant's study included a secondary analysis for irritation during the induction phase. The following table summarizes subjects with likely irritation due to ZuraPrep™.

Table 26. Potential Irritation of ZuraPrep™

Subject	Visual Scores of Skin Irritation				Comment
	30 Minutes	24 Hours	48 Hours	72 Hours	
(b) (6)	5	3	3	0	Irritation
	4	3	2	2	Irritation
	3	3	2	2	Irritation
	5	3	3	2	Irritation
	5	3	2	2	Irritation
	5	3	2	0	Irritation
	5	3	3	0	Irritation
	5	3	2	2	Irritation
	4	3	3	3*	Irritation
	5	5	3	2	Irritation
	3	1	2	2	Irritation

*Even though the 72-hour evaluation of Subject (b) (6) presented a score of 3, improvement over the 72 hour test period was observed, as determined from the narrative comments of the evaluator (Table 2A in Addendum 5).

Safety:

During the study, 15 subjects experienced 19 AEs. One AE was serious, one AE was related to test product, and two AEs were possibly related to test product. All 19 AEs resolved.

Serious AE: Subject reported leg fracture after being knocked over by dog. Subject required surgery and discontinued study.

AE: contact dermatitis and folliculitis. Subject was instructed to return for safety evaluation due to reaction score of 3 for reference product. One month later (was out of town), subject was evaluated by investigator and diagnosed for contact dermatitis and folliculitis which resolved with doxycycline and fluocinonide cream. Report does not include detail about site of contact dermatitis diagnosis.

Reviewer's comments:

This study was adequate in design and conduct for evaluation of contact sensitization potential of the test product. The study results indicate that ZuraPrep™ has the potential for contact sensitization.

The results of the secondary analysis support the findings of the standalone cumulative irritation study, Protocol ZX-ZP-0018, showing that ZuraPrep™ has the potential for cumulative irritation.

Evaluation of Phototoxicity Potential

Study Number: PB610115

Protocol: ZX-ZP-0016

Principal Investigator: Jonathan Dosik, MD, TKL Research Inc.

Study title: A 4-day, randomized study to evaluate the irritation potential of ZuraPrep™ when application to skin is followed by light exposure in healthy volunteers, using a phototoxicity patch test design

Conducted: 6/24/2015 – 8/10/2015; Date of Report: 12/16/2015

Study population: 34 male and female subjects 18 years and older with Fitzpatrick skin type I through III

Study design: This was a randomized, single center, blinded, controlled, intra-subject comparison study.

Test patches included:

- ZuraPrep™: 200µL
- ZuraPrep™ without isopropyl alcohol (vehicle): 200µL
- Untreated patch (negative control)

Patch consisted of 2 cm x 2 cm Webril pad and covered with nonporous, plastic film adhesive bandage (3M medial tape).

Study procedures:

Day 1:

- Minimal Erythema Dose (MED) was determined (in seconds of exposure time) for each subject prior to initiation of study (50cm² area of infrascapular back).
- Each subject had 9 application sites (6 irradiated and 3 non-irradiated) on the infrascapular back. The test products were applied in 3 sets (Set A, B, and C). After 24 hours, Set A and B were irradiated while Set C was not irradiated. All sites were evaluated 24 and 72 hours after irradiation.

Day 2:

- MED calculated
- Patches removed and application sites evaluated using scales below. Sites were then irradiated as described below:
 - Set A sites: irradiated with 16 J/cm of UVA (320 - 400 nm) followed by 0.5 times MED UVB/UVA exposure.
 - Set B sites: irradiated with 16 J/cm² of UVA (320 - 400 nm) followed by 0.5 times MED UVB/UVA and 15 J/cm² visible light exposure.
 - Set C: no irradiation. This set served as a non-irradiated control.

Day 3:

- All sites evaluated using scales below 24 hours after irradiation

Scoring Scales

Table 9-3 Grading of Responses

Response	Symbol	Numerical Equivalent Score
Erythema		
No reaction	-	0
Mild, but definite erythema	+	1.0
Moderate erythema	++	2.0
Marked/severe erythema	+++	3.0
Edema		
No reaction	0	0
Mild, but definite edema	**	1.0
Definite edema with erosion/vesiculation	***	1.5

Table 9-4 Response Notations

Response/Comment	Notation
Hyperpigmentation	Hr
Hypopigmentation	Ho
Vesiculation	V
Papular response	P
Papulovesicular response	PV
Damage to epidermis: oozing, crusting and/or superficial erosions	D
Itching	I
Spreading of reaction beyond patch study site (ie, reaction where material did not contact skin)	S
Follicular irritation with or without pustule formation (folliculitis)	f
Subject absent	X
Patch dislodged	PD
Not patched	NP
No reaction	0

Safety monitoring: No laboratory testing or vitals were taken during this study. Urine pregnancy testing was done in women of childbearing potential. Adverse events (AE) were reported during the conduct of this study. AEs were recorded and included the severity and relationship to drug.

Observed adverse effects which could be denoted using the scoring scale was not considered an AE. In addition, tape-related irritation was not recorded as an AE.

Study results: The summary of dermal responses during the challenge phase are presented in Table 11-2, below.

Table 11-2 Summary of Dermal Responses – All Randomized Subjects

Response [1]	ZuraPrep™			Test Article Vehicle - ZuraPrep™ without IPA			Untreated		
	Irradiated SET A	Irradiated SET B	Non-Irradiated	Irradiated SET A	Irradiated SET B	Non-Irradiated	Irradiated SET A	Irradiated SET B	Non-Irradiated
0 hours (Day 2), n(%)									
0	34 (100.0)	33 (97.1)	34 (100.0)	34 (100.0)	34 (100.0)	34 (100.0)	34 (100.0)	34 (100.0)	34 (100.0)
1	0	1 (2.9)	0	0	0	0	0	0	0
24 hours (Day 3), n(%)									
0	9 (26.5)	12 (35.3)	27 (79.4)	9 (26.5)	12 (35.3)	33 (97.1)	13 (38.2)	13 (38.2)	34 (100.0)
1	23 (67.6)	20 (58.8)	5 (14.7)	25 (73.5)	22 (64.7)	1 (2.9)	20 (58.8)	21 (61.8)	0
3	2 (5.9)	2 (5.9)	2 (5.9)	0	0	0	1 (2.9)	0	0
48 hours (Day 4), n(%)									
0	27 (79.4)	27 (79.4)	28 (82.4)	29 (85.3)	30 (88.2)	33 (97.1)	30 (88.2)	30 (88.2)	34 (100.0)
1	5 (14.7)	5 (14.7)	4 (11.8)	4 (11.8)	3 (8.8)	0	3 (8.8)	4 (11.8)	0
2	0	0	0	1 (2.9)	1 (2.9)	1 (2.9)	0	0	0
3	1 (2.9)	1 (2.9)	1 (2.9)	0	0	0	1 (2.9)	0	0
3.5	1 (2.9)	1 (2.9)	1 (2.9)	0	0	0	0	0	0
Average of 24 & 48 hours									
N	34	34	34	34	34	34	34	34	34
Mean(SD)	0.60 (0.72)	0.55 (0.74)	0.32 (0.79)	0.46 (0.36)	0.40 (0.36)	0.04 (0.26)	0.43 (0.55)	0.37 (0.33)	0.00 (0.00)
P values									
ZuraPrep™, Irr SET A vs:	-	0.6401	0.0033	0.1394	0.0361	<0.0001	0.0739	0.0163	<0.0001
ZuraPrep™, Irr SET B vs:	-	-	0.0132	0.3114	0.1025	<0.0001	0.1859	0.0522	<0.0001
ZuraPrep™, Non-irr vs:	-	-	-	0.1394	0.3916	0.0042	0.2430	0.5854	0.0009
Test Article Vehicle, Irr SET A vs:	-	-	-	-	0.5331	<0.0001	0.7552	0.3500	<0.0001
Test Article Vehicle, Irr SET B vs:	-	-	-	-	-	0.0002	0.7552	0.7552	<0.0001
Test Article Vehicle, Non-irr vs:	-	-	-	-	-	-	<0.0001	0.0007	0.6401

Irradiation was associated with dermal response with no statistical significant difference between irradiated ZuraPrep™, irradiated vehicle, and irradiated control sites. Non-irradiated ZuraPrep™ sites had statistically significantly greater dermal irritation compared to non-irradiated vehicle and control sites. No retesting was necessary.

Safety: No AEs were reported in this study.

Reviewer’s comments:

Based on the results of this study, it is reasonable to conclude that the ZuraPrep™ does not have the potential for phototoxicity.

Evaluation for Photoallergy Potential

Study number: PB710115

Protocol: ZX-ZP-0019

Principal Investigator: Jonathan Dosik, MD, TKL Research, Inc.

Study title: A 6-week, randomized study to evaluate the potential of ZuraPrep™ and vehicle to induce a photoallergic skin reaction in healthy volunteers, using a controlled photopatch test design.

Conducted: 6/2/2015 – 9/8/2015. Date of Report: 1/5/2016

Study population: 49 male and female healthy volunteers 18 years and older with Fitzpatrick skin type I-III.

Study design: This was a randomized, single center, blinded, controlled, within-subject comparison study.

Test patches included:

- ZuraPrep™: 200µL
- ZuraPrep™ without isopropyl alcohol (vehicle): 200µL
- Untreated patch (negative control)

Patch consisted of 2 cm x 2 cm Webril pad and covered with nonporous, plastic film adhesive bandage (3M medical tape).

Study procedures:

Minimal Erythema Dose (MED) was determined (in seconds of exposure time) for each subject prior to initiation of study (50cm² area of infrascapular back).

This study consisted of three phases:

Induction phase (Weeks 1-3): Over 3 weeks, two sets of study material was applied (Set A and B), evaluated, and irradiated (if designated) twice weekly for a total of 6 applications. Patches were applied on Mondays and Thursdays. After 24 hours, the product patches were removed and the sites evaluated. On all Tuesdays and Fridays, the sites were irradiated, as described below:

- Set A sites: irradiated with 2 times the subject's MED of UVA/UVB (full spectrum) irradiation
- Set B sites: irradiated with 2 times the subject's MED of UVA/UVB (full spectrum) irradiation and 15 J/cm² visible light.

Evaluations were performed on:

- Tuesday and Friday immediately after patch removal
- Thursday of the Week 1 and Monday and Thursday of Week 2 and 3
- Immediately prior to product application

Rest phase (Weeks 4 and 5): This phase lasted 13-17 days during which there was no patches application or irradiation.

Challenge phase (Week 6): During this phase, patches were applied to naive skin sites per predetermined randomization scheme and left in place for 24 hours. After 24 hours, patches were removed and irradiated with filtered light as described below:

- Set C sites: irradiated with 6 J/cm² of UVA (320 - 400 nm) followed by 0.5 times MED UVB/UVA exposure.
- Set D sites: irradiated with 6 J/cm² of UVA (320 - 400 nm) followed by 0.5 times MED UVB/UVA and 15 J/cm² visible light exposure.
- Set E sites: no irradiation. This set served as a non-irradiated control.

Skin reactions were scored 24, 48 hours, and 72 hours after irradiation.

Re-challenge: If potential photosensitivity reaction observed at any irradiated product site, re-challenge would be performed.

Scoring Scale: The same scale was use as the one used for phototoxicity evaluation (see above).

Safety monitoring: No laboratory testing or vitals were taken during this study. Urine pregnancy testing was done in women of childbearing potential. AEs were reported during the conduct of this study. AEs were recorded and included the severity and relationship to drug.

Observed adverse effects which could be denoted using the scoring scale was not considered an AE. In addition, tape-related irritation was not recorded as an AE.

Study results: The summary of dermal responses during the challenge phase are presented in Table 11-3, below.

Table 11-3 Summary of Dermal Responses with Notations During Challenge – Population I

Time Post-Irradiation	ZuraPrep™			Test Article Vehicle – ZuraPrep™ without IPA			Untreated		
	Irr SET C	Irr SET D	Non-Irr SET E	Irr SET C	Irr SET D	Non-Irr SET E	Irr SET C	Irr SET D	Non-Irr SET E
0 hours, n (%)									
0,0	49 (100.0)	49 (100.0)	49 (100.0)	49 (100.0)	49 (100.0)	49 (100.0)	49 (100.0)	49 (100.0)	49 (100.0)
24 hours, n (%)									
0,0	26 (53.1)	25 (51.0)	43 (87.8)	36 (73.5)	35 (71.4)	49 (100.0)	34 (69.4)	34 (69.4)	49 (100.0)
0,HR	1 (2.0)	1 (2.0)	0	1 (2.0)	1 (2.0)	0	1 (2.0)	0	0
1,0	22 (44.9)	23 (46.9)	6 (12.2)	12 (24.5)	13 (26.5)	0	14 (28.6)	14 (28.6)	0
1,HR	0	0	0	0	0	0	0	1 (2.0)	0
48 hours, n (%)									
0,0	30 (61.2)	27 (55.1)	41 (83.7)	38 (77.6)	39 (79.6)	48 (98.0)	40 (81.6)	38 (77.6)	49 (100.0)
0,HR	6 (12.2)	7 (14.3)	0	7 (14.3)	6 (12.2)	1 (2.0)	6 (12.2)	5 (10.2)	0
1,0	13 (26.5)	15 (30.6)	8 (16.3)	4 (8.2)	4 (8.2)	0	3 (6.1)	6 (12.2)	0
72 hours, n (%)									
0,0	36 (73.5)	36 (73.5)	41 (83.7)	43 (87.8)	44 (89.8)	49 (100.0)	44 (89.8)	44 (89.8)	49 (100.0)
0,HR	2 (4.1)	2 (4.1)	0	4 (8.2)	3 (6.1)	0	3 (6.1)	3 (6.1)	0
1,0	8 (16.3)	8 (16.3)	6 (12.2)	2 (4.1)	2 (4.1)	0	2 (4.1)	2 (4.1)	0
1,HR	2 (4.1)	2 (4.1)	2 (4.1)	0	0	0	0	0	0
1,I	1 (2.0)	1 (2.0)	0	0	0	0	0	0	0
Number Sensitized [2]	0	0	0	0	0	0	0	0	0

No more than mild definite erythema was observed at the irradiated sites. The incidence of erythema was comparable at the irradiated Vehicle and untreated sites and higher for the irradiated ZuraPrep™ sites. No subject met the criteria for reactions indicating photosensitization. No re-challenge was necessary.

Photoirritation potential was evaluated during the induction period. Grade 2 irritation (moderate erythema or mild but definite erythema plus mild but definite edema) with epidermal damage (oozing, crusting, superficial erosions, or a combination of the three) occurred at some ZuraPrep™ sites.

Safety: Three subjects experienced treatment-emergent AEs (TEAEs):

- Right shoulder muscle strain (severe, not related to study treatment, discontinued)
- Diarrhea (moderate, not related to study treatment, resolved)
- Appendicitis (serious, severe, not related to study treatment, discontinued)

Reviewer’s comments:

Based on the results of this study, it is reasonable to conclude that ZuraPrep™ does not have the potential for photoallergenicity.

Reviewer’s conclusion regarding four dermal safety studies submitted by the applicant:

Based on results of dermal safety studies submitted by the applicant, it is reasonable to conclude that ZuraPrep isopropyl alcohol 70% solution has the potential for irritation and sensitization, and thus should be adequately conveyed in labeling.

Based on the results of this study, it is reasonable to conclude that ZuraPrep™ does not have the potential for phototoxicity or photoallergenicity.

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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/

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09/19/2018

SNEZANA TRAJKOVIC
09/20/2018