

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210872Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



**MEETING MINUTES**

IND 117045

Zurex Pharma  
Attention: R. Andrew Morgan  
Executive Vice President,  
Regulatory Affairs and Quality Assurance Operations  
2113 Eagle Drive  
Middleton, WI 53562

Dear Mr. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for isopropyl alcohol, 70%, sponge.

We also refer to the meeting between representatives of your firm and the FDA on March 13, 2018. The purpose of the meeting was to discuss the results of your two pivotal phase 3 efficacy studies, and to obtain guidance on the content of your planned 505(b)(2) NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** March 13, 2018, 2:00 – 3:00 p.m.  
**Meeting Location:** FDA, White Oak Campus, Bldg. 22, Room 1415

**Application Number:** IND 117045  
**Product Name:** isopropyl alcohol 70%, sponge

**Indication:** Patient preoperative skin preparation  
**Sponsor/Applicant Name:** Zurex Pharma

**Meeting Chair:** Theresa Michele, MD  
**Meeting Recorder:** Celia Peacock, RDN, MPH

**FDA ATTENDEES**

Office of Drug Evaluation IV, Immediate Office (ODEIV/IO)  
Jagjit Grewal, MPH, Associate Director for Regulatory Affairs

Division of Nonprescription Drug Products  
Theresa Michele, MD, Director  
Elizabeth Donohoe, MD, Medical Officer  
Jane Sohn, PhD, Nonclinical Team Leader  
Francisco Martinez-Murillo, PhD, Interdisciplinary Scientist Team Leader  
Anita Kumar, PhD, Interdisciplinary Scientist  
Hana Mujahid, PhD, Interdisciplinary Scientist  
Keisha Findley, PhD, Interdisciplinary Scientist  
Celia Peacock, RND, MPH, Regulatory Project Manager  
Helen Lee, PharmD, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics VII (OB/DBVII)  
Rima Izem, PhD, Mathematical Statistician Team Leader  
Yueqin Zhao, PhD, Mathematical Statistician Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products (OPQ)  
Swapan De, PhD, Chemistry Team Leader

Office of Translational Science, Office of Clinical Pharmacology/DCPIII

Luke Oh, PhD, Clinical Pharmacology Reviewer

Sojeong Yi, PhD, Clinical Pharmacology Reviewer

## **SPONSOR ATTENDEES**

### Zurex Pharma

Carmine J. Durham, CEO

R. Andrew Morgan, RPH, Executive Vice President, RA and Quality Operations

Dawn R. Parks, Senior Director, Quality and RA

Consultants to Zurex Pharmaceuticals

(b) (4)

## **1.0 BACKGROUND**

Zurex Pharma (Zurex or the Sponsor) proposes to market a single-use plastic applicator containing isopropyl alcohol 70% solution, 10.5 mL, (b) (4). Per the Sponsor's briefing package, the (b) (4) indication is as a patient preoperative skin preparation for use in pre-surgical settings as an antiseptic/antimicrobial agent to reduce the bacteria that potentially can cause skin infection.

Zurex submitted an IND on April 16, 2014, followed by a Special Protocol Assessment (SPA) on March 27, 2015, for clinical protocol ZX-ZP-0060, entitled, "Pivotal Clinical Evaluation of the Antimicrobial Effectiveness of Topically Applied ZuraPrep™". FDA responded on June 15, 2015, with an "SPA No Agreement" letter. On August 31, 2015, FDA met with Zurex to discuss issues related to the pivotal study design and planned analysis.

At a pre-phase 3 meeting on June 17, 2016, FDA and Zurex met to discuss the proposed phase 3 pivotal protocol design and the completed in vivo pilot study.

On November 21, 2017, Zurex submitted a pre-NDA meeting request to discuss the phase 3 efficacy study results and the format, content, and timing of its planned 505(b)(2) NDA. Per the meeting package, Zurex states the following meeting objectives:

1. Confirm ZuraPrep's regulatory filing status as 505(b)(2) NDA
2. Confirm Zurex has completed all required studies for filing the NDA
3. Confirm that the FDA agrees that ZuraPrep does not trigger the Pediatric Research Equity Act (PREA)
4. Confirm CMC stability lot size for submission
5. Obtain FDA's feedback on the summaries of the results from our two completed pivotal phase 3 in vivo efficacy studies performed by MicroBioTest (MBT) and BioScience Laboratories, Inc. (BSL)
6. Discuss requirements of electronic submission format of clinical study reports

7. Discuss if sections 2.7.1 and 2.7.2 in Module 2 are required
8. Discuss content and format of the ISS and ISE in Module 5

FDA sent Preliminary Comments to Zurex on March 12, 2018. Zurex indicated in a March 13, 2018, email that they request additional discussion for questions 1, 9, and 10.

## 2.0 DISCUSSION

The Sponsor's questions and responses to the FDA preliminary comments are **bolded**; FDA's preliminary responses are *italicized*, and meeting discussion is in normal font.

Post-meeting comments are included, where appropriate, under meeting discussion. Also, note Section 3.0 below: "ADDITIONAL POST-MEETING COMMENTS".

### Question 1

**As discussed previously with the Division, Zurex is planning to submit a 505(b)(2) NDA for ZuraPrep solution, containing 70% v/v Isopropyl Alcohol (IPA) as the active pharmaceutical ingredient. We will rely upon FDA's findings of safety for ChloroPrep NDA 020832 as ZuraPrep and ChloroPrep both contain the active ingredient IPA at 70% v/v. In addition, having ChloroPrep as the active control in our in vivo safety and efficacy studies, the results confirmed establishment of a scientifically valid bridge for such reliance. Therefore, no additional nonclinical or clinical safety studies are needed with respect to the active ingredient to support the topically applied ZuraPrep antiseptic for the preoperative indication we seek. Does the FDA agree to this regulatory filing strategy; if not, why not?**

### FDA Response to Question 1

*Confirmation of establishment of a scientifically valid bridge between your product and ChloroPrep is a review issue; therefore, we cannot determine if additional studies may be needed at this time. Also, see our responses to Questions 3, 4, and 7.*

*In regard to clinical safety, we note that your product includes IPA 70% v/v as an active antiseptic ingredient whereas ChloroPrep contains chlorhexidine gluconate (CHG) 2% w/v in addition to IPA 70% v/v. Also, differences in inactive ingredients between your product formulation and ChloroPrep may alter the dermal absorption of IPA and could raise potential safety concerns as compared to the relied upon listed drug. Therefore, to establish an adequate bridge to FDA's findings of safety for ChloroPrep, you need to address the potential for dermal absorption of 70% IPA in humans in a maximal use condition comparing your final, to-be-marketed product compared to ChloroPrep. To determine what circumstance constitutes a maximal use condition of your product, we recommend that you consider a case that would be likely to have the highest exposure considering the proposed indication in terms of dose per application, total skin area to be applied, and dose per cm<sup>2</sup>.*

To address the potential for dermal absorption of 70% IPA in humans from your final, to-be-marketed product compared to ChloroPrep, we suggest that you consider the following approaches:

- 1) You may provide literature support to demonstrate the dermal absorption of IPA 70% v/v at the maximal use condition as a surgical skin preparation, in addition to the results of in vitro skin permeation studies with the human skin comparing your final, to-be-marketed product compared to ChloroPrep.
- 2) Or, you may conduct an in vivo human pharmacokinetic study (i.e., Maximal Usage Trial) to address comparative bioavailability of your final, to-be-marketed product compared to ChloroPrep at a maximal use condition. Regarding study design of Maximal Usage Trial, refer to the following:
  - “Guidance for Industry: Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data”  
(<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM473464.pdf>)
  - Bashaw, ED, DC Tran, CG Shukla, et al., January 2015, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, *Ther Innov Regul Sci*, 49(1):108-115.  
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4663190/>)

We note that the Health Care Antiseptics Final Rule was published December 20, 2017. Isopropyl alcohol (70 to 91.3%) is listed as a deferred ingredient in the Final Rule for the indication of patient antiseptic skin preparation, which includes patient preoperative skin preparation, among other indications.

See the “505(b)(2) REGULATORY PATHWAY” section below for additional information.

### **Zurex Comments to FDA Response to Question 1**

**We commit to conduct an in vitro skin permeation study and search literature for available articles to demonstrate the dermal absorption of IPA at the maximal use conditions. However, the newly introduced request comes at such a late time in our development program and we do not have the financial means to complete the study prior to NDA submission. Therefore, we request that the proposed in vitro permeation study be designated as a Phase 4 commitment. Zurex will commit to working collaboratively with the Division to develop the in vitro skin permeation protocol and timeline to complete the study activities. We believe this is in line with the current thinking and approach the agency has undertaken with the broader industry for topical antiseptic ingredients and by listing IPA as a deferred ingredient in the Final Rule. This Phase 4 commitment is a reasonable approach with low safety risk and allows our company to move forward within our resource constraints to meet our NDA submission timeline, does the Agency agree?**

**Additionally, we would be interested to know if the Agency is aware of any reference articles that could be informative regarding dermal absorption of IPA 70% v/v at the maximal use condition as a topical antiseptic?**

### Meeting Discussion Question 1

Zurex stated that it is willing to conduct an in vitro permeation study, but timing is an issue. Zurex asked if FDA would accept this study as a phase IV commitment. Zurex noted that they do not want to delay submitting their NDA, and alternatively proposed to submit the NDA for FDA review, while concurrently conducting the in vitro study with study data to be submitted during the application review cycle. FDA responded that a phase IV commitment to evaluate dermal absorption is not appropriate for this OTC product. Zurex noted that ChloroPrep was not required to conduct absorption studies for NDA approval, and therefore, it might be difficult to establish a scientific bridge to this product due to this lack of information. FDA noted that regulatory science evolves over time, and stated that dermal absorption studies are now required for dermal OTC products. FDA does not generally re-adjudicate previous decisions unless there are specific concerns that warrant such action.

Zurex stated that IPA is a monograph product and available in the OTC market. Since FDA has granted a deferral for safety absorption studies for IPA under the OTC monograph, while remaining on the market, Zurex asked why their product can't enter the marketplace also with a deferral for safety absorption studies. FDA stated that Zurex is following an NDA pathway, and is therefore held to NDA products' guidelines and requirements. FDA agreed to have further discussions on this issue, and will share any additional comments as a post-meeting discussion.

FDA noted that for purposes of NDA filing, Zurex could develop and provide a scientific rationale to address the bridging requirement for reliance upon FDA's previous findings of safety for ChloroPrep. The bridge may be based on information already available to the sponsor and relevant published literature. Whether the scientific rationale is adequate to justify reliance upon the listed drug and/or published literature would be a review issue. FDA further offered that there may be relevant literature cited in the 2015 Health Care Antiseptic Proposed Rule. See link: <https://www.regulations.gov/document?D=FDA-2015-N-0101-0001>.

FDA noted that if Zurex plans to rely on ChloroPrep for safety, a missing piece of data is proof that the use of IPA with CHG does not affect the absorption of IPA. Zurex would need to show that dermal absorption of IPA alone is the same as, or less than, that of IPA with CHG. The applicant's scientific bridging rationale, which may include published literature, must address this issue.

FDA stated it will provide a template in post-meeting comments to illustrate how the literature data addressing dermal absorption for IPA could be presented in the NDA submission.

### FDA Post-meeting Comments

1. FDA has no further comments with regard to the OTC drug monograph.
2. If you plan to submit literature data, we recommend that you provide a tabulated summary of literature data regarding human dermal absorption of isopropyl alcohol at a maximal use condition of your product.

The table below is provided as an example and may be formatted differently as needed. If you provide an estimated value instead of an actual value, clarify how you derived the value with reasonable justifications. Do not include information related to ethanol.

Source	Indication	Strength (w/w)	Dose of IPA per application (g)	Number of applications /time duration	Total dose applied (g)	(Estimated) Applied body surface area (cm <sup>2</sup> )	Total applied dose per cm <sup>2</sup> (g/cm <sup>2</sup> )	Highest Observed Blood Concentration (mg/L)	Estimated Absorbed Dose (if applicable) (g or mg)
Maximal use condition of Zurex's Product	Pre-OP skin preparation	70% (v/v) = X% (w/w)	XX g in 10.5 mL	10.5-mL application * X Single-use		X cm <sup>2</sup>	X mg/cm <sup>2</sup>		
Literature A									
Literature B									
Literature C									

2. Provide information in the table below to evaluate whether the establishment of a scientific bridge from ChloroPrep to your product is appropriate in terms of the extent of dermal exposure for isopropyl alcohol.

	ChloroPrep CHG 2%/IPA 70%	Zurex's Product IPA 70%
Strength	70% (v/v) = XX % (w/w)	70% (v/v) = XX % (w/w)
Amount of IPA in a single product (g)	X g in X mL	X g in X mL
Maximum skin coverage (cm <sup>2</sup> )	X cm <sup>2</sup>	X cm <sup>2</sup>
Applied dose per cm <sup>2</sup> (mg/cm <sup>2</sup> )	X mg/cm <sup>2</sup>	X mg/cm <sup>2</sup>

### Question 2

Upon completion of a thorough review of the PREA regulations, Zurex has concluded ZuraPrep is exempt from PREA (21 U.S.C. 355c). ZuraPrep will be submitted as a 505(b)(2) NDA relying upon FDA's finding of safety for ChloroPrep containing 70% v/v IPA as active for topical preoperative use identical to the 70% v/v IPA active in ZuraPrep. Additionally, for the preoperative indication we seek, ZuraPrep's labeling for use and

administration will be identical to ChloroPrep. Therefore, none of the criteria outlined in Section III of the March 2016 Pediatric Study Plan Guidance that trigger PREA (new active ingredient, indication, dosage form, dosing regimen or route of administration) apply. Zurex corresponded with our DNDP project manager regarding whether or not ZuraPrep would trigger PREA who, on behalf of DNDP, provided guidance via email to submit a waiver request with justification. Zurex considered this advice but has determined that since our product does not trigger PREA, submitting a waiver request with justification is not necessary. Because none of PREA criteria apply to our application, does the FDA agree we are exempt for this requirement? If not, please explain why not?

FDA Response to Question 2

*We agree that this product does not trigger PREA; therefore, the requirement to obtain an Agreed iPSP prior to the submission of your marketing application does not apply.*

Question 3

For NDA filing, Zurex will provide at least 18-months of room temperature stability data, as well as, accelerated (6 months) and intermediate (12 months) stability data on the to-be-marketed formulation/container closure system ( (b) (4) applicator) for (b) (4) clinical/stability lots representative of (b) (4) commercial scale lot size and seek a 24-month initial expiration date. Please confirm this is acceptable for NDA filing; if not, please explain why not?

FDA Response to Question 3

*Yes, the proposed stability data package to be included in the NDA is acceptable. The expiration date of the drug product will be a review issue and will be assessed per ICH Q1E. We recommend that you finalize the drug product specifications (release and stability) based on ICH Q6A and ICH Q3B.*

*We refer you to the additional CMC comments below. These additional comments address critical quality issues; resolve these issues prior to submission of your NDA.*

Question 4

As discussed in our April 16, 2013 PIND meeting ([Reference ID: 3307949](#)), prior to initiating clinical trials, (b) (4)

(b) (4)

FDA Response to Question 4

(b) (4)

**Question 5a**

**Please confirm the responder rate results for the positive control will not have an impact on the Division's acceptance of the trial results with respect to validity.**

FDA Response to Question 5a

*The advice letters that FDA sent to you on July 15, 2016, and July 10, 2017, specify the expected performance criteria for a patient preoperative skin preparation indication for your proposed product. Although it seems that your provided results offer a promising performance outcome, we will consider the different analytical approaches and will assess the totality of the evidence during our evaluation of the product's efficacy, which will ultimately constitute a review issue once we evaluate all existing data.*

**Question 5b**

**Please confirm that ATE superiority and non-inferiority will be the data upon which the Agency will make your product efficacy determination.**

FDA Response to Question 5b

*No, we cannot confirm. The results presented in the meeting package are promising. However, we will make our efficacy determination based on the totality of evidence after a thorough review of the NDA.*

*We also refer you to our response to Question 5a.*

**Question 6**

**We believe that ZuraPrep's study design and effectiveness results have met the Agency's current thinking for effectiveness requirements for approval of a preoperative antiseptic. Reference [Attachment 4 & 5](#) for the trial synopsis. Upon review of the above presented log<sub>10</sub> reductions, responder rates and average treatment effect analysis, does the Agency agree? If not, please state why.**

FDA Response to Question 6

No, we cannot confirm; see our responses to Questions 5a and 5b. In addition, we noticed that for some treated subjects with ChloroPrep or ZuraPrep, the 6-hour bacterial count measurement was not lower than the baseline measurement. In the NDA, provide details regarding why these subjects did not meet persistency at 6 hours.

Question 7

**Details on the regulatory development path and necessary studies for topical patient preoperative skin preparations are outlined in several FDA communications and American Association for Testing and Materials (ASTM) methods. ZuraPrep's active ingredient Isopropyl Alcohol 70% v/v is present in OTC and OTC/NDA products having demonstrated a long history of safe and effective antiseptic use. The FDA has not required that we specifically conduct clinical pharmacology studies for ZuraPrep. Additionally, ZuraPrep will be filed as a 505(b)(2) NDA, with reliance upon FDA's findings of safety and efficacy for ChloroPrep (2% w/v chlorhexidine gluconate and 70% v/v Isopropyl Alcohol). We will also rely upon the FDA's Inactive Ingredient Database for ingredients found safe for topical use to support the safety of ZuraPrep's inactive ingredients. We have assured the safety of methylene blue by virtue of the results of our dermal minipig study. We intend to describe this information under Module 2 sections 2.7.1 and 2.7.2. However, that stated, for our 505(b)(2) NDA, are sections 2.7.1 and 2.7.2 needed; if so, does the Agency agree with the content to be included? If not, why not?**

FDA Response to Question 7

*In regard to your nonclinical data, as section 2.7.1 refers to the SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS and section 2.7.2 refers to the SUMMARY OF CLINICAL PHARMACOLOGY STUDIES, this approach seems reasonable. Include nonclinical data addressing excipient safety in the nonclinical sections of the NDA.*

*Based on the information you have provided, it does not appear that submission of any information under section 2.7.1 will be required. We refer you to the following guidances:*

*Guidance for Industry M4E: The CTD — Efficacy*

<https://www.fda.gov/downloads/Drugs/Guidances/ucm073290.pdf>

*Link to draft guidance for industry Submitting Marketing Applications According to the ICH-CTD Format —General Considerations*

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073308.pdf>

*However, to establish a bridge from ChloroPrep to your product in terms of safety, you need to address the comparability between your product and ChloroPrep with regard to the dermal absorption of IPA in humans. Data related to these studies would be submitted under section 2.7.2.*

*See our response to Question 1 on establishing an adequate bridge to FDA's findings of safety for ChloroPrep.*

*In addition, you state "... with reliance upon FDA's finding of safety and efficacy for ChloroPrep...". Confirm that you intend to rely, in part, upon FDA's findings of only safety for ChloroPrep.*

### **Zurex Comments to FDA Response to Question 7**

**Regarding the response to Question 7 asking for confirmation that we intend to rely, in part, upon FDA's findings of only safety for ChloroPrep – that is correct, we will provide our own efficacy data. No further discussion needed.**

### **Question 8a**

**Having two independent phase 3 pivotal efficacy studies and 3 pilot efficacy studies of similar design for section 2.7.3, the summary presentation will include pooled data from both pivotal efficacy studies, at all endpoints (primary and secondary), as well as each study independently. With only two (2) treatment-emergent adverse events to summarize in our two pivotal efficacy studies, the safety data from the clinical program can be summarized entirely within section 2.7.4. Therefore, we will be providing individual study data and pooled data for sections 2.7.3 and 2.7.4 in Module 2. We also plan to include summaries of adverse event data on the use of topical isopropyl alcohol 70% v/v from the published literature, the World Health Organization Uppsala Monitoring Center Vigibase, the FDA Adverse Event Reporting System, and the National Poison Data System. We believe this is an acceptable approach, does the Agency agree?**

### **FDA Response to Question 8a**

*We do not generally agree to pooling the data (for section 2.7.3) from the different pivotal studies for the assessment of effectiveness. We expect you will provide a summary presentation of each study independently, and present data analysis according to the advice provided in our previous communications (December 14, 2014, June 15, 2015, July 15, 2016, and July 10, 2017).*

*In regard to safety data, we agree that it may be appropriate to pool your safety data in section 2.7.4 and provide data for each study separately in Module 5. However, without clarity on what specific data you plan to submit in support of your NDA, we cannot provide a definitive answer. We note that Module 2 is reserved for high level overviews and data summaries. If your evidence of efficacy includes clinical study reports, datasets, and/or meta-analyses of the literature, Module 5 would be more appropriate for such information, as Module 2.7 has size limitations. If the text portion of your ISS is relatively small, it may also serve as the Summary of Clinical Safety in Module 2. We refer you to the following guidances:*

*Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*

*<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf>*

*Guidance for Industry: M4: The CTD - Efficacy Questions and Answers*

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073293.pdf>

*We also expect that you will provide results of your dermal safety studies as well as any adverse events observed in all clinical studies, including skin coverage and drying time studies. Provide summaries in a narrative format with a thorough analysis of adverse events and safety concerns for each study. Also, provide a tabular listing of all clinical studies you conducted to support your NDA. All data from clinical studies should reflect use of your to-be-marketed formulation.*

*Provide a summary of the data that supports your NDA, as well as an overall assessment of the supporting data. Provide the location of the information you are referring to, as well as hyperlinks that will allow access to the information for review within the NDA.*

*With regard to your postmarketing safety data, we expect you will provide a comprehensive, cumulative review of the safety data from the identified postmarketing databases and a summary of the literature with a risk-benefit assessment specific to the sole active ingredient in your product, IPA, inclusive of the last 5 years; if available, include data related to concentrations of IPA that differ from your proposed 70% IPA product.*

*Tabulate, summarize, and analyze postmarketing adverse event data as follows:*

- *Seriousness and outcome for each case*
- *Relationship to the drug exposure*
- *Concomitant drugs*
- *Underlying medical conditions*
- *Product specific attributes (dose, dosage strength, and duration of use)*
- *Event year*
- *Subject demographics (gender, age, and racial subgroups)*

*Provide a separate analysis to address the postmarketing safety of IPA in the pediatric population, including a separate analysis of infants less than 2 months of age. If any studies were conducted, provide narratives for deaths, serious adverse events, and study discontinuations due to adverse events. Include separate tables for deaths, SAEs, and non-serious AEs.*

*If you rely in part on the published literature to support safety, you will need to explain the relevance of each publication to the safety of your proposed product, summarize and analyze information relevant to the safety of 70% IPA, include a list of retrieved references, and provide full-text articles in English upon request.*

*During the review, FDA may request additional safety information if warranted.*

### **Question 8b**

**Are there other adverse event data systems that the FDA requires that we search to support the safety of our product?**

FDA Response to Question 8b

No.

**Question 8c**

**Because we have only 2 treatment-emergent adverse events to report from our clinical studies and expect few adverse events reported on topically applied isopropyl alcohol in the literature or other databases, may we cross reference the ISE and the ISS to sections 2.7.3 and 2.7.4 respectively?**

FDA Response to Question 8c

*We agree with your plan to cross-reference the ISE and ISS to sections 2.7.3 and 2.7.4, respectively. We expect you will provide a summary of the safety information relevant to your proposed indication in your submission [Module 2.7.4] as well as discussions and conclusions for your overall safety database, and updated analyses by adverse event severity, gender, and age group.*

*We also expect that you will provide complete ISE and ISS in Module 5 in the NDA. See our response to Question 8a.*

**Question 9**

**Please confirm we are exempt from CDISC data standards. If we are not, is the above proposal acceptable for NDA filing; if not, why not?**

FDA Response to Question 9

*Yes, based on information you have provided, you are exempt from CDISC data standards. However, legacy data format can be used for the studies that started prior to December 17, 2016. SAS v5 transport file is the correct format for study data submission. Excel format is not acceptable for study data submission.*

*We do expect you to submit subject level data for study ZX-ZP-0073 and ZX-ZP-0074 in an electronic format. For fileability, the data on safety and efficacy should be complete and well documented so that we can easily assess traceability of your results and reproduce the main findings. We encourage you to send a mock data set (sample of a data) and/or documentation (define files for all datasets) so that we can provide more feedback prior to submitting the NDA.*

**Zurex Comments to FDA Preliminary Response to Question 9**

**We have a mock data set attached for the pivotal efficacy study ZX-ZP-0073 for your review and comment. Please advise on the timing for your feedback so that we can pursue our target NDA submission date (June).**

Meeting Discussion Question 9

FDA acknowledged receipt of the mock dataset and stated this will be addressed in post-meeting comments. FDA requested that the sponsor also submit the data dictionary for the SAS dataset. PDF format is acceptable for the define document for review.

*FDA Post-meeting Statistics Comments on Submitted Datasets*

FDA reviewed the datasets and data dictionary submitted for study ZX-ZP-0073, and found that the data format and documentation, in general, to be acceptable. However, Zurex needs to clarify whether the treatment (“Tmt”) included in the datasets (Variable: Tmt) is the treatment being randomized to or the treatment actually received; include both treatment variables if there are protocol deviation(s).

Include the following items in your dataset:

1. Demographics dataset with one record per subject. It is required for the analysis tool.
2. Numeric visit for dataset ‘ZP0073F2’.
3. Define.pdf
4. CRF.pdf

Also, see Section 3.0 ADDITIONAL POST-MEETING COMMENTS

**Question 10**

**For all trials initiated prior to Dec 17, 2016, a pdf file of the comprehensive study report will be submitted. Hard copy CRF’s (used as primary data capture forms) have been utilized, scanned to pdf, and are available upon request for the two large pivotal efficacy trials. The efficacy trials resulted in only two (2) treatment emergent adverse events (none serious). MedDRA coding has not been utilized; however, all treatment emergent AE’s will be reported in a verbatim summary, as well as, in detail in the final clinical study report with pdf scans of the subject CRF’s included. Please confirm this is acceptable for NDA filing; if not, why not?**

*FDA Response to Question 10*

*The fileability of the NDA will be determined during the filing review period (i.e., 60 days after the NDA is received by FDA). FDA regulations require that the case report forms (CRFs) from subjects who discontinue treatment in association with an adverse event be submitted in the NDA (21 CFR 314.50(f)(2)); analysis of these subjects constitutes a critical part of the safety evaluation. In addition to providing the CRFs for the categories of patients defined by ICH E3 (i.e., deaths, other serious adverse events, and withdrawals for adverse events) within the individual study reports, provide CRFs for all enrolled subjects who withdrew for any reason after study start.*

**Zurex Comments to FDA Preliminary Response to Question 10**

**Zurex agrees to include the CRF’s for subjects discontinued from treatment in association with an adverse event. With respect to submitting CRF’s for all subjects enrolled who withdrew for any reason after study start, we are confused on the definition of “enrolled” and “studystart” with respect to our pivotal trials. The table below breaks out the discontinued subjects in each study. As you can see the number of CRF’s to be submitted would be large if non-treated subjects are included. Therefore, please define which group you wish Zurex to provide for review?**

	Consented	Screened	Screen BL did not qualify for	Treated	Completed
Pivotal – MBT ZX-ZP-	681	633	180 <sup>1</sup>	440	440
Pivotal – BSL ZX-ZP-	2227 <sup>2</sup>	1526	763	640	639

<sup>1</sup> 13 subjects met minimum BL, but withdrew or were excluded prior to treatment (2 were extra screens, study complete).

<sup>2</sup> Subject discontinuations other than low screen baseline (BL): 106 = extra screened, study complete; 146 = qualification failure; 361 = no show; 4 = AE; 147 = schedule conflict; 12 = PI dismissal; 46 = voluntary withdrawal; 2 = other.

#### Meeting Discussion Question 10

FDA clarified that it expects Case Report Forms to be submitted for all subjects exposed to any product (vehicle, test, controls) who experienced an adverse events and/or withdrew for any reason (including those subjects who do not meet the 2nd baseline criteria and do not continue on with the study).

#### Question 11

**Please confirm our development program is complete and that we have addressed submission requirements for a fileable NDA for the 10.5-mL ZuraPrep Solution.**

#### FDA Response to Question 11

*This is a review issue; see our responses to the questions above.*

#### *Additional Comments*

##### Proprietary Name

*We note the use of a product name, ZuraPrep, in the Briefing Document for IND 117045. If you intend to have a proprietary name for your proposed product, we recommend you submit a request for a proposed proprietary name review as soon as possible.*

*The content requirements for such a submission can be found in the draft guidance for industry entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names:*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

##### Planned Flammability Study

*Based on information provided in your Meeting Package, we note that you intend to submit a (b)(4) flammability study based on prior recommendation by FDA. We are no longer requiring these studies as the flammability characteristics are well documented and related safety issues can be adequately addressed in the Drug Facts labeling.*

Chemistry, Manufacturing, and Controls

1. *In the NDA, provide detailed information for the proposed 10.5 mL applicator. We understand that the applicator used during the clinical studies does not have 510(k) clearance and it has not been used in previously approved products.*
2. *Your protocol dated October 23, 2015, indicated presence of high levels (controlled at NMT (b) (4) %) of (b) (4) in the drug product (b) (4). Provide acceptance criteria for each of these impurities.*
3. *The assay value of isopropyl alcohol in the drug product should be (b) (4) % throughout the shelf life of the drug product. The proposed assay value of (b) (4) % is not acceptable (amendment dated October 23, 2015).*
4. *Base the impurities/degradants specifications for the drug product on ICH Q3B (R2) limits or justified for safety.*

**505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s)

in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>

1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX "TRADENAME"	Previous finding of effectiveness for indication A
3. Example: NDA YYYYYY "TRADENAME"	Previous finding of safety for Carcinogenicity, labeling section B
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

### **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

### 3.0 ADDITIONAL POST-MEETING COMMENTS

#### Clinical

You may find the following reference helpful in planning submission of your NDA: the comprehensive table of contents headings and hierarchy document is available at: <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm315023.pdf>

In general, if you plan to omit eCTD sections that seem otherwise applicable (i.e., required or pertinent), clarify why the section is omitted. We acknowledge that not all headings are applicable to all submissions or submission types.

Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER electronic submissions staff at: [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov).

#### Nonclinical

When you demonstrated the use of your proposed product during the meeting, we noted the plastic (b)(4) for your drug product. Provide a safety assessment of extractables and leachables with submission of your NDA. See Comment below under Chemistry, Manufacturing and Controls.

#### Chemistry, Manufacturing and Controls

Provide extractable and leachable studies to assure compatibility and to qualify container closure systems for the drug product. Refer to following guidances for the CMC requirements on container closure system.

*Guidance for industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999) accessible at:*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>

*Guidance for Industry: Q and A for the Container Closure Systems for Packaging Human Drugs and Biologics (2002) accessible*

*at:*<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070553.pdf>

#### **4.0 ACTION ITEMS**

None

#### **5.0 ATTACHMENTS AND HANDOUTS**

Zurex March 13, 2018 comments in response to FDA's March 12, 2018 preliminary responses document.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THERESA M MICHELE  
04/12/2018



IND 117045

**MEETING MINUTES**

Zurex Pharma  
Attention: Andrew Morgan  
Executive Vice President, RA and Quality Assurance Operations  
2113 Eagle Drive  
Middleton, WI 53562

Dear Mr. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ZuraPrep™ (isopropyl alcohol, 70%), solution.

We also refer to the End of Phase 2/Pre-phase 3 meeting held on June 17, 2016 between representatives of your firm and the FDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

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

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End of Phase 2/Pre-phase 3

**Date:** June 17, 2016  
**Time:** 1:30 – 2:30 PM

**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1311  
Silver Spring, Maryland

**Application Number:** IND 117045

**Product Name:** ZuraPrep (isopropyl alcohol, 70%)  
**Indication:** patient preoperative skin preparation

**Meeting Chair:** Theresa Michele, MD  
**Meeting Recorder:** Celia Peacock, RND, MPH

**FDA ATTENDEES**

*Division of Nonprescription Drug Products*

Theresa Michele, MD, Director  
Jane Filie, MD, Lead Medical Officer  
Steve Osborne, MD, Lead Medical Officer  
Elizabeth Donohoe, MD, Medical Officer  
Anita Kumar, PhD, Interdisciplinary Scientist  
Celia Peacock, RND, MPH, Regulatory Project Manager  
Lori Griner, PhD, ORISE Fellow

*Office of Biostatistics*

Yueqin Zhao, PhD, Biostatistics Reviewer

## SPONSOR ATTENDEES

### Zurex Pharmaceuticals

Carmine J. Durham, CEO

R. Andrew Morgan, RPH, Executive Vice President, RA and Quality Operations

Dawn R. Parks, Senior Director, Quality and RA

### Consultants to Zurex Pharmaceuticals



## 1.0 BACKGROUND

ZuraPrep™ is a patient preoperative skin preparation solution for use in pre-surgical settings. Zurex Pharma (Zurex) submitted a Special Protocol Assessment (SPA) on March 27, 2015 for clinical protocol ZX-ZP-0060, entitled, “Pivotal Clinical Evaluation of the Antimicrobial Effectiveness of Topically Applied ZuraPrep”. FDA responded on June 15, 2015 with an “SPA No Agreement” letter. A Type A meeting occurred on August 31, 2015 to discuss issues related to the pivotal study design and planned analysis. On December 23, 2015, Zurex submitted an amendment stating its concern that the meeting minutes dated September 30, 2015 (from the August 31, 2015 Type A meeting) did not sufficiently capture the meeting outcomes and discussion. FDA responded with an Advice letter dated February 22, 2016 noting that the official meeting minutes accurately reflected the meeting discussion. In addition, FDA provided additional explanations in response to the sponsor’s concerns.

Zurex submitted an End of Phase 2/Pre-phase 3 meeting request on March 16, 2016 seeking agreement on its proposed Phase 3 pivotal protocol design. In the meeting package, Zurex states that it has completed an in vivo pilot study and is interested in sharing the results with FDA.

Zurex received the FDA Preliminary Comments on June 13, 2016, and submitted a response on June 15, 2016 stating that it wished to obtain further clarification on Questions 2 and 3.

The sponsor’s questions and additional topics for discussion during the meeting are in **bold** font; FDA’s preliminary responses are in *italics*, and meeting discussion is in normal font.

## 2.0 DISCUSSION

### Question 1

For ease of review, presented in the Table 5 (also included as [Table 13](#) in the statistical appendix of [report # ZX-ZP-0068](#)) is the difference between the vehicle and saline arms of which the maximum difference for any comparison is 0.60 across all study populations, which is well below the absolute 1.0 log<sub>10</sub> CFU/cm<sup>2</sup> difference threshold indicated in the Advice letter.

Table 5: Differences in Log <sub>10</sub> CFU/cm <sup>2</sup> Reductions Vehicle and Saline, all study populations				
Population	Body Area	Differences in Log <sub>10</sub> CFU/cm <sup>2</sup> Reductions from Baseline* (95% Adjusted CI)		
		30 Seconds	10 Minutes	6 Hours
Intent-To-Treat	Abdomen	0.39 (-0.18 to 0.96)	0.60 (0.08 to 1.12)	0.35 (-0.19 to 0.89)
	Groin	0.14 (-0.43 to 0.70)	0.49 (-0.02 to 1.00)	0.38 (-0.16 to 0.91)
No Replacements	Abdomen	0.34 (-0.31 to 0.98)	0.52 (-0.08 to 1.11)	0.36 (-0.25 to 0.96)
	Groin	0.19 (-0.45 to 0.83)	0.54 (-0.04 to 1.13)	0.44 (-0.16 to 1.04)
Per-Protocol	Abdomen	0.39 (-0.21 to 0.99)	0.60 (0.07 to 1.14)	0.32 (-0.25 to 0.90)
	Groin	0.03 (-0.55 to 0.62)	0.40 (-0.12 to 0.93)	0.38 (-0.18 to 0.95)

\* Light gray = within 1.0 log<sub>10</sub> CFU/cm<sup>2</sup>.

Therefore, having confirmed that the vehicle's activity is not different from the saline control, completing formulation characterization, we will conduct a 3 arm Phase 3 pivotal study design with test article ZuraPrep, reference product ChloroPrep, and a saline negative control. Do you agree with this approach, and if not, why not?

#### FDA Preliminary Response to Question 1

Based on the data provided, we agree that a three arm pivotal trial is acceptable; however, we recommend that you include test product, active control and vehicle control as arms. According to our current effectiveness standards (as specified in 2015 TFM, FR 80 25166 at 25178), for the study to be valid, the test product and active control must meet the performance criteria, and the test and active control performances must be superior to the vehicle control.

### Question 2

Does the Agency agree how we will treat treatment day baseline failures (i.e., exclude from efficacy analysis per predefined protocol inclusion/exclusion criteria as historically done) and define protocol subject populations for safety and efficacy analysis, and if not, why not?

#### FDA Preliminary Response to Question 2

We do not agree. For the primary analysis, you can use the modified Intent-to-Treat (mITT) population. The mITT consists of all randomized subjects who have met all the inclusion criteria but none of the exclusion criteria at baseline (pre-treatment). Subjects who failed the baseline bacterial count criteria would be excluded from this analysis population and would not be considered non-responders. Adjudicate post-randomization and post-treatment protocol violations as failures in this primary analysis.

*The sample size for this study needs to account for the baseline failure rate. Treatment assignment should be randomized for all subjects in the study. Note that a deterministic assignment of treatment to a new site based on which treatments the failed sites were assigned to would violate randomization.*

### **Zurex Request for Clarification Question 2**

**As clearly stated above, the subjects that fail the baseline bacterial count criteria for treatment day baseline would be excluded and not considered non-responders in the primary analysis for the mITT.**

**Also, based on the guidance provided, treatment day assignments will be randomized for all subjects in the study. Additional randomization groups will be utilized in the event additional subjects are needed to account for subjects excluded from the primary analysis, i.e. baseline failures. Each subsequent randomization group will be independently randomized. Please confirm that this addresses the FDA's statement about deterministic assignment of treatments.**

**We need more clarification of the statement, "Adjudicate post-randomization and post-treatment protocol violations as failures in the primary analysis," to ensure a successful pivotal clinical trial execution. For example:**

- Would a subject who didn't come back for the 6 hour sampling point, or withdrew from the study after the 30 second or 10 minute sampling time point, be treated as a non-responder in the primary efficacy criteria for the missing time point or would they be considered a non-responder for all time points?**
- Subjects with protocol deviations assigned as minor by the PI, such as missing the 30 second time point sampling window by 2 seconds, would not be treated as non-responders within the adjudication you note above and all the data from the subject would be included in the primary analysis, please confirm.**
- A protocol deviation where a subject did not date the informed consent form at the time of screening but did upon return for treatment. This should not be treated as a non-responder, please confirm.**
- A laboratory error where an incorrect dilution media was inadvertently used. All data would not be useable and excluded, i.e. not treated as a non-responder, please confirm.**

### **Meeting Discussion Question 2**

Zurex asked for additional clarification on the term 'deterministic assignment of treatment'. FDA stated that this is defined as the assignment of treatment to subjects as being determined by the study investigator and not randomized.

Zurex noted its concern that there are only two laboratories in the U.S. who conduct these types of studies, and that treatment failures, especially in the groin studies, vary significantly between the two laboratories. Zurex highlighted that this variability makes it difficult to determine how many patients to recruit. FDA recommended that Zurex look at its pilot study for guidance. FDA additionally offered that Zurex could consider randomizing patients in blocks sequentially.

Patients who fail at baseline would be replaced by subjects in the next randomized block. The sample size for this study needs to account for the baseline failure rate. FDA recommended that Zurex submit the revised statistical analysis plan and randomization scheme for review.

FDA reiterated that the protocol violations here refer to those protocol violations that lead to missing values. The main idea is to minimize missing values and minimize protocol violations, as these would penalize the study.

FDA further recommended that while designing the pivotal protocol, Zurex defines up front how much of a protocol deviation is acceptable and what is a major and a minor violation so that the endpoint is satisfactory. Any “acceptable” protocol deviations should be defined in the protocol or statistical analysis plan.

### **Question 3**

**Please see protocol sections 3.2 and 8 for a detailed description of the planned efficacy analysis in draft protocol# ZX-ZP-0073. Does the agency agree with our efficacy analysis criteria, and if not, why not?**

#### **FDA Preliminary Response to Question 3**

*As noted in the September 30, 2015 meeting minutes, the May 1, 2015 proposed rule (80 FR 25166) proposes various design and methods considerations that are provisional and undergoing assessment pending a final rule. You can use responder rate at 10 minutes for your primary analyses; however, the responder rate at 30 seconds and 6 hours should then be secondary endpoints rather than exploratory endpoints. We will take into consideration all the data, and the results obtained will guide the labeling of your product, if approved.*

*We recommend that efficacy data be collected at 30 seconds, 10 minutes and 6 hours after application and drying time are complete. Therefore, for your pivotal studies base the primary analysis on the proportion of patient successes (responders) as a binary endpoint. Success for a patient is defined as meeting the required 3 log reduction from baseline at the groin site and 2 log reduction at the abdomen site. The primary efficacy criteria for the test product is that the lower bound of a 95% confidence interval for the responder rate  $\geq 70\%$  at 10 minutes in both the groin and the abdomen sites. Important study validity goals are for the active control to meet  $\geq 70\%$  responder rate criterion at 10 minutes at groin and abdomen and that both the test product and active control are superior to vehicle.*

*We noted that you propose to use Bonferroni correction to control for testing for both the groin and abdomen areas. However, efficacy criteria for these two areas are co-primary, so there is no need for additional type 1 error correction.*

### **Zurex Request for Clarification Question 3**

**We will use the responder rate at 10 minutes as the primary efficacy endpoint. We also agree to the 6 hour responder rate as a secondary endpoint. We have reservations about including the responder rate at 30 seconds as a secondary endpoint when we already have demonstrated failure in our pilot study.** (b) (4)

(b) (4)

### Meeting Discussion Question 3

Zurex noted its concern that during the pivotal study, the majority of the products will not win at 30 seconds for responder rates, and Zurex is concerned about how the results at the 30-second time point will be viewed by FDA during the NDA review. FDA reiterated its recommendation that efficacy data be collected at 30 seconds, 10 minutes and 6 hours after the product is dry following application. FDA recommended collecting the responder rate at 30 seconds reporting it as a secondary endpoint. FDA noted that it is asking for this data because real world product use at a 30-second time point is often a reality in hospitals. FDA acknowledged that it may be difficult to win at 30 seconds, which is why FDA will use the 10 minute time point as the primary endpoint. Upon submission of the NDA, the FDA will review the totality of the data.

Zurex stated that it understood FDA's comments on the 30-second time point and responder rates and that moving forward it will generate the data as per FDA recommendation.

FDA noted that Zurex needs to conduct the skin coverage study with the proposed 10.5 mL applicator. Additionally, when Zurex conducts the three arm (test product, active control and vehicle control) pivotal clinical studies, the vehicle must be at the same pH as the test product.

### Question 4

**As noted in our 4 arm pilot study, the NDA reference product (ChloraPrep) did not achieve the primary efficacy criteria at 30 seconds in the groin (*Table 4*) and it is unlikely that any product can consistently achieve 70% responder rate for both body areas at 30 seconds. With the reference product not achieving the primary efficacy criteria at 30 seconds and the May 1 2015 proposed rule being provisional and undergoing assessment pending the final rule, does the Agency agree with basing our pivotal patient population on the historical 10 minute responder rate data, and if not, why not?**

### FDA Preliminary Response to Question 4

*We agree. We recommend that you use an approved active control (comparator) that you feel confident will show the study validity. Perform the clinical simulation studies based on the efficacy criteria described in the response to Question 3. The results of the active control and vehicle in your pivotal study will be a review issue.*

### Question 5

(b) (4)

**3.0 ACTION ITEMS**

None

**4.0 ATTACHMENTS AND HANDOUTS**

None

**5.0 POSTMEETING ADDENDUM**

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THERESA M MICHELE  
07/15/2016