CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210872Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 24, 2018
From	Francis E. Becker, M.D., F. A. C. P
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 210872, SD-1
Applicant	Zurex Pharma, Inc.
Date of Submission	June 29, 2018
PDUFA Goal Date	April 29, 2018
Proprietary Name	ZuraGard
Established or Proper Name	Isopropyl Alcohol 70% Solution
Dosage Form(s)	Surgical solution; 10.5 mL sponge applicator
Applicant Proposed Indication(s)/Population(s)	Presurgical skin preparation: • For preparation of the (b) (4) skin prior to surgery • Helps (b) (4) reduce bacteria that potentially can cause skin infection
Applicant Proposed Dosing Regimen(s)	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.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Patient preoperative skin preparation: • adult and pediatric patients (b) (4) • use with care in premature infants or infants 2 months of age.
Recommended Dosing Regimen(s) (if applicable)	Same as applicant proposed dosing regimen.

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

I recommend approval of ZuraGard Isopropyl Alcohol 70% Solution 10.5 mL for use as a preoperative skin preparation. ZuraGard 70% Isopropyl Alcohol Solution will provide an additional option for preoperative skin preparation. It will also provide an alternative for patients who are intolerant or allergic to other active ingredients, such as chlorhexidine or provodine iodine, or for whom these other active ingredients are contraindicated.

Surgical site infections (SSIs) remain a substantial cause of morbidity, prolonged hospitalization, and death. The National Healthcare Safety Network (NHSN) reported over 16,000 SSIs following nearly 850,000 operative procedures for an overall rate of 1.9% between 2006-2008.[1] In 2014 estimates of SSI incidence rates ranged from 2%-5%.[2] SSIs rank as the most costly of the hospital-acquired infections with an annual cost in the United States estimated at $3.5 to $10 billion.[3] According to the Center for Disease Control, SSIs are associated with a mortality rate of 3%, with 75% of SSI-associated deaths being directly attributable to the SSI.[4]

In two pivotal trials (**ZX-ZP-0073** and **ZX-ZP-0074)**, the efficacy of ZuraGard 10.5 mL for the preoperative skin indication was adequately demonstrated, as evidenced by responder rates greater than 70% (lower bound of 95% confidance interval based on $\log_{10}$ reduction in bacterial count from baseline) at 10 minutes for both body regions; statistical superiority to the vehicle and non-inferiority to ChloraPrep (active control) at 10 minutes and 30 seconds for both body regions based on average treatment effects; and persistent antimicrobial properties in the groin region at 6 hours. All primary endpoints were met, and although both studies failed to demonstrate persistent antimicrobial properties, defined in the 2017 Final Rule as responder rate of 100% at 6 hours, in the abdomen, this was a secondary endpoint, and it is noteworthy that the actual responder rates were close, that is, 99.4% and 99.1%, in Study **ZX-ZP-0073** and Study **ZX-ZP-0074**, respectively. Furthermore, for both ZuraGard and ChloraPrep at both the abdominal and groin sites in both studies, the log reductions at the 6 hour timepoint were similar to the log reductions achieved at 30 seconds, which were lower than baseline mean $\log_{10}$ CFU/cm^2 values, demonstrating that both ZuraGard and ChloraPrep did not exceed baseline counts at 6 hours. In addition, a pilot clinical study (**ZX-ZP-0068**) and four in vitro time-kill studies were supportive of the pivotal studies. Therefore, based on the totality of the data, the efficacy of ZuraGard for the proposed indication has been demonstrated and is acceptable for approval.

The safety profile of ZuraGard is consistent with the known safety profile of other isopropyl alcohol (IPA) products. In the clinical studies, adverse

[1] Mu Y, Edwards JR, Horan TC, Berríos-Torres SI, Fridkin SK. Improving risk-adjusted measures of surgical site infection for the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2011;32(10):970-986.

[2] Anderson DJ, Podgorny K, Berrios-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014; 35:605e627.

[3] Ibid

[4] Awad, S.S., "Adherence to surgical care improvement project measures and post- operative surgical site infections". Surgical Infection (Larchmt), 13(4): (2012): 234-7.

events were rare, generally mild, and included skin irritation, itching, and rash. Dermal safety studies demonstrated that ZuraGard has the potential for irritation and sensitization but does not have the potential for phototoxicity or photoallergenicity. No new safety signals were identified in postmarketing databases or in the published literature. The labeling will appropriately advise to "stop use and ask a doctor if irritation, sensitization, or allergic reaction occurs." As with other alcohol-containing antiseptic products, there is a risk of flammability associated with intra-operative electrocautery, electrosurgery, or laser surgery, particularly when the surgical site is not completely dry after the prep is applied. However, this risk is adequately mitigated in the proposed labeling which includes class labeling boxed flammability warnings and precise instructions for use to ensure that adequate drying time is allowed and no ignition source (e.g. cautery, laser) is used. Due to its irritant properties, IPA products are contraindicated for lumbar puncture or in contact with the meninges or on open wounds or as a general skin cleanser, and IPA products should not be used around the eyes, ears, or mouth. A recent literature review article assessed the evidence regarding ototoxicity of surgical antiseptic preparations and concluded that there is some evidence that iodine, chlorhexidine, hydrogen peroxide, and alcohol based antiseptics have ototoxicity[5]. Therefore, product labeling will include appropriate warnings to not use "for lumbar puncture or in contact with the meninges" or "on open skin wounds or as a general skin cleanser," and to keep this product "out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain." These warnings are present in labeling of other similar antiseptic products. Lastly, labeling is included to "use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." This is consistent with labeling in other similar products because it is known that the risk of chemical burns or skin irritation in this age group is increased. However, it is important to note that IPA-based products may still remain an acceptable option for infants requiring surgery. Providone iodine containing products, which are commonly used for preop skin reparation, should be avoided in infants because of the known risk of transient hypothyroidism, which may affect the developing brain and potentially result in diminished intellectual capacity.

In conclusion, the Benefit-Risk assessment remains favorable for approval of ZuraGard Isopropyl Alcohol 70% Solution 10.5 mL for preoperative skin preparation.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In US, over 16,000 surgical site infections (SSIs) reported following nearly 850,000 operative procedures for an overall rate of 1.9% between 2006-2008. • In 2014, estimates of SSI incidence rates ranged from 2%-5%. • Mortality of 3% associated with SSIs • 75% of SSI-associated deaths being directly attributable to the SSI • Cost of SSI treatment in US estimated at $3.5-$10 billion annually.	SSIs remain a substantial cause of morbidity, mortality, and prolonges hospitalization after surgical procedures. Causes are multifactorial, but bacteria from surgical sites are often the source of infection. Prevention of SSIs is a critical focus in patient care with far-reaching implications.

[5] Singh and Blakely, J Otolaryngol Head Neck Surg., 47:18, 2018.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are numerous preoperative skin preparations available. • Alcohol-based antiseptic agents (isopropyl alcohol) are available combined with other active ingredients, such as chlorhexidine and provodine iodine.	Prevention of SSIs requires multiple preventive measures. Use of alcohol-based antiseptic agents is recognized as an important preventative measure.
Benefit	• The results of 2 pivotal efficacy studies (ZX-ZP-0073 and ZX-ZP-0074), supported by a pilot study and in vitro time-kill studies, are adequate to demonstrate efficacy for the proposed indication "for preparation of the skin prior to surgery; helps reduce bacteria that potentially can cause skin infection."	ZuraGard 70% Isopropyl Alcohol Solution will provide and additional option for preoperative skin preparation and will provide an alternative for patients who are intolerant or allergic to other active ingreidients, such as chlorhexidine or provodine iodine, or for whom these other active ingredients are contraindicated.
Risk and Risk Management	• In the clinical studies, AEs were rare, generally mild, and included skin irritation, itching, and rash. • Dermal safety studies demonstrated that ZuraGard has the potential for irritation and sensitization, but does not have the potential for phototoxicity or photoallergenicity. • No new safety signals were identified in postmarketing databases or in the published literature. • Use with care in infants under 2 months of age because the risk of skin irritation and chemical burns in this age group is increased. • ZuraGard is flammable and should be allowed to completely dry.	The safety profile of ZuraGard is favorable for approval and is consistent with the known safety profile of other IPA products. Risk of flammability and use in infants will be adequately addressed in labeling.

2. Background

Zurex Pharma, Inc (the Sponsor) is seeking approval of isopropyl alcohol (IPA) 70% (v/v) solution in an applicator size of 10.5 mL for a patient preoperative skin preparation as an antiseptic/antimicrobial agent to reduce the bacteria that potentially can cause an infection. The Sponsor submitted the NDA under the 505(b)(2) pathway, relying on FDA's previous findings of safety for the reference listed drug, ChloraPrep (2% w/v chlorhexidine gluconate [CHG] and 70% v/v IPA), which is approved under NDA 20832. ChloraPrep and the Sponsor's proposed product contain the same active ingredient (IPA 70% v/v) and have the same dosage form, route of administration, and indication for use.

The to-be-marketed dosage form of the proposed product comprises a single-use 10.5 mL plastic applicator with a sterile barrier to ensure that the applicator surfaces are sterile. The solution is proposed to be applied topically to the patient using back and forth strokes (b) (4) for (b) (4) 30 seconds on dry surgical sites and (b) (4) 2 minutes on moist surgical sites. The solution is allowed to completely dry for a minimum of 3 minutes on dry, hairless sites or up to an hour on hair. To highlight the coverage area once applied to the skin, the product formulation includes an excipien (b) (4) methylene blue (b) (4)

Isopropyl alcohol (IPA) is a wide spectrum antimicrobial ingredient that provides rapid antimicrobial effect while it evaporates from the skin. Alcohols (ethanol and isopropyl alcohol) are considered antiseptics and disinfectants.[6] FDA has categorized isopropyl alcohol at concentrations from 71.3% to 91.3% (v/v in water) as an active ingredient deferred from final rule making in the Health Care Antiseptic Monograph (82 FR 60474) for the patient preoperative skin preparation indication. It is believed that IPA dehydrates the bacterial cell and denatures its proteins. IPA-induced coagulation of proteins occurs at the cell wall, the cytoplasmic membrane and the various plasma proteins, particularly those that function as membrane-bound enzymes.[7] Coagulation of various proteins leads to loss of cellular functions.

A variety of patient preoperative skin preparation products are available OTC for use prior to surgery. The patient preoperative skin preparation indication was established under the OTC drug monograph for healthcare antiseptics (21 CFR 310). On 20 December, 2017, FDA published its HealthCare Antiseptic Final Rule (82 FR 60474). NDA drugs include a variety of CHG products, including CHG alone, and CHG/alcohol or isopropyl alcohol (IPA). Iodine/IPA products are also available under NDAs. Products available

[6] McDonnell, G and and AD Russell, 2001, Antiseptics and Disinfectants: Activity, Action, and Resistance, Clinical Microbiology Review, 12(1)147-79.
[7] Ayi Y, Dolan J, Fendler EJ, Larson EL. 2001, Alcohols. In: Block SS ed., Disinfection, Sterilization, and Preservation. 5th ed. Philadelphia, PA: Lippincott, Williams, and Wilkens; pp 29-53.

under the OTC drug monograph include a number of different ingredients, including alcohol (ethyl alcohol), benzalkonium chloride, benzethonium chloride, iodine, and IPA. To date, no products containing IPA as the sole active ingredient have been approved for preoperative skin preparation indication under an NDA.

Development of the proposed IPA product was initiated by the Sponsor in 2012 (IND 117045). Since then, there have been numerous interactions and communications between the Sponsor and FDA. Highlights of these interactions are as follows:

- Pre-IND Meeting (16 April 2013): (b) (4)

(b) (4)

- EOP2 Meeting (17 June 2016): The details of a pivotal study were discussed. The FDA acknowledged that the Sponsor's Pilot Clinical Evaluation (**ZX-ZP-0068**) revealed that the only ingredient that demonstrated antimicrobial activity was IPA 70% (see Pre-IND Meeting discussion above). The Sponsor was advised that a 3-arm (test product, active control, and vehicle control) pivotal study was acceptable and that responder rate at 10 minutes should be the primary endpoint. Responder rates at 30 seconds and 6 hours should be secondary (not exploratory) endpoints.
- Advice (10 July 2017): The following new efficacy analyses was recommended for the two pivotal studies: average treatment effect, non-inferiority bound of 0.5 $\log_{10}$ versus ChloraPrep, and superiority bound of 1.2 $\log_{10}$ versus vehicle.

- Pre-NDA Meeting (13 March 2018): The Sponsor was informed that a summary of biopharmaceutics (Module 2.7.1) is not required. It was agreed that the potential for dermal absorption of 70% IPA in humans in a maximum use condition comparing final product to ChloraPrep will be established via literature and presented in Module 2.7.2.[8] The Sponsor was informed that ZuraPrep does not trigger the Pediatric Research Equity Act (PREA) and an interim pediatric study plan is not required prior to NDA submission. Details of data required for NDA submission (ISS, ISE, efficacy data not to be pooled, etc) were discussed. The Sponsor was informed that flammability studies are no longer required.

Note that upon submission of this NDA, the Sponsor's proposed proprietary name was ZuraPrep. However, during the NDA review, FDA determined that this name was unacceptable (see **Section 12**). The Sponsor subsequently proposed the proprietary name ZuraGard, which was found to be acceptable by FDA. However, since the NDA was submitted prior to proprietary name agreement, many of the study reports and summaries use the name ZuraPrep. Therefore, this review uses both names to describe the Sponsor's proposed IPA product. However, it is understood that the agreed upon proprietary name is ZuraGard.

3. Product Quality

Isopropyl alcohol (IPA) is transparent, colorless, flammable liquid with a slight ethanol/acetone-like odor. It is synthetic in origin and is a well-established chemical solvent with little tendency to form degradants/impurities when stored appropriately. The proposed drug product formulation is a non-sterile, blue solution of IPA in water, as shown in **Table 1** below. To highlight the coverage area once the solution is applied to the skin, the drug product formulation includes an excipient (b) (4) methylene blue (b) (4) The to-be-marketed dosage form comprises a single-use, 10.5 mL plastic applicator containing ZuraGard solution with a sterile barrier system to ensure that the applicator surfaces are sterile (see **Figure 1** below). The applicator container closure system is comprised (b) (4)

[8] See Section 5 Clinical Pharmacology below. During the current review cycle, the submitted literature was deemed inadequate and, consequently, the Sponsor submitted an in vitro permeation study.

Table 1. Components of ZuraGard (Isopropyl Alcohol 70%) Solution

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
Trisodium citrate (b) (4)		Excipient		USP
Methylparaben		Excipient		NF
Propylparaben		Excipient		NF
Methylene blue (b) (4)		Excipient		USP
Purified water		Excipient		USP
NF = National Formulary; USP = United States Pharmacopeia.				
(b) (4)				

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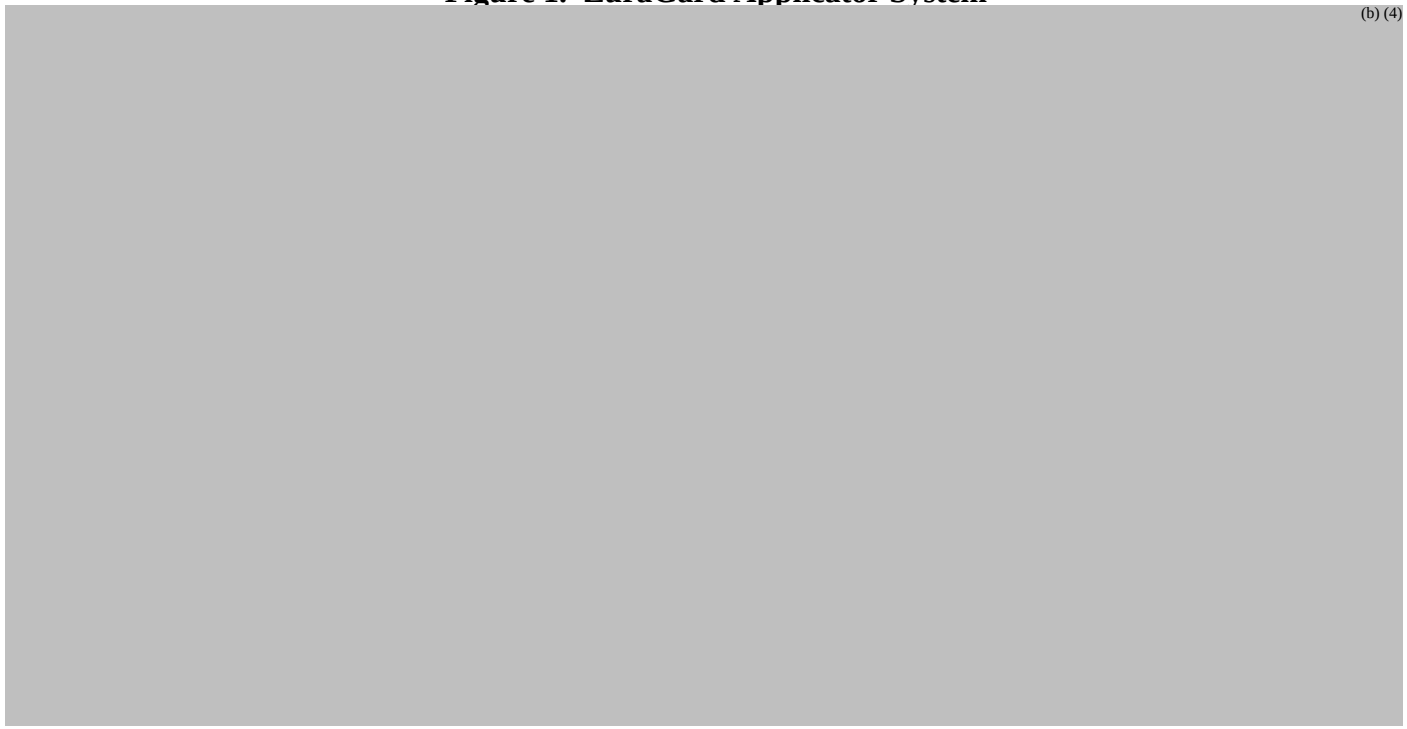
Figure 1. ZuraGard Applicator System



The Quality Review Team for this application is listed in **Table 2** below. In his Executive Summary, Dr. Swapan De, Application Technical Lead, concluded that, regarding Chemistry, Manufacturing and Controls, the application may be approved. He wrote, "Regarding quality aspects of the submitted application the drug substance, drug product, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application…...In addition, a consult review is performed by CDRH to evaluate the safety and functionality aspects of the drug product, a single-use 10.5-mL plastic applicator containing 70% isopropyl alcohol solution with a sterile barrier system. The CDRH review was found acceptable on 3/19/2019. The drug product is granted a 24-month shelf life when stored at 25^{o}C/60%RH."

Table 2. Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffrey Medwid, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process & facility	Tarun Mehta	OPF/DPAII/BranchVI
Microbiology	Jason God	OPF/DPAII/BranchVI
CDRH	Marc Neubauer	CDRH/ODE
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Teshara Bouie	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
Environmental Assessment (EA) and Labeling	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

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For details of Quality Review Team assessments, the reader is referred to OPQ Portfolio Review.[9] Highlights of the review are as follows:

- Dr. Luong concluded that long-term stability data support the proposed product shelf-life of 24 months. Dr. Luong also assessed the Chemical Characterization Report (**ZX-ZP-0077**) and concluded that, because the solution only comes in contact with the applicator and foam/sponge at the time of usage as the solution flows (b) (4) through the applicator and sponge onto the patient's skin, extractable impurities from the applicator and foam "pose low risk." Dr. Luong initially expressed concern about one impurity, (b) (4) According to ICH M7, an acceptable intake for an individual impurity is (b) (4) mcg per day. However, Dr. Luong noted in her review that "the clinical team confirmed that at most 2 applicators will be used in a single surgery. (b) (4)

[9] NDA 210872 OPQ Prortfolio Review: March 21, 2019.

CDTL Comment: An Information Request (IR) was sent to the Sponsor via email on February 11, 2019. The IR requested that the Sponsor "Propose a maximum number of 10.5 mL applicators to be used for a single preoperative application and provide justification for your proposal." The Sponsor responded on February 14, 2019 as follows:

> *Knowing product usage is based upon surgical procedures, hospital protocols which may outline preoperative product use, and/or staff surgeon/scrub tech's standing orders for antiseptic (cleaning intact skin) pre-surgical procedures, the number of 10.5-ml applicators used for a single preoperative application may vary. Therefore, as confirmed in the coverage and dry time study (ZX-ZP-0083), we are proposing a maximal treatment area for a single 10.5-ml applicator as approximately 8.4" x 8.4" (457cm^2). If the maximal treatment area exceeds 8.4" x 8.4" during a procedure, an additional applicator may be used.* (b) (4)

*The clinical team found this proposed maximum use for the 10.5 mL applicator acceptable and reasonable. To address this issue and circumvent use on larger prep areas, the statement "For head, neck, and small prep areas" will be included on the PDP for the 10.5 mL applicator following the statement "Surgical Solution" (see also **Section 12**).* (b) (4)

- The CDRH team was involved in reviewing the container closure system as well as the microbiology aspect of this device. CDRH recommended approval of the container closure system. CDRH further stated that they will not be reviewing this type of device anymore because it is low risk.
- The Sponsor is requesting a categorical exclusion from the requirement to submit an Environmental Assessment for ZuraPrep Solution as action on this NDA does not increase the use of the active moiety and, to the best of the Sponsor's knowledge, no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the environment. OPQ concluded that this request was adequate and acceptable.
- Tarum Mehta (Process and Facility) reported that, "following a review of the application and inspectional documents, there are no significant outstanding manufacturing or facilities risks that prevent approval of this application. The manufacturing facilities for NDA 210872 are found to be acceptable." Furthermore, the NDA "is deemed adequate for Manufacturing Process perspective."

(b) (4)

- Dr. God confirmed that "release and stability microbial limits for isopropyl alcohol solution comply with USP <1111> for a cutaneous product." Overall, microbial limits are considered adequate and will continue to be tested on long-term stability samples at 0, 12, and 24 months.

4. Nonclinical Pharmacology/Toxicology

Nonclincial Pharmacology/Toxicology Review was conducted by D. Charles Thompson, RPh, PhD, DABT (Team Leader: Jane J. Sohn, PhD)[11]. Dr. Thompson concluded that, from nonclinical standpoint, the NDA is approvable. Dr. Thompson also concluded that the Sponsor's submitted labeling is acceptable from a nonclinical perspective.

Dr. Thompson pointed out that, based on the Sponsor's stated intention to rely on FDA's previous findings of safety for a similar 70% IPA drug product (ChloraPrep, NDA 20832), FDA advised the Sponsor that the only new nonclinical data that would be needed to support an NDA was a 21-day dermal toxicity study in minipigs (provided that drug product impurity levels do not require safety qualification). Such a study was submitted with the original IND 117045 and found to be adequate and negative for any safety concerns regarding the drug product, including the potential for any significant systemic absorption of the methylene blue excipient (R.T. Dorsam, 2014).

Also at FDA's request, the Sponsor provided assessments of the safety-in-use of the proposed drug product excipients and drug product degradant and container closure system impurities. Regarding the excipients, only the levels of (b) (4) citrate (b) (4) and methylene blue (b) (4) are noted to exceed levels previously used as excipients in approved topical solutions. The Sponsor provided an excipient risk assessment document entitled, "Safety Data Review of ZuraPrep Ingredients."[12] The document reviewed publicly available data and information and concluded, "the available safety data for citric acid (b) (4), (b) (4) citrate (b) (4) methylene blue (b) (4), methylparaben, propylparaben and 70% isopropyl alcohol indicates no toxicological concerns for use as formulation ingredients in the antimicrobial drug ZuraPrep at the proposed maximum topical application of (b) (4) for the final formulation….In addition, there are no safety concerns from the topical application of a (b) (4) citrate (b) (4) in the final formulation of ZuraPrep." Dr. Thompson concluded, "Based on the absence of adverse findings in the above-noted minipig dermal toxicity study and the totality of the information discussed in the Sponsor's submitted excipient risk assessment document (Baldrick and Klein, 2013), this reviewer finds the safety of the proposed excipient use and use levels to have been adequately addressed from a nonclinical perspective."

[11] NDA 210872 Pharmacology/Toxicology NDA/BLA Review and Evaluation; January 9, 2019.
[12] Baldrick and Klein, 2013.

Dr. Thompson also noted that drug product degradant impurities that exceed the ICH Q3B(R2)-prescribed qualification limits consist of a number of different (b) (4) (b) (4) The safety of each of these (b) (4) impurities was also addressed by the absence of adverse findings in the minipig dermal toxicity study and the totality of the information discussed in the Sponsor's submitted (b) (4) impurity risk assessment document.[13] Dr. Thompson reported that the safety conclusion of this risk assessment is driven largely by FDA/CFSAN findings that (b) (4) is GRAS for multiple food uses with no limitation other than current good manufacturing practice (21 CFR 184.1386). Dr. Thompson concurred with the Sponsor and concluded, "the preponderance of available information supports a finding that the proposed drug product impurity specification limits for the various (b) (4) (b) (4) do not raise safety concerns from a nonclinical perspective."

Lastly, drug product impurities that may potentially arise from the containier closure system (i.e., leachable/extractable impurities) were addressed by the Sponsor via submission of a contracted, third-party risk assessment document prepared by the medical device CRO, (b) (4). Based on this risk assessment and the totality of the data, Dr. Thompson concluded that, "the Sponsor has demonstrated reasonable due diligence in assessing the potential risks posed by leachable/extractable impurities in their drug product and that these risks are likely to be low, if not negligible, under the anticipated conditions of use of the product. However, a final determination as to the validity and reliability of the device study data upon which the Sponsor's risk assessment is based is deferred pending final input from OPQ and/or CDRH reviewers."

5. Clinical Pharmacology

Office of Clinical Pharmacology review[14] was conducted by the Clinical Pharmacology Team (Sojeong Yi, PhD and Soo Hyeon Shin, PhD, Division of Clinical Pharmacology III; and Dennis Bashaw, PharmD, Immediate Office). The Team concluded that, "from a clinical pharmacology standpoint, the information provided was acceptable to support the approval of ZuraGard for use as a preoperative skin preparation as formulated."

The NDA was submitted under the 505(b)(2) pathway, relying on FDA previous findings of safety for the reference listed drug, ChloraPrep, containing 2% w/v chlorhexidine gluconate (CHG) and 70% v/v IPA, which is approved under NDA 20832. The Sponsor proposed to support establishment of a bridge between ZuraGard and ChloraPrep in terms of clinical pharmacology safety and address

[13] Stewart, 2013.
[14] NDA 210872 Office of Clinical Pharmacology Review; March 21, 2019.

potential dermal absorption of IPA from ZuraGard based on published literature. However, as ZuraGard does not have identical composition from either ChloraPrep or the products used in the literature, the published literature was deemed insufficient to support the Sponsor's proposal. It is noted that, unlike ZuraGard containing IPA 70% v/v only, ChloraPrep contains CHG w/v in addition to IPA 70% v/v. Furthermore, some excipients in ZuraGard are not contained in ChloraPrep. Thus, it is possible that dermal absorption of IPA could be altered when only IPA is topically applied compared to when IPA is applied with the presence of CHG. Additionally, given that some excipients in ZuraGard are not contained in ChloraPrep, those excipients could also alter the dermal absorption of IPA. To address this issue, during this review cycle, the Sponsor submitted in vitro permeation test (IVPT) results comparing the skin permeation of IPA between ZuraGard and ChloraPrep to support bridging between the two products in terms of potential dermal absorption of IPA and systemic safety.

For the proposed 10.5 ml applicator, the Sponsor defined the maximum treatment area as 8.4 in x 8.4 in (=70.56in^2 = 457 cm^2). Thus, the Sponsor defined maximum potential dermal IPA exposure from the proposed single 10.5 mL applicator as (b) (4) mg IPA/cm^2 to 457 cm^2 skin area, assuming 100% of the product contained in the applicator is delivered to the skin with no product evaporation. This is consistent with the ChloraPrep product, as shown in **Table 3** below.

Table 3. Maximum Potential Dermal Exposure of Isopropyl Alcohol of ChloraPrep 10.5 nL Applicator versus the ZuraGard 10.5 nL Applicator.

	ZuraGard (IPA 70% v/v)	ChloraPrep (IPA 70% v/v + CHG 2% w/v)
IPA Strength	70.0% (v/v) = (b) (4) mg/mL	70.0% (v/v) = (b) (4) mg/mL
Amount of IPA in a single product (g) [a]	(b) (4)	
Maximum skin coverage (cm^2) per an applicator	8.4 in.×8.4 in. (=70.56 in^2 = 457 cm^2)	8.4 in.×8.4 in. (=70.56 in^2 = 457 cm^2)
Maximum applied dose per cm^2 (mg/cm^2) [b]	(b) (4)	

CHG = chlorhexidine gluconate; IPA = isopropyl alcohol.

a. Amount of isopropanol (IPA) in a single 10.5-mL applicator (b) (4)

b. Assumes total IPA content (b) (4) of 10.5-mL applicator applied to 457 cm2 area of skin. The maximum applied dose assumes that all of the product in the applicator is delivered to the skin with no product evaporation.

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Regarding the potential for dermal absorption of 70% IPA, the Clinical Pharmacology Team pointed out in their review that multiple publications demonstrate that IPA is absorbed following topical application. However, the extent of systemic exposure to IPA is expected to vary depending on the frequency of application, surface area involvement, formulation, and other factors when used as an active ingredient in topical antiseptic products. Per the literature survey cited in the 2015 Proposed Rule on Health Care Antiseptics[15], the highest blood concentration of IPA observed across studies was less than 20 mg/L following various topical application scenarios with IPA-containing products. Of note, clinical effects such as mild CNS depression are associated with elevated blood isopropyl alcohol levels exceeding approximately 500 mg/L, and patients with blood levels ≥1500 mg/L are comatose[16]. Symptoms of mild IPA intoxication include headache, dizziness, ataxia, hypoglycemia, tachycardia, miosis, abdominal pain, nausea, vomiting, and hematemesis; symptoms of severe toxicity include respiratory depression, hypotension, and coma.

It is estimated that 70-90% of absorbed IPA is metabolized to acetone by alcohol dehydrogenase in the liver. Acetone is eliminated via the kidney or in exhaled air; otherwise, it can be further metabolized to acetate and formate, and ultimately to carbon dioxide. IPA's reported half-life in humans ranges from 2-4 hours. Acetone, the main metabolite of IPA, remains in the blood longer than IPA with longer half-life of about 17-27 hours and is known to be a CNS depressant.[17,18]

Literature Review

The Clinical Pharmacology team reported that the literature provided was inadequate by itself to support establishment of a bridge between ZuraGard and ChloraPrep in terms of potential dermal absorption. The products used in the literature were not identical to ZuraGard, and the literature was inadequate to allow for cross-studies comparison (i.e. dermal absorption of IPA with vs. without the presence of CHG) given the fact that those study designs vary in terms of the applied amount of IPA and exposed skin area.

The Sponsor submitted four published studies in relation to dermal absorption of IPA in humans after use of antiseptics, which are detailed in the Clinical Pharmacology Review and are summarized in **Table 4** below. Three of the studies (Below et al,[19], Kirschner et

[15] Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph by the FDA on May 1, 2015 (80 FR 25165

[16] Puschel, K. Percutaneous Alcohol Intoxication. Eur J Pediatr. 1981 Jul; 136(3):317-8.

[17] Jones AW. Elimination half-life of acetone in humans: case reports and review of the literature. J Anal Toxicol. 2000 Jan-Feb;24(1):8-10.

[18] Natowicz M, Donahue J, Gorman L, Kane M, McKissick J, Shaw L. Pharmacokinetic analysis of a case of isopropanol intoxication. Clin Chem 1985 Feb; 31(2):326-8.

[19] Below et al. Dermal aand pulmonary absorption of propan-1-ol and propan-2-ol from hand rube. Am J Infect Control. 2012;40:250-257.

al[20]; and Turner et al[21]) used antiseptics containing IPA 10 to 63.1% w/w, whereas the fourth study (Brown et al[22]) used an antiseptic containing both CHG 0.5% and IPA 70% v/v.

[20] Kirschner et al. Transdermal resorption of an ethanol- and 2-propranol-containing skin disinfectant. Langenbeck's Archiv Surg. 2009; 394: 151-157.
[21] Turner et al. Dermal absorption of isopropyl alcohol from a commercial hand rub: implications for its use in hand decomtamination. J Hosp Infect. 2004;56:287-290.
[22] Brown et al. Can alcohol-based hand-rub solutions cause you to lose your driver's license? Comparative cutaneous absorption of various alcohols. Antimicrob Agents Chemother. 2007;51(3):1107-1108.

Table 4. Dermal Absorption of Isopropyl Alcohol from the Published Literature

Source	Indication	IPA Strength	IPA Dose per Application (g)	Number of Applications/ Time Duration	Total Dose Applied (g)	(Estimated) Applied Body Surface Area (cm^2)	Total Applied Dose per cm^2 (g/cm^2)	Highest Observed Blood Concentration (mg/L)	Estimated Absorbed Dose[a] (% Applied Dose)
proposed labeling[d]									
Below et al, 2012	hygienic/ surgical hand rub	63.1% (w/w) = 631 mg/mL	2.21	Hygienic: 20 applications/ 30 seconds per application in 30 minutes	44.25	850[e]	0.0520	Dermal and pulmonary 5.3 (median)	Dermal and pulmonary 0.50 (median)[g]
			11.06	Surgical: 10 applications/ 3 minutes per application over 80 minutes	110.62	1850[e]	0.0597	Dermal and pulmonary 5.8 (median)	Dermal and pulmonary 0.22 (median)[g]
Turner et al, 2004	Surgical hand rub	52.6% (w/w) = 526 mg/mL	1.58	24 applications/ the per application duration was not reported but application occurred every 10 minutes over 4 hours	37.9	850[e]	0.0445	1.8	~0.20
With Chlorhexidine Gluconate (0.5%), No Occlusion									
Brown et al, 2007	Antiseptic hand rub	70.0% (v/v) = 550 mg/mL	0.66	30 applications/ 2 minutes per application (1 hour total duration)	19.8	850[e]	0.0233	< 2	< 0.42
			0.82		24.6	850[e]	0.0290	< 2	< 0.34
No Chlorhexidine Gluconate, Continuous Wet Application									
Kirschner et al. 2009	Pre-OP skin preparation, continuous wet application	10.0% (w/w) = 100 mg/mL	2.00	1 application/ 10 minutes	2.00	200	0.0100	~3.0	~6.3

IPA = isopropyl alcohol; Pre-OP = preoperative.
[a] = Assumes an average adult human of 70 kg will contain about 42 L of water and IPA distributes homogenously in total available body water.
[b] = Total amount of isopropanol (IPA) in a single ZuraPrep 10.5-mL applicator is (b) (4) assuming a density of (b) (4)
[c] = Actual IPA dose administered in study *ZX-ZP-0083*.
(b) (4)
(b) (4)
[e] = Assumes an average adult human hand has a total surface area of between 400 cm^2 (female) and 450 cm^2 (male) and two hands (850 cm^2) are rubbed with IPA.
[g] = The increase in the absorbed amount of IPA (b) (4) from dermal plus pulmonary versus dermal alone was not statistically significant.

Electronically copied and reproduced from Clinical Pharmacology Review (Table 4; page 19)
Source: Summary of Clinical Pharmacology Studies

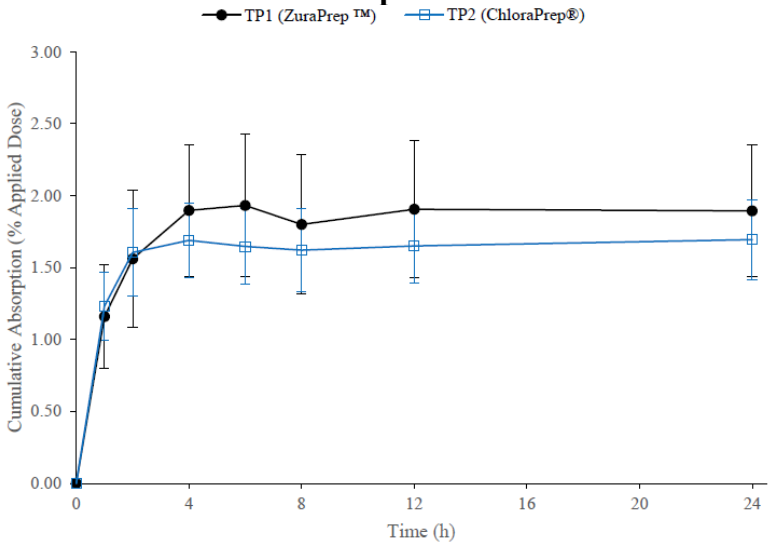
The Clinical Pharmacology Team reported that, in the literature submitted, "the estimated proportion of IPA absorbed was low, ranging from approximately 0.4% to 6.3% of the applied IPA dose and the highest blood level of IPA across the literature was 5.8 mg/L which is far below than 500 mg/L that may cause mild CNS depression. Still, the literature submitted could not fully address potential dermal absorption of IPA from ZuraGard after use as a preoperative skin preparation, because the products used in the

literature were not the same as ZuraGard in terms of the composition. Additionally, none of the literature covered the maximal usage condition that we typically consider for a preoperative skin preparation, i.e., single application to 50% BSA." The Sponsor "stated that based on cross-study comparison, the highest blood concentration of IPA following topical application of IPA without CHG (i.e., 1.8 mg/L to 5.8 mg/L) is not markedly different from the concentration after topical application of IPA with CHG (i.e., < 2 mg/L). However, the literature data was inadequate to allow for a cross-studies comparison because study designs vary in terms of the applied amount of IPA and the exposed skin area."

In Vitro Permeation Test (IVPT) Results

The submitted In Vitro Permeation Test (IVPT) compared skin permeation of IPA between ZuraGard and ChloraPrep. The Clinical Pharmacology Team determined that the study results indicate that the dermal absorption of IPA from ZuraGard and ChloraPrep were comparable in vitro. The Team wrote that despite the compositional differences between the two formulations, "from a Clinical Pharmacology perspective, ZuraGard does not appear to pose a significantly higher systemic absorption potential of IPA compared to ChloraPrep," as evidenced graphically in the cumulative absorption and flux profiles (**Figures 2** and **3**) below.

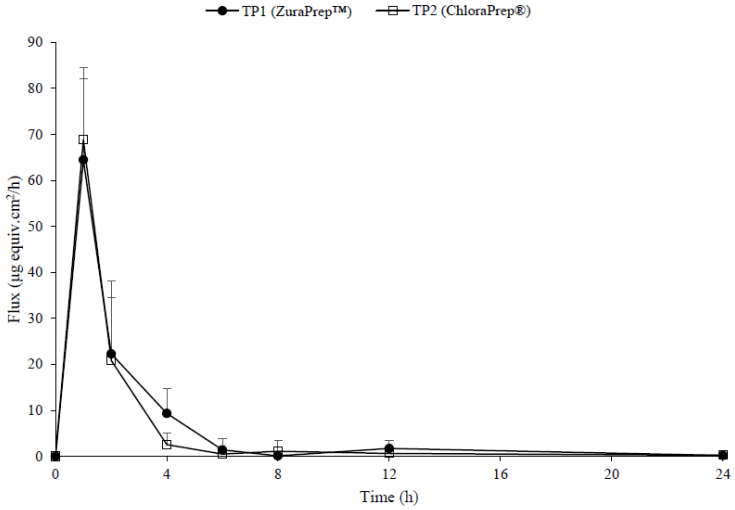
Figure 2. Comparison of Cumulative Absorption Profiles for ZuraGard and ChloraPrep



Mean ± SD, n=12 per test product

Electronically copied and reproduced from Clinical Pharmacology Review (Source: Figure 12, Reference No. ZX-ZP-099).

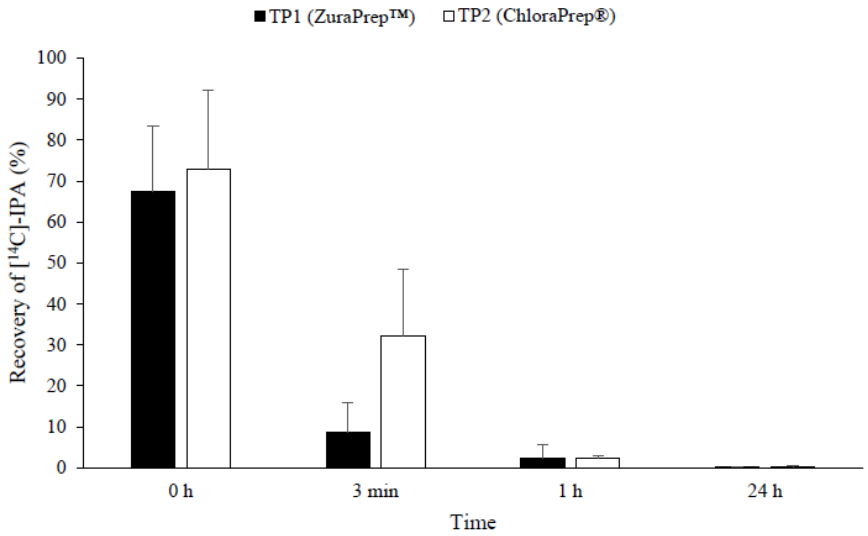
Figure 3. Comparison of Flux Profiles for ZuraGard and ChloraPrep



Mean ± SD, n=12 per test product
Electronically copied and reproduced from Clinical Pharmacology Review (Source: Figure 13, Reference No. ZX-ZP-099).

Furthermore, the Clinical Pharmacology Team determined that the study demonstrated that the ZuraGard solution evaporates more rapidly compared to ChloraPrep solution, as shown graphically in **Figure 4** below. The Team wrote, "as rapid evaporation represents less amount of solution available to potentially be absorbed through skin and reach systemic circulation, the results do not pose a safety issue concerning systemic absorption of IPA from ZuraGard."

Figure 4. Comparison of Recovery of [14C]-IPA Following Topical Application of ZuraGard or ChloraPrep for Volatility Testing to Aluminum Foil.



Electronically copied and reproduced from Clinical Pharmacology Review (Source: Figure 3, Reference No. ZX-ZP-099).

Conclusions

The Clinical Pharmacology team concluded that "the in vitro bridging approach used here for a single-use application of IPA 70% (v/v) as formulated in this NDA is justifiable from a clinical pharmacological perspective, taking into consideration both the literature data provided and the in vitro permeation study results." Additionally, the Clinical Pharmacology team pointed out that it is unlikely that ZuraGard used as preoperative skin preparation could cause a significant systemic exposure to IPA based on the following rationale:

1. Given that the typical usage pattern of preoperative skin preparation (i.e., single-use application), ZuraGard will be used only a few times in one's lifetime aside from an exceptional case such as a massive traumatic situation that requires multiple surgeries in a short period or in the case of patients with a cerebral shunt which may need multiple revisions throughout their lives (albeit at significant intervals).
2. Potential formulation effect on the dermal absorption of IPA is expected to be minimal. IPA itself is known to be dermally absorbed to some extent and acts as a skin permeation enhancer. As the majority of the composition is IPA with 70% v/v in the proposed product, the rest of other excipients are less likely to further increase the dermal

absorption of IPA. Additionally, IVPT conducted by the Sponsor suggested that skin permeation of IPA from ZuraGard was not significantly higher compared to that from ChloraPrep, i.e. without vs. with the presence of CHG 2% w/v.

CDTL Comment: As pointed out by the Clinical Pharmacology Team in their review, the above Clinical Pharmacology Team determination is not applicable to other products containing IPA (or other antiseptic agent) where chronic use and multiple administrations over a day are to be expected (e.g., a hand rub or a hand wash) or where prior information of human exposure is lacking as in the case of a new excipient that may have unexpected effects on skin retention or surface permanence.

6. Clinical Microbiology

Clinical Microbiology Review was conducted by Anita Kumar, PhD, Interdisciplinary Scientist, DNDP (TL: Francisco Martinez-Murillo, PhD). Based on her review, Dr. Kumar recommended that "the in vitro and clinical simulation studies in this application be approved for the indication 'patient preoperative skin preparation'."

For details of the microbiology data submitted by the Sponsor, please see Dr. Kumar's thorough review[23]. Briefly, Dr. Kumar reviewed the results of four in vitro and four clinical in vivo microbiology studies, as shown in **Table 5** below.

[23] NDA 210872 Clinical Microbiology NDA Review; 29 March 2019.

Table 5. Clinical In Vivo and In Vitro Microbiology Studies – NDA 210872

Study No.	Title of Study
	Clinical In Vitro Microbiology Evaluations
(b) (4) 130734-202 (ZX-ZP-0014)	Determination of the Minimum Inhibitory Concentrations and Minimum Bactericidal Concentrations of Two Test Products, One Active Ingredient, One Reference Product, and One Negative Control When Challenged With Various Microorganism Strains
(b) (4) 30733-201 (ZX-ZP-0015)	An In Vitro Time-Kill Evaluation of Two Test Products, One Active Ingredient, One Reference Product, and One Negative Control for Their Antimicrobial Properties When Challenged With Various Microorganism Strains
(b) (4) 130548-201	Determination of the Dose-Response of Various Microorganism Strains to One Test Product, Five Active Ingredients, and Two Controls Using an In Vitro Time-Kill Procedure
(b) (4) 365-102 (ZX-ZP-0043)	Evaluation of Potential for Development of Antimicrobial Resistance
	Clinical In Vivo Microbiology Studies
MBT 865-104 (ZX-ZP-0068)	Pilot Clinical Evaluation to Characterize the In Vivo Effects of Topically Applied ZuraPrep™ and ZuraPrep™ Vehicle (March 18, 2016)
MBT 865-105 (ZX-ZP-0073)	Pivotal Clinical Evaluation of the Antimicrobial Effectiveness of Topically Applied ZuraPrep™
BSLI 150316-103 (ZX-ZP-0074)	Pivotal Clinical Evaluation of ZuraPrep™, a Patient Preoperative Skin Preparation
(b) (4) 365-106 (ZX-ZP-0083)	Evaluation of the Skin Area Covered and Dry Time of a Preoperative Skin Preparation

Electronically copied and reproduced from Dr. Kumar's Clinical Microbiology Review

Clinical In Vitro Microbioogy Studies:

Study ZX-ZP-0014 ((b) (4) 130734-202): Determination of Minimum Inhibitory Concentrations (MIC) and Minimum Bacterial Concentrations (MBC) of Two Test Products, One Active Ingredient, One Reference Product, and One Negative Control When Challenged With Various Microbiology Strains

In this study, in vitro antimicrobial spectrum and minimum bactericidal concentration (MBC) of ZuraGard solution was determined against 180 different microorganism strains (2 laboratory strains and 10 fresh clinical isolates of 15 different microorganism species), including both Gram-positive and Gram-negative bacteria, and yeast. Test product ZuraGard was bactericidal for 155 of the 180 strains when diluted 1:16. In contrast, ZuraGard's vehicle was bactericidal for 33 of the 180 strains when diluted 1:16, suggesting, according to Dr. Kumar, that the vehicle has weak subtherapeutic activity.

Study ZX-ZP-0015 (b) (4) 130733-201): An In vitro Time-Kill Evaluation of Two Test Products, One Active Ingredient, One Reference Product, and One Negative Control for Their Antimicrobial Properties When Challenged With Various Microorganism Strains

This time-kill study performed at full strength concentration for ZuraGard final product, 70% v/v isopropyl alcohol independently, and ChloraPrep product, showed a >3.0 $\log_{10}$ (>99.9%) reduction in viable microbial cells within 30 seconds for all 148 challenge strains tested, in the three test products. Dr. Kumar noted that the killing effect or antimicrobial activity of a drug needs to reach ≥3 $\log_{10}$ reduction to be considered active. The minimum $\log_{10}$ reduction observed was 5.1 for ZuraGard, 4.7 for 70% v/v isopropyl alcohol, and 5.1 for ChloraPrep. ZuraGard's vehicle showed activity against 51 of the 148 organisms tested. However, the Sponsor demonstrated, through pilot clinical simulation study **ZX-ZP-0068**, discussed in **Section 7** below, that the log reduction achieved by ZuraGard's vehicle and a normal saline negative control were similar, indicating that ZuraGard's excipients do not significantly contribute towards the effectiveness of the test product. Dr. Kumar concluded that, overall, the results of this time-kill study showed that ZuraGard provides immediate killing of the tested microorganisms at exposure times of 30, 60, and 120 seconds, and is an effective bactericidal agent.

Study ZX-ZP-0043 ((b) (4) 865-102): Evaluation of Potential for Development of Antimicrobial Resistance of ZuraPrep

This study was intended to determine the potential for development of resistance to ZuraGard and 70% v/v isopropyl alcohol by sequential passage of several clinically relevant microorganisms through increasing concentrations of an antimicrobial/antibiotic included in the culture medium. Ten repository isolates and 4 clinical isolates from 8 species were evaluated for a total of 42 isolates. The study results did not show any higher MIC values with clinical isolates compared to ATCC laboratory strains and the baseline. In addition, an evaluation of the potential for antibiotic cross-resistance due to isopropyl alcohol was performed by comparing the MICs of several antibiotics both before and after extended exposure to sublethal concentrations of isopropyl alcohol. Similar to the final product testing, no changes to MICs were observed for isopropyl alcohol. Dr. Kumar concluded that the study results "indicate that ZuraGard and isopropyl alcohol do not induce or select for resistance in clinically relevant bacteria and do not mediate cross-resistance with clinically useful antibiotics."

Study (b) (4) 130548-201: Determination of the Dose-Response of Various Microorganism Strains to One Test Product, Five Active Ingredients, and Two Controls Using an In Vitro Time-Kill Procedure

This study was an in vitro time-kill kinetic evaluation of ZuraGard test product, 5 ingredients (citrate (b) (4) solution, methylene blue solution, methylparaben solution, propylparaben solution, isopropyl alcohol), and 2 controls (0.9% sodium chloride irrigation, United States Pharmacopeia (USP), and purified water), versus suspensions of 15 different microorganism strains (15 American Type Culture Collection strains). Test product ZuraGard and the 5 ingredients were evaluated at concentrations of 99% (v/v), 75% (v/v), 50% (v/v), and 25% (v/v); the controls were evaluated at a single concentration, 99% (v/v). The percent and $\log_{10}$ reductions from the initial population of each challenge microorganism were determined following 30-second, 60-second, 120-second, and 5-minute exposures to each test material. Test materials were considered bactericidal at the concentration and contact time that demonstrated a 3 $\log_{10}$ (99.9%) or greater reduction in bacterial viability as compared to the initial inoculum. ZuraGard achieved a $\geq$3 $\log_{10}$ reduction from baseline for all bacterial species evaluated, demonstrating a broad antimicrobial activity at all time points tested. Every individual ingredient alone, with the exception of isopropyl alcohol, failed to achieve a 3 $\log_{10}$ reduction from baseline that would be considered bactericidal. Thus, Dr. Kumar concluded that "the results from this dose-response study confirm that ZuraGard contains only one therapeutically active ingredient, 70% v/v isopropyl alcohol."

7. Clinical/Statistical- Efficacy

As discussed in **Section 6**, Dr. Kumar reviewed the results of four in vitro and four clinical in vivo microbiology studies and concluded that the application was acceptable for approval for the indication "patient preoperative skin preparation." The four in vitro studies are discussed in **Section 6** above. In this section, the four in vivo studies will be discussed.

The clinical in vivo studies consisted of one pilot clinical evaluation study (**ZX-ZP-0068)** and two pivotal clinical simulation studies (MicroBioTest **ZX-ZP-0073** and BioScience Laboratories **ZX-ZP-0074**), which were designed to evaluate the antimicrobial efficacy and safety of ZuraGard, active control ChloraPrep, and ZuraGard's vehicle on the abdominal and groin/inguinal regions of the body. In addition, a skin coverage area and drying time study (**ZX-ZP-0083**) was done.

The two pivotal studies were also reviewed by the Division of Biostatistics VII, Office of Biostatistics (Sai Dharmarajan, PhD, Mat Soukup, PhD, and Mark Levinson, PhD).[24] The Biostatistics Team concluded that "from a statistical standpoint, there is sufficient evidence that ZuraPrep 10.5 mL is effective and adds benefit beyond the vehicle." Specifically, the Biostatistics Team concluded that:

- Responder rates of ZuraPrep 10.5 mL were greater than 70% at 10 minutes for both body regions;

[24] NDA 210872 Statistical Review and Evaluation; 19 March 2019.

- ZuraPrep is statistically superior to the vehicle and non-inferior to the ChloraPrep at 10 minutes and 30 seconds, for both body regions based on average treatment effects, the effectiveness criteria outlined in the 2017 Final Rule; and
- ZuraPrep 10.5 mL showed persistent antimicrobial properties in the groin region at 6 hours.

Furthermore, the Biostatistics Team noted that "the validity of the studies was confirmed as ChloraPrep 10.5 mL, an approved product, met the 70% responder rate criteria and was found to be statistically superior to the vehicle control in ATE analysis at 10 minutes post-application." However, "both studies failed to demonstrate persistent antimicrobial properties in the abdomen."

Study ZX-ZP-0068 (MBT 865-104): Pilot Clinical Evaluation to Characterize the In Vivo Effects of Topically Applied ZuraGard and ZuraGard Vehicle

This study was a Phase 2, randomized, four-arm, paired-comparisons, pilot trial to evaluate whether ZuraGard's vehicle (ZuraGard product without IPA) and saline solution are equally therapeutically inactive and are not substantially different in antimicrobial $\log_{10}$ reduction from baseline at the timepoints described in the 1994 TFM (10 minutes and 6 hours after application), as well as at the newly proposed 30 second timepoint (1 May 2015 TFM, 80 FR 25166).

For details regarding study protocol, the reader is referred to Dr. Kumar's review. Briefly, each subject received two of the four planned treatments: ZuraGard 10.5 mL Applicator; ChloraPrep 10.5 mL Applicator; ZuraGard's vehicle; and normal saline. The trial was conducted at MicroBioTest, Sterling, VA. The primary objective of this study was to characterize the in vivo effects of the ZuraGard's vehicle in comparison to the normal saline control. The in vivo performance of the investigational products with the proposed sampling interval at 30 seconds and 10 minutes were evaluated. The study measured the antimicrobial activity of ZuraGard as compared to the positive product, ChloraPrep 10.5 mL Applicator ([redacted] (b) (4) Tint), and of the ZuraGard's vehicle compared to a negative control, normal Saline.

Healthy male or female volunteers of at least 18 years of age with no dermatological conditions or known history of sensitivity were enrolled into this study. On the screening day, the baseline counts were required to be at least 1.0×10^3 CFU/cm^2 per abdominal site (left and right) and at least 1.0×10^5 CFU/cm^2 per groin site (left and right) for inclusion in the study. A total of 89 subjects were treated. Eighty-two subjects were treated on both the abdomen and groin, 4 on the abdomen only, and 3 on the groin site only.

The primary goal of the study was the reduction of skin flora on the abdominal and groin sites 30-seconds and 10-minutes following application of the test treatments, relative to the treatment day baseline $\log_{10}$ counts. The study was analyzed per the 1994 Tentative Final Monograph (TFM) standards for Effectiveness Testing of a Patient Preoperative Skin Preparation (59 FR 31402 at 31450-31452), and by the 2015 Health Care antiseptics Proposed Rule (80 FR 25166 at 25166). As the primary endpoint, the 1994 TFM indicates that the test product and the active control should achieve a 2 $\log_{10}$ per cm^2 mean reduction on the abdomen site and a 3 $\log_{10}$

per cm^2 mean reduction on the groin site at 10 minutes post application. The 2015 Proposed Rule (80 FR 25166 at 25178 to 25179) indicates 30 seconds as the primary efficacy time point and a >70% lower bound of the 95% confidence interval for the responder rate for test and active control.

In this study, both ZuraGard and ChloraPrep met the primary effectiveness criteria at abdominal and groin sites at 30 seconds and 10 minute timepoints: at least 2 log_{10} per cm^2 reduction from baseline on the abdominal site and 3 log_{10} per cm^2 reduction from baseline on the groin site; and count values below baseline at 6 hours. Furthermore, the differences in the bacterial log_{10} per cm^2 reductions from baseline between normal saline and ZuraGard's vehicle were demonstrated to be below 0.6 log_{10} per cm^2. Dr. Kumar pointed out that these results are consistent with the standards provided in the FDA February 22, 2016 Advice letter, which specifies that ZuraGard's vehicle and normal saline are considered equivalent when the comparisons of mean log_{10} per cm^2 reduction from baseline are below 1 log_{10} per cm^2 for both body areas at all timepoints (30 seconds, 10 minutes, and 6 hours). Thus, Dr. Kumar concluded that these results were acceptable.

The secondary efficacy goal was to have the lower bound of the 95% confidence interval for the responder rate to be ≥70% at 10 minutes. Both the test product (ZuraGard) and the active control (ChloraPrep) met the 70% lower bound responder rate at 10 minutes and 6 hours for the abdomen area. However, at the groin area, ZuraGard and ZuraPrep met the 70% responder rate at 6 hours but not at the 10 minute timepoint. At 30 seconds, neither ZuraGard or ChloraPrep could achieve the 70% responder rate at either the abdomen or groin site. Dr. Kumar concluded that this is acceptable because this was a pilot study to characterize the ZuraGard vehicle when compared to saline, given that the primary objective (per 1994 TFM log reduction criteria) was achieved, and considering the totality of evidence as described in the two pivotal studies.

<u>Studies ZX-ZP-0073 (MicroBiotest) and ZX-ZP-0074 (BioScience Labs): Pivotal Clinical Evaluation of the Antimicrobial Effectiveness of Topically Applied ZuraPrep</u>

Two pivotal clinical simulation studies were designed to evaluate the immediate (30 seconds and 10 minutes) and persistent (6 hour) antimicrobial efficacy on abdomen and groin sites of patient preoperative skin preparations (ZuraGard test product, ChloraPrep control, and ZuraGard's vehicle). The two trials were randomized, vehicle and active controlled, evaluator blinded, single-center paired-comparison in healthy volunteers, who received 2 of 3 possible study products on the abdomen and 2 of 3 possible study products on the groin. The three products were ZuraPrep 10.5 mL Applicator; ChloraPrep 10.5 mL Applicator (b) (4) Tint (positive control); and ZuraGard's vehicle (negative control). The healthy volunteers were at least 18 years of age with no dermatological conditions or known sensitivity to natural rubber latex, adhesive skin products, IPA, chlorhexidine gluconate, or other investigational product ingredients. Prepping procedure consisted of 30 seconds of product application time on abdomen and 2 minutes on the groin site, followed by 3 minutes of drying time. Sampling was performed at 30 seconds, 10 minutes, and 6 hours after the post-application drying time.

Each study consisted of 3 phases: a pre-treatment phase (14-day washout to allow for the removal of any antimicrobial agents from the subject's skin), a screening phase, and a treatment phase (scheduled at least 72 hours after screening baseline collection). Baseline bacterial count in Colony Forming Units (CFU) were assessed on screening day and on treatment day. Subjects meeting treatment day baseline sampling criteria (1×10^3 CFU/cm^2 abdominal site and 1.0×10^5 CFU/cm^2 groin site) were randomized to receive two of the three investigational products (one product on the right side, one product on the left side). Following application of products, each treatment site was further subdivided into four areas of the same dimension for post-application sampling of skin flora at baseline, 30 seconds, and 6 hours. The study was evaluator-blinded, that is, study staff/investigators performing study material application or bacterial sample collections were not blinded, while study staff performing the bacterial enumeration were not involved in study material application or the collection of samples. This is acceptable, as the (b) (4) tint of the ChloraPrep product and the blue tint of the ZuraPrep product would make blinding during the application and sample collection phases virtually impossible.

The procedures used in these pivotal studies were based on the American Society for Testing and Materials standards (ASTM E1173-01, reapproved 2009: Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations) and the FDA's 1994 Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products (59 FR 31402). In addition, the two study protocols were aligned with the 2015 Health Care Antiseptics Proposed Rule, which provided revisions to the effectiveness criteria set forth in the 1994 TFM while continuing to recommend bacterial log reduction studies, and the Final Rule for Health Care Antiseptic Products (82 FR 6047 to 60487; published on 20 December 2017) which added criteria to include non-inferiority of the test product to an active control by a margin of 0.5 and superiority of the test product to a negative control by an indication-specific margin. This assessment is to be based on Average Treatment Effect (ATE), which is defined as the estimated difference of the effect of two treatments correcting for baseline count.

Thus, the two trials were similarly designed with two co-primary objectives:

- To demonstrate non-inferiority of ZuraPrep to the active control by a margin of ≤ 0.5 and superiority of ZuraPrep to the vehicle control by a margin of ≥ 1.2 on Average Treatment Effect (ATE). The ATE was estimated from a linear regression of post-treatment bacterial counts ($\log_{10}$ scale at 10 minutes) correcting for the baseline pre-treatment measurement.
- To demonstrate that the lower bound of the 95% confidence interval (CI) was greater than 70% for the responder rate at 10 minutes. At 10 minutes, a responder on the abdomen is defined as having at least a 2 $\log_{10}$/cm^2 bacterial reduction compared to baseline, and a responder on the groin region is defined as having at least a 3 $\log_{10}$/cm^2 bacterial reduction compared to baseline.

Secondary responder rate endpoints were responder rates at 30 seconds and 6 hours post-treatment for the abdominal and groin regions. At 30 seconds, a responder is defined as done at 10 minutes. At 6 hours, a responder is defined as having counts below

baseline for the groin and abdomen region. A secondary ATE endpoint was ATE at 30 seconds, estimated using the same linear regression as for the primary endpoint. Additional secondary endpoints are reduction in bacterial counts (log_{10} scale) at 30 seconds, 10 minutes, and 6 hours, and mean bacterial counts (log_{10} scale) at baseline and all post-application time points.

In Study **ZX-ZP-0073,** a total of 440 subjects were treated on the abdomen and groin, as shown in **Table 6** below. Of these, there were 344 subjects who had qualifying Treatment Day baseline bacterial counts on the abdomen and groin, 34 subjects who had qualifying Treatment Day baseline bacterial counts on the abdomen and 19 subjects who had qualifying Treatment Day baseline bacterial counts on the groin. This resulted in a total of 751 evaluable abdomen sites and 724 evaluable groin. Most subjects were male (~57%), and the most common races were Caucasian (40%), Asian (~27%), Black/African American (~19%), and Hispanic (~10%).

In Study **ZX-ZP-0074**, a total of 641 subjects were randomized, 640 subjects were treated, and 639 subjects completed testing (**Table 6**). A total of 416 subjects were treated at both abdomen and groin sites, 69 subjects were treated at the groin site only, and 155 were treated at the abdomen only. Of the 640 treated subjects, 67 subjects failed baseline criteria at both abdomen and groin sites, resulting in 573 subjects used in the efficacy analysis. The majority of treated subjects were male (~75%) and the most common race was Causasion (90%).

Table 6. Demographic Characteristics of Clinical Studies

Study	Number of Subjects		
	ZX-ZP-0074 (N = 640)	ZX-ZP-0073 (N = 440)	ZX-ZP-0068 (N = 89)
Age, years			
Mean (standard deviation)	30[a]	38.43 (15.32)	38.88 (14.31)
Minimum, maximum	18, 85	18, 80	19, 75
Sex, n (%)			
Female	164 (25.63)	190 (43.18)	32 (35.96)
Male	476 (74.38)	250 (56.82)	57 (64.04)

Study	Number of Subjects		
	ZX-ZP-0074 (N = 640)	ZX-ZP-0073 (N = 440)	ZX-ZP-0068 (N = 89)
Race, n (%)			
Asian	8 (1.25)	119 (27.05)	39 (43.82)
Black/African American	9 (1.41)	84 (19.09)	12 (13.48)
Hispanic/Latino	20 (3.13)[b]	45 (10.23)	7 (7.87)
Caucasian	576 (90.00)	176 (40.00)	30 (33.71)
Other	47 (7.34)[c]	16 (3.64)	1 (1.12)

Abbreviations: CSR = clinical study report

[a] Median is presented; mean and standard deviation were not reported.

[b] Subjects double-counted as another race.

[c] A total of 23 subjects who chose not to disclose race are included with 'other' race.

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Study Results

Primary Analysis by Responder Rate and 95% CI Lower Bound at 10 Minutes

As shown in **Table 7** below, in both pivotal studies, ZuraGard met the primary efficacy criteria of responder rate 95% CI lower bound ≥70% at 10 minutes on the abdomen and groin sites. In Study **ZX-ZP-0073**, at 10 minutes, the responder rate 95% CI lower bound for the abdominal region was 94.0% for ZuraGard and 94.3% for ChloraPrep. For the groin region, at 10 minutes, the responder rate 95% CI lower bound was 89.4% for ZuraGard and 87.5% for ChloraPrep. In Study **ZX-ZP-0074**, at 10 minutes, the responder rate 95% CI lower bound for the abdominal region was 76.2% for ZuraGard and 74.5% for ChloraPrep. For the groin region, at 10 minutes, the

responder rate 95% CI lower bound was 70.3% for ZuraGard and 67.5% for ChloraPrep. For both abdominal and groin regions in both studies, the responder rates of the test product ZuraGard and the active control ChloraPrep at 10 minutes were significantly higher than that of the vehicle control.

Table 7. Responder Rate at 10 Minutes (mITT population) – Studies ZX-ZP-0073 and ZX-ZP-0074

	Abdomen			Groin		
Study	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)
ZX-ZP-0074	11.8 (5.2, 21.9)	80.9 (76.2, 85.0)	79.4 (74.5, 83.7)	1.4 (0.0, 7.3)	75.2 (70.3, 79.7)	72.4 (67.5, 77.0)
ZX-ZP-0073	17.4 (9.3, 28.4)	96.5 (94.0, 98.2)	96.8 (94.3, 98.4)	16.2 (8.4, 27.1)	92.7 (89.4, 95.3)	91.1 (87.5, 94.0)

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Priimary Anal;ysis by Average Treatment Effect (Superiority and Noninferiority) at 10 Minutes

In both Study **ZX-ZP-0073** and Study **ZX-ZP-0074**, ZuraGard met the expected ATE criteria. The upper limit of the 95% confidence interval for the non-inferiority of ZuraGard vs. ChloraPrep was below 0.5, and the lower limit of the 95% confidence interval for the superiority of ZuraGard vs. its vehicle was above 1.2.

In Study **ZX-ZP-0073**, at 10 minutes, the ATE noninferiority point estimate of ZuraGard to ChloraPrep was 0.039 (95% CI: -0.18 to 0.10), and 0.021 (95% CI: 0.09 to 0.05) for the groin and abdominal sites, respectively. The ATE superiority point estimate of ZuraGard to its vehicle control was 2.595 (95% CI: 2.34 to 2.84), and 1.87 (95% CI: 1.74 to 1.99) for the groin and abdominal sites, respectively, as shown in **Table 8** below.

Table 8. Study ZX-ZP-0073 Analysis by Average Treatment Effect

Body Area	Treatments	30 Seconds		10 Minutes	
		ATE Difference	95% CI	ATE Difference	95% CI
Groin	Non-inferiority (ChloraPrep vs ZuraPrep)	-0.078	(-0.264 to 0.108)	-0.039	(-0.184 to 0.106)
	Superiority – ZuraPrep vs Vehicle	2.300	(1.983 to 2.618)	2.595	(2.347 to 2.843)
	Superiority – ChloraPrep vs Vehicle	2.222	(1.904 to 2.540)	2.556	(2.308 to 2.804)
Abdomen	Non-inferiority - ChloraPrep vs ZuraPrep	-0.111	(-0.238 to 0.016)	-0.021	(-0.096 to 0.054)
	Superiority – ZuraPrep vs Vehicle	1.892	(1.673 to 2.111)	1.870	(1.740 to 1.999)
	Superiority – ChloraPrep vs Vehicle	1.781	(1.562 to 2.000)	1.849	(1.719 to 1.979)
ATE = average treatment effect; CI = confidence interval.					

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In Study **ZX-ZP-0074**, at 10 minutes, the ATE noninferiority point estimate of ZuraGard to ChloraPrep was -0.020 (95% CI: -0.21 to 0.17), and -0.045 (95% CI: -0.20 to 0.11) for the groin and abdominal sites, respectively. The ATE superiority point estimate of ZuraGard to its vehicle control was 2.54 (95% CI: 2.1 to 2.77), and 1.97 (CI 1.69 to 2.24) on the groin and abdominal sites, respectively, as shown in **Table 9** below.

Table 9. Study ZX-ZP-0074 Analysis by Average Treatment Effect

Body Area	Treatments	30 Seconds		10 Minutes	
		ATE Difference	95% CI	ATE Difference	95% CI
Groin	Non-inferiority (ChloraPrep vs ZuraPrep)	-0.024	(-0.217 to 0.169)	-0.020	(-0.212 to 0.172)
	Superiority – ZuraPrep vs Vehicle	2.609	(2.283 to 2.934)	2.454	(2.129 to 2.778)
	Superiority – ChloraPrep vs Vehicle	2.584	(2.259 to 2.909)	2.434	(2.110 to 2.757)
Abdomen	Non-inferiority - ChloraPrep vs ZuraPrep	-0.023	(-0.196 to 0.150)	-0.045	(-0.208 to 0.117)
	Superiority – ZuraPrep vs Vehicle	2.048	(1.756 to 2.341)	1.972	(1.697 to 2.247)
	Superiority – ChloraPrep vs Vehicle	2.025	(1.733 to 2.318)	1.927	(1.651 to 2.202)
ATE = average treatment effect; CI = confidence interval.					

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Secondary Analyses by Responder Rate

Secondary analyses included responder rate at 30 seconds and 6 hours.

Secondary Analysis by Responder Rate and 95% CI Lower Bound at 30 Seconds

As shown in **Table 10** below, for the secondary endpoint at 30 seconds analysis, both ZuraGard and ChloraPrep met the responder rate of ≥70% on the abdominal site. However, on the groin site, ZuraGard was able to achieve 74.6% responder rate but ChloraPrep only achieved 68.1% responder rate. Dr. Kumar considered these results acceptable since both ZuraGard and ChloraPrep successfully met the primary efficacy goals (lower bound of a 95% CI for the responder rate ≥70% at 10 minutes in both the groin and the abdomen sites).

Table 10. Responder Rate at 30 Seconds (mITT population, Studies ZX-ZP-0073 and ZX-ZP-0074)

	Abdomen			Groin		
Study	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)
ZX-ZP-0074	4.4 (0.9, 12.4)	76.5 (71.5, 81.1)	76.3 (71.2, 80.8)	1.4 (0.0, 7.3)	70.8 (65.7, 75.6)	71.0 (66.0, 75.7)
ZX-ZP-0073	4.4 (0.9, 12.2)	84.2 (79.9, 87.9)	80.6 (76.0, 84.7)	2.9 (0.4, 10.2)	74.6 (69.5, 79.2)	68.1 (62.7, 73.1)

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Secondary Analysis by Responder Rate and 95% CI Lower Bound at 6 Hours

The lower bound of the 95% CI for the 6-hour responder rate exceeded 70% for the abdomen and groin in all treatment groups at 6 hours post application. However, the Sponsor was only able to demonstrate persistent antimicrobial activity for ZuraPrep 10.5 mL, defined in the 2017 Final Rule as responder rate of 100% at 6 hours, in the groin region for both studies. In the abdomen region, the responder rate at 6 hours was 99.4% and 99.1% in Study **ZX-ZP-0073** and Study **ZX-ZP-0074**, respectively, as shown in **Table 11** below.

Table 11. Resoponder Rate with 95% CI at 6 Hours Post-Application

Study	Abdomen			Groin		
	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)
ZX-ZP-0074	N = 324	N = 320	N = 68	N = 343	N = 352	N = 74
	86.8 (76.4, 93.8)	99.1 (97.3, 99.8)	99.1 (97.3, 99.8)	100.0 (96.0, 100.0)	100.0 (99.1, 100.0)	99.4 (98.0, 99.9)
ZX-ZP-0073	N = 342	N = 340	N = 69	N = 330	N = 326	N = 68
	97.1 (89.9, 99.7)	99.4 (97.9, 99.9)	100.0 (98.9, 100.0)	100.0 (94.7, 100.0)	100.0 (98.9, 100.0)	100.0 (98.9, 100.0)
Abbreviations: CI = confidence interval;						

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Additional Secondary Analysis

All efficacy objectives were met with respect to ATE at 30 seconds in both studies.

Regarding mean log_{10} reduction, both ZuraGard and ChloraPrep met the secondary efficacy criteria at 10 minutes and 30 seconds (≥2 log_{10} reduction on abdomen and ≥3 log_{10} reduction on the groin from baseline in both studies. For both ZuraGard and ChloraPrep at both the abdominal and groin sites in both studies, the log reductions at the 6 hour timepoint were similar to the log reductions achieved at 30 seconds, which were lower than baseline mean log_{10} CFU/cm^2 values. Therefore, both ZuraGard and ChloraPrep did not exceed baseline counts at 6 hours, as shown in **Table 12** and **Table 13** below.

Table 12. Mean Log_{10} CFU/cm^2 values with Standard Deviation (SD) – Study ZX-ZP-0073

Body Area		N	Baseline		30 Seconds		10 Minutes		6 Hours	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Abdomen	ChloraPrep	340	3.43	0.50	0.53	0.92	0.08	0.52	1.00	0.96
	Vehicle	69	3.37	0.50	2.30	0.67	1.91	0.67	2.19	0.69
	ZuraPrep	342	3.42	0.52	0.42	0.83	0.05	0.48	0.97	0.91
Groin	ChloraPrep	326	5.40	0.45	1.57	1.29	0.62	1.01	2.41	0.98
	Vehicle	68	5.36	0.37	3.77	0.71	3.15	0.83	3.34	0.93
	Zuraprep	330	5.43	0.48	1.51	1.27	0.59	0.98	2.43	0.99

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Table 13. Mean Log_{10} CFU/cm^2 values with Standard Deviation (SD) – Study ZX-ZP-0074

Body Area		N	Baseline		30 Seconds		10 Minutes		6 Hours	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Abdomen	ChloraPrep	320	3.63	0.49	0.90	1.23	0.72	1.09	0.68	0.98
	Vehicle	68	3.66	0.55	2.95	0.82	2.66	0.98	2.28	1.16
	ZuraPrep	324	3.69	0.48	0.92	1.19	0.70	1.09	0.66	0.96
Groin	ChloraPrep	352	5.85	0.50	2.06	1.38	1.84	1.38	2.04	1.28
	Vehicle	74	5.89	0.49	4.66	0.67	4.29	0.57	3.79	0.76
	Zuraprep	343	5.87	0.50	2.04	1.33	1.83	1.32	1.90	1.28

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Study ZX-P-0083 ((b) (4) 865-106): Evaluation of the Skin Area Covered and Dry Time of a Preoperative Skin Preparation
This study was intended to establish the observed drying time and skin coverage for the ZuraGard 10.5 mL applicator. Twenty applicators were used on 20 subjects. The investigational product was applied topically using back and forth strokes of the sponge for 30 seconds over the treatment area (8.1" x 8.4" of the subject's back) and the skin was allowed to dry. The containers were weighed before and after the procedure to determine the volume used. The drying time was independently observed by three technnicians.

The average amount of product used was 2.58 grams, and the average drying time was 100.2 seconds (range: 77-136 seconds), as shown in **Table 14** below.

Table 14. Summary of Dry Time and Coverage per Dose

	Coverage Area Dose (g/cm^2)	Dry Time (sec)	Dose (g)	Coverage per Dose (cm^2/g)
Mean	0.00567	100.2	2.58	178
Median	0.00584	102.7	2.66	171
Min	0.00474	77.0	2.16	161
Max	0.00622	136.0	2.83	211

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Thus, for the ZuraGard 10.5 mL applicator, the coverage area is 2.58 g/0.00567 g/cm^2 = 455 cm^2. The average coverage in square inches is 70.52 in^2. Dr. Kumar observed that the labeling for ZuraGard 10.5 mL applicator specifies that the coverage area is 8.4" x 8.4" or 457 cm^2. In addition, the labeling states, "discard the applicator after a single use along with any portion of the solution not required to cover the prepped area. It is not necessary to use the entire amount available." Dr. Kumar concluded that "the defined coverage area for ZuraGard 10.5 mL applicator is acceptable."

CDTL Comments: In summary, in two pivotal trials, the efficacy of ZuraGard 10.5 mL for the preoperative skin indication was adequately demonstrated, as evidenced by responder rates greater than 70% at 10 minutes for both body regions; statistical superiority to the vehicle and non-inferiority to ChloraPrep at 10 minutes and 30 seconds for both body regions based on average treatment effects; and persistent antimicrobial properties in the groin region at 6 hours. All primary endpoints were met, and although it is noted that both studies failed to demonstrate persistent antimicrobial properties, defined in the 2017 Final Rule as responder rate of 100% at 6 hours, in the abdomen, this was a secondary endpoint, and the actual responder rates were close, that is, 99.4% and

*99.1% in Study **ZX-ZP-0073** and Study **ZX-ZP-0074**, respectively. Furthermore, for both ZuraGard and ChloraPrep at both the abdominal and groin sites in both studies, the log reductions at the 6 hour timepoint were similar to the log reductions achieved at 30 seconds, which were lower than baseline mean log_{10} CFU/cm^2 values, demonstrating that both ZuraGard and ChloraPrep did not exceed baseline counts at 6 hours. Therefore, based on the totality of the data, the efficacy of ZuraGard for the proposed indication has been demonstrated and is acceptable for approval.*

8. Safety

Division of Nonprescription Drug Products (DNDP)

General safety review was conducted by Edwin H. Chin, MD, MPH, Medical Officer, DNDP. Dr. Chin's review focused on the safety data from the following studies:

- Pivotal efficacy and safety studies (**ZX-ZP-0073** and **ZX-ZP-0074**)
- Pilot efficacy and safety studies (**ZX-ZP-0035**, **ZX-ZP-0055**, and **ZX-ZP-0068**)
- Phototoxicity study (**ZX-ZP-0016**)
- Cumulative irritation study (Study **ZX-ZP-0017**)
- Contact sensitization study (Study **ZX-ZP-0018**)
- Photosensitization study (**ZX-ZP-0019**)
- Skin area covered and dry time study (**ZX-ZP-0083**)

Note that the phototoxicity, cumulative irritation, and contact sensitization studies were also reviewed by the Division of Dermatology and Dental Products (DDDP) and will be discussed in detail in the DDDP section below.

In the submitted studies, 1500 subjects were exposed to the ZuraPrep product (applied at least once). In addition, 1369 subjects were exposed to the reference product (ChloraPrep), 660 were exposed to the ZuraPrep Vehicle (ZuraPrep without IPA), 312 were exposed to Normal Saline, and 40 were exposed to sodium lauryl sulfate. Dr. Chin concluded that overall, "a sufficient number of subjects were used in the studies to generate data to support the safety of ZuraPrep," and I agree. Exposure periods for the cumulative irritation, contact sensitization, and phototoxicity studies were up to 21 days. In the contact sensitization study, application of test product was 3 times weekly for 3 weeks, followed by a 14-day Rest Period, then applied again for a 48-hour challenge phase. In the photosensitization study, test product was applied to test sites and exposed to irradiation approximately 24 hours later, then applied

twice weekly over a 3-week Induction Phase, followed by a 13 to 17-day Rest Period, and applied again to test sites for a 24-hour Challenge Phase.

The demographic distribution of subjects is outlined in **Table 15** below. Subjects ranged in age from 18 to 85 years, were predominantly Caucasian in 8 of the 10 studies and primarily Asian in the remaining 2 studies. Dr. Chin concluded that "the study population appears to have been sufficiently large and diverse to represent the expected target population," and "the pivotal studies' methods met the criteria for maximal human exposure outlined in the TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 1994, pp. 31450-31452)." I agree.

Table 15. Demographic Characteristics of Subjects Across ZuraPrep Program

	Studies									
	ZX-ZP-0016	ZX-ZP-0017	ZX-ZP-0018	ZX-ZP-0019	ZX-ZP-0035	ZX-ZP-0055	ZX-ZP-0068	ZX-ZP-0073	ZX-ZP-0074	ZX-ZP-0083
	(N=34)	(N=40)	(N=225)	(N=55)	(N=64)	(N=36)	(N=89)	(N=440)	(N=640)	(N=20)
Age (Years)										
Mean (SD)	53.1 (10.99)	49[a]	35[a]	50.1 (14.03)	24[a]	35.7 (14.73)	38.9 (14.31)	38.4 (15.32)	30[a]	35.4 (16.55)
Range	24, 75	19, 67	18, 82	18, 74	18, 74	20, 67	19, 75	18, 80	18, 85	20, 77
Sex, n (%)										
Male	6 (17.6)	8 (20.0)	85 (37.8)	11 (20.0)	47 (73.4)	20 (55.6)	57 (64.0)	250 (56.8)	476 (74.4)	20 (100)
Female	28 (82.4)	32 (80.0)	140 (62.2)	44 (80.0)	17 (26.6)	16 (44.4)	32 (36.0)	190 (43.2)	164 (25.6)	0
Race, n (%)										
Asian	2 (5.9)	0	7 (3.1)	0	2 (3.1)	10 (27.8)	39 (43.8)	119 (27.1)	8 (1.3)	9 (45.0)
Black	0	0	4 (1.8)	0	1 (1.6)	2 (5.6)	12 (13.5)	84 (19.1)	9 (1.4)	1 (5.0)
Caucasian	32 (94.1)	39 (97.5)	204 (90.7)	55 (100)	52 (81.3)	20 (55.6)	30 (33.7)	176 (40.0)	576 (90.0)	8 (40.0)
Other or not provided[b]	0	1 (2.5)	10 (4.4)	0	9 (14.2)	4 (11.1)	8 (9.0)	61 (13.9)	47 (7.3)	2 (10.0)
Ethnicity, n (%)										
Not Hispanic/ Latino	34 (100)	39[b] (97.5)	219[b] (97.3)	45 (81.8)	58[b] (90.6)	34[b] (94.4)	82[b] (92.1)	395[b] (89.8)	581 (90.8)	19[b] (95.0)

Abbreviations: SD = standard deviation

[a] Median age.

[b] Ethnicity was captured as race in Study ZX-ZP-0017, Study ZX-ZP-0018, Study ZX-ZP-0035, Study ZX-ZP-0055, Study ZX-ZP-0068, Study ZX-ZP-0073, and Study ZX-ZP-0083 and is included with "Other".

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Due to the within-subject comparison study designs employed in the ZuraPrep clinical program, most treatment-emergent adverse events (TEAEs) were not attributed to a specific test product. These TEAEs were included for each test product applied to the subject

during the study. For TEAEs attributed to a particular test site, the events are counted only for the test product applied at that site. Therefore, the discussion of TEAEs focuses on ZuraPrep, unless the event was attributed to a specific product.

Across the ZuraPrep clinical program, the percentage of subjects with at least 1 treatment-emergent AE was 1.9% for ZuraPrep. Most AEs were reported in the cumulative irritation, contact sensitization, and photosensitization studies, where the exposure periods were at least 21 days (28 of 35 events for ZuraPrep; 80%). No adverse events were reported in Study **ZX-ZP-0016**, Study **ZX-ZP-0055**, Study **ZX-ZP-0068**, Study **ZX-ZP-0073**, or Study **ZX-ZP-0083**. The incidences of specific terms were all <1.0% for ZuraPrep, as shown in **Table 16** below.

Table 16. Treatment-emergent Adverse Events Across the ZuraPrep Clinical Program

Adverse Event Verbatim Term, n (%)	ZuraPrep (N=1500)	ChloraPrep (N=1369)	ZuraPrep Vehicle (N=660)	Normal Saline (N=312)	Sodium Lauryl Sulfate (N=40)
At least 1 adverse event	28 (1.9)	23 (1.7)	21 (3.2)	19 (6.1)	4 (10.0)
Sniffly/Nasal discharge/Stuffy nose/Stuffy, runny nose	4 (0.3)	4 (0.3)	4 (0.6)	4 (1.3)	1 (2.5)
Rash	3 (0.2)	3 (0.2)	1 (0.2)	1 (0.3)	0
Cut	2 (0.1)	0	0	0	0
Nausea/Upset stomach	2 (0.1)	2 (0.1)	2 (0.3)	2 (0.6)	1 (2.5)
Stomach flu/Flu-like illness	2 (0.1)	2 (0.1)	2 (0.3)	2 (0.6)	0
Appendicitis	1 (0.1)	0	1 (0.2)	0	0
Back pain	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Broken leg	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Broken toe	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Contact dermatitis	1 (0.1)	1 (0.1)	0	0	0
Diarrhea	1 (0.1)	0	1 (0.2)	0	0
Fatigue	1 (0.1)	1 (0.1)	0	0	0
Fever	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Folliculitis	1 (0.1)	1 (0.1)	0	0	0
Headache	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Hip pain	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Illness, cold	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Irritation	1 (0.1)	1 (0.1)	0	0	0
Itching/Itchy eyes and back	1 (0.1)	2 (0.1)	1 (0.2)	2 (0.6)	0
Lightheaded	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	1 (2.5)
Neck pain	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Scratch	1 (0.1)	0	0	0	0
Shaky	1 (0.1)	1 (0.1)	1 (0.2)	0	0
Shoulder muscle strain	1 (0.1)	0	1 (0.2)	0	0
Sneezing	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Sore throat	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	1 (2.5)
Tonsillitis	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	1 (2.5)
Burning	0	0	0	1 (0.3)	0

Note: Due to the within-subject comparison study designs employed in the ZuraPrep clinical program, treatment-emergent adverse events were included for each test product applied during the study, except for specific treatment-emergent adverse events identified for a particular test site, which are included only for the test product applied at that site.

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Most of the treatment-emergent adverse events were considered by the investigator to be mild in intensity. Four subjects had treatment-emergent adverse events that were considered moderate or severe in intensity including moderate flu-like illness (Study **ZX-ZP-0018** Subject (b) (6), moderate diarrhea (Study **ZX-ZP-0019** Subject (b) (6)), severe appendicitis (Study **ZX-ZP-0019** Subject (b) (6)), and severe shoulder strain (Study **ZX-ZP-0019** Subject (b) (6)). An additional subject (Study **ZX-ZP-0018** Subject (b) (6) had a serious treatmen-emergent adverse event of a broken leg that did not have intensity indicated on the adverse event form. Each of these events was considered unrelated to test products. There were no deaths inany of the clinical trials.

Six subjects had TEAEs that were considered by the investigator to have possible, probable, or definite relationship to test products. These AEs were associated with test product application sites and included 2 subjects with rash, 2 subjects with itching, 1 subject with cut, and 1 subject with irritation, folliculitis, and contact dermatitis. However, as noted above, due to the within-subject comparison designs in some of the studies, it was often not possible to attribute the TEAE to a specific product, as illustrated in the following narratives of the six subjects:

- Study **ZX-ZP-0018** Subject (b) (6): 51 year old Caucasian female developed itching at the Normal Saline and ChloraPrep sites on Day 10 and burning at the Normal Saline site of Day 12. The events were considered mild, possible related to test products, and were noted as resolved.
- Study **ZX-ZP-0018** Subject (b) (6): 50-year-old Caucasian male who was instructed on the last day of the Challenge Phase (Day 41) to return for safety evaluation due to an irritation score of 3 at the ChloraPrep site. The subject was out of town for a month and upon returning had irritation scores of 5 on the ZuraPrep and ChloraPrep sites. The subject was referred for evaluation and was diagnosed with contact dermatitis and folliculitis which resolved with doxycycline and fluocinonide cream. The events were considered mild and definitely related to test products.
- Study **ZX-ZP-0018** Subject (b) (6): 72-year-old Caucasian female who developed itchy back and itchy eyes on Day 3 (subject was exposed to ZuraPrep, ChloraPrep, ZuraPrep Vehicle, and Normal Saline). The event was considered mild, possibly related to test products, and was noted as resolved.
- Study **ZX-ZP-0035** Subject (b) (6): 48-year-old Hispanic female who, following the 12-hour sampling at the left groin site, was noted to have a cut measuring approximately 3 mm in length adjacent to the adhesive bandage between sampling sites. The event was considered mild, possibly related to test products, and was noted as resolved.
- Study **ZX-ZP-0074** Subject (b) (6): 22-year-old Caucasian female who developed a rash at all ZuraPrep and ChloraPrep test sites 2 days after dosing. The event was considered mild, definitely related to test products, and was noted as resolved.
- Study **ZX-ZP-0074** Subject (b) (6): 31-year-old Caucasian male who developed a rash at ZuraPrep and ChloraPrep test sites on the abdomen 2 days after dosing. The event was considered mild, probably related to test products, and was noted as resolved.

All of the efficacy studies (Studies **ZX-ZP-0035**, **ZX-ZP-0055**, **ZX-ZP-0068**, **ZX-ZP-0073**, and **ZX-ZP-0074**) had an exposure period of 24 hours or less and test products were used per intended application. Across the efficacy studies, the percentages of subjects with at least 1 treatment-emergent adverse event was <1% across all test products.

All of the specific verbatim terms reported in the efficacy studies were considered mild in intensity. A total of 3 subjects, described above, had TEAEs that were considered related to test products including 2 events of rash (Study **ZX-ZP-0074** Subject (b) (6), and Subject (b) (6)) and 1 event of cut (Study **ZX-ZP-0074** Subject (b) (6)).

Table 17. TEAEs in ZuraPrep Studies Where Test Products Were used Per Intended Application

Adverse Event Verbatim Term, n (%)	ZuraPrep (N=1126)	ChloraPrep (N=1104)	ZuraPrep Vehicle (N=306)	Normal Saline (N=47)
At least 1 adverse event	7 (0.6)	4 (0.4)	1 (0.3)	0
Cut	2 (0.2)	0	0	0
Rash	2 (0.2)	2 (0.2)	0	0
Scratch	1 (0.1)	0	0	0
Fatigue	1 (0.1)	1 (0.1)	0	0
Shaky	1 (0.1)	1 (0.1)	1 (0.3)	0

Note: Due to the within-subject comparison study designs employed in the ZuraPrep clinical program, treatment-emergent adverse events were included for each test product applied during the study, except for specific treatment-emergent adverse events identified for a particular test site, which are included only for the test product applied at that site.
Electronically copied and reproduced from Sponsor's submission: ISS, page 29, Table 6.

Dr, Chin observed that that the pivotal safety and efficacy study **ZX-ZP-0073** and the pilot study **ZX-ZP-0055**, both of which were conducted by the same primary investigator (MicroBioTest) in Sterling Virginia, were notable for the absence of AEs and skin irritation in the safety population. In contrast, Study **ZX-ZP-0074**, which was conducted at Bioscience Laboratories in Bozeman, Montana, reported 7 AEs in its safety population, with irritation scores showing only erythema for ZuraPrep, ChloraPrep, and Vehicle at 30 seconds, 10 minutes, and 6 hours for both the abdominal and groin sites, as shown in **Table 18** and **Table 19** below.

Table 18. Skin Irritation Scores for Groin Sites – Study ZX-ZP-0074

Erythema	ZuraPrep™	ChloraPrep®	Vehicle
Baseline			
0 – No Reaction	441 (100.%)	441 (100.%)	441 (100.%)
1 – Mild/transient redness	0	0	0
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0
30 seconds			
0 – No Reaction	214 (48.53%)	147 (33.33%)	24 (27.27%)
1 – Mild/transient redness	220 (49.89%)	287 (65.08%)	60 (68.18%)
2 – Moderate redness	7 (1.59%)	7 (1.59%)	4 (4.55%)
3 – Severe redness	0	0	0
10 minutes			
0 – No Reaction	374 (84.81%)	317 (71.88%)	65 (73.86%)
1 – Mild/transient redness	67 (15.19%)	123 (27.89%)	23 (26.14%)
2 – Moderate redness	0	1 (0.23%)	0
3 – Severe redness	0	0	0
6 hours			
0 – No Reaction	429 (97.28%)	430 (97.51%)	85 (96.59%)
1 – Mild/transient redness	12 (2.72%)	11 (2.49%)	3 (3.41%)
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0

Electronically copied and reproduced from Dr. Chin's Review (adapted from Table 23 ZX-ZP-0074 Study Report, page 71.

Table 19. Skin Irritation Scores for Abdomen Sites – Study ZX-ZP-0074

Erythema	ZuraPrep™	ChloraPrep®	Vehicle
Baseline			
0 – No Reaction	519 (100.0%)	520 (100.0%)	104 (100.0%)
1 – Mild/transient redness	0	0	0
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0
30 seconds			
0 – No Reaction	373 (71.87%)	301 (57.88%)	58 (56.31%)
1 – Mild/transient redness	143 (27.55%)	218 (41.92%)	45 (43.69%)
2 – Moderate redness	3 (0.58%)	1 (0.19%)	0
3 – Severe redness	0	0	0
10 minutes			
0 – No Reaction	458 (88.25%)	434 (83.46%)	88 (85.44%)
1 – Mild/transient redness	61 (11.75%)	86 (16.54%)	15 (14.56%)
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0

6 hours 0 – No Reaction 1 – Mild/transient redness 2 – Moderate redness 3 – Severe redness	 504 (97.30%) 13 (2.51%) 1 (0.19%) 0	 498 (95.95%) 20 (3.85%) 1 (0.19%) 0	 99 (96.12%) 4 (3.88%) 0 0

Electronically copied and reproduced from Dr. Chin's Review (adapted from Table 24 ZX-ZP-0074 Study Report, page 73).

Clinical laboratory testing, routine vital signs, and eclectrocardiographic monitoring were not performed in the clinical studies. For the topical test products utilized in these studies, this was a reasonable approach.

CDTL Comments: It is unclear why there were no AEs reported at the two MicroBiotest sites, in contrast to BioScience site. However, overall, the total number of AEs across all studies is low and consistent with the known safety profile of similar preoperative antiseptic products. Furthermore, as described below, the dermal studies and postmarketing safety evaluation are also consistent with the safety results from the clinical trials.

Postmarketing Safety Evaluation

The Sponsor submitted postmarketing data for other products containing IPA. Databases included FAERS, World Health Organization Uppsala Monitoring Center VigiBase, and the National Poison Data System (NPDS). The NPDS showed that for 2016, 80% of human exposure cases were associated with ingestion of IPA products. The Sponsor also submitted case reports from the medical literature of dermal toxicity following dermal exposure. Dr. Chin reviewed the submitted postmarketing data and concluded that the data "did not reveal any concerning safety signals as most databases showed most events were skin related events that might be expected with use." Furthermore, Dr. Chin reported that the case reports from the medical literature "did not demonstrate safety signals readily applicable to ZuraPrep when used as intended."

*CDTL Comments: The case reports described adverse events, primarily neurologic, related to use of IPA or other alcohol products as baths, soaks, and rubdowns. Some of the cases involved rubdowns occurring over several days, and some of the soaks involved wrapping areas of the body with alcohol soaked towels for several hours. Under these circumstances, it is anticipated that absorption of IPA and other alcohol products would be significantly enhanced. As described in **Section 5** above, the Clinical Pharmacology team pointed out that it is unlikely that ZuraGard used as preoperative skin preparation could cause a significant systemic exposure to IPA. Therefore, I agree with Dr. Chin's conclusion that the risk of any of neurologic adverse events with use of ZuraPrep as intended and labeled is nearly nonexistent.*

Division of Dermatology and Dental Products (DDDP)

A review of the submitted phototoxicity and dermal sensitivity studies was conducted by Melissa Reyes, MD, MPH, DTMH, Medical Officer, DDDP.[25] Dr. Reyes concluded, "based on the results of the 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." She further concluded that, based on the results, "it is reasonable to conclude that ZuraPrep does not have the potential for phototoxicity or photoallergenicicty."

The following studies were submitted by the Sponsor and reviewed by Dr. Reyes. For details of study design, please see Dr. Reyes' Review:

- Study ZX-ZP-0016 (phototoxicity): a 4-day, single-center, controlled, within-subject comparison study of ZuraPrep and ZuraPrep vehicle under occlusive patch conditions to determine the irritation potential of ZuraPrep and ZuraPrep vehicle when topical application to the skin is followed by light exposure. An untreated patch served as negative control. All subjects had 9 application sites (6 irradiated and 3 non-irradiated) on the back designated for test sample application and irradiation. ZuraPrep, ZuraPrep vehicle, and a blank patch (untreated) were applied in 3 sets to the application sites. After 24 hours, 2 of the 3 sets were irradiated. All sites were examined for dermal reactions at 24 and 48 hours post irradiation (see **Table 20** below. A total of 34 subjects had test products applied and completed the study.

Table 20. Study ZX-ZP-0016: 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

Electronically copied and reproduced from Sponsor's submission: ZX-ZP-0016 Study Report; Table 9-3, page 21.

[25] DDDP Consult #1946; NDA 210872; September 20, 2018.

In this study, irradiation was associated with dermal response with no statistically significant differences between irradiated ZuraPrep, irradiated vehicle, and irritated control sites. Non-irradiated ZuraPrep sites had statistically significantly greater dermal irritation compared to non-irradiated vehicle and control sites. These results indicate that neither ZuraPrep or ZuraPrep vehicle is phototoxic. Dr. Reyes concluded that "it is reasonable to conclude that the ZuraPrep does not have the potential for phototoxicity."

- Study ZX-ZP-0017 (cumulative irritation): a single-center, 21-day, controlled, randomized, within-subject comparison study of ZuraPrep, ZuraPrep vehicle, ChloraPrep (reference product), 0.1% Sodium Laurel Sulfate (positive control), and 0.9% Physiological Saline (negative control) under occlusive patch conditions in healthy adult volunteers. Each of the products were randomly assigned to 1 of the 5 patch application sites on the back of each subject. Individual products were applied daily to its assigned site for 21 consecutive days. The patches remained in place for approximately 23 hours, after which they were removed, and the sites were evaluated and scored for irritancy within 10 minutes of removal (see **Table 21** below). Failure of a site having an irritation score of ≥3 to show inmprovement within a 48 hour period would have been considered an AE, but did not occur. Forty subjects were treated with test products and 34 completed testing.

Table 21. 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 site discontinued
†Adverse Event; subject discontinued from testing.
Electronically copied and reproduced from Sponsor's submission: Final Study Report 130820-302, Protocol ZX-ZP-0017, Table 1, page 20.

In this study, the mean irritation score of exposed sites to ZuraPrep was greater than the ZuraPrep vehicle and positive control, but less than sites exposed to ChloraPrep after 21 days of exposure. The total cumulative irritation scores after 21 days of repeated application of test products were 1653 for ZuraPrep, 1461 for the ZuraPrep vehicle, and 1846 for ChloraPrep. Total cumulative irritation scores for Sodium Lauryl Sulfate and Physiological Saline were 1125 and 312, respectively. Dr. Reyes concluded that, overall, "ZuraPrep was shown to have irritation potential under the study's provocative conditions."

- Study ZX-ZP-0018 (contact sensitization): a clinical evaluation to determine the allergic contact sensitizing potential of topically applied ZuraPrep and ZuraPrep vehicle after repetitive patch applications to the skin of healthy adult male and female volunteers in a single-center, double-blind, randomized, controlled, within-subject comparison design. ChloraPrep and 0.9% Physiological Saline were employed as reference product and negative control, respectively. Each of the products was assigned randomly to 1 of 4 patch application sites on the back of each subject. The study consisted of the standard 3 phases: an Induction Phase, a Rest Phase, and a Challenge Phase. In the Induction Phase, each test product was reapplied to its assigned skin site 3 times weekly for 3 weeks. The patches remained in place for 48 hours on weekdays and 72 hours on weekends. Skin sites were evaluated following each patch and scored for irritancy (same scale as used in Study **ZX-ZP-0017**; see **Table 21** above). This was followed by the Rest Phase, during which no treatment was performed. The Challenge Phase began on the day following the Rest Phase. Test product patches were applied to respective assigned sites on each subject's back opposite the side which was exposed to test product materials during the Induction Phase. After 48-hour exposure, patches were removed and the sites were scored for skin irritiaion at 30 minutes, 24, 48, and 72 hours following removal. Two hundred twenty-five subjects were treated with test products, and 208 completed all phases of testing.

  In this study, of the 208 subjects who completed testing, 1 subject displayed sensitizing characteristics related to ZuraPrep and ChloraPrep. Additionally, 1 subject showed a potential sensitivity to ChloraPrep, although the Sponsor noted that irritation was also a likely possibility for this case. Seven subjects displayed more mild signs of possible sensitization escalating in irritation scores of 2 to 3 at 72 hours (2 related to ZuraPrep, 3 related to ChloraPrep, and 2 related to 0.9% Physiological Saline). These data indicate that ZuraPrep and ChloraPrep have some minimal, yet similar, sensitizing potential. ZuraPrep vehicle showed no signs of sensitization. Dr Reyes concluded that "the study results indicate that ZuraPrep has the potential for contact sensitization."

- Study ZX-ZP-0019 (photosensitization): a 6-week, single-center, controlled, randomized, within-subject comparison study of ZuraPrep and ZuraPrep vehicle under occlusive patch conditions to determine the ability of ZuraPrep and ZuraPrep vehicle to induce a photoallergic skin reaction using a controlled photopatch testing procedure. A total of 6 application sites (2 cm x 2 cm each) were marked on one side of the subject's back and test products were applied in 2 sets (2 untreated blank patches) to the application sites. After 24 hours, the designated sites were exposed to irradiation, which was performed twice weekly over the

3-week Induction Phase. After the Induction Phase, the subjects entered a Rest Phase of 13-17 days, followed by the Challenge Phase. During the Challenge Phase, a total of 9 application sites (2 cm x 2 cm each) applied test products or intreated (blank) patch in 3 sets. After 24 hours, 2 sets were irradiated and third set remained non-irradiated. All sites were examined for dermal reactions (same scale as in Study **ZX-ZP-0016**; see **Table 20** above) at approximately 24, 48, and 72 hours post irradiation. A total of 55 subjects had test products and 49 completed the study.

During the Induction Phase, there was statistically significantly more irritation at the irradiated ZuraPrep sites than at the irradiated vehicle and untreated sites ($p<0.0001$), likely attributable to the presence of the active ingredient, IPA. There were no statistically significant differences in irritation between the vehicle and untreated sites.

During the Challenge Phase, the maximum response observed among the subjects was Grade 1 irritation, which was noted at some irradiated sites for each of the 3 treatments. Grade 1 irritation was noted at some non-irradiated ZuraPrep sites; no irritation was noted at any non-irradiated vehicle or untreated sites.

Based on the results of the study, there was no evidence of photosensitization to ZuraPrep or the vehicle for ZuraPrep. Dr. Reyes concluded that, "it is reasonable to conclude that ZuraPrep does not have the potential for photoallergenicity."

CDTL Comments: In summary, based on the results of the dermal safety studies submitted by the Sponsor, I agree with Dr. Reyes that ZuraPrep isopropyl alcohol 70% solution has the potential for irritation and sensitization, and does not have the potential for phototoxicity or photoallergenicicty.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application as it is not a new class switch and does not raise significant public health issues.

10. Pediatrics

As this application does not include a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration, PREA is not triggered. The product will include labeling to use with caution in children younger than 2 months due to risk of skin irritation and chemical burns.

11. Other Relevant Regulatory Issues

N/A.

12. Labeling

Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Review

Proprietary name review was conducted by the DMEPA Team (Grace P. Jones, PharmD, BCPS, Safety Evaluator; Sevan Kolejian, PharmD, MBA, Acting Team Leader; and Danielle Harris, PharmD, BCPS, Deputy Director)[26]. In the NDA submission, the Sponsor proposed the name, (b) (4) (b) (4) (b) (4) The DMEPA team concluded that the proposed proprietary name, (b) (4), was unacceptable.

The DMEPA team conducted name simulation studies in which 56 practitioners participated and found that the responses did not overlap with any currently marketed products. (b) (4) and communicated these findings to DNDP via email on September 20, 2018.

The DNDP team concurred with the DMEPA conclusion. (b) (4)

[26] NDA 210872 Proprietary Name Review, Division of Medication Error Prevention and Analysis (DMEPA), September 25, 2018.

(b) (4) In conclusion, DMEPA wrote, (b) (4)

Therefore, a Proprietary Name Request Unacceptable letter dated September 28, 2018 was sent to the Sponsor. On December 6, 2018, the Sponsor submitted a New Request for Proprietary Name Review, presenting ZuraGard Solution (Isopropyl Alcohol 70%) as the proposed proprietary name. The DNDP team again conducted name simulation studies in which 10 practitioners participated and found no overlap with any currently marketed products. Furthermore, the responses did not sound or look similar to any currently marketed products. The POCA search identified 108 names with a combined phonetic and orthographic score ≥55% or an indivisual phonetic score ≥70%. The DMEPA team reviewed the 108 names and determined that none of the names will pose a risk for confusion with ZuraGard. DNDP concurred and had no concerns with the proposed proprietary name, ZuraGard. Thus, DMEPA concluded that the proposed proprietary name, ZuraGard, was acceptable.

DMEPA had the following comments which were subsequently conveyed to the Sponsor:

We have completed our review of the proposed proprietary name, ZuraGard, and have concluded that this name is acceptable.

In addition, we have the following comments related to your product:

> *In your Request for Proprietary Name Review, you state that the derivation of your proposed proprietary name, ZuraGard, is associated with the manufacturer's name, Zurex Pharma, Inc. We understand that the proposed isopropyl alcohol product is your first NDA submission* (b) (4)
>
> > *Proprietary names should not incorporate the sponsor's name across multiple products (e.g., ABCName1, ABCName2, ABCName3, etc.). This practice can result in creating multiple similar proprietary names, which might increase the risk of confusion among the products. The practice can be problematic when products are stored alphabetically in distributor or pharmacy locations or when products are ordered from alphabetized lists. For more information, please see the Draft Guidance for Industry: Best Practices in Developing Proprietary Names for Drugs (2014) available at: https://www.fda.gov/downloads/drugs/guidances/ucm398997.pdf*

If any of the proposed product characteristics as stated in your submission, received on December 6, 2018, are altered prior to approval of the marketing application, the name must be resubmitted for review.

Division of Medication Error Prevention and Analysis (DMEPA) Human Factors, Label, and Labeling Review

The DMEPA team (Grace P. Jones, PharmD, BCPS; and and Chi-Ming (Alice) Tu, PharmD, BCPS) also conducted a human factors and labeling review. The DMEPA team reviewed the proposed container labels and carton labeling and noted 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 as the DFL.

The DMEPA team observed that the proposed product would be used in hospital surgical room environments by healthcare professionals, 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. DMEPA noted that, "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."[27]

DMEPA identified some medication error issues with the submitted container labels and carton labeling, which, along with DMEPA's rationale for concern and proposed recommendation to minimize the medication error, are shown in **Table 22** and **Table 23** below:

Table 22. 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.

Electronically copied and reproduced from DMEPA Review; Table 2, page 3.

[27] NDA 210872 DMEPA Human Factors, Label, and Labeling Review; 18 March 2019.

Table 23. 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.

Electronically copied and reproduced from DMEPA Review; Table 3, page 3.

In conclusion, the DMEPA team wrote, "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 [**22** above] and 3 [**23** above] 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." The DMEPA comments were subsequently convetyed to the Sponsor.

Interdisciplinary Science (IDS) Labeling Team Review

IDS labeling review was conducted by Hana Mujahid, PhD (Team Leader: Francisco Martinez-Murillo, PhD), DNDP. On 15 February 2019, the Sponsor submitted draft labeling and font and format specifications with the proposed proprietary name "ZuraGard" for the 10.5 mL applicator, (b) (4) (secondary packaging), outer carton, and package insert. In response to FDA's information requests dated 13 March 2019 and 21 March 2019, the Sponsor submitted revised labeling and font and format specifications on 27 March 2019 which addressed the outstanding labeling requests. Dr. Mujahid reviewed both the original (15 February 2019) and revised (27 March

2019) submitted labeling for the 10.5 mL applicator, 10.5 mL applicator secondary packaging (applicator (b) (4)), 10.5 mL applicator 25-count outer carton, and 10.5 mL applicator package insert for 25-count outer carton.

The majority of FDA requested revisions described in the Information Requests of 13 March 2019 and 21 March 2019 related to regulatory requirements related to font and formatting issues. Revisions were also requested to ensure consistency between outside drug facts for the outer container and the principal display panel.

In addition, revisions were requested to ensure that labeling is consistent with class labeling for topical antiseptic drug products indicated for patient preoperative skin preparation. On 14 November 2013, FDA sent a CBE supplement letter to sponsors requesting class labeling preperative skin preparation antiseptic products to help reduce the risk of contamination and subsequent infections. The class labeling changes requested at that time included: 1) revision of product labels to indicate the sterility or non-sterility of the drug product; 2) secondary packaging (b) (4) single use applicators that are sterilized in an enclosed package should include a sterility statement regarding the status of the applicator; and 3) an applicator that is sterilized should include the statement, "Applicator is sterile if package is intact."

For a detailed review of the Sponsor's submitted labeling and IDS Labeling Team assessment of the original and revised labeling, the reader is referred to Dr. Mujahid's review.[28] Important highlights are as follows:

- The placement and format of the statements "Non-sterile Solution" and "Applicator is sterile if package is intact" on the PDP was not consistent with class labeling safety changes requested in the CBE of 2013. On 21 March 2019, FDA requested that the Sponsor relocate and reformat the sterility statements and avoid the use of white font on the light blue background.
- The Labeling Team observed that in the proposed labeling, the maximal treatment area for one 10.5 mL applicator is approximately 8.4" x 8.4". The Team noted that applicators of this size and relative treatment area are not intended to be used in excess to cover large prep areas. To circumvent use on larger prep areas, the Team recommended that the statement "For head, neck, and small prep areas" be included on the PDP following the statement "Surgical Solution." (see also CDTL comment in **Section 3**)
- The Sponsor was advised to revise the second bullet in the boxed flammability warning. 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

[28] NDA 210872 Labeling Review for ZuraGard; 8 April 2019

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. 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 ChloraPrep™ (NDA 020832), DuraPrep™ (NDA 021586), and SoluPrep™ (NDA 208288).

- The Sponsor's proposed labeling included under the "**Do not use**" subheading "on patients allergic to isopropyl alcohol or any other ingredient in this product" [first bullet] and "for lumbar puncture or in contact with meninges." [second bullet]. It was agreed that such language should be included in labeling. However, in order to be consistent with class labeling, revisions to the exact wording were requested.
- In 2011 (CBE Supplement Request Letter for NDA 20832; 21 October 2011), FDA determined that class labeling change was warranted for chlorhexidine (CHG) topical antiseptic products due to reports of chemical burns in neonates. FDA requested that the infant warning statement "use with care in premature nfants or infants under 2 months of age. These products may cause irritation and chemical burns" be placed as the first bulleted statement under the "**Directions**" in the Drug Facts Labeling. Dr. Mujahidin pointed out that use of topicals in infants (particularly under occlusive dressings) has also been associated with development of measurable blood levels, local toxicity (irritancy, necrosis) and systemic toxicity. Furthermore, increased absorption may occur in infants less than 2 months of age.[29] Therefore, the inclusion of the infant warning is acceptable, and the Labeling Team requested revisions to the wording to improve clarity and for consistency across OTC approved labeling for this drug category.

The Sponsor revised proposed labeling according to FDA requests. The Sponsor's proposed Drugs Facts for the package insert (original submission of 15 February 2019 and the revised version per FDA requests on 27 March 2019) are shown below. Dr. Mujahidin concluded that, "in accordance with the Agency's request, the sponsor has amended the content, format, and order or the statements in the revised proposed labeling submitted on March 27, 2019 amd it is acceptable." Dr. Mujahidin recommended that an Approval letter be issued.

[29] Mancini A.J. Skin. Pediatrics 113 (4 Suppl): 1114-1119, 2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CDTL Comments: At the time of this writing, all IRs and comments from DMEPA and IDS regarding labeling have been addressed by the Sponsor. DMEPA and the IDS Labeling Team have concluded that the revised proposed label is acceptable for approval, and I agree.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

None. Communcications with the Sponsor have adequately addressed all issues as described in **Section 12** above.

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/

FRANCIS E BECKER
04/25/2019 04:07:17 PM

THERESA M MICHELE
04/26/2019 02:29:42 PM
I concur with the findings and conclusions in this summary review and agree that the product has demonstrated an appropriate benefit-risk profile for approval. There will be no separate Division Director summary review.