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APPLICATION NUMBER:

210872Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA Number	210872
Link to EDR	\\CDSESUB1\evsprod\NDA210872\210872.enx
Submission Date	06/29/2018 (SDN 1) 12/12/2018 (SDN 10)
Submission Type	Original NDA, 505(b)(2)
Brand Name	ZuraGard
Generic Name	Isopropyl Alcohol 70% (v/v)
Dosage Form and Strength	Solution in applicator sizes of 10.5 mL
Route of Administration	Topical
Proposed Indication	Patient Preoperative Skin Preparation
Applicant	Zurex Pharma, Inc
Associated IND	117045
OCP Review Team	Sojeong Yi, PhD / Soo Hyeon Shin, PhD Division of Clinical Pharmacology III
OCP Final Signatory	Dennis Bashaw, PharmD, Immediate Office

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1. EXECUTIVE SUMMARY

The Applicant is seeking an approval of isopropyl alcohol (IPA) 70% (v/v) solution in an applicator size of 10.5 mL for a patient preoperative skin preparation (hereafter called ‘ZuraGard’ which is conditionally granted as the proprietary name as of now). This original NDA was submitted under the 505(b)(2) pathway, relying on the Agency's previous findings of safety for the reference listed drug, ChloroPrep containing 2% w/v chlorhexidine gluconate (CHG) and 70% v/v IPA, which is approved under NDA 020832. As this is a 505(b)(2) application, it is not subject to nor should it be considered as having an impact on the OTC Monograph status of IPA, which is subject to a separate regulatory process.

The Applicant proposed to support establishment of a bridge between ZuraGard and ChloroPrep in terms of clinical pharmacology safety and address potential dermal absorption of IPA from ZuraGard based on published literature. However, as ZuraGard does not have identical composition from either ChloroPrep or the products used in the literature, the published literature provided was deemed insufficient to support the Applicant’s proposal. During this review cycle, the Applicant supplemented in vitro permeation test (IVPT) results comparing the skin permeation of IPA between ZuraGard and ChloroPrep to support bridging between the two products in terms of potential dermal absorption of IPA and systemic safety.

1.1 Recommendations

The Office of Clinical Pharmacology reviewed this submission and found 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.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

ZuraGard Solution and its proposed usage

ZuraGard is solution containing IPA 70% (v/v) in a 10.5-mL plastic applicator with a sterile barrier system to ensure that the applicator surfaces are sterile, which is intended to be used as a patient preoperative skin preparation solution in presurgical settings to reduce the bacteria that potentially can cause skin infection. For the proposed 10.5-mL applicator, the maximum treatment area is 8.4 in × 8.4 in (=70.56 in² = 457cm²).

ZuraGard is designed for single-use topical application to the intact skin prior to a surgical procedure. On dry surgical sites (e.g., abdomen or arm), the product should be applied for approximately 30 seconds while it is to be used for 2 minutes on moist surgical sites (e.g., inguinal fold). The proposed label directs the user to wait until the solution is completely dry (minimum of

3 minutes on the hairless skin and up to 1 hour in hair) before draping the surgical site or starting the surgical site or starting the procedure.

Comparison of ZuraGard Solution (IPA 70% v/v) to ChloroPrep Solution (IPA 70% v/v / CHG 2% w/v)

The proposed rationale for bridging ZuraGard to ChloroPrep as the reference listed product was based upon a similar product composition (particularly having IPA as an active ingredient and at the same content level, 70% v/v) and identical delivered IPA dose, in the same dosage form and route of administration, for the same indication (**Table 1**). However, it has to be noted that unlike ZuraGard containing IPA 70% v/v only, ChloroPrep contains CHG 2% w/v in addition to IPA 70% v/v. Additionally, some excipients in ZuraGard are not contained in ChloroPrep, i.e., (b) (4) citric acid, (b) (4) methylparaben, propylparaben, methylene blue.

The Applicant defined the maximum potential dermal IPA exposure from the proposed single 10.5-mL applicator as (b) (4) mg IPA/cm² to 457 cm² skin area, assuming 100% of the product contained in the applicator is delivered to the skin with no product evaporation (**Table 1**). It is consistent with the approved IPA dose for ChloroPrep 10.5 mL applicator.

Reviewer’s comment: We typically consider that the maximal use condition of a surgical skin preparation is application to 50% body surface area (BSA), which represents a use in a single major surgery such as a cardiovascular procedure. (b) (4)

Table 1. Maximum Potential Dermal Exposure of Isopropyl Alcohol of ChloroPrep 10.5-mL Applicator versus the ZuraGard 10.5 mL Applicator

	ZuraGard (IPA 70% v/v)	ChloroPrep (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.

Source: Summary of Clinical Pharmacology Studies, Table 2.7.2-4

The potential for dermal absorption of 70% IPA

Multiple publications demonstrate that IPA is absorbed following topical application, but 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 Antiseptics¹, 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 comatose². 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^{3,4}.

The potential for dermal absorption of IPA with and without the presence of CHG

One of the key compositional differences between the proposed product (i.e., ZuraGard) and the reference listed product (i.e., ChloroPrep) is the presence of CHG (2% w/v) in ChloroPrep but not in ZuraGard (**Table 2, Table 3**). The 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 ChloroPrep (**Table 2, Table 3**), those excipients could, again, alter the dermal absorption of IPA. These differences could result in higher dermal absorption of IPA, which brings up the potential for additional safety concerns beyond those for ChloroPrep.

The IVPT results provided by the Applicant compared skin permeation of IPA between ZuraGard and ChloroPrep. It indicated that the skin permeation of IPA from ZuraGard and ChloroPrep are comparable in vitro, suggesting that ZuraGard does not appear to pose a significantly higher

¹ 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 05/01/2015 (80 FR 25165)

² Puschel, K. Percutaneous Alcohol Intoxication. *Eur J Pediatr.* 1981 Jul;136(3):317-8.

³ 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.

⁴ 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.

dermal absorption potential of IPA compared to ChloroPrep despite the compositional differences between these two specific formulations.

Table 2. Components of ZuraGard (Isopropyl Alcohol, 70% v/v) Solution

Component	Amount	Function	Quality Standards
Isopropyl alcohol CAS number: 67-63-0	70% (v/v) equiv. to (b) (4) mg/mL	Active ingredient/drug substance/ antiseptic (b) (4)	USP
(b) (4) citric acid (b) (4) CAS number: 77-92-9	(b) (4)	Excipient (b) (4)	USP
(b) (4) sodium citrate (b) (4) CAS number: 6132-04-3	(b) (4)	Excipient	USP
Methylparaben CAS number: 99-76-3	(b) (4)	Excipient	NF
Propylparaben CAS number: 94-13-3	(b) (4)	Excipient	NF
Methylene blue (b) (4) CAS number: 7220-79-3	(b) (4)	Excipient	USP
Purified water	(b) (4)	Excipient	USP
CAS = Chemical Abstracts Service; equiv. = equivalent; NF = National Formulary; USP = United States Pharmacopeia. (b) (4)			

Source: Summary of Clinical Pharmacology Studies, Table 2.7.2-2

Table 3. Components of ChloroPrep (2% w/v Chlorhexidine Gluconate and 70% v/v Isopropyl Alcohol)

Component	Amount	Function	Quality Standards
Chlorhexidine gluconate CAS number: 55-56-1	2% w/v	Active ingredient/drug substance/ antiseptic	BP
Isopropyl alcohol CAS number: 67-63-0	70% (v/v)	Active ingredient/antiseptic	USP
Purified water	(b) (4)	Inactive ingredient: (b) (4)	USP
BP = British Pharmacopoeia; CAS = Chemical Abstracts Service; USP = United States Pharmacopeia.			

Source: Summary of Clinical Pharmacology Studies, Table 2.7.2-3

2.3 Outstanding Issues

In the initial NDA submission, the literature provided by the Applicant was deemed insufficient to evaluate in vivo dermal absorption of IPA after the topical application of ZuraGard under the rubric of maximal use. The literature data provided by the Applicant was previously reviewed and discussed by the FDA in the 2015 Proposed Rule on Health Care Antiseptics (80 FR 25165, pp 25165-25205); subsequently, in the 2017 Final Rule (82 FR 60474, pp 60474-60503). In the final

rule IPA was identified as a Category III ingredient with insufficient information for a GRASE (Generally Recognized as Safe and Efficacious) determination. At that time the FDA deferred regulatory action on IPA in order to allow sufficient time for additional information on efficacy and safety including in vivo dermal absorption data to be generated. Also, as the products used in the literature provided are not identical to ZuraGard, theoretically the potential formulation effect on dermal absorption of IPA could not be ruled out and would require additional “bridging” information.

In the situation here, the literature provided was also inadequate by itself to support establishment of a bridge between ZuraGard and ChloroPrep in terms of potential dermal absorption. The products used in the literature are not identical to ZuraGard, and the literature data was inadequate to allow for a 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 the exposed skin area.

Therefore, through the filing communication dated Sep 7, 2018, the FDA requested additional supportive material (e.g., results of an in vitro permeation study or an in vivo human pharmacokinetic study) which can support the establishment a bridge between ZuraGard and ChloroPrep. In response to the FDA’s request, on Dec 12, 2018, the Applicant supplemented in vitro permeation study results comparing the skin permeation rate of IPA between the final to-be-marketed formulation of ZuraGard and ChloroPrep.

Nonetheless, 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, great weight is given to the fact that, as formulated, it is unlikely that ZuraGard used as preoperative skin preparation 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 Applicant suggested that skin permeation of IPA from ZuraGard was not significantly higher compared to that from ChloroPrep, i.e. without vs. with the presence of CHG 2% w/v.

However, this 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.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY ASSESSMENT

3.1 The literature review on topical applications of IPA

The Applicant referred to four published studies in relation to dermal absorption of IPA in humans after use of antiseptics; three of which (Below et al, 2012; Kirschner et al, 2009; Turner et al, 2004) used antiseptics containing IPA 10 to 63.1% w/w whereas one study used an antiseptic containing both CHG 0.5% and IPA 70% v/v (Brown et al, 2007) (**Table 3**).

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.

Additionally, the Applicant 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.

Brown et al. (2007) assessed dermal absorption of IPA after intensive use (30 times per hour) of alcohol-based hand-rub solutions by 19 healthcare workers. The commercial hand rub formulation (DeBug, Orion Laboratories, Australia) contained 0.5% CHG in addition to 70% IPA. Following dermal administration, serum IPA levels were at or below the limit of detection (< 2 mg/L) at all time points (up to 12 hours post-applications).

Below et al. (2012) assessed systemic absorption following the use of a surgical hand rub containing 63.14% (w/w) IPA in 12 adults. A 4 mL of rub was applied and rubbed into the hands and forearms ($\approx 2540 \text{ cm}^2$). This procedure was repeated 5 times over 3 minutes to keep hands and forearms covered with the hand rub, followed by a 5-minute waiting period outside the room. Ten surgical hand rubs were performed, resulting in a total exposure time of 30 minutes over an 80-minute period. Samples were collected seven times for 120 minutes after the last surgical hand rub. The median value of C_{max} for IPA was 5.8 mg/L (25th – 75th percentile: 3.27 – 7.47 mg/L).

The estimated amount dermally absorbed was median 321 mg (25th – 75th percentile: 472 – 575 mg), which accounted for 0.4% (0.3 – 0.5%) of total applied amount, 110.62 g of IPA.

Turner et al. (2004) examined IPA blood alcohol levels in healthy adults (N = 10 subjects) following repeated dermal application of an IPA-containing hand rub (52.6% [w/w] IPA; Sterisol hand disinfectant, Sterisol AB, Sweden) every 10 minutes over a 4-hour period (3 mL of product per application). At the end of the testing period, measurable blood IPA levels (range 0.5 to 1.8 mg/L) were recorded in 9/10 (90%) subjects. The estimated absorbed dose was < 0.2% of the applied dose.

Kirschner et al. (2009) reported on dermal absorption of 10% IPA (20 mL [15 mL initially and 5 mL 5 min later]) applied with a 200-cm² gauze swab that was kept on the skin continuously for 10 minutes (0.1 mL/cm² treated skin area) in 14 healthy adults. The results showed that use of IPA alone (10% IPA in water) or as a mixture with ethanol (Softasept® N, B. Braun Melsungen AG, containing 74.1% ethanol and 10% IPA) did not result in any significant increase of total blood alcohol levels following dermal administration. The highest serum IPA level obtained in the period from 15 to 60 minutes after dermal administration of 10% IPA alone was approximately 3.0 mg/L (median level of 1.0 mg/L, range 0.5 to 3.0 mg/L). The estimated absorbed dose under occlusion was approximately 6.3% of the applied dose.

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									
<i>Below et al, 2012</i>	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 ^f	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 ^f	0.0597	Dermal and pulmonary 5.8 (median)	Dermal and pulmonary 0.22 (median) ^g
<i>Turner et al, 2004</i>	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 ^f	0.0445	1.8	~0.20
With Chlorhexidine Gluconate (0.5%), No Occlusion									
<i>Brown et al, 2007</i>	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 ^f	0.0233	< 2	< 0.42
			0.82		24.6	850 ^f	0.0290	< 2	< 0.34
No Chlorhexidine Gluconate, Continuous Wet Application									
<i>Kirschner et al, 2009</i>	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)									
^j = 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.									

Source: Summary of Clinical Pharmacology Studies, Table 2.7.2-6

3.2 In Vitro Permeation Test for IPA

As a response to the Information Request dated Aug 13, 2018 and the filing communication by Clinical Pharmacology dated Sep 7, 2018, the Applicant submitted the protocol and final report for IVPT (ZX-ZP-0099) comparing the in vitro skin permeation of IPA from ZuraGard and ChloroPrep through human skin. The provided IVPT study results indicate that the dermal absorption of IPA from ZuraGard and ChloroPrep are comparable in vitro. From Clinical Pharmacology's perspective, ZuraGard does not appear to pose a significantly higher systemic absorption potential of IPA compared to ChloroPrep.

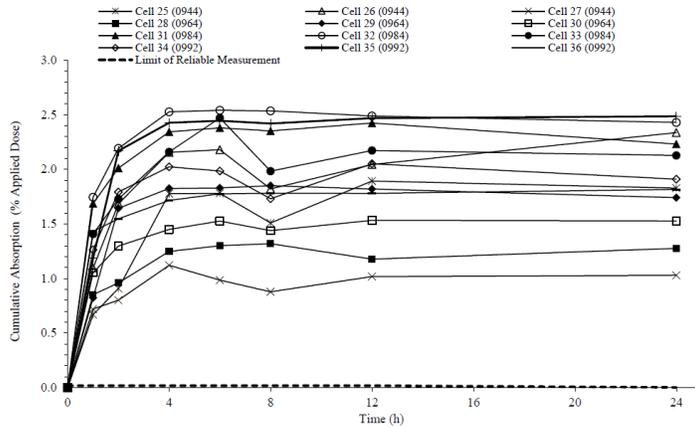
3.2.1 Study Design

Test Product	ZuraGard, labelled with ^{(b) (4)} mg/mL of [¹⁴ C]-IPA
Reference Product	ChloroPrep, labelled with ^{(b) (4)} mg/mL of [¹⁴ C]-IPA
Analyte	[¹⁴ C]-IPA
Type of Diffusion Cells	Static diffusion cells
Temperature	Skin temperature of 32 ± 1 °C, maintained by a circulating water bath
Dose/Permeation Area	0.64 cm ²
Dose Application Method	Positive displacement pipette
Dose Amount	6.4 µL (10 µL/cm ²)
Donor compartment	Unoccluded
Membrane Type	Human skin (abdomen)
Membrane Preparation	Dermatome
Membrane Thickness	380 – 400 µm
# of Donors	4
# of Replicates	12 per product
Skin Integrity Test	Electric resistance; skin sample with a resistance less than 10.9 kΩ was excluded
Receptor Solution	Phosphate buffered saline containing polyoxyethylene 20 oleyl ether (PEG, 6%, w/v), sodium azide (0.01%, w/v), streptomycin (0.1 mg/mL) and penicillin (100 units/mL), pH 7.43
Receptor Chamber Volume	5 mL
Dose Duration	24 hours
Sampling Duration	12 hours
Sampling Timepoints	1, 2, 4, 6, 8 12, and 24 hours post-dose
Sampling Volume	300 µL
Receptor Stirring speed	Not reported
Analytical Method	Liquid scintillation counting; limit of measurement: 30 d.p.m above background
Mass Balance Components	Dislodgeable dose at 24 hours post-dose (obtained from skin wash, tissue swab, pipette tip, and donor chamber wash), stratum corneum, unexposed skin, epidermis, and dermis

Reviewer's comments: *The maximum treatment area for one applicator per the proposed label is 457 cm² and one applicator contains 10.5 mL of ZuraGard solution. When the applicator is applied to the maximum treatment area, the nominal dose of product applied would be 23 µL/cm². Per the Applicant, the selected dose of 10 µL/cm² represents a realistic maximum use clinical exposure as in clinical practice, larger amounts of solution would tend to run-off. Given the limited size of permeation area on diffusion cells and the absence of room for solution to run-off the edge of the permeation area, the selected dose for IVPT study appears to be reasonable.*

3.2.2 Results

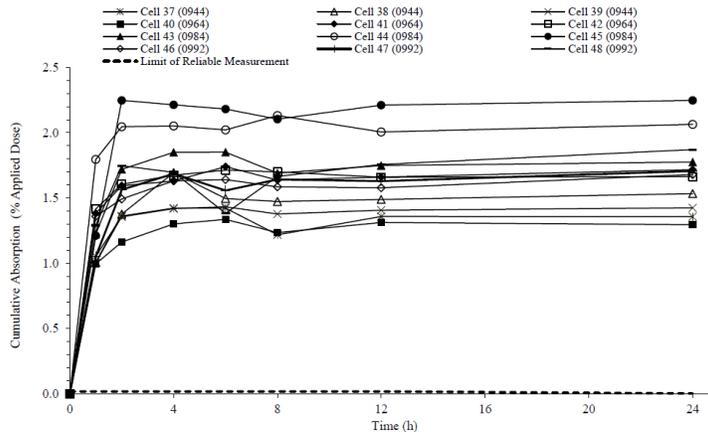
Figure 1. Individual Absorption Profiles for [¹⁴C]-IPA (% Applied Dose) in Receptor Fluid Following Topical Application of [¹⁴C]-IPA in ZuraGard to Human Split Thickness Skin



Note: Limit of reliable measurement 0-12 hours = 0.0179%, 24 hours = 0.0022% (<30 d.p.m.)

Source: Figure 4 from Reference No. ZX-ZP-0099

Figure 2. Individual Absorption Profiles for [¹⁴C]-IPA (% Applied Dose) in Receptor Fluid Following Topical Application of [¹⁴C]-IPA in ChloroPrep to Human Split Thickness Skin

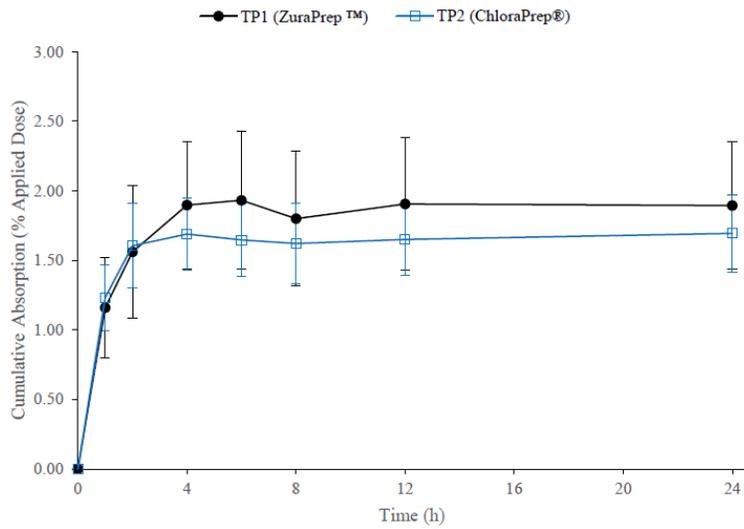


Note: Limit of reliable measurement 0-12 hours = 0.0169%, 24 hours = 0.0020% (<30 d.p.m.)

Source: Figure 8 from Reference No. ZX-ZP-0099

Reviewer's comments: *Decrease in cumulative absorption values of several cells noted (for example, from 4 to 8 hours) were noted in Figures 1 and 2. It appears that it was due to experimental errors as the cumulative absorption values should either increase or remain constant over time. Because the decrease was observed after the majority of absorption occurred and during the time when there was minimal absorption, this reviewer does not believe the noted decrease affect the conclusion of the IVPT study review.*

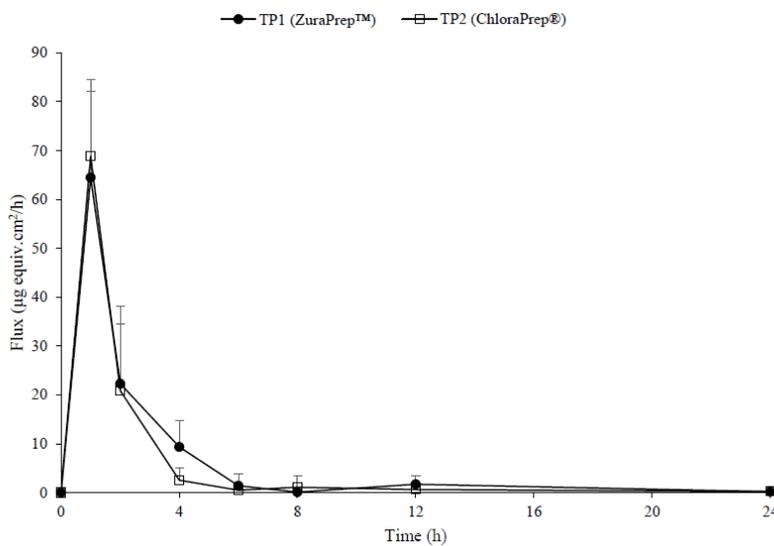
Figure 3. Comparison of Cumulative Absorption Profiles for ZuraGard and ChloroPrep



Mean ± SD, n=12 per test product

Source: Figure 12 from Reference No. ZX-ZP-0099

Figure 4. Comparison of Flux Profiles for ZuraGard and ChloroPrep



Mean ± SD, n=12 per test product

Source: Figure 13 from Reference No. ZX-ZP-0099

Reviewer's comments: It appears that the overall flux profiles and cumulative absorption amounts of the Test and Reference products are comparable from the graphical evaluation of Figures 3 and 4.

Table 5. Distribution of [¹⁴C]-IPA (% Applied Dose) at 24 hours Post Dose Following Topical Application of ZuraGard to Human Split-Thickness Skin

	Cell Number and Donor Number												Mean	SD	
	Cell 25 0944	Cell 26 0944	Cell 27 0944	Cell 28 0964	Cell 29 0964	Cell 30 0964	Cell 31 0984	Cell 32 0984	Cell 33 0984	Cell 34 0992	Cell 35 0992	Cell 36 0992			
Skin Wash 24 h	*0.01	*0.01	*0.01	*0.01	*0.00	*0.01	*0.01	*0.01	*0.01	*0.01	*0.02	*0.02	*0.01	*0.01	*0.01
Tissue Swab 24 h	0.00	0.01	0.01	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.05	0.01	0.01	0.01
Pipette Tip 24 h	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Donor Chamber Wash	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Total Dislodgeable Dose	0.01	0.02	0.03	0.01	0.01	0.01	0.02	0.02	0.02	0.04	0.06	0.02	0.02	0.02	0.02
Stratum Corneum 1-2	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 3-5	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 6-10	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 11-15	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 16-20	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum	*0.00	*0.00	*0.01	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Unexposed Skin	0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00
Total Unabsorbed	0.03	0.05	0.04	0.02	0.03	0.02	0.03	0.03	0.02	0.05	0.07	0.03	0.04	0.02	0.02
Epidermis	0.01	0.01	0.01	0.01	0.00	0.00	0.01	0.01	0.00	0.02	0.01	0.01	0.01	0.01	0.01
Dermis	0.02	0.02	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.02	0.02	0.01	0.01	0.01	0.01
Receptor Fluid	1.83	2.34	1.03	1.28	1.74	1.53	2.23	2.43	2.13	1.91	2.49	1.82	1.89	0.46	0.46
Receptor Chamber Wash	*0.10	*0.13	*0.02	*0.03	*0.14	*0.05	*0.12	*0.05	*0.10	*0.14	*0.04	*0.03	*0.08	*0.05	*0.05
Total Absorbed	1.93	2.46	1.05	1.31	1.88	1.57	2.35	2.48	2.23	2.05	2.53	1.85	1.97	0.48	0.48
Dermal Delivery	1.96	2.50	1.07	1.33	1.90	1.59	2.37	2.50	2.24	2.09	2.56	1.87	2.00	0.48	0.48
Mass Balance	1.99	2.55	1.11	1.35	1.93	1.61	2.39	2.53	2.27	2.14	2.63	1.90	2.03	0.49	0.49

* = Results calculated from data less than 30 d.p.m. above background
 ° = Mean includes results calculated from data less than 30 d.p.m above background

Source: Table 3 from Reference No. ZX-ZP-0099

Table 6. Distribution of [¹⁴C]-IPA (% Applied Dose) at 24 hours Post Dose Following Topical Application of ChloroPrep to Human Split-Thickness Skin

	Cell Number and Donor Number												Mean	SD	
	Cell 37 0944	Cell 38 0944	Cell 39 0944	Cell 40 0964	Cell 41 0964	Cell 42 0964	Cell 43 0984	Cell 44 0984	Cell 45 0984	Cell 46 0992	Cell 47 0992	Cell 48 0992			
Skin Wash 24 h	*0.05	*0.03	*0.06	*0.06	*0.03	*0.07	*0.06	*0.02	*0.08	*0.08	*0.04	*0.10	*0.06	*0.02	*0.02
Tissue Swab 24 h	0.07	0.11	0.10	0.06	0.06	0.06	0.07	0.09	0.15	0.09	0.06	0.06	0.06	0.03	0.03
Pipette Tip 24 h	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Donor Chamber Wash	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Total Dislodgeable Dose	0.13	0.14	0.16	0.12	0.09	0.14	0.14	0.11	0.23	0.18	0.11	0.16	0.14	0.04	0.04
Stratum Corneum 1-2	*0.00	0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 3-5	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 6-10	*0.00	0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 11-15	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum 16-20	*0.00	*0.00	0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00	*0.00
Stratum Corneum	*0.01	0.02	0.01	*0.01	*0.01	*0.01	*0.01	*0.00	*0.00	*0.00	*0.00	*0.00	*0.01	*0.01	*0.00
Unexposed Skin	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00
Total Unabsorbed	0.14	0.17	0.18	0.14	0.11	0.16	0.16	0.13	0.25	0.19	0.12	0.17	0.16	0.04	0.04
Epidermis	0.01	0.04	0.04	0.01	0.02	0.02	0.03	0.02	0.03	0.03	0.03	0.03	0.03	0.01	0.01
Dermis	0.01	0.01	0.01	0.02	0.02	0.03	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.01
Receptor Fluid	1.36	1.53	1.43	1.30	1.72	1.66	1.77	2.06	2.25	1.68	1.71	1.87	1.69	0.28	0.28
Receptor Chamber Wash	*0.09	*0.03	*0.02	*0.07	*0.03	*0.03	*0.14	*0.03	*0.04	*0.04	*0.03	*0.04	*0.05	*0.03	*0.03
Total Absorbed	1.45	1.56	1.45	1.37	1.74	1.70	1.91	2.10	2.29	1.72	1.73	1.91	1.74	0.27	0.27
Dermal Delivery	1.47	1.61	1.50	1.40	1.78	1.75	1.96	2.12	2.33	1.76	1.78	1.95	1.79	0.27	0.27
Potentially Absorbable Dose	1.48	1.63	1.51	1.41	1.79	1.76	1.96	2.12	2.34	1.77	1.78	1.95	1.79	0.27	0.27
Mass Balance	1.61	1.78	1.68	1.54	1.89	1.91	2.12	2.25	2.58	1.96	1.90	2.12	1.94	0.29	0.29

* = Results calculated from data less than 30 d.p.m. above background
 ° = Mean includes results calculated from data less than 30 d.p.m. above background

Source: Table 8 from Reference No. ZX-ZP-0099

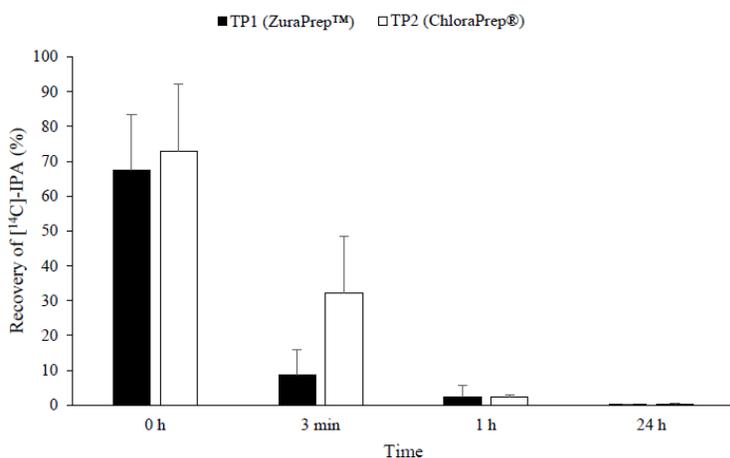
Reviewer's comments: The total absorbed dose (% applied dose) was minimal for both Test and Reference products with the mean (\pm SD) of 1.97 (\pm 0.48) and 1.74 (\pm 0.27), respectively. The reviewer's statistical analysis suggests that there is no statistically significant difference between the two products ($p=0.1615$, unpaired t -test).

The amounts of [¹⁴C]-IPA retained in skin layers (epidermis and dermis) at 24 hours post-dose were very low from both products. Rather, the amount recovered from receptor fluid (i.e. the amount that passed through the skin layers) represented the major portion of the total mass balance indicating minimal skin retention and rapid penetration of IPA. Note that the low mass balance is probably due to the volatility nature of formulations which were demonstrated from the volatility assessment in the next section.

3.2.3 Volatility assessment

Sections of aluminum foil instead of skin membrane were placed on diffusion cells. Each cell was dosed with 10 μL/cm² of either ZuraGard solution or ChloraPrep solution using a positive displacement pipette. The donor chamber was not occluded, and the temperature of aluminum foil was maintained at 32 ± 1 °C, mimicking the IVPT study conditions. At 0 h, 3 min, 1 h and 24 h post dose, the exposure was terminated (n=3 per each time point) and the remaining amount on aluminum foil and apparatus was analyzed.

Figure 5. Comparison of Recovery of [¹⁴C]-IPA Following Topical Application of ZuraGard or ChloraPrep for Volatility Testing to Aluminum Foil



Source: Figure 3 from Reference No. ZX-ZP-0099

Reviewer's comments: *It appears that ZuraGard solution evaporates more rapidly compared to ChloraPrep solution. 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.*

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/s/

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