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APPLICATION NUMBER:

208288Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208288
Link to EDR	\\CDSESUB1\evsprod\NDA208288\208288.enx
Submission Date	2/9/2018 (SDN 59)
Submission Type	Resubmission (Class 2) to original NDA
Brand Name	SoluPrep Film-Forming Sterile Surgical Solution
Generic Name	Chlorhexidine Gluconate 2%(w/v)/Isopropyl Alcohol 70% (v/v)
Dosage Form and Strength	Solution in applicator sizes of 10.5 mL and 26 mL for different types of surgical procedures.
Route of Administration	Topical
Proposed Indication	Patient Preoperative Skin Preparation
Applicant	3M Health Care Business
Associated IND	76549
OCP Review Team	Sojeong Yi, PhD
OCP Final Signatory	Chinmay Shukla, PhD

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1. EXECUTIVE SUMMARY

This NDA is the second resubmission following a Complete Response decision (dated September 1, 2017) following the review of the first resubmission. The Applicant is seeking an approval of SoluPrep Film-Forming Sterile Surgical Solution 10.5 mL and 26 mL containing chlorhexidine gluconate (CHG) 2% (w/v) and isopropyl alcohol (IPA) 70% (v/v) as a patient preoperative skin preparation.

The complete response decision dated September 1, 2017 was based on deficiencies in nonclinical safety assessment for two impurities of CHG, i.e., (b) (4) as the proposed specifications of the two impurities were above the qualification threshold per the ICH guidance. Based on the agency's recommendation, the Applicant conducted a human maximal use trial (MUsT) (Study EM-05-014226) with the goal of assessing systemic exposure to (b) (4) under maximal use conditions. In this resubmission, the results of the MUsT as well as a nonclinical study report and additional safety updates were submitted.

1.1 Recommendations

From a Clinical Pharmacology standpoint, NDA 208288 is acceptable provided the Applicant adequately addresses the labeling comments.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology/Clinical Pharmacokinetics and General Dosing

SoluPrep Film-Forming Sterile Surgical Solution (SoluPrep)

SoluPrep Film-Forming Sterile Surgical Solution (hereafter SoluPrep) is designed for single-use topical application to the intact skin prior to a surgical procedure. SoluPrep contains CHG 2% (w/v) and IPA 70% (v/v) as well as a film-forming acrylate copolymer which produces a water-insoluble film following application to the skin. SoluPrep is to be provided as a sterile solution in a sterile applicator. This NDA includes 3 different presentations of the product, a colorless solution in a 10.5-mL applicator, a green-tinted solution in a 10.5-mL applicator, and a green-tinted solution in a 26-mL applicator.

Proposed dosing regimen

For 10.5-mL and 26-mLapplicator, the maximum treatment areas are 178.8 in^2 (=1153.5 cm^2) and 387.5 in^2 (=2500 cm^2), respectively. Per the proposed label, the smaller product (10.5 mL) is to be applied to head, neck or small preparation and the larger product (26 mL) is for large preparation area below the neck.

On dry surgical sites (e.g., abdomen or arm), the product should be applied for 30 seconds while it is to be applied for 2 minutes on moist surgical sites (e.g., inguinal fold). Following application, one should wait until the applied solution is completely dry (minimum of 3 minutes on hairless skin and up to 1 hour in hair) before draping the surgical site or starting the surgical site procedure.

Maximal usage conditions

In both the previous resubmission and the current resubmission, the Applicant states that up to four 26-mL SoluPrep products may potentially be used in a single major surgery, such as a cardiovascular procedure, which represents a "maximal use" circumstance[1]. It is estimated that four 26-mL SoluPrep products, i.e., a total of 104 mL solution, maximally can be applied to 10,000 cm^2 of skin area (2,500 cm^2 per a 26-mL applicator × 4) which is approximately 58% of the average total body surface area (BSA) of adults, i.e. 1.73 m^2.

Reviewer comments: *The maximal BSA of drug application is considered reasonable.*

Dermal absorption of CHG, (b) (4) under a maximal use conditions

In Study EM-05-014226, 24 healthy male and female adults received a single application of four 26-mL applicators of SoluPrep to 10,000 cm^2 of the subject's intact skin in the chest/abdomen, upper and lower back, and front and back legs. The surface area was mapped to accommodate four 2500 cm^2 treatment areas and one 26-mL applicator of SoluPrep was applied topically to each area. Each 26-mL applicator contained at least (b) (4) mg (b) (4) and at least (b) (4) mg (b) (4) . Subjects were advised to refrain from showering and vigorous physical activity for 48 hours after the application such that the applied "film forming material" containing CHG, (b) (4) remained intact on the skin surface. The mean (range) actual amount of SoluPrep solution applied per subjects was 46.0 g (Range: 38.1 g to 54.3 g). This was a single treatment and blood samples were collected at 0, 2, 4, 8, 12, 24, and 48 hours after the application.

The pharmacokinetic results indicated that all of the resulting plasma concentrations of CHG and CHG-related impurities, (b) (4) were below the lower limit of quantitation (LLOQ), i.e., < 1 ng/mL. Of note, the plasma concentrations of isopropyl alcohol were not measured in this study. These results suggest that there were no quantifiable systemic concentrations of CHG and the two impurities, (b) (4) under the studied maximal use conditions of single use of SoluPrep (i.e., four 26-mL applicators topically applied to 10,000 cm^2 skin area) as a preoperative skin preparation on intact skin. The determination of acceptability of the maximal use PK data the systemic exposure below the LLOQ for the calculation of safety margins based on animal toxicity data is deferred to Pharm/Tox.

[1] Section 2.6.4 Pharmacokinetics Written Summary, Page 10

Bioanalytical assay validation for measurement of CHG, [redacted] (b) (4) using LC-MS/MS was acceptable. The LLOQ was 1 ng/mL for each analyte. Sample storage time from the first sample collection until the last bioanalysis (12 days) was within the established long-term stability period (26 days).

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

We recommend that dermal absorption data relevant to the usage of SoluPrep be indicated for both chlorhexidine gluconate and isopropyl alcohol based on the results of MUsT in addition to the literature submitted in the previous resubmission, which was reviewed by Clinical Pharmacology (see review in DARRTS dated 08/24/2017). The following changes are recommended in the Applicant's proposed labeling. The underlined text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.
. Of note, the following labeling recommendation has been further modified from the labeling recommendation in the previous resubmission. See the Clinical Pharmacology Review dated 08/24/2017 for the labeling recommendation of the previous resubmission.

Proposed	Recommended
12 Clinical Pharmacology	**12 Clinical Pharmacology**
[redacted] (b) (4)	
	The systemic absorption of chlorhexidine after topical application of SoluPrep was evaluated following a single application to 24 female and male adult subjects. Plasma concentrations of chlorhexidine were all below the level of quantitation (< 1 ng/mL) following a topical application of four 26-mL SoluPrep applicators to approximately 1550 in^2 (10,000 cm^2) surface area

	of intact skin. The systemic absorption of isopropyl alcohol after topical application of SoluPrep was not studied. Isopropyl alcohol is slightly absorbed approximately 1% of the amount applied to the intact skin. In a published study, a different product containing 49.8% (w/w) isopropyl alcohol was applied to subjects aged 1 month to 23 years for a preoperative skin preparation resulting in detectable blood concentration of IPA ranged from 0.83 to 12.25 mg/L at 1 hour after application.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY ASSESSMENT

3.1 Individual Study Review

Title: SoluPrep™ Film-Forming Sterile Surgical Solution Human Pharmacokinetics Maximum Usage Trial to Evaluate Systemic Absorption of Chlorhexidine Gluconate Qualification Level Related Substances (EM-05-014226)

Study site: This study was conducted in a single site, [redacted] (b) (4)

Objectives:

The primary objective of the study was to evaluate the systemic absorption of the active pharmaceutical ingredient-related degradants for chlorhexidine gluconate (CHG) topical solution impurities, [redacted] (b) (4), in a maximal use trial (MUsT).

The secondary objective of this study was to evaluate the safety and tolerability of SoluPrep in healthy subjects.

Reviewer's note: *When the MUsT protocol was first submitted on 11/29/2017 under IND 76,549, the applicant originally proposed to evaluate only* [redacted] (b) (4). *Per the e-mail*

correspondence dated 12/19/2017 with the applicant, subject enrollment and treatment had been completed whereas data analysis was still pending. Considering such situation, instead of giving comments on study design, we recommended that the sponsor measure isopropyl alcohol and CHG in addition to (b) (4) *from the collected plasma samples in order to maximize the utility of the completed MUsT study (See the Clinical Pharmacology Review dated 12/28/2017 on the protocol under IND 76,549). The advice letter including those recommendations was sent to the sponsor on 1/4/2018, but there were not subsequent protocol amendment or responses from the sponsor. In this resubmission, we note that the applicant later included CHG as an additional analyte but not isopropyl alcohol. Not measuring the systemic concentrations of isopropyl alcohol in this MUsT does not preclude the approval as discussed in the previous resubmission (See the Clinical Pharmacology Review dated 08/24/2017 regarding the clinical pharmacology information of CHG and isopropyl alcohol from the literature submitted). For the labeling purpose, the information regarding the systemic absorption of isopropyl alcohol will be based on the literature which was submitted in the previous resubmission whereas the lack of quantifiable systemic absorption of CHG can be indicated using the data from this MUsT.*

Study design:

1. **Subjects:** male and female healthy subjects ≥18 years of age, N=24
2. **Investigational product:** SoluPrep Film-Forming Sterile Surgical Solution containing chlorhexidine gluconate (CHG) 2% (w/v) and isopropyl alcohol (IPA) 70% (v/v) was supplied in a 26-mL applicator. In addition, (b) (4) were chemically synthesized and added to the test article to provide levels of the impurities of at least (b) (4) . In each 26-mL applicator, there were at least (b) (4) mg (b) (4) and at least (b) (4) mg (b) (4).

   Reviewer's note: *The amount of* (b) (4) *added to the test article seems to be consistent with the limit of the proposed specifications, i.e., NMT* (b) (4) *% for* (b) (4) *and NMT* (b) (4) *% for* (b) (4).

3. **Dosing method**
   a. Frequency/duration of dosing: single dose
   b. Total involved surface area to be treated: Four 26 mL applicators were applied topically to an ~1550 in^2 (10,000 cm^2) surface area of the subject's intact skin on the chest/abdomen, upper and lower back, and front and back legs. The surface area was mapped to accommodate four ~387.5 in^2 (2500 cm^2) treatment areas. One 26 mL-applicator of the study product was applied topically to each area. Total four 26 mL applicators were used.
   c. Site preparation/application method: On Day -1, subjects had their treatment areas clipped to provide a cleaner surface for application. Study product was applied with

repeated back-and-forth strokes for 2 minutes on each 2500 cm^2 treatment area and allowed to dry for 3 minutes. Each applicator was weighed before and after it was used.

The duration of exposure to study products was intended to be approximately 48 hours. Therefore, subjects were advised to refrain from showering and vigorous physical activity that might have caused sweating during Day 1 to Day 3 after the drug application. Subjects wore loose-fitting clothing (e.g., scrubs) for the duration of admission and changed clothing at least once per day. Additionally, subjects were instructed to avoid touching and scratching treatment areas and to keep hands away from their mouths to avoid accidental/incidental oral ingestion of study product.

Reviewer's note: *The application method in the study such as hair-clipping, repeated back-and-forth strokes for 2 min, and drying for 3 min is consistent with the proposed method in the labeling. Also, the applied area, i.e., 10,000 cm^2 including the chest/abdomen, upper and lower back, and front and back legs reasonably represents the maximal use condition of preoperative skin preparation.*

4. **PK blood sampling:** After application of study product to the fourth treatment area was completed and allowed to dry for 3 minutes (time 0 hours), post-treatment blood samples for PK assessment were collected at 2, 4, 8, 12, 24, and 48 hours.
5. **Safety assessment**: See Clinical Review dated 4/20/2018 by Dr. Podruchny for details.
6. **Bioanalytical method:**
   An LC-MS/MS bioanalytical method for the quantitation of chlorhexidine, (b) (4) in human K_2EDTA plasma was validated (Report (b) (4)-RPT 17318). Sample volume was 100 µL and the injection volume was 5 µL. The summary validation results are presented in **Table 1** and **Error! Reference source not found.**. Overall, the bioanalytical method validation was acceptable and the actual sample storage duration (12 days) was within the established long-term matrix stability (26 days).

Table 1. Plasma Bioanalytical Method Validation Summary (Chlorhexidine)

Attribute	**Analyte**
	Chlorhexidine
Linear Range	1–100 ng//mL
LLOQ	1 ng/mL
Selectivity, Carryover	No interference > 20% of the peak area of LLOQ, no carryover
Recovery	Chlorhexidine: 81.9 – 88.3%; Chlorhexidine -d_8 (IS): 77.5%
Dilution integrity	500 ng/mL diluted 10-fold
QC Concentration	3, 10, and 75 ng/mL
Intra-Day Precision (% CV)	At LLOQ (1 ng/mL): 4.3% to10.0%; at other QC levels: 1.8% to 11.2%
Intra-Day Accuracy (% Bias)	At LLOQ (1 ng/mL): -9.3% to 5.0% at other QC levels: -10.3% to 4.1%

Inter-Day Precision over 3 days (% CV)	At LLOQ (1 ng/mL): 9.3%; at other QC levels: 5.0% to 7.9%
Inter-Day Accuracy over 3 days (% difference)	At LLOQ (1 ng/mL): -0.7%; at other QC levels: -6.0% to -1.5%
Freeze and Thaw Stability	3 cycles at -20°C and at -70°C
Storage Stability	20 h at room temperature* (plasma) 25 h at 4°C (extract) 26 days and at -70°C (plasma)
Auto-sampler Stability of Processed Samples	119 h at room temperature*
Master Stock Solution Stability in Solvent	6 h at room temperature* 49 d at -20°C

CV = coefficient of variation; LLOQ = lower limit of quantitation; QC = quality control
*The exact room temperature was not specified.

(b) (4)

Result:

1. **Disposition of subjects**
   Out of 135 subjects who were screened, 24 subjects were enrolled and all subjects completed study. Overall, 5 (20.8%) subjects were female and 19 (79.2%) subjects were male. Seven (29.2%) subjects were White, and 17 (70.8%) subjects were Black or African American. The mean age was 36.8 years; the mean body weight was 116.42 kg; the mean height was 175.94 cm; and the mean body mass index was 37.55 kg/m^2.

2. **Pharmacokinetic results:**
   The mean actual amount of SoluPrep solution applied per subjects was 46.0 g (Range: 38.1 g to 54.3 g). The plasma concentrations of CHG and CHG-related impurities, (b) (4) were all below the LLOQ, i.e., < 1 ng/mL. These results suggest that there is no quantifiable systemic absorption of CHG and the two impurities, (b) (4) when SoluPrep was applied under maximal use conditions (i.e., four 26-mL applicators topically applied to 10,000 cm^2 skin area) as a preoperative skin preparation on intact skin.

3. **Safety assessment**
   Four subjects experienced adverse events which included rhinitis, upper respiratory infection, dental abscess, and itching. See Clinical Review dated 4/20/2018 by Dr. Podruchny for details.

***Reviewer's note**: To assess whether there were any detected plasma levels of CHG or the two impurities of CHG* (b) (4) *which might indicate dermal absorption (though not quantifiable), an information request was sent to the Applicant on 5/30/2018.*
The Applicant responded to the IR on 6/15/2018 providing chromatograms from 20% of serially selected subjects. Based on the submitted data, this reviewer was not able to clearly indicate the

limit of detection. However, nonexistence of systemic absorption cannot be completely ruled out based on submitted chromatograms.

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/s/

SOJEONG YI
06/26/2018

CHINMAY SHUKLA
06/27/2018

Office of Clinical Pharmacology Review

NDA Number	208288
Link to EDR	\\CDSESUB1\evsprod\NDA208288\208288.enx
Submission Date	03/03/2017 (SDN 45) 06/29/2017 (SDN 53)
Submission Type	Resubmission to original NDA
Brand Name	SoluPrep Film-Forming Sterile Surgical Solution
Generic Name	Chlorhexidine Gluconate 2%(w/v)/Isopropyl Alcohol 70% (v/v)
Dosage Form and Strength	Solution in applicator sizes of 10.5 mL and 26 mL for different types of surgical procedures.
Route of Administration	Topical
Proposed Indication	Patient Preoperative Skin Preparation
Applicant	3M Health Care Business
Associated IND	76549
OCP Review Team	Sojeong Yi, PhD
OCP Final Signatory	Dennis Bashaw, PharmD

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1. EXECUTIVE SUMMARY

3M Health Care Business (3M) provided this resubmission seeking an approval of SoluPrep Film-Forming Sterile Surgical Solution 10.5 mL and 26 mL containing chlorhexidine gluconate (CHG) 2% (w/v) and isopropyl alcohol (IPA) 70% (v/v) for a patient preoperative skin preparation. The original NDA was submitted on July 6, 2015, under the 505(b)(2) pathway, relying on published literature but the Agency issued a Complete Response Letter dated May 6, 2016, because of major issues in efficacy and quality.

In the original NDA, a clinical pharmacology-related deficiency was also identified indicating that inadequate literature was submitted for IPA and a combination of CHG/IPA to evaluate dermal absorption in humans while the literature for CHG absorption submitted was sufficient to support NDA approval. (See Division Director Summary Review dated 05/06/2016 by Dr. Michele.) Thus, the agency recommended as followed:

> *You may rely on adequate literature for IPA and CHG/IPA to demonstrate absorption after use as a surgical skin preparation with a similar level of skin coverage to that proposed for the largest size product (26 mL), rely upon FDA's findings of safety for a listed drug(s), or conduct a maximal use pharmacokinetic study with the final, to-be-marketed formulation of your product.* (See the Complete Response Letter dated 05/06/2016.)

In this resubmission, to resolve the deficiency in clinical pharmacology data, the sponsor provided the following:

- A literature review with regard to the human pharmacokinetic data evaluating CHG and IPA as a preoperative skin preparation and for the combination CHG/IPA
- A proposal to establish clinical pharmacology safety for IPA of SoluPrep based on the cross-reference to safety and effectiveness data of DuraPrep Surgical Solution [Iodine Povacrylex (0.7% Available Iodine) and IPA (74% w/w)] under NDA 21-586
- Results from an in vitro skin permeation test for CHG using SoluPrep compared to that of ChloraPrep

1.1 Recommendations

The Division of Clinical Pharmacology 3 reviewed this resubmission and found that from a clinical pharmacology standpoint the information provided was acceptable to support the approval of the combination of CHG 2% (w/v) and IPA 70% (v/v) (as formulated in this NDA) as a film-forming solution for use as a preoperative skin preparation.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

SoluPrep Film-Forming Sterile Surgical Solution (SoluPrep)

SoluPrep contains CHG 2% (w/v) and IPA 70% (v/v) as well as a film-forming acrylate copolymer which stays dissolved until it is applied on the skin to produce a water-insoluble film. SoluPrep is to be provided

as a sterile solution in a sterile applicator. This NDA includes 3 different presentations of the product, a colorless solution in a 10.5 mL applicator, a green-tinted solution in a 10.5 mL applicator, and a green-tinted solution in a 26 mL applicator.

Chlorhexidine Gluconate (CHG)

A strong electrostatic binding property of CHG leads to antimicrobial effects. Even though CHG has been recognized minimally absorbed in adults after topical application, some publications reported measurable systemic exposure in neonates and premature infants after topical antiseptic application, particularly if CHG is combined with a skin penetration enhancer such as alcohol[1]. Per the proposed label of SoluPrep, it should be used with care in premature infants or infants under 2 months of age because of potential irritation or chemical burns. On the other hand, the current labeling of ChloraPrep, a marketed product containing CHG 2%/IPA 70% includes 'Do not use' warning for children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption.

When ^{14}C-labeled CHG was orally administered to a human, no radioactivity was detected in the blood. The radioactivity excreted in urine and feces was all found to be unchanged forms. The half-life of radioactivity was estimated about 4 days[2].

Isopropyl Alcohol (IPA)

IPA exhibits a broad spectrum of antimicrobial activity. Multiple publications demonstrate that IPA is absorbed following topical application, but the systemic exposure to IPA is expected to be low when used as an active ingredient in topical antiseptic products, depending on both the frequency of application, surface area involvement, and other factors. The highest blood concentration of IPA observed across studies was less than 20 mg/L following various topical application scenarios with IPA-containing products[3]. (See also Table 3.) 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[4]. 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 about 17-27 hours and is known to be a CNS depressant[5, 6].

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[1] Chapman AK, Aucott SW, Milstone AM. Safety of chlorhexidine gluconate used for skin antisepsis in the preterm infant. J Perinatol. 2012 Jan; 32(1):4-9.
[2] Winrow MJ, Metabolic studies with radiolabelled chlorhexidine in animals and man. J Periodontal Res Suppl. 1973;12:45-8.
[3] 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)
[4] Puschel, K. Percutaneous Alcohol Intoxication. Eur J Pediatr. 1981 Jul;136(3):317-8.
[5] 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.
[6] 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.

2.2 Application Regimen

Proposed usage

SoluPrep is designed for single-use topical application to the intact skin prior to a surgical procedure. For 26-mL and 10.5-mL applicator, the maximum treatment areas are 178.8 in^2 (=1153.5 cm^2) and 387.5 in^2 (=2500 cm^2), respectively. Per the proposed label, the smaller product (10.5 mL) is to be applied to head, neck or small preparation and the larger product (26 mL) is for large preparation area below the neck.

On dry surgical sites (e.g., abdomen or arm), the product should be applied for 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.

Maximal usage condition

The sponsor stated that up to four 26-mL SoluPrep products may potentially be used in a single major surgery, such as a cardiovascular procedure, which represents a "*maximal use*" circumstance[7]. It is estimated by the Sponsor that four 26-mL SoluPrep products, i.e., a total of 104 mL solution, maximally can be applied to 10,000 cm^2 of skin area which is approximately 58% of 1.73 m^2, the average body surface area of adults.

2.3 Outstanding Issues

In the original NDA review, the literature demonstrating the dermal absorption of CHG was deemed acceptable whereas those for IPA and the CHG/IPA combination were inadequate. Thus, in this resubmission, the sponsor intended to address the dermal absorption of IPA and the combination of CHG/IPA with the literature review and in vitro permeation study data.

However, while the literature submitted suggested that the systemic exposure to CHG and IPA used as active ingredients in topical antiseptic products is expected to be low, it was found that none of the literature submitted had evaluated in vivo bioavailability of the two active ingredients with the CHG 2%/IPA 70% combination product proposed by the Sponsor at the intended usage level (i.e., a single application of up to four 26-mL products to 10,000 cm^2). In fact, the products used in the literature primarily contained either CHG or IPA not both, had lower strengths of either one of the two active ingredients than the proposed CHG 2%/IPA 70% combination, or were applied to smaller skin areas than the expected maximal application area for the proposed product. Subsequently, the literature provided was not sufficient to demonstrate the dermal absorption of either IPA or the CHG/IPA combination under a maximal usage condition for a preoperative skin preparation (i.e., a single application of four 26-mL products). Also, the in vitro skin permeation test for CHG that the sponsor conducted using SoluPrep cannot be considered representative of in vivo dermal absorption data unless there is in vivo data generated from a maximal usage trial with which to anchor the in vitro methodology with.

Nonetheless, the single-use application of the combination of CHG 2% (w/v) and IPA 70% (v/v) as formulated in this NDA as a film-forming solution is justifiable from a clinical pharmacological perspective, because it is unlikely to cause a significant systemic exposure to either CHG or IPA given

[7] Section 2.6.4 Pharmacokinetics Written Summary, Page 11

that this type of single-use product 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 life (albeit at significant intervals). To determine the risk of the potential systemic exposure, we additionally considered the known information about CHG and IPA based on the literature submitted; CHG generally shows minimal absorption following topical administration except when it is applied to neonates and preterm infants; and IPA is slightly absorbed after topical administration while it depends on both the frequency of application, surface area involvement, and other factors, so the expected IPA blood level after a single use of SoluPrep is far lower than 500 mg/L that is known to be associated with a mild adverse effect of IPA in addition to the fact that IPA is readily eliminated via exhaled air and urine following metabolism once it is absorbed through the skin.

However, this determination is not applicable to other products 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 ingredient.

2.4 Summary of Labeling Recommendations

The following major labeling recommendations for Target Product Information will be conveyed to the sponsor and under discussion.

Section 12. Clinical Pharmacology

We recommend that dermal absorption data relevant to the usage of SoluPrep be described for both chlorhexidine gluconate and isopropyl alcohol at a minimum based on the literature submitted.

Proposed	Recommended
12 Clinical Pharmacology	**12 Clinical Pharmacology**
(b) (4)	(b) (4)
no clinical pharmacokinetic or pharmacodynamic studies (b) (4) conducted. It is generally recognized that chlorhexidine is not or is only minimally absorbed through mature intact skin.	No clinical pharmacokinetic or pharmacodynamic studies (b) (4) conducted (b) (4) While it has been generally recognized that chlorhexidine is ~~not or is only~~ minimally absorbed through the mature (i.e., adult) intact skin, some studies have found detectable chlorhexidine blood levels up to 1021 ng/mL in neonates after repeated topical application of chlorhexidine solution.
(b) (4)	(b) (4)
	Isopropyl alcohol is slightly absorbed

	approximately 1% of the amount applied to the intact skin. In a published study, a product containing 49.8% (w/w) isopropyl alcohol was applied to subjects aged 1 month to 23 years for a preoperative skin preparation resulting in detectable blood concentration of IPA ranged from 0.83 to 12.25 mg/L at 1 hour after application.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY ASSESSMENT

3.1 Dermal absorption of chlorhexidine (CHG) from the product

Throughout the review of both the original NDA and this resubmission, while the submitted human data for dermal absorption of CHG alone was deemed sufficient to support the safety profile of CHG for single-use application of CHG 2% for a preoperative skin preparation, the dermal absorption of 2% CHG in IPA 70% solution has not been demonstrated. Given that the combination of CHG with isopropyl alcohol may result in enhanced absorption of CHG, relative to that of CHG in aqueous solution, additional in vivo absorption studies (including a MUsT) would be necessary in the situation where the formulation used in this NDA would be proposed for other indications that utilize a higher frequency of administration, such as a hand wash or hand scrub.

The literature review on topical applications of CHG

In the original NDA submission, eight publications were cited, and these were primarily focused on CHG absorption in neonates and related symptoms[8] after topical antiseptic use. In 7 out of 8 publications, CHG 0.5% 4% in aqueous solution was applied to infants for antiseptic bath, catheter site dressing, or umbilical cord care resulting in some detectable blood levels of CHG ranged from 0 to 1021 ng/mL.

On the other hand, **Garland et al. (2009)**[9] evaluated dermal absorption of CHG for ChloraPrep containing 2% CHG and 70% IPA with the same combination of active ingredients as SoluPrep. It was applied weekly to ten critically ill infants with ≥ 1500 g body weight and 7 days to 2 months of age for dressing on the peripherally inserted central catheter (PICC) site. Five of 10 infants showed measurable serum concentration of CHG (> 10 ng/mL) even following the first application. After several weeks, seven infants presented serum concentrations of CHG with a range of 13 - 100 ng/mL.

**Reviewer's comment: Aside from this paper by Garland et al., the literature submitted was about products containing only CHG without 70% IPA solution. Even Garland et al. applied ChloraPrep to only neonates with limited skin areas, so it does not necessarily demonstrate the dermal absorption of SoluPrep as a preoperative skin preparation at the equivalent surface area exposures contemplated with this product.*

In this resubmission, of the literature additionally provided, two publications were pertinent to the dermal absorption of CHG in humans after use of 4-5% CHG solution for hand washing or skin disinfectant.

[8] Section 2.7.4 Summary of Clinical Safety, 'Percutaneous Absorption of Chlorhexidine', Page 27
[9] Garland JS, Alex CP, Uhing MR, Peterside IE, Rentz A, Harris MC. Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antisepsis for central venous catheter placement in neonates. J Perinatol 2009; 29(12): 808–813.

Johnsson et al. (1987)[10] measured CHG levels in cord and venous blood samples obtained 32 neonates who had been applied 0.2 mL Hibiscrub solution (CHG 4%) every day to the dry cord and the surrounding skin. CHG levels of cord blood were detectable in 7 out of 32 neonates ranging from 0 to 249 ng/mL while none of the venous blood was except only one sample with 496 ng/mL in a neonate.

Case et al. (1980)[11] applied ^{14}C-labeled CHG as a 5% aqueous solution or Hibiscrub[12] (a hand wash containing 4% CHG) to 50 cm^2 of intact forearm skin of 5 adults, respectively, and then left for 3 hours under a non-occlusive condition. From collected blood, urine, and feces up to 10 days, none of the samples showed detectable levels of radioactivity (< 5 ng/ml for blood; < 0.02% of applied dose for urine; < 0.006% of applied dose for feces) aside from two fecal samples representing 0.009% of applied dose. In the second study, Case et al. also repeatedly applied 5% CHG in aqueous solution as a skin scrub to the intact hands and forearms in 15 adults 5 times a day, 5 days a week for 3 weeks (total 75 times). Blood samples were withdrawn on days 0, 5, 12, 16, and 19 but no detectable blood level of CHG was observed. In their third study, they measured the blood levels of CHG in 25 hospital staff that had used Hibiscrub on a regular basis (average 5 times per day) for at least 6 months. Blood samples were collected periodically at 1 to 2 hours after scrubbing throughout the 6-month period but CHG was not detected in any samples (<10 ng/mL).

***Reviewer's comment:** Case et al. studied dermal absorption of CHG in adults unlike the other publications submitted but these studies neither adequately demonstrated the dermal absorption of CHG from SoluPrep because of differences in formulations and usage patterns. The CHG-containing products that Case et al. used were 4-5% CHG in aqueous solution where SoluPrep is 2% CHG in 70% IPA solution which may increase the dermal absorption of CHG. Also, Case et al. used the CHG-containing products as a hand wash that was applied to a relatively smaller skin area (i.e., two hands and forearms) followed by rinsing off with water while SoluPrep can be applied to a broader skin area up to approximately 50% body surface area and is typically left on the skin during a surgical procedure.*

In vitro skin permeation test for CHG using 2% CHG/70% IPA combination product

Instead of in vivo human data of CHG/IPA combination product, the sponsor provided a publication in which skin permeation of CHG 2% from IPA 70% solution was tested using excised human skin, i.e., a Franz cell diffusion model. Additionally, the sponsor conducted a similar in vitro test using SoluPrep compared to ChloraPrep, a marketed product containing both CHG 2% and IPA 70%.

In the in vitro skin permeation study by Karpanen et al. (2009)[13], excised human skin was exposed to both aqueous and isopropanol CHG for each 2 minutes and 30 minutes. Overall, following 30- minute exposures, the skin permeation from both aqueous and alcoholic solutions was limited. At skin depths of ≥ 300 μm, the concentration of CHG detected from both solutions was negligible (< 0.0008 μg/mg

[10] Johnsson J, Seeberg S, Kjellmer I. Blood concentrations of chlorhexidine in neonates undergoing routine cord care with 4% chlorhexidine gluconate solution. Acta Paediatr Scand. 1987 Jul;76(4):675-6.
[11] D. E. Case, J. McAinsh, A. Rushton, M. J. Winrow. Chlorhexidine: Attempts to Detect Percutaneous Absorption in Man. Special Problems in Chemotherapy pp 367-374
[12] Hibiscrub contains inactive ingredients such as fragrance, gluconolactone, isoproply alcohol 4% w/v, lauramine oxide, poloxamer 237, purified water and red 40.
[13] Karpanen TJ, Worthington T, Conway BR, Hilton AC, Elliott TS, Lambert PA. Permeation of chlorhexidine from alcoholic and aqueous solutions within excised human skin. Antimicrob Agents Chemother. 2009 Apr;53(4):1717-9

tissue). Following the 30 minute exposure, there was no significant difference in the skin penetration of CHG between alcoholic and aqueous solutions within the model.

Similarly, the sponsor evaluated the skin permeation of CHG from SoluPrep compared to ChloraPrep using a Franz cell diffusion model (Report number: TEST-PLAN-RPT-05-279792). Excised human full-thickness skin was exposed to both products for 6 hours, which covers a duration of the typical surgical procedure. In the superficial layers of skin (0-300 μm), SoluPrep showed lower concentration than ChloraPrep whereas both products showed minimal skin permeation in deeper skin depths (300-600 μm) (Table 1).

Table 1. CHG penetration profile for SoluPrep compared to ChloraPrep after 6 hours of exposure in excised human skin tested in Franz cell

Sample section (um)	SoluPrep FF prep (CHG μg per mg of tissue)						ChloraPrep (CHG μg per mg of tissue)						Controls (CHG μg per mg of tissue)	
	1	2	3	4	5	Average	1	2	3	4	5	Average	Positive	Negative
0-100	0.62	0.45	0.36	0.48	0.20	0.42	0.39	0.50	1.95	1.96	4.09	1.78	3.12	0.01
101-200	0.30	0.33	0.20	0.30	0.12	0.25	0.12	0.46	1.00	0.71	1.51	0.76	1.43	0.02
201-300	0.20	0.29	0.24	0.11	0.10	0.19	0.08	0.22	0.57	0.31	0.56	0.35	1.13	-0.01
301-400	0.20	0.35	0.28	0.16	0.05	0.21	0.09	0.15	0.32	0.16	0.30	0.20	1.77	-0.01
401-500	0.21	0.29	0.26	0.07	0.10	0.19	0.10	0.14	0.20	0.09	0.19	0.14	1.05	0.00
501-600	0.21	0.27	0.19	0.04	0.04	0.15	0.07	0.19	0.13	0.05	0.13	0.11	0.99	0.00
601-700	0.10	0.21	0.14	0.03	0.03	0.10	0.05	0.08	0.08	0.04	0.09	0.07	0.98	0.00

Reviewer's comment: *While the aforementioned results imply that dermal permeation potential of CHG in the CHG/IPA combination is limited and CHG of SoluPrep is less permeable than that of ChloraPrep, it cannot be regarded as primary data to support the dermal absorption of SoluPrep. As an in vitro-in vivo correlation cannot be established without in vivo data, in vitro skin permeation data cannot supplant in vivo absorption data generated via a maximal usage trial.*

Conclusion

Based on the literature review, the series of studies by Case et al. suggests that CHG is minimally absorbed in adults after multiple topical applications whereas some publications indicate that CHG may be absorbed in neonates particularly when it is repeatedly applied. Relatively higher absorption in neonates seems to be attributed to their thinner and underdeveloped skin characteristics compared to the intact and matured skin of adults. The clinical relevance of the detectable CHG blood concentrations is unknown despite no systemic adverse events observed in the literature reporting the CHG absorption in humans.

Still, SoluPrep's dermal absorption for CHG after use as a preoperative skin preparation could not be fully demonstrated with the literature provided because the CHG-containing products employed in the literature primarily were aqueous solutions, not combined with 70% IPA which may potentially enhance the absorption of CHG. The study by Garland et al. only used ChloraPrep containing both 2% CHG and 70% IPA to disinfect catheter site in ten infants, but the size of the drug applied area was too small to represent a typical usage of preoperative skin preparation. In addition, the in vitro skin permeation data cannot be linked to in vivo dermal absorption in absence of in vivo data generated a maximal usage trial using the combination product.

Nevertheless, given the single-use application of the combination of CHG 2% (w/v) and IPA 70% (v/v) as formulated in this NDA, CHG absorption is unlikely to lead to significant systemic exposure that may cause any safety concern based on the known information of CHG's pharmacokinetic properties as discussed above. However, this finding cannot be applicable to other CHG-containing products with other indications to be repeatedly used such as an antiseptic hand rub or a disinfectant.

3.2 Dermal absorption of isopropyl alcohol (IPA) from the product

The literature review on topical applications of IPA

The sponsor referred to 17 publications in relation to pharmacokinetics of IPA, but only 5 out of 17 references were relevant to dermal absorption of IPA in humans after use of antiseptics. However, those 5 references were limited to the assessment of the dermal absorption with products containing IPA only, not both CHG 2% and IPA 70%. Additionally, the information provided for IPA was still at lower exposures than what would be expected under a maximal usage condition as a preoperative skin preparation.

Out of 5 studies, the two studies by Below et al. (2012)[14] and Wittmann et al. (1992)[15] were most relevant to the use of SoluPrep. The conditions where Below et al. studied were closest to SoluPrep in term of IPA strength (i.e., 63.14% w/w vs. 64.1% w/w) and the surface area involved with a 26-mL product, i.e., two hands and forearms (≈ 2540 cm^2) vs. 2500 cm^2. Wittmann et al. used the IPA-containing product as a preoperative skin preparation.

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 (≈ 2540 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 (25^{th} – 75^{th} percentile: 3.27 – 7.47 mg/L). The estimated amount dermally absorbed was median 321 mg (25^{th} – 75^{th} percentile: 472 – 575 mg), which accounted for 0.4% (0.3 – 0.5%) of total applied amount, 110.62 g of IPA. The other results under scenarios with less exposure for IPA are summarized in Table 3.

***Reviewer's comment:** the sponsor estimated the applied area of two hands and forearms for surgical hand rub at 2540 cm^2 although the exact size of the applied areas was not disclosed in the publication. While the sponsor did not clarify the estimation method for the applied area, it seems reasonable based on the reviewer's assessment referring to 'Exposure Factors Handbook (UP EPA 2011)': the average surface area in adult male > 21-year-old for hands and forearms is 1070 cm^2 and 1480 cm^2, respectively.*

Wittmann et al. (1992) investigated the absorption of IPA after preoperative skin preparation of 26 children and young adults aged 1 month to 23 years with a product containing 49.8% IPA. The applied

[14] Below, H., et al., "Dermal and Pulmonary Absorption of Propan-1-ol and Propan-2-ol From Hand Rubs," American Journal of Infection Control, 40:250-257, 2012.
[15] Wittmann S, Gilg T, Dietz HG, Grantzow R, Peschel O, von Meyer L. Isopropanol and acetone serum levels after presurgical disinfection with isopropanol containing antiseptics. Blutalkohol. 1992;29:326-35.

area ranged 210 – 1920 cm^2 accounting for 1 to 16% of total body surface area in each individual whereas the total amount applied of IPA is unknown. Blood samples were taken before and at 10 minutes and 60 minutes after skin preparation. The ranges of IPA serum levels were 0.78 – 10.94 mg/L and 0.83 – 12.25 mg/L at 10 min and 60 min after applications, respectively.

The other three publications cited, i.e., **Brown et al. (2007)[16], Turner et al. (2004)[17],** and **Kirschner et al. (2009)[18]**, studied IPA-containing products with even lower strengths than SoluPrep or smaller applied areas under different usage patterns from a surgical skin preparation. The results of the other three studies are summarized in Table 3.

Cross-reference to the clinical pharmacology safety for IPA of DuraPrep (NDA 21-586)

The sponsor proposed to establish the clinical pharmacology safety of IPA of SoluPrep by cross-referencing information of safety and effectiveness from NDA 21-586 for DuraPrep Surgical Solution [Iodine Povacrylex (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w)].

However, the cross-reference to NDA 21-586 of DuraPrep is deemed inapplicable because DuraPrep differs from SoluPrep in terms of active ingredients, formulation, and application regimen (Table 2). The safety and effectiveness data of IPA in DuraPrep is confounded by iodine so it cannot be used to establish the clinical pharmacology safety of IPA of SoluPrep. Furthermore, dermal absorption of IPA was not evaluated in NDA 21-586 of DuraPrep and DuraPrep is applied with a lower dose of IPA per cm^2 than SoluPrep (5.701 mg/cm^2 vs. 5.840 mg/cm^2) (Table 2).

Table 2. Comparison of exposure to IPA between SoluPrep and DuraPrep

	SoluPrep (NDA 208288)	DuraPrep (NDA 21586)
Active ingredients	CHG 2%/IPA 70%	Iodine 0.7%/IPA 74%
Strength of IPA	70% (v/v)= 64.1% (w/w)	74% (w/w)
Amount of IPA in a single product (g)	14.60 g in 26 mL	16.55 g in 26 mL
Maximum skin coverage (cm^2)	19.5*19.5 $inch^2$ = 380.25 $inch^2$ = 2500 cm^2	15*30 $inch^2$ = 450 $inch^2$ = 2903 cm^2
Applied dose per cm^2 (mg/cm^2)	5.840 mg/cm^2	5.701 mg/cm^2

Conclusion

Based on the literature provided, assuming no other factors increasing dermal absorption of IPA, the relative proportion of IPA absorbed is expected to be very low, approximately 0.4%-1.1% of the applied

[16] Brown TL, Gamon S, Tester P, et al. Can alcohol-based hand-rub solutions cause you to lose your driver's license? Comparative cutaneous absorption of various alcohols. Antimicrobial Agents and Chemotherapy. 2007;51(3):1107-8.
[17] Turner P, Saeed B, Kelsey MC. Dermal absorption of isopropyl alcohol from a commercial hand rub: implication for its use in hand decontamination. J Hosp Infect. 2004;56:287-90.
[18] Kirschner MH, Lang RA, Breuer B, et al. Transdermal resorption of an ethanol- and 2-propanol-containing skin disinfectant. Langenbecks Arch Surg. 2009;394:151-7.

dose. The highest blood level of IPA across the publications provided was 12.25 mg/L which is far below than 500 mg/L that may cause mild CNS depression.

However, SoluPrep's potential dermal absorption for IPA after use as a preoperative skin preparation could not be fully addressed with the literature submitted because none of the literature covered the maximal usage condition of SoluPrep, i.e., single application of four 26-mL products to 10,000 cm^2 area. Moreover, the potential impact of 2% CHG on dermal absorption of IPA has not been addressed yet.

Even so, from a clinical pharmacology perspective, considering both the typical usage pattern of preoperative skin preparation (i.e., single-use application) and the known pharmacokinetic information of IPA (e.g., readily eliminated from the bloodstream through metabolism into acetone and CO_2 followed by excretion via urine and air), the submitted data is acceptable to justify the usage of SoluPrep as a preoperative skin preparation; in other words, it is not likely to cause significant systemic exposure that may arise an safety concern, e.g., > 500 mg/L. This determination is not warranted for other IPA-containing products where chronic uses are expected, however.

Table 3. Study results of dermal absorption of isopropyl alcohol following topical applications (SDN 53)

Source	Indication	Strength (w/w)	Dose of IPA per application (g)	Number of applications /time duration	Total IPA dose applied (g)	(Estimated) Applied body surface area (cm^2)	Total applied IPA dose per cm^2 (mg/cm^2)	Highest Observed IPA Blood Concentration (mg/L)	Estimated Absorbed Dose (if applicable) (g or mg)
Maximal use condition of SoluPrep	Pre-OP skin preparation	64.1%	14.60 g in 26 mL	Four 26-mL applicators Single-use	58.40 g (Four 26-mL applicators)	2500 cm^2 *4 = 10000 cm^2 (for a major surgery)	5.840 mg/cm^2	NA	NA
Below et al. (2012)	Hygienic hand rub Experiment 1	63.14%	2.21 g in 4 mL (calculated by dividing 44.25g/20) 4 mL applied to the hands and rubbed for 30 seconds. After waiting 1 minute this procedure was repeated for a total of 20 hand rubs	20 hygienic hand rubs (4 mL/rub) for 10 minute exposure over 30 min	44.25 g	1104.5 cm^2	40.06 mg/cm^2	5.3 mg/L	310 mg (0.7 % of applied dose)
Below et al. (2012)	Surgical hand rub Experiment 1	63.14%	2.21 g in 4 mL Each 3 minute application cycle = 20 mL	Ten 20-mL applications. 30 minute exposure over an 80-minute time period.	110.62 g	2540 cm^2	43.55 mg/cm^2	5.8 mg/L	472 mg (0.4 % of applied dose)

Table 3. Study results of dermal absorption of isopropyl alcohol following topical applications (SDN 53) (continued)

Source	Indication	Strength (w/w)	Dose of IPA per application (g)	Number of applications /time duration	Total IPA dose applied (g)	(Estimated) Applied body surface area (cm^2)	Total applied IPA dose per cm^2 (mg/cm^2)	Highest Observed IPA Blood Concentration (mg/L)	Estimated Absorbed Dose (if applicable) (g or mg)
Below et al. (2012)	Hygienic hand rub Experiment 1	45.0%	1.53 g in 4 mL (calculated by dividing 44.25g/20) 4 mL applied to the hands and rubbed for 30 seconds. After waiting 1 minute this procedure was repeated for a total of 20 hand rubs	20 hygienic hand rubs (4 mL/rub) for 10 minute exposure over 30 min	30.64 g	1104.5 cm^2	27.74 mg/cm^2	4.9 mg/L	310 mg (1.0 % of applied dose)
Below et al. (2012)	Surgical hand rubs Experiment 1	45.0%	1.53 g in 4 mL Each 3 minute application cycle = 4 mL X 5 = 20 mL/cycle. Ten cycles were performed.	Ten 20-mL applications = 200 mL. 30 minute exposure over an 80-minute time period.	76.6 g	2540 cm^2	30.16 mg/cm^2	10.0 mg/L	569 mg (0.7 % of applied dose)
Below et al. (2012)	Hygienic and Surgical hand rub Experiment 3	63.14%	2.21 g in 4 mL 1-Hygienic hand rub and 3-Surgical hand rub	Surgeons were exposed to a mean total of 33 mL of hand rub for 5 minute over 280 minutes.	18.25 g	2624 cm^2	7 mg/cm^2	1.74 mg/L	151 mg (0.8% of applied dose)
Below et al. (2012)	Hygienic and Surgical hand rub Experiment 2	45.0%	1.53 g in 4 mL 1-Hygienic hand rub and 3-Surgical hand rub	Surgeons were exposed to a mean total of 33 mL of hand rub for 5 minute exposure over 280 minutes.	12.64 g	2624 cm^2	4.8 mg/cm^2	2.56 mg/L	137 mg (1.1% of applied dose)

Table 3. Study results of dermal absorption of isopropyl alcohol following topical applications (SDN 53) (continued)

Source	Indication	Strength (w/w)	Dose of IPA per application (g)	Number of applications /time duration	Total IPA dose applied (g)	(Estimated) Applied body surface area (cm^2)	Total applied IPA dose per cm^2 (mg/cm^2)	Highest Observed IPA Blood Concentration (mg/L)	Estimated Absorbed Dose (if applicable) (g or mg)
Kirschner et al. (2009)	Skin disinfectant	10.0%	1.66 g in 20 mL	15 mL applied using a 200 cm2 gauze swab for 10 minutes. Waiting 5 min another 5 mL applied to ensure the skin area was kept wet continuously. The gauze swab remained on the skin for 10 minutes.	1.66 g	200 cm^2	8.3 mg/cm^2	3.0 mg/L	All data indicate that there was no clinical relevant sign of enhancement of dermal absorption within 1 hour after application
Brown et al. (2007)	Hand rub	62.9%	0.8256 g in 1.5 mL	30 applications over 60 minutes	24.768 g	1034 cm^2	23.95 mg/cm^2	All serum IPA levels were un-recordable. Lower limit of quantitation: 0.002 g/100 mL [%]	No detectable serum absorption could be detected. Lower limit of detection 0.0001 g/100 mL [%]
Turner et al. (2004)	Hand rub	52.6%	1.436 g in 3 mL	24 applications over 4 hours	34.464 g	1069 cm^2	32.24 mg/cm^2	1.8 mg/L	Not provided. The results of this small study indicate that IPA can be absorbed through intact skin in healthy human adults.

Table 3. Study results of dermal absorption of isopropyl alcohol following topical applications (SDN 53) (continued)

Source	Indication	Strength (w/w)	Dose of IPA per application (g)	Number of applications /time duration	Total IPA dose applied (g)	(Estimated) Applied body surface area (cm^2)	Total applied IPA dose per cm^2 (mg/cm^2)	Highest Observed IPA Blood Concentration (mg/L)	Estimated Absorbed Dose (if applicable) (g or mg)
Wittmann et al. (1992)	Preoperative skin disinfection	55.314%	0.498 g in 1 mL	Skin disinfection for planned surgical procedure. Details of product application (number/time duration) was not provided.	The IPA quantity used for disinfection couldn't be determined.	363 cm^2	The IPA quantity used for disinfection couldn't be determined, therefore the applied dose per cm^2 could not be calculated.	12.25 mg/L	Between 1.19 and 141.18 mg.

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/s/

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