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APPLICATION NUMBER:

210872Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	210872
Supporting document/s:	1
Applicant's letter date:	29 June 2018
CDER stamp date:	29 June 2018
Product:	ZuraGard™ (Isopropyl Alcohol 70% v/v) Solution
Indication:	Patient preoperative skin preparation
Applicant:	Zurex Pharma, Inc. 2113 Eagle Drive Middleton, WI ·53562
Review Division:	Nonprescription Drug Products
Reviewer:	D. Charles Thompson, RPh, PhD, DABT
Team Leader:	Jane J. Sohn, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Sherry A. Stewart, PharmD

Disclaimer

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1 Executive Summary

1.1 Introduction

Zurex Pharma, Inc., has submitted a 505(b)(2) NDA 210872 in support of market approval for ZuraGard™ (originally proposed as ZuraPrep) (Isopropyl Alcohol 70% v/v) Solution, a drug-device combination product proposed for use as a topical antiseptic/ antimicrobial agent in patient preoperative skin preparation.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor is relying on previous FDA findings of safety for a related product, ChloraPrep® (NDA 020832), for their primary nonclinical support. The only original nonclinical data required by FDA were those from a 21-day dermal toxicity study in minipigs. Such a study was submitted and found to be adequate and negative for any evidence of safety concerns regarding the drug product, including the potential for any significant systemic absorption of the methylene blue excipient. Assessments of the safety of the proposed excipients and of proposed and/or anticipated drug product impurities were also submitted and are supportive of the safety of the drug product under anticipated clinical use.

1.3 Recommendations

1.3.1 Approvability: Approvable

1.3.2 Additional Nonclinical Recommendations: None

1.3.3 Labeling

The Sponsor's proposed labeling for inclusion on the drug package insert is as shown below. This is acceptable from a nonclinical perspective.

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2 Drug Information

2.1 Drug

CAS Registry Number: 67-63-0

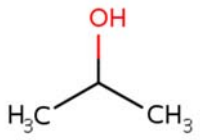
Generic Name: Isopropyl alcohol; isopropanol; 2-propanol

Code Name: N/A

Chemical Name: 2-propanol

Molecular Formula/Molecular Weight: C_3H_8O/60.095

Structure:



Pharmacologic Class: Antiseptic

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 020832 (ChloraPrep® [2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol]; Becton Dickinson and Co.); IND 117045

2.3 Drug Formulation

The proposed drug product formulation is a non-sterile, blue solution of isopropanol (IPA) in water as summarized in the Sponsor's Table 2.3.P.1-1 below. 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 Sponsor's schematic diagram reproduced below).

Table 2.3.P.1-1. Components of ZuraPrep (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)				

(b) (4)

2.4 Comments on Novel Excipients

As noted in the original review of IND 117045 (R.T. Dorsam, 2014), the levels of (b) (4) citrate (b) (4) and methylene blue (b) (4) exceed levels previously used as excipients in approved topical solutions. Dr. Dorsam did note that "Both ingredients have extensive prior human exposure and appear reasonably safe at these doses in the context of these proposed trials." Per Agency guidance, the Sponsor conducted a 21-day repeated dose dermal toxicity study in minipigs and submitted it to the IND for review (R.T. Dorsam, 2014).

In addition, the Sponsor also included with the original IND 117045 submission, and again with the current NDA submission, a risk assessment document entitled, "Safety Data Review of ZuraPrep™ Ingredients." The document was written by Paul Baldrick and Emmeline Klein and dated 5 February 2013. Of note, at the time the document was written, the Sponsor was asserting that (b) (4) Methylparaben and propylparaben are (b) (4)

(b) (4) in the formulation." The Sponsor has subsequently amended their position to assert that ZuraGard™ is a single-active drug product (i.e., isopropanol 70%).

The submitted document (Baldrick and Klein, 2013) reviews publicly available data and information in arriving at the following overall conclusion regarding the safety of each of the individual constituents and of the ZuraGard™ formulation as a whole:

> "A review of the available safety data for citric acid (b) (4) (b) (6) (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™ (b) (4) respectively, for citric acid (b) (4) (b) (6) (b) (4), methylene blue (b) (4), methylparaben, propylparaben and 70% isopropyl alcohol). In addition, there are no safety concerns from the topical application (b) (4) as contained in the final formulation of ZuraPrep™. Finally, Zurex Pharma Inc. is planning to perform a 14-day [subsequently amended to 21-day per FDA guidance] dermal toxicity study in the minipig to assess the tolerance and toxicity of 70% isopropyl alcohol and the final formulation of ZuraPrep™."

Regarding the safety of methylene blue, it should also be noted that, subsequent to Dr. Dorsam's original IND 117045 review, FDA approved PROVAYBLUE® (methylene blue injection, 5 mg/mL) (NDA 204630, approved 8 April 2016), indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia. These data were not pivotal to the approval of NDA 210872.

Approved labeling for PROVAYBLUE® describes nonclinical safety findings for methylene blue, including positive signals in in vitro and in vivo genetic toxicity studies, oral embryofetal development studies in rats and rabbits, and 2-year oral carcinogenicity studies in rats and mice (see Dr. B.J. Gehrke review, NDA 204630, dated 2 March 2016, and others referenced therein). Of note, the label for PROVAYBLUE® identifies that MB is a carcinogen and induces abortions and malformations. Importantly, these data do not appear to be relevant to the proposed nonprescription product, based on data that MB was not detected circulating in plasma following repeated dermal application in the minipig toxicity study previously discussed above.

Based on internal discussions of all the carcinogenicity and EFD data with Dr. Paul Brown (OND/IO, email 11 November 2018), it is concluded that the proposed levels of MB do not raise safety concerns from the nonclinical perspective.

In conclusion, as part of a Pre-NDA meeting with the Sponsor discussing nonclinical data requirements to support an NDA, FDA confirmed that "the nonclinical data and information submitted to date appear to support the safety of the proposed drug product formulation with a preoperative skin preparation indication" (Meeting Minutes, 12 April 2018). This reviewer concurs with this overall assessment and agrees that the proposed

use and use levels of excipients in the drug product are acceptable from a nonclinical perspective.

2.5 Comments on Impurities/Degradants of Concern

The Sponsor was advised in a Pre-NDA meeting (Meeting Minutes, 12 April 2018) to "ensure that your NDA addresses and provides adequate safety qualification support for any drug product impurities" and also to "provide a safety assessment of extractables and leachables with submission of your NDA."

Degradant Impurities

In their NDA submission, the Sponsor proposes DP specifications that include the following:

Isopropyl alcohol (%v/v)	(b) (4)	SOP-TM-0002
Identification (FTIR)[a]	Conforms to standard	USP <854>
Total impurities (%)	NMT (b) (4)	
(b) (4)	NMT	
	NMT	SOP-TM-0005
	NMT	
	NMT	
	NMT	
	(b) (4) mg/mL	SOP-TM-0001

In addressing the safety of the drug product impurities that exceed the ICH M7 threshold of toxicological concern and the ICH Q3B(R2) qualification threshold, namely, (b) (4)

The risk assessment document also references the JECFA acceptable daily intake of 14 mg/kg body weight of (b) (4) The administered test article in the studies evaluated by JECFA in its assessment was described as (b) (4) (b) (4) (b) (4)

(b) (4)

To further address systemic toxicity, Dr. Stewart provides justification for the proposed amount of impurities based on the amount of (b) (4) that animals received in the 21-day repeat dose dermal study (Study #ZX-ZP-0003/8276397). Review of the certificate of analysis (CoA) of Lot #ZP0003A shows that the test article applied to animals contained (b) (4) This is consistent with Dr. Stewart's calculation that approximately (b) (4) of labeled concentration of the test article was (b) (4) and, thus, animals received an applied dose of approximately (b) (4) mg/kg/day of (b) (4).

Regarding local toxicity/tolerability, this was assessed in the 21-day minipig dermal toxicity study, in which animals were exposed to approximately (b) (4) related impurities, as previously discussed above. This is comparable to the level of NMT (b) (4) impurities that the Sponsor proposes. Importantly, minimal toxicity was observed in this study (R.T. Dorsam, 2014).

The Sponsor's justification for the specified impurities is summarized below with the excerpted conclusion from Dr. Stewart's risk assessment document.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

"In conclusion, the topical application of ZuraPrep™ containing up to (b) (4) mg/mL (b) (4) (b) (4) is unlikely to be a cause of concern with respect to human safety."

This reviewer concurs with the Sponsor's submitted overall safety assessment of the (b) (4) impurities as summarized above. The totality of the information discussed, in conjunction with the low order of dermal toxicity demonstrated in the Sponsor's 21-day toxicity study in minipigs (R.T. Dorsam, 2014), provide reasonable assurance of safety and support the acceptability of the proposed drug product specification levels (b) (4).

Container Closure System Impurities

In addition, per FDA guidance, the Sponsor submitted a risk assessment document addressing the potential for, and any potential human health hazards posed by, leachable/ extractable impurities entering the drug product formulation from the container closer system. (b) (4)

Review of the device studies described in this risk assessment is deferred and the reader is referred to the OPQ review and/or the consultative input from CDRH for evaluation of the sufficiency and adequacy of these studies and their interpretation. The OPQ team reviewed the leachable/extractable information contained in the submission and did not identify any safety concerns for consideration by the Pharm/Tox team.

2.6 Proposed Clinical Population and Dosing Regimen

The product is proposed for use as a preoperative patient skin antiseptic agent. The drug product formulation is contained in a 10.5-mL applicator sponge device that is to be applied to a maximal skin surface area of approximately 8.4 inches x 8.4 inches (457 cm^2). Depending on whether the skin application area is dry or moist, the product should be applied in a back-and-forth scrubbing motion for from 30 seconds to 2 minutes and then allowed to completely dry before initiating the surgical procedure. The product is labeled to be used "…with care in premature infants or infants 2 months of age."

2.7 Regulatory Background

NDA 210872 was originally received on 29 June 2018 following development under IND 117045, which was received on 16 April 2014 and allowed to proceed (R.T. Dorsam, 2014). The Sponsor submits the application as "…a 505(b)(2) submission, relying upon the Food and Drug Administration's findings of safety for ChloraPrep (New Drug Application 020-832) as ZuraPrep and ChloraPrep both contain the same active

ingredient isopropyl alcohol 70% v/v, and have the same dosage form, route of administration, and indication for use." A Pre-NDA meeting was held with the Sponsor on 13 March 2018 (Meeting Minutes, T.M. Michele, 12 April 2018). In this meeting the Sponsor was advised that the previously submitted and reviewed (R.T. Dorsam, 2014) 21-day dermal minipig study would be the only nonclinical safety data required to support an NDA submission, with the following caveats:

> "A final determination as to the adequacy of the data will be a review issue after a full evaluation of all available information at the time of the NDA submission. Ensure that your NDA addresses and provides adequate safety qualification support for any drug product impurities….When you demonstrated the use of your proposed product during the meeting, we noted the plastic (b) (4) for your drug product. Provide a safety assessment of extractables and leachables with submission of your NDA."

3 Studies Submitted

The following nonclinical studies were included in the submission:

- Study 8276397 (ZX-ZP-0003): 21-Day Dermal Toxicity Study with ZuraPrep™ in Minipigs.
- Study 8285539 (ZX-ZP-0021): Validation of a Method for the Determination of Methylene Blue in Minipig Plasma by HPLC with MS/MS Detection.
- Study 15T_48780_04 (ZX-ZP-0063): ZuraPrep™ Applicator Foam Pad—Cytotoxicity Study Using the ISO Agarose Overlay Method.
- Study 15T_48780_06 (ZX-ZP-0064): ZuraPrep™ Applicator Foam Pad—ISO Closed Patch Sensitization Study in Guinea Pigs.
- Study 15T_48780_05 (ZX-ZP-0065): ZuraPrep™ Applicator Foam Pad—ISO Skin Irritation Study in Rabbits.
- Study 05T_35190_02: Methlock 0.05% with MP/PP—USP and ISO Modified Systemic Toxicity Study (Solution).
- Study 05T_35190_04: Methlock 0.05% with MP/PP—USP Modified Intracutaneous Study with Histopathology (Solution).
- Study 16T_50770_02/16T_50770_03 (ZX-ZP-0077): ZuraPrep™ 10.5mL Vial/Cap (Ampule)—ISO 10993-18 - Chemical Characterization.
- Study 16T_50772_13/16T_50772_14 (ZX-ZP-0 079): ZuraPrep™ 10.5mL Applicator Body—ISO 10993-18 - Chemical Characterization.
- Study 16T_50766_02/16T_50766_03 (ZX-ZP-0080): ZuraPrep™ 10.5mL Foam—ISO 10993-18 - Chemical Characterization.

Also included in the submission were the following risk assessment documents:

- P. Baldrick and E. Klein (2013). Safety Data Review of ZuraPrep™ Ingredients.
- (b) (4) (b) (4).

- (b) (4)
- J. Murphy, L. Dupuis, and S. Cooper (2018). Risk Assessment of Oral Dose (Topical) products to meet the Elemental Impurities requirements of ICH Q3D and USP <232> and <233>.

3.1 Studies Reviewed

The following studies were reviewed previously under IND 117045 (R.T. Dorsam, 2014) and are incorporated herein by reference:

- Study 8276397 (ZX-ZP-0003): 21-Day Dermal Toxicity Study with ZuraPrep™ in Minipigs.
- Study 05T_35190_02: Methlock 0.05% with MP/PP—USP and ISO Modified Systemic Toxicity Study (Solution).
- Study 05T_35190_04: Methlock 0.05% with MP/PP—USP Modified Intracutaneous Study with Histopathology (Solution).

3.2 Studies Not Reviewed

Review of the following studies is deferred pending consultative input by CDRH:

- Study 15T_48780_04 (ZX-ZP-0063): ZuraPrep™ Applicator Foam Pad—Cytotoxicity Study Using the ISO Agarose Overlay Method.
- Study 15T_48780_06 (ZX-ZP-0064): ZuraPrep™ Applicator Foam Pad—ISO Closed Patch Sensitization Study in Guinea Pigs.
- Study 15T_48780_05 (ZX-ZP-0065): ZuraPrep™ Applicator Foam Pad—ISO Skin Irritation Study in Rabbits.
- Study 16T_50770_02/16T_50770_03 (ZX-ZP-0077): ZuraPrep™ 10.5mL Vial/Cap (Ampule)—ISO 10993-18 - Chemical Characterization.
- Study 16T_50772_13/16T_50772_14 (ZX-ZP-0 079): ZuraPrep™ 10.5mL Applicator Body—ISO 10993-18 - Chemical Characterization.
- Study 16T_50766_02/16T_50766_03 (ZX-ZP-0080): ZuraPrep™ 10.5mL Foam—ISO 10993-18 - Chemical Characterization.

3.3 Previous Reviews Referenced

- NDA 204630: Carcinogenicity Assessment Committee (CAC/CAC-EC) Report, Brenda J. Gehrke, PhD, 25 March 2014.
- IND 117045: Pharmacology/Toxicology IND Review and Evaluation, Robert T. Dorsam, PhD, 13 June 2014.
- NDA 204630: Pharmacology/Toxicology NDA Review and Evaluation, Brenda J. Gehrke, PhD, 28 May 2014.
- NDA 204630: Pharmacology/Toxicology Memorandum, Brenda J. Gehrke, PhD, 2 March 2016.
- IND 117045: Meeting Minutes, Theresa M. Michele, MD, 12 April 2018.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 21-Day Dermal Toxicity Study with ZuraPrep™ in Minipigs

Study no.:	8276397 (ZX-ZP-0003)
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	13 June 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Zuraprep™, lot ZP0003A

Methods

Doses:	See Sponsor's tabular summary below
Frequency of dosing:	Daily for 21 consecutive days
Route of administration:	Topical application to the clipped dorsal interscapular skin (approximately 15 cm x 25 cm, or 375 cm^2). The material was applied uniformly using a scrubbing motion for approximately 2 minutes. The area was then wrapped with an occlusive dressing. The dressing was removed each day after 6 hours. The site was then wiped with soap and paper towels that were moistened with tap water.
Dose volume:	21.5 mL/animal/day applied using a disposable syringe.
Formulation/Vehicle:	70% isopropyl alcohol
Species/Strain:	Minipig/ (b) (4)
Number/Sex/Group:	3
Age:	6-7 months at dosing initiation
Weight:	M: 12.6-15.1 kg; F: 13.4-18.3 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	"The acclimation period was 8 weeks instead of 2 weeks. The occlusive dressing was found to be off a single animal on Day 1, a female on Day 11, and 3 males plus 1 female on Day 12. Other minor protocol deviations also occurred during the study, though none of these deviations significantly impact the interpretation of the study."

3.1.5 Study Design

Group[a]	No. of Animals Male	No. of Animals Female	Dose Volume (mL/animal/day)
1 (Vehicle Control Article)	3	3	21.5
2 (Control Article)	3	3	21.5
3 (Test Article)	3	3	21.5

a Group 1 received vehicle control article (70% isopropyl alcohol) and Group 2 received control article (sterile saline).

Summary Description and Conclusions

This study was previously reviewed under IND 117045 by Dr. Robert Dorsam, whose summary is reproduced below. The reader is referred to the original review (R.T. Dorsam, 2014) for further details.

> "A 21-repeat dose toxicology study in minipigs was conducted with 3 animals/sex/group receiving 21.5 mL of isopropyl alcohol, saline, or Zuraprep over a 15 X 25 cm area (375 cm2) of skin. In this study, animals received 57.3 µL of Zuraprep per square cm of skin area. Males and females in the Zuraprep group had similar body weight, food consumption, clinical signs, hematology parameters, clinical chemistry parameters when compared with the groups that received saline and isopropyl alcohol. Aside from the expected blue discoloration from methylene blue, there were no gross pathological or histopathological changes in the animals that received Zuraprep. The dermal response was monitored throughout the study; however, no dermal irritation was observed for animals in the Zuraprep group. The sponsor also attempted to measure plasma levels of methylene blue, though all plasma levels were below the level of detection (0.3 ng/mL). The Zuraprep group had low systemic exposure to methylene blue in this study. Zuraprep was not irritating after 21 consecutive days of treatment."

10 Special Toxicology Studies

The following studies were previously reviewed under IND 117045 by Dr. Robert Dorsam, whose summaries are reproduced below. These studies (b) (4) The reader is referred to the original review (R.T. Dorsam, 2014) for further details.

Study title: USP Modified Intracutaneous Study with Histopathology Solution: Test Article – MethLock 0.05% with MP/PP (Zuragen)

Study no.:	05T_35190_04
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	28 May 2005
Test species:	Rabbit/New Zealand White (2 males)
Test article:	MethLock 0.05% with methylparaben/ propylparaben; lot MBP040105, batch B501040.
Control article:	0.9% sodium chloride USP solution

Summary Description and Conclusions

"Intracutaneous injection of MethLock MP/PP in two rabbits (5 injection sites/rabbit) resulted in slight erythema at 24, 48, and 72 hours post injection. Histopathological changes were limited to a single focus of macrophages in one injection site of test article. Under the conditions of this study, the MethLock MP/PP was non-irritating" (R.T. Dorsam, 2014).

Study title: USP and ISO Modified Systemic Toxicity Study Solution: Test Article – MethLock 0.05% with MP/PP (Zuragen)

Study no.:	05T_35190_02
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6 June 2005
Test species:	Mouse/Crl:CF-1 BR (10 males/group)
Test article:	MethLock 0.05% with methylparaben/ propylparaben; lot MBP040105, batch B501040.
Control article:	0.9% sodium chloride USP solution
Dose	10 µL/g body weight
Route	Intravenous
Modification	The protocol for USP and ISO 10993 was modified to increase the observations from 72 hours to 7 days and to use Zuragen rather than an extract.

Summary Description and Conclusions

"Mice were monitored for 7 days after receiving intravenous injections of Zuragen (10 µL/g body weight) or saline. All mice survived through the completion of the study. During the 7-day post-dose observation period, mice had normal clinical signs and similar body weights as control animals that were injected with saline" (R.T. Dorsam, 2014).

11 Integrated Summary and Safety Evaluation

With this 505(b)(2) NDA 210872, Zurex Pharma, Inc., proposes market introduction of ZuraPrep™ (isopropyl alcohol 70%) solution as a topical antiseptic/ antimicrobial agent for use as a patient preoperative skin preparation drug product. The to-be-marketed dosage form consists of a single-use, 10.5-mL plastic (b) (4) applicator containing the non-sterile ZuraPrep solution with a sterile barrier system to ensure that the applicator surfaces (b) (4) are sterile.

Development for this drug/ device combination product was carried out under IND 117045. 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 020832), 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 submission 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 request, the Sponsor has 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, it was only the levels of (b) (4) citrate (b) (4) and methylene blue (b) (4) that are noted to exceed levels previously used as excipients in approved topical solutions. 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.

Drug product degradant impurities that exceed the ICH Q3B(R2)-prescribed qualification limits consist (b) (4) The safety of (b) (4) impurities is 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 (b) (4) The safety conclusion of this risk assessment is driven largely by FDA/CFSAN findings that (b) (4) is (b) (4) for multiple food uses with no limitation other than current good manufacturing practice (b) (4) Cosmetic uses of (b) (4) were also reviewed and discussed. Overall, this reviewer concurs with the Sponsor's assertion and concludes that the preponderance of available information supports a finding that the proposed drug product impurity specification limits (b) (4) do not raise safety concerns from a nonclinical perspective.

Finally, drug product impurities that may potentially arise from the container closure system (i.e., leachable/extractable impurities) were also addressed by the Sponsor via submission of a contracted, third-party risk assessment document prepared by the (b) (4) The Sponsor concludes, based on this risk assessment, that "…the likelihood of a toxic effect from the ZuraPrep applicator is negligible and that the applicator can be considered safe for use as intended." Based on the totality of the data and information provided, this reviewer finds 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.

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/s/

DONALD C THOMPSON
01/07/2019 04:34:37 PM

JANE J SOHN
01/09/2019 09:24:48 AM
I concur.