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APPLICATION NUMBER:

208288Orig1s000

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:	208288
Supporting document/s:	59
Applicant's letter date:	9 February 2018
CDER stamp date:	9 February 2018
Product:	SoluPrep Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate & 70% v/v isopropyl alcohol)
Indication:	Patient preoperative skin preparation
Applicant:	3M Health Care Business (3M) 3M Center, Bldg. 0275-05-W-06 St. Paul, MN 55144-1000
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:	Celia R. Peacock, MPH, RDN

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208288 are owned by 3M for which the above-mentioned applicant has obtained a written right of reference. Any information or data necessary for approval of NDA 208288 that the applicant does not own or have a written right to reference constitutes one of the following: (1) published literature or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are included for descriptive purposes only and are not relied upon for approval of NDA 208288.

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1 Executive Summary

1.1 Introduction

The current submission constitutes the Sponsor's second resubmission of the 505(b)(2) NDA 208288 following two previous FDA Complete Response (CR) actions. The application proposes market registration of a drug product comprised of a sterile, film-forming antiseptic solution (chlorhexidine gluconate (CHG; 2% w/v) and isopropanol (IPA; 70% v/v)), along with 10.5-mL and 26-mL applicators, that is indicated for preoperative patient skin antisepsis in the OTC healthcare setting.

(b) (4) resulted in increased drug product instability relative to the approved non-sterile product, which has prompted the Sponsor to propose drug product impurity specifications that exceed safety qualification limits.

In the previous review cycle, Pharmacology/Toxicology recommended a Complete Response based on inadequate safety assessment of two drug product impurities. To address the deficiency, FDA recommended that the Sponsor submit new and adequate nonclinical data, or provide data from an adequately designed and conducted maximal use trial (MUsT) demonstrating that there is clinically insignificant systemic absorption of the two impurities of concern.

1.2 Brief Discussion of Nonclinical Findings

The current submission contains an amended study report for a repeat-dose dermal toxicity study in rabbits. The previous version of the study report, reviewed in the last cycle, was found to be inadequate to support the safety of the proposed increased impurity specifications.

The amended report provides data from new microscopic histopathological evaluations of organ tissues that had been collected and preserved in original terminal procedures, but were not originally examined. These new data do not identify any new and/or increased safety concerns with respect to the elevated impurity levels of the aged test article employed. However, provision of the new organ tissue analyses alone does not overcome the other deficiency of the original dermal rabbit study, which is an inadequate dosing regimen to support previous estimates of human systemic exposure to the two impurities of concern.

In lieu of conducting a new animal dermal toxicity study, the Sponsor elected to provide data from a clinical pharmacokinetic study (MUsT). Clinical Pharmacology determined this MUsT to be adequate and to validly demonstrate no quantifiable systemic (plasma) exposure to the two impurities of concern, based on the Sponsor's stated lower limit of quantitation (LLOQ; S. Yi, PhD, 27 June 2018). The LLOQ for this application is considered sufficient to address remaining nonclinical safety concerns, based on previously reviewed nonclinical data provided by the Sponsor (D.C. Thompson, 24 July 2017). Pharmacology/Toxicology did not evaluate if the LLOQ is consistent with state-of-the-art analytical capabilities that should be employed to detect compounds of concern.

To be clear, from a nonclinical perspective, Clinical Pharmacology's assessment and interpretation of the MUsT was considered in conjunction with the previously submitted data from adequate and negative assessments of the impurities for genotoxicity and rabbit dermal toxicity in arriving at a determination of safety of the proposed impurity specifications. In general, clinical MUsT data should be evaluated on a case-by-case basis by Pharmacology/Toxicology to determine whether such information can be leveraged to inform nonclinical assessment of safety. Pharmacology/Toxicology did not review the LLOQ of the Sponsor's MUsT from an analytical perspective. See the Integrated Summary for further details.

1.3 Recommendations

1.3.1 Approvability: The application is approvable from a nonclinical perspective, relying on the Clinical Pharmacology assessment that the MUsT study was adequately conducted to quantify and demonstrate clinically insignificant systemic (plasma) exposure to the two impurities of concern.

1.3.2 Additional Nonclinical Recommendations: None**.**

1.3.3 Labeling: See previous review (D.C. Thompson, 24 July 2017)**.**

2 Drug Information

2.1 Drug

CAS Registry Number: 18472-51-0 (CHG); 67-63-0 (IPA)

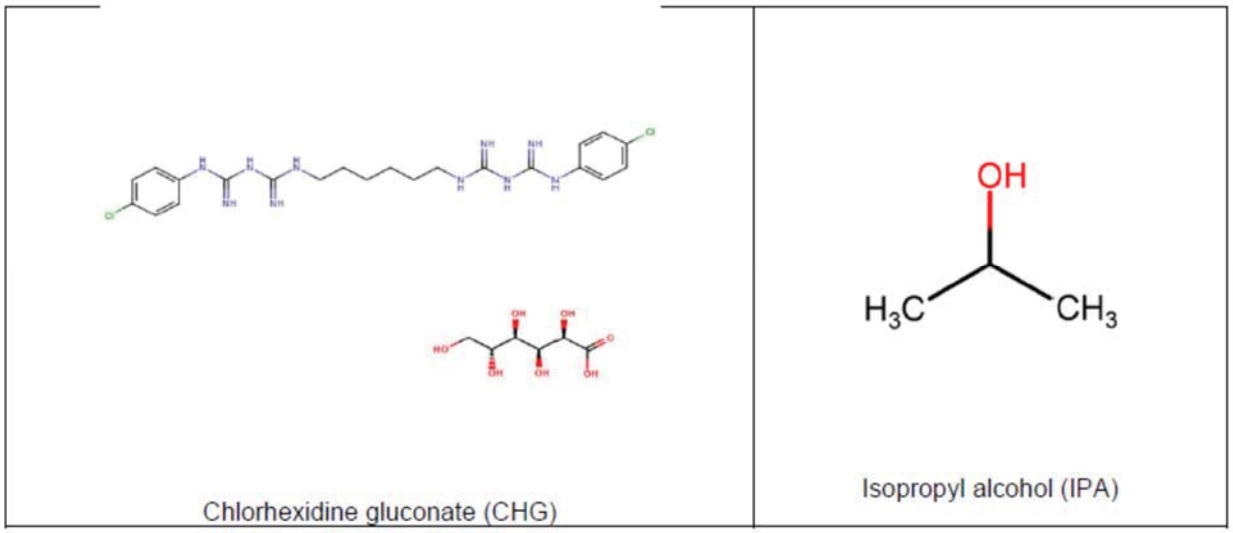
Generic Name: Chlorhexidine gluconate (CHG); isopropyl alcohol (IPA)

Code Name: N/A

Chemical Name: 1,1'-Hexamethylene bis(5-(p-chlorophenyl)biguanide), digluconate (CHG); 2-propanol or isopropanol (IPA)

Molecular Formula/Molecular Weight: $C_{22}H_{30}Cl_2N_{10}•2C_6H_{12}O_7$/897.7626 (CHG); C_3H_8O/60.095 (IPA)

Structure:



Pharmacologic Class: antiseptic

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 76,549

2.3 Drug Formulation

The proposed drug product formulation and presentation remain unchanged from the previous review cycle. Briefly, the proposed product is a drug-device combination, consisting of a film-forming antiseptic drug solution (tinted and non-tinted formulations) contained in a single-use, [(b) (4)] sealed glass ampoule (10.5 and 26 mL), which is housed in a [(b) (4)] plastic applicator having a [(b) (4)] sponge at the end. See Nonclinical Review #1 for further detail (D.C. Thompson, 24 July 2017).

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Due to drug product instability resulting from [(b) (4)] proposed specifications for two impurities, [(b) (4)] (NMT [(b) (4)] %) and [(b) (4)] [(b) (4)] (NMT [(b) (4)] %) remain above the qualification threshold per the ICH guidance for industry *Q3B(R2) Drug Product Impurities*. The reader is referred to previous Nonclinical Reviews and CR Letters for the application for further details and background information.

See also review of the amended study report for a repeat-dose dermal toxicity study in rabbits under General Toxicology and an updated interpretation of the rabbit study findings in view of the clinical MUsT data under the Integrated Summary.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed drug product is intended for use in preoperative patient skin antisepsis. Estimated daily patient exposure to CHG anticipated to result from product use remains unchanged from that discussed previously (D.C. Thompson, 24 July 2017).

2.7 Regulatory Background

NDA 208288 was originally received on 6 July 2015 following development under IND 76,549. Following first-cycle review, multiple deficiencies were identified in the application (Clinical, Clinical Pharmacology, Product Quality, Microbiology, and Nonclinical), which precluded approval and resulted in a CR action (CR letter, 6 May 2016). An initial resubmission was received on 3 March 2017 and was also determined to be deficient (CR letter, 1 September 2017). The current submission constitutes the Sponsor's resubmission of the NDA following the latest CR action.

3 Studies Submitted

As noted below, the only nonclinical study submitted in the current resubmission is an amended version of Study 16-014, a repeat-dose dermal toxicity study in rabbits. As was communicated in the most recent CR letter (CR Letter, 1 September 2017), review of the original version of Study 16-014 (D.C. Thompson, 24 July 2017) determined that microscopic histopathological evaluation was performed on an insufficient battery of organ tissues from study animals to fully assess the potential for systemic toxicity of the two drug product impurities of concern. The amended version of Study 16-014 now included in the current resubmission differs from the originally submitted version of the study report in two respects only:

- "Per Protocol Amendment 1, additional tissues were designated to be microscopically examined. Additional data have been included in the amended pathology report."
- "Per Protocol Amendment 2, qualitative microscopic examination and characterization of cell populations and M:E ratio relative to Group 1 of the bone marrow was conducted. Additional data have been included in the amended clinical pathology report."

These new study data reflect new evaluations of biological samples (organ tissues and bone marrow smears) collected and preserved as part of terminal procedures during the original study conduct (experimental termination date: 4 March 2016), but that were electively not evaluated at the time.

Thus, the review that follows of this amended Study 16-014 report will focus exclusively upon these newly submitted study data and their impact on overall study interpretation. The reader is referred to the previous nonclinical review (D.C. Thompson, 24 July 2017) for a full discussion and evaluation of the design, conduct, and findings of the original study.

3.1 Studies Reviewed

- Study 16-014: Systemic Toxicity of Aged vs. Fresh Solutions of MTDID 25415 Following Repeated Dermal Application to the Rabbit [AMENDED].

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- NDA 208288: Office of Clinical Pharmacology Review, S. Yi, PhD, 27 June 2018.
- NDA 208288: Pharmacology/Toxicology NDA Review and Evaluation #1, D.C. Thompson, RPh, PhD, DABT, 24 July 2017.
- NDA 208288: Complete Response Letter, T.M. Michele, MD, 1 September 2017.
- NDA 208288: Complete Response Letter, T.M. Michele, MD, 6 May 2016.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Systemic Toxicity of Aged vs. Fresh Solutions of MTDID 25415 Following Repeated Dermal Application to the Rabbit

Study no.:	16-014 [AMENDED]
Study report location:	EDR (Rabbit Dermal)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8 February 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MTDID 25415 (Aged), batch PPE-05RPROJ- 05-129395-0084-0084, CLIN C and CLIN D pooled; MTDID 25415 (Fresh), batch PPE-05R-PROJ-05-129395-0080-0080, 42-0027-7331-7 (b) (4) (b) (4)

Key Study Findings

- The Study Director for this study, as well as the Clinical and Anatomic Pathologists, were the same in all cases for both the amended and original study reports.
- Newly reported data from microscopic histopathological examinations of an expanded battery of organ tissues, including qualitative cytological evaluations of bone marrow smears, revealed no discernable effects that could be clearly attributed to the differences between fresh and aged drug product test articles and, specifically, to the elevated levels of impurities of the aged test article.
- Thus, these new data provide no evidence to support a change in the overall interpretation of the findings from the original review of Study 16-014 (D.C. Thompson, 24 July 2017), other than to now conclude that an adequate battery of organ tissues has been subjected to microscopic histopathological evaluation.

Methods

Doses:	4 doses @ 3.7 mL/dose; this equates with an applied dose of approximately (b) (4) mg/animal/day of the (b) (4) impurity and (b) (4) mg/animal/day of the (b) (4) impurity.
Frequency of dosing:	Once daily on Days 1, 5, 9, and 13 for 23-24 hr/day
Route of administration:	Topical dermal in the clipped inter-scapular area of the dorsum (approximately 12 cm x 20 cm, or 240 cm^2, area per application; not stated by the Sponsor, but this equates with approximately 16% BSA based 1500 cm^2 total BSA in a reference rabbit); test article was spread evenly over application site with the syringe tip and allowed to air dry for at least 5 minutes; the application area was then covered with Tegaderm™, followed by wrapping the entire trunk of the animal with Vetrap®; after a minimum 23 hours of exposure, the wrap and covering were removed and the application site gently wiped clean with a 10% Ivory soap in tap water solution.
Dose volume:	3.7 mL
Formulation/Vehicle:	Water
Species/Strain:	Rabbit/New Zealand White Hra:(NZW)SPF
Number/Sex/Group:	5 sex/dose group
Age:	7.0-7.5 Months
Weight:	M: 3.46-3.60 kg; F: 3.18-3.55 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None affecting the integrity or interpretation of the study data.

Summary Description and Conclusions

A report of Study 16-014 was originally included by the Sponsor in the first NDA Resubmission of 3 March 2017. Review of the study at that time (D.C. Thompson, 24 July 2017) concluded that an insufficient battery of organ tissues had been subjected to microscopic histopathological evaluation to adequately assess the potential for systemic toxicity of the two DP impurities of concern ((b) (4) (b) (4)). This inadequacy was identified as a primary deficiency of the application in the subsequent CR Action taken by the Agency (CR Letter, 1 September 2017).

In addressing the identified deficiency in the current resubmission, the Sponsor has amended the original report of Study 16-014 to include data from new microscopic examination of organ tissues and bone marrow smears, as summarized in the

Sponsor's table below (**bold/<u>underline</u>** text indicates newly evaluated tissues). Findings from these new evaluations are discussed in the appropriately headed paragraphs that follow.

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination
Adrenal glands	X	X	X
Aorta		X	<u>X</u>
Bone with bone marrow, femur (process distal end with tibiofemoral joint only)		X	<u>X</u>
Bone with bone marrow, femur (proximal)		X	<u>X</u>
Bone with bone marrow, sternum		X	<u>X</u>
Bone marrow smear		X	<u>X</u>
Brain	X	X	X
Epididymides		X	<u>X</u>
Esophagus		X	<u>X</u>
Eyes (with optic nerve)		X	<u>X</u>
Gallbladder		X	<u>X</u>
GALT (Gut-Associated Lymphoid Tissue)		X	<u>X</u>

Gross lesions (including tissue masses)		X	X
Heart	X	X	X
Kidneys	X	X	X
Large intestine, cecum		X	X
Large intestine, colon		X	X
Large intestine, rectum		X	X
Larynx		X	X
Liver	X	X	X
Lung with bronchi		X	X
Lymph node, mandibular		X	X
Lymph node, mesenteric		X	X
Mammary gland (process females only)		X	X
Nerve, sciatic		X	X
Ovaries	X	X	X
Oviducts		X	X
Pancreas		X	X
Pituitary gland		X	X
Prostate gland		X	X
Salivary gland, mandibular		X	X
Salivary gland, parotid		X	X

Seminal vesicles		X	X
Skeletal muscle, biceps femoris		X	X
Skin (treated)		X	X
Skin (untreated)		X	X
Small intestine, duodenum		X	X
Small intestine, ileum		X	X
Small intestine, jejunum		X	X
Spinal cord, cervical		X	X
Spinal cord, lumbar		X	X
Spinal cord, thoracic		X	X
Spleen	X	X	X
Stomach, cardia		X	X
Stomach, fundus		X	X
Stomach, pylorus		X	X
Testes	X	X	X
Thymus	X	X	X
Thyroid gland (with parathyroid)	X	X	X
Tongue		X	X
Trachea		X	X
Ureters		X	X
Ureters		X	X
Urinary bladder		X	X
Uterus with cervix		X	X
Vagina		X	X

Hematology

A signed and dated amended Study Clinical Pathologist's report was included in the submission. Bone marrow smears from all animals were stained (Wright-Giemsa) and evaluated microscopically. Qualitative characterization of all cell populations and myeloid: erythroid (M:E) ratios were reported.

Findings indicate there were no meaningful differences in bone marrow cytology between animals treated with fresh or aged drug product, as summarized by the Study Clinical Pathologist: "Minimal differences in individual findings in animals treated with aged test article relative to fresh test article were considered within an acceptable range for biologic variation. Megakaryocytes were generally observed in adequate numbers.

Both erythroid and myeloid cell lines were well represented and matured appropriate to completion. Cells from all lines appeared morphologically unremarkable."

Histopathology

Adequate Battery: Yes, as per amended tissue inventory (see above).

Peer Review: Not performed.

Histological Findings: A signed and dated amended Study Pathologist's report was included in the submission. Among the tissues newly subjected to microscopic examination, there were no discernible effects that were clearly attributable to the aged test article and, in particular, to its elevated levels of impurities.

11 Integrated Summary and Safety Evaluation

NDA 208288 proposes market authorization for SoluPrep Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate & 70% v/v isopropyl alcohol), which would be the first sterile pre-surgical skin antiseptic product available to U.S. health care practitioners. The application was originally received on 6 July 2015 following development under IND 76,549. The current submission constitutes the Sponsor's second resubmission following CR Actions by the Agency, the most recent on 1 September 2017.

The primary deficiency underlying the latest CR Action relates to proposed drug product impurity specifications for two impurities ((b) (4) (b) (4) that exceed the qualification threshold (≤ 1%) proscribed under ICH Q3B(R2). The elevated impurity levels derive from drug product instability resulting from (b) (4)

The Sponsor was advised in the last CR letter that part of the safety qualification data prescribed under ICH Q3B(R2) that they had submitted in the first resubmission—namely, the repeat-dose dermal toxicity study in rabbits (Study #16-014)— "…does not include a sufficient tissue battery to assess systemic toxicity." This aspect of the deficiency has been adequately addressed by the Sponsor, as discussed above, by their submission of additional data from new microscopic histopathological evaluations of organ tissues that were collected and preserved during conduct of the original study, but not examined microscopically. These new data do not identify any effects that are clearly attributable to the aged drug product test article and, specifically, to its elevated levels of impurities. Thus, they provide no evidence that changes the overall interpretation of the findings from that of the original review of Study 16-014 (D.C. Thompson, 24 July 2017), other than to now support a conclusion that an adequate battery of organ tissues has been subjected to microscopic histopathological evaluation.

However, in that same 1 September 2017 CR letter, the Sponsor was also advised that "…the doses administered in your rabbit dermal study do not appear to support your proposed impurity specifications for the 26 mL applicator, using the available data. This relies upon your proposed maximal use for the 26 mL applicator, the proposed impurity stability specifications, and conversion of the doses administered to animals to human equivalent doses….To resolve this deficiency, provide an adequate qualification study in a single animal species (e.g., a single extended dose study) or otherwise adequately address the systemic exposure to…" the impurities in question.

While Study #16-014 is now considered adequate from the perspective of the total battery of organ tissues subjected to microscopic histopathological examination, the adequacy of the doses employed in the rabbit study was not addressed by the additional tissue evaluation.

The Sponsor elected to address the identified deficiencies in the rabbit study dosing regimen by submitting data from a clinical pharmacokinetic study (MUsT). Clinical Pharmacology has determined this MUsT to be adequate and to validly demonstrate no quantifiable systemic (plasma) exposure to the two impurities of concern, based on the Sponsor's stated (b) (4) ng/mL lower limit of quantitation (LLOQ; S. Yi, PhD, 27 June 2018). For perspective, this (b) (4) ng/mL LLOQ equates to a quantifiable point estimate body burden of approximately (b) (4) µg/person of each impurity, based on an assumption of instantaneous equilibration into a reference total plasma volume of 3 L/person. By comparison, human subjects in the MUsT were topically dosed once with approximately (b) (4) mg of the (b) (4) impurity and (b) (4) mg of the impurity at (b) (4), based on clinical test article batch analyses indicating (b) (4) % and (b) (4) % of each respective impurity. Therefore, the (b) (4) µg/person LLOQ is approximately (b) (4) -fold lower than the amount of impurity applied topically to each study subject.

Furthermore, potential patient exposures to the impurities will likely be lower than the exposures in MUsT subjects. While the MUsT employed a test article containing (b) (4) % (b) (4) and (b) (4) % of the impurity at (b) (4) is proposing lower specifications of (b) (4) % (b) (4) and (b) (4) % of the impurity (b) (4). For example, preoperative treatment at a maximum usage of 4 x 26-mL applicators with the proposed lower specifications results in applied doses of approximately (b) (4) and (b) (4) mg/person of (b) (4) and the impurity (b) (4), respectively. These expected maximum doses for patients are lower than the doses employed in the MUsT (i.e., (b) (4) mg of the (b) (4) impurity and (b) (4) mg of the impurity (b) (4)).

Overall, Pharmacology/Toxicology interprets the Sponsor's reported clinical MUsT findings and associated level of analytical sensitivity in light of the totality of the nonclinical safety data provided for the impurities to date. These data include an adequate genotoxicity assessment that, briefly, incorporated isolation, purification, and testing of each impurity in a bacterial mutagenesis assay and an in vitro assay for chromosomal aberrations, all of which were valid and negative for any evidence of potential mutagenic risk (D.C. Thompson, 24 July 2017). Also provided were data from GLP-compliant assessments of local skin irritation and skin sensitization potential in

intact animals (rabbits and mice, respectively) that employed complete DP solution formulations that were either fresh or aged [redacted], the latter containing elevated levels of the two noted individual impurities and of total impurities. These data indicate a lack of any clinically relevant skin intolerance to drug product or impurities, from the nonclinical perspective.

Finally, Pharmacology/Toxicology perspective reflects the now confirmed lack of any clinically relevant test article-related local dermal or systemic findings in the amended rabbit dermal toxicity study. As discussed in the previous review (D.C. Thompson, 24 July 2017), this study incorporated repeated topical dermal doses (≥23 hr/day under occlusion) to the animals of approximately [redacted] mg/animal/day of [redacted] and [redacted] mg/animal/day of the impurity [redacted], applied over an area of approximately 240 cm^2. In the previous review, Pharmacology/Toxicology assumed 100% systemic bioavailability in the absence of any submitted animal TK data and human PK data. However, Clinical Pharmacology review supports an upper bound of likely human systemic exposure of approximately [redacted] µg/person, although this value reflects an estimate of systemic exposure only in the plasma, at a snapshot in time. It is still not possible to determine the plasma concentrations of the impurities of concern in the rabbit study and, therefore, a calculation of a safety margin is not possible. Further, Pharmacology/Toxicology notes the upper bound of likely human systemic exposure of approximately [redacted] µg/person represents a low level of risk, considering that the impurities of concern are not genotoxic. Importantly, the impurities are derived from CHG, as illustrated by the structures submitted by the Sponsor, and the MUsT data are reassuring that any systemic absorption of [redacted] is likely to be limited.

Therefore, in consideration of the totality of the information described herein, including the newly submitted clinical MUsT data indicating clinically negligible systemic absorption of the impurities of concern, nonclinical safety support of the proposed drug product impurity specifications is now considered to be adequate. The application is, thus, considered approvable from a nonclinical perspective.

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/s/

DONALD C THOMPSON
06/29/2018

JANE J SOHN
06/29/2018
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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Review Addendum

NDA: 208288
CDER stamp date: March 3, 2017
Product: SoluPrep Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate & 70% v/v isopropyl alcohol)
Indication: Patient preoperative skin preparation
Applicant: 3M Health Care Business (3M)
Division: Nonprescription Drug Products
Author: Jane J. Sohn, Ph.D., Team Lead

This is an addendum to the nonclinical review dated July 24, 2017 by Dr. D. Charles Thompson.

FDA's Discipline Review Letter dated August 11, 2017 included a nonclinical recommendation to address deficiencies in impurity qualification. In addition, it included a CMC recommendation to tighten specification limits for individual and total impurities.

At the time of this review, 3M had committed to establishing tentative specifications for (b) (6) and the impurity (b) (6) at NMT (b) (6)% and NMT (b) (6)%, respectively, per recommendation by CMC (refer to the CMC review dated August 23, 2017).

The decrease in the tentative specifications does not fully address the two nonclinical issues identified in the Discipline Review Letter. The first nonclinical issue was regarding inadequate dosing in the dermal rabbit study (#16-014). The decreased tentative specifications could address the inadequate dosing to *potentially* provide an adequate exposure margin >1 (rabbit: human) for the impurities in the 10.5 mL applicator. However, the decreased tentative specifications do not adequately address the proposed impurity specifications for the 26 mL applicator, which results in a higher dose of impurities than the 10.5 mL applicator.

The second nonclinical issue in the Discipline Review Letter was regarding the inadequate characterization of systemic toxicity in the dermal rabbit study. Relying on the data submitted to the NDA on March 3, 2017, Pharm/Tox is precluded from determining a systemic exposure margin for impurity (b) (4); an inadequate tissue battery was evaluated in study 16-014. This issue concerns both the 10.5 mL and 26 mL applicators. The Applicant submitted data on July 31, 2017 to address the inadequacy of the tissue battery. The Division communicated in the Discipline Review Letter that review of the data submitted on July 31, 2017 may trigger a major amendment. The Applicant chose to withdraw the new data on August 22, 2017, after receiving the Discipline Review Letter. As a result of the data withdrawal, Pharm/Tox cannot adequately assess the systemic toxicity of impurity (b) (4) for either the 10.5 or 26 mL applicator.

In conclusion, by withdrawing the data submitted on July 31, 2017, the Applicant has chosen not to pursue the potential approval of the 10.5 mL applicator under a major amendment. Doses in study #16-014 do not support the potential systemic exposure to impurities from the proposed 26 mL applicator. The animal to human dose conversion relies on the Applicant's proposed stability specifications, and proposed use of the 26 mL applicator. The Clinical Pharmacology team (teleconference on August 17, 2017) has also determined that the results from a Franz Cell assay do not provide adequate data on the systemic absorption of the impurities.

Recommendation:
A complete response is recommended due to inadequate qualification of impurities. The impurity (b) (4) are above the qualification threshold in the ICH guidance for industry *Q3B(R2) Drug Product Impurities*.

As stated previously in the review dated July 24, 2017, absent the Clinical Review Team finding that the benefit-risk assessment of the proposed sterile product outweighs any potential safety risk due to the impurities, it is recommended that additional impurity qualification data is needed.

The Applicant may respond with an adequate qualification study in a single animal species (e.g., a single extended dose study), or otherwise address the systemic exposure to (b) (4) . Alternatively, the Applicant can control the level of impurities to that of a relevant approved product.

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/s/

JANE J SOHN
08/23/2017

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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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1.2 Brief Discussion of Nonclinical Findings

Nonclinical data contained in the current submission were generated solely for the purposes of qualifying the safety of elevated levels of two DP degradant impurities. The data recommended for qualification are prescribed in ICH Q3B(R2). In vitro data on bacterial mutagenicity and mammalian cell chromosome aberration potential were submitted on each impurity individually and were considered sufficient and adequate, confirming negative genotoxic activity potential. In vivo data addressing the skin irritation and skin sensitization potential of fresh versus aged finished DP solution in rabbits and mice, respectively, also confirmed a lack of clinically relevant toxicity. However, a pivotal dermal general toxicity study of the same fresh versus aged DP solution in rabbits is considered inadequate by design and conduct and the data cannot be relied upon to qualify the safety of the two DP degradant impurities at currently proposed product specifications and clinical use exposure scenarios.

1.3 Recommendations

1.3.1 Approvability: Not approvable

1.3.2 Additional Non Clinical Recommendations: The pivotal repeated dose dermal toxicity study to qualify elevated levels of the two DP degradant impurities was not adequately designed and conducted. In response to subsequent IR communications, the Sponsor has agreed to provide an amended final study report containing results from microscopic analyses of all organ tissues preserved at necropsy during the original study (Study 16-014). In addition, if the Sponsor has determined that the impurities would not be absorbed into the systemic circulation, they should provide data supporting such a determination. In the absence of such data, the other study design deficiencies preclude adequate safety qualification of the drug product at currently proposed impurity specification levels. If the Sponsor cannot commit to lowering these impurity specifications, then a new, adequately designed and conducted general dermal toxicology study will be required to qualify the safety of the two DP degradant impurities.

1.3.3 Labeling: The Sponsor included with their submission documents with proposed 'Target Product Information' labeling text. This document is laid out generally in standard Physician Labeling Rule (PLR) format as for Prescribing Information (PI) for an Rx drug. Text from the relevant nonclinical sections of the proposed document are

excerpted in their entirety below, overlaid with this reviewer's recommended editorial changes showing in Tracked Changes formatting.

8 Use in Specific Populations

Pediatric Use:
Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns.

12 Clinical Pharmacology

Chlorhexidine is a cationic biguanide that exhibits broad-spectrum antimicrobial activity, which is thought to be related to its ability to disrupt cell membranes of bacterial cells. Isopropyl alcohol is a secondary aliphatic alcohol that, at the proposed concentration of 70%, also exhibits antiseptic properties, most likely resulting from protein denaturation.

(b) (4) [redacted] ~~n~~No clinical pharmacokinetic or pharmacodynamic studies (b) (4) have been conducted with the drug product formulation.

~~It is generally recognized that chlorhexidine is not or is only minimally absorbed through mature intact skin.~~

(b) (4) [redacted]

13 Nonclinical Toxicology

Chlorhexidine gluconate and isopropyl alcohol both have long histories of (b) (4) use (b) (4) [redacted] o studies addressing the mutagenicity, carcinogenicity, or developmental/reproductive toxicity of the drug product formulation or its active ingredients were conducted in support of marketing of this drug product.

(b) (4) [redacted]

2 Drug Information

2.1 Drug

CAS Registry Number: 18472-51-0 (CHG); 67-63-0 (IPA)

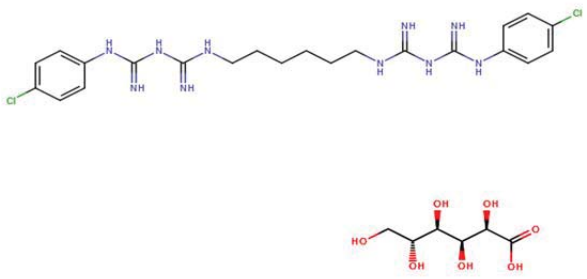
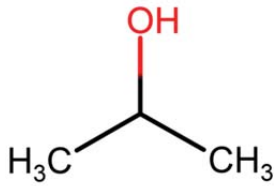
Generic Name: Chlorhexidine gluconate (CHG); isopropyl alcohol (IPA)

Code Name: N/A

Chemical Name: 1,1'-Hexamethylene bis(5-(p-chlorophenyl)biguanide), digluconate (CHG); 2-propanol or isopropanol (IPA)

Molecular Formula/Molecular Weight: $C_{22}H_{30}Cl_2N_{10}•2C_6H_{12}O_7$/897.7626 (CHG); C_3H_8O/60.095 (IPA)

Structure:

 Chlorhexidine gluconate (CHG)	 Isopropyl alcohol (IPA)

Pharmacologic Class: topical antiseptic

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 76,549

2.3 Drug Formulation

The proposed product is a drug-device combination, consisting of a film-forming antiseptic drug solution (tinted and non-tinted formulations; see Sponsor's drug product composition summary table below) contained in a single-use, (b) (4) sealed glass ampoule (10.5 and 26 mL), which is housed in a (b) (4) plastic applicator having a (b) (4) sponge at the end (see Sponsor's figures below). (b) (4) The antiseptic drug solution is dispensed through the sponge during use as indicated for preoperative patient skin antisepsis. "Each applicator is sealed in a rectangular (b) (4) pouch with a peelable top (one unit per pouch) (b) (4)

Table 2.3.P.1-1 Composition of Tinted and Untinted Drug Solution

Component	Function	Level in Tinted	Level in Untinted
Chlorhexidine Gluconate (b) (4) Chlorhexidine Gluconate Solution, USP, Ph.Eur.)	Active Drug Substance	2.0% w/v (2.3% w/w)	2.0% w/v (2.3% w/w)
(b) (4) Isopropyl Alcohol, USP	Active Drug Substance /	70% v/v (64.1% w/w)	70% v/v (64.1% w/w)
Purified Water, USP	(b) (4)		
Acetyltributyl citrate, NF			
3M Acrylate Copolymer: (b) (4)			
Yellow #5, FD&C			
Blue #1, FD&C			
Trisodium HEDTA*			
TOTAL		100%	100%

*HEDTA = hydroxylethyl ethylenediamine triacetic acid

2.3.P.7.1.2 Applicator – 10.5 mL

The 3M CHG/IPA Film-forming Preoperative Skin Preparation applicator consists of the parts shown below:

(b) (4)

2.3.P.7.2.2 Applicator – 26 mL

The 3M CHG/IPA Film-forming Preoperative Skin Preparation Applicator consists of the parts shown below:

(b) (4)

[redacted]

2.4 Comments on Novel Excipients

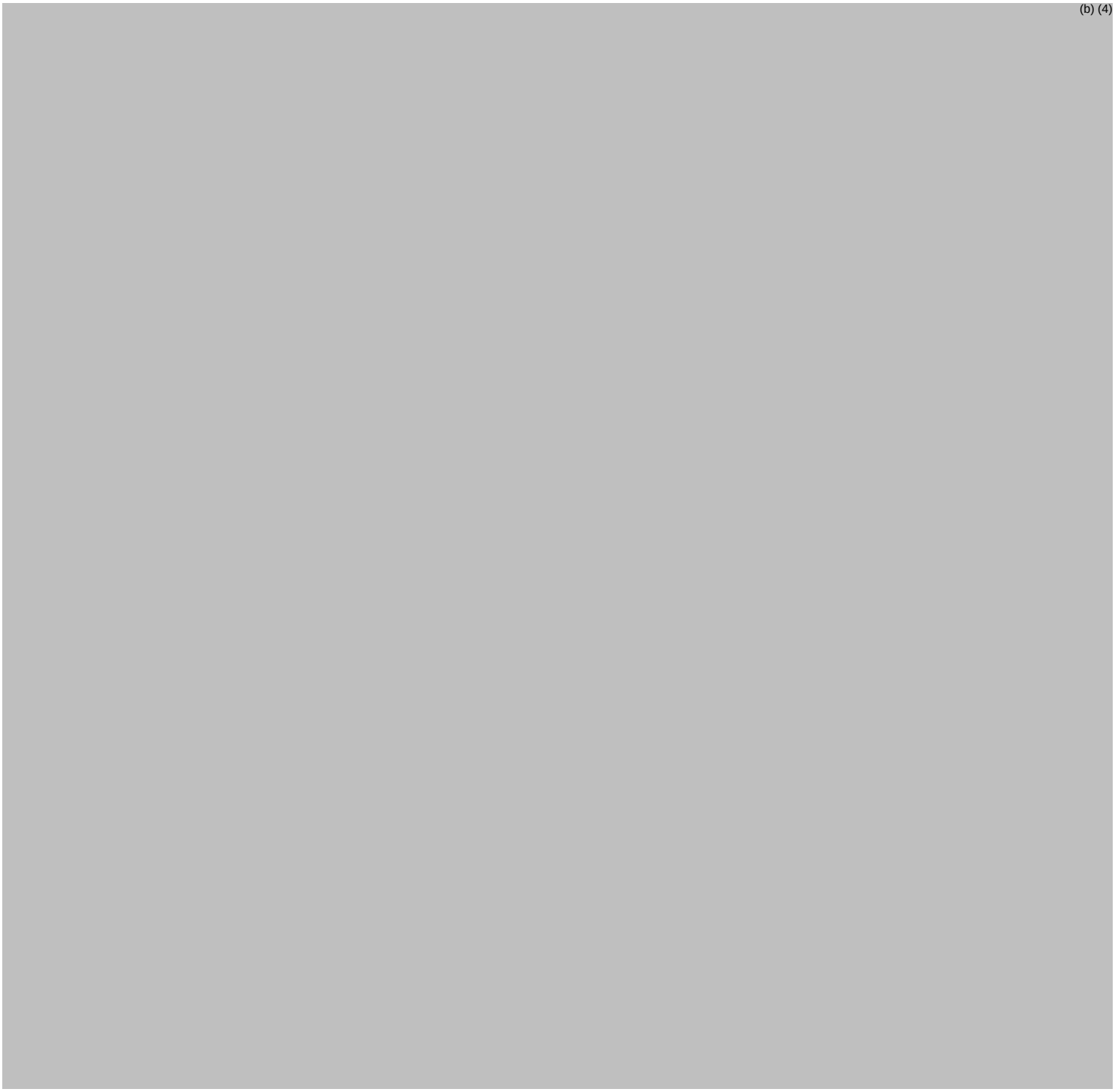
None

2.5 Comments on Impurities/Degradants of Concern

See previous nonclinical and CMC reviews (Section 3.3 below: W. Harrouk, 22 January and 23 March, 2016; S. De, 25 March 2016). As discussed there, drug development stability testing identified two impurities for which the Sponsor had proposed specifications that exceeded the ICH Q3B(R2)-specified qualification threshold of ≤ 1%. These impurities are identified in the summary table below. (b) (4)

[redacted]

(b) (4)



Following communication exchanges between the Agency and the Sponsor with respect to whether qualification of these impurity specifications would be required and what that qualification program might entail (outlined in Dr. Harrouk's 22 January 2016 memorandum), it was determined that the Sponsor's proposed impurity specifications precluded NDA approval. The CR letter (6 May 2016) identified the Sponsor's proposed impurity specifications as a primary deficiency of the application and stated that the

impurities would need to be qualified for safety via a nonclinical testing program as outlined in the ICH Q3B(R2) guidance.

The current submission proposes upwardly-revised individual impurity specifications that continue to exceed qualification thresholds prescribed in ICH Q3B(R2), as well as a total impurities content specification that exceeds (b) (4) % (see relevant portion of Sponsor's Table 3.2.P.5.1-1 below). Based on internal discussions with the OPQ reviewer (E. Luong), it was confirmed that the Sponsor's current proposed specifications would not be consistent with Agency guidance and would likely be revised downward based on stability testing results. The Sponsor has not to date submitted any proposal for lowering the noted specifications.

Table 3.2.P.5.1-1 Specifications for 3M™ CHG/IPA Film-forming Preoperative Skin Preparation Solution

Test	Method / Source	Acceptance Criteria
Total Impurities Content (%w/w with respect to CHG label claim)	TM-05-207970	(b) (4)
Individual Impurities Content: (b) (4) (%w/w relative to CHG label)	TM-05-207970	

The nonclinical studies submitted by the Sponsor in support of the safety of these proposed specifications are listed in Section 3.3 below and are reviewed in subsequent sections.

In regards to compatibility with the container closure system, the Sponsor states (2.3.P.2.6) that "The CHG and the IPA do not interact with the glass ampoules as demonstrated by 3M stability studies. The drug solution has transient contact with the foam, barrel and gasket and no interactions have been noted. No extractables of concern are observed."

2.6 Proposed Clinical Population and Dosing Regimen

The proposed drug product is intended for use in preoperative patient skin antisepsis. Refer to Dr. Harrouk's previous review (23 March 2016) for a discussion of estimated daily patient exposure to CHG anticipated to result from product use.

2.7 Regulatory Background

NDA 208288 was originally received on 6 July 2015 following development under IND 76,549. Following first-cycle review, multiple deficiencies were identified in the application (Clinical, Clinical Pharmacology, Product Quality, Microbiology, and Nonclinical), which precluded approval and resulted in a CR action (CR letter, 6 May

2016). The current submission constitutes the Sponsor's resubmission of the NDA following the CR action.

3 Studies Submitted

3.1 Studies Reviewed

- Study 16-012: ISO Skin Irritation Study in Rabbits.
- Study 16-013: Assessment of Skin Sensitization to MTDID 25415 (Aged) and MTDID 25415 (Fresh) in the Mouse (Local Lymph Node Assay).
- Study 16-014: Systemic Toxicity of Aged vs. Fresh Solutions of MTDID 25415 Following Repeated Dermal Application to the Rabbit.
- Study 16-077: Bacterial Reverse Mutation Assay for MTDID 46013.
- Study 16-078: In Vitro Mammalian Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes (HPBL) for MTDID 46012.
- Study 16-079: Bacterial Reverse Mutation Assay for MTDID 46012.
- Study 16-080: In Vitro Mammalian Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes (HPBL) for MTDID 46013.

3.2 Studies Not Reviewed

- MTDID 46012: QSAR DEREK and LeadScope Model Applier Assessments per ICH M7.
- MTDID 46012: Computational Toxicity Assessment Using the LeadScope Model Applier.
- MTDID 46013: QSAR DEREK and LeadScope Model Applier Assessments per ICH M7.
- MTDID 46013: Computational Toxicity Assessment Using the LeadScope Model Applier.

3.3 Previous Reviews Referenced

- NDA 208288: Quality Assessment Review #1, Swapan K. De, PhD, 25 March 2016.
- NDA 208288: Pharm/Tox Memorandum, Wafa Harrouk, PhD, 22 January 2016.
- NDA 208288: Pharmacology/Toxicology NDA Review and Evaluation, Wafa Harrouk, 23 March 2016.
- NDA 208288: Complete Response Letter, Theresa M. Michele, MD, 6 May 2016.
- NDA 208288: Bacterial Mutagenicity Assessment, CDER/OTS/OCP/DARS-Chemical Informatics Group, 15 December 2015.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Systemic Toxicity of Aged vs. Fresh Solutions of MTDID 25415 Following Repeated Dermal Application to the Rabbit

Study no.:	16-014 (137-231)
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8 February 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MTDID 25415 (Aged), batch PPE-05R-PROJ-05-129395-0084-0084, CLIN C and CLIN D pooled; MTDID 25415 (Fresh), batch PPE-05R-PROJ-05-129395-0080-0080, 42-0027-7331-7 (b) (4) (see summary table comparison of aged vs. fresh test articles below per CoA; however, complete drug product composition not provided for either test article)

Criteria	MTDID 25415 (fresh)	MTDID 25415 (aged)
CHG (%w/w)	2.0	1.8
IPA (%v/v)	72	71
(b) (4) (ppm)	(b) (4)	
Tot Imp (%w/w)		
(b) (4) %w/w)		
(%w/w)		

Key Study Findings

- One female administered aged test article died after blood collection on Day 16, apparently unrelated to drug treatment.
- Dermal skin reaction scoring data suggest that the dermal responses to low- (fresh) versus high-impurity (aged) drug product were generally similar, especially after a single 24-hour exposure under occlusion. However, after repeated such exposures, female skin appears to be more susceptible to adverse responses than male skin and, further, adverse responses were slightly more pronounced with the aged drug product than with the fresh drug product.
- An inadequate collection of organ tissues was examined microscopically for histopathology. Of those tissues examined, it is unclear if the apparent differences in observation incidences between animals exposed to fresh versus aged drug product can be affirmatively attributed to the differences in impurity levels of the two test articles.

Methods

Doses:	4 doses @ 3.7 mL/dose; this equates with an applied dose of approximately (b) (4) mg/animal/day of the (b) (4) impurity and (b) (4) mg/animal/day of the (b) (4) impurity.
Frequency of dosing:	Once daily on Days 1, 5, 9, and 13 for 23-24 hr/day
Route of administration:	Topical dermal in the clipped inter-scapular area of the dorsum (approximately 12 cm x 20 cm, or 240 cm^2, area per application; not stated by the Sponsor, but this equates with approximately 16% BSA based 1500 cm^2 total BSA in a reference rabbit[1]); test article was spread evenly over application site with the syringe tip and allowed to air dry for at least 5 minutes; the application area was then covered with Tegaderm™, followed by wrapping the entire trunk of the animal with Vetrap®; after a minimum 23 hours of exposure, the wrap and covering were removed and the application site gently wiped clean with a 10% Ivory soap in tap water solution.
Dose volume:	3.7 mL
Formulation/Vehicle:	Water
Species/Strain:	Rabbit/New Zealand White Hra:(NZW)SPF
Number/Sex/Group:	5 sex/dose group
Age:	7.0-7.5 Months
Weight:	M: 3.46-3.60 kg; F: 3.18-3.55 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None affecting the integrity or interpretation of the study data.

Observations and Results

Mortality

Observed twice daily. One female administered aged test article died after blood collection on Day 16, apparently unrelated to drug treatment. All other animals survived to scheduled necropsy.

Clinical Signs

Cageside observations were performed twice daily; detailed clinical observations were performed pretest and on Days 7, 14, and 17. Skin reactions (erythema and edema) were assessed pretest and at approximately 1, 24, 48, and 72 hours following removal

[1] Table 3, pg. 19, Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, CDER, 2005.

of each patch application. Skin reactions were scored using Draize methodology as summarized in the Sponsor's Tables C and D below.

Clinical observation findings indicate dry and red discolored dorsal skin was reported in both test groups and was considered to be related to test article exposure, but no difference between aged and fresh test article was apparent.

Table C. Erythema and Eschar Formation

Score	Classification
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well-defined erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness) to slight eschar formation (injuries in depth)
Maximum possible = 4	

Table D. Edema Formation

Score	Classification
0	No edema
1	Very slight edema (barely perceptible)
2	Slight edema (edges of area well defined by definite raising)
3	Moderate edema (raised approximately 1 millimeter)
4	Severe edema (raised more than 1 millimeter and extending beyond area of exposure)
Maximum possible = 4	

Dermal skin reaction scoring is summarized in the table below. These data suggest that the dermal responses to low- (fresh) versus high-impurity (aged) drug product were generally similar, especially after a single 24-hour exposure under occlusion. However, the data also suggest that after repeated such exposures, female skin is more susceptible to adverse responses than is male skin and, further, that adverse responses were slightly more pronounced with the aged drug product than with the fresh drug product. At all scoring points for males and females, the erythema and eschar scores were at their highest at 1 hour after patch removal and generally declined thereafter; edema was only observed in females sporadically and, in some cases, not until 24 hours after patch removal.

Summary of Observed Mean Skin Reaction Scores (n=5*)

		MTDID 25415 Fresh				MTDID 25415 Aged			
		Male		Female		Male		Female	
Day	Time**	Ery&Esc	Edema	Ery&Esc	Edema	Ery&Esc	Edema	Ery&Esc	Edema
Day 1	1hr	0	0	0	0	0	0	0	0
	24hr	0	0	0	0	0	0	0	0
	48hr	0	0	0	0	0	0	0	0
	72hr	0	0	0	0	0	0	0	0
Day 5	1hr	0.2	0	0.8	0	0.4	0	0.8	0
	24hr	0.2	0	0.6	0	0.2	0	0.6	0
	48hr	0.2	0	0.4	0	0	0	0.2	0
	72hr	0.2	0	0.4	0	0.2	0	0.2	0
Day 9	1hr	1.0	0	2.0	0	1.0	0	2.2	0
	24hr	0.8	0	1.6	0.4	0.8	0	1.8	0.6
	48hr	0.4	0	1.0	0.6	0.6	0	1.6	0.6
	72hr	0	0	0.4	0	0	0	0.6	0
Day 13	1hr	0.8	0	1.6	0	0.6	0	1.2	0.2
	24hr	0.6	0	1.6	0	0	0	1.0	0.4
	48hr	0	0	0.6	0	0	0	0.5	0
	72hr	0.2	0	0.6	0	0	0	0.25	0

*Except for n=4 for Day 13 @ 48 and 72 hr (Female, Aged)
**Post wrap removal

Body Weights

Recorded pretest and on Days 7, 14, and 17. The Sponsor's summary table of mean body weights observed on study is provided below. They conclude that "No test-article related effects were noted on body weight. Body weights and body weight gains were comparable between groups." This reviewer finds such a conclusion not entirely accurate, as on an individual animal basis, all males exposed to fresh drug product gained weight from Day -1 to Day 17, whereas 2 males exposed to aged drug product lost weight. Among females, all animals gained weight except for 2 animals exposed to fresh drug product.

Table G. Body Weights, kg

	Male Animals			Female Animals		
Treatment	Pretest	Day 17	(%)	Pretest	Day 17	(%)
MTDID 25415 (Fresh)	3.550	3.636	+2.4%	3.398	3.416	+0.5%
MTDID 25415 (Aged)	3.536	3.566	+0.8%	3.370	3.528	+4.7%

(%) – Percent difference from pretest

Feed Consumption

Recorded daily. No meaningful differences in feed intake were apparent between animals exposed to fresh versus aged drug product.

Ophthalmoscopy

Not performed.

ECG

Not performed.

Hematology

A signed and dated Clinical Pathologist's report was included in the submission. Blood was collected via jugular vein on Day 16, the day prior to scheduled necropsy. No meaningful differences in hematology parameter values were apparent between fresh and aged drug product-exposed animals.

Clinical Chemistry

A signed and dated Clinical Pathologist's report was included in the submission. Blood was collected via jugular vein on Day 16, the day prior to scheduled necropsy. No meaningful differences in clinical chemistry parameter values were apparent between males exposed to fresh and aged drug product; however, several parameter values were increased in females exposed to aged product as compared to fresh product (see Sponsor's summary table excerpts below). At the individual animal level, this finding equated with 3/5 females that received aged TA having AST values that were above the control range. For ALT, 4/5 females administered aged TA had values that were above the control range; the value for one animal (#2017), in particular, is the cause of the notable increase in the mean.

Summary of Clinical Chemistry Values - FEMALE

Endpoint	Study Interval	MTDID 25415 (Fresh) Mean	SD	N	MTDID 25415 (Aged) Mean	SD	N
AST U/L	Terminal	16.0	3.54	5	27.0	11.96	5
ALT U/L	Terminal	32.4	5.32	5	53.4	22.04	5
Creatinine mg/dL	Terminal	1.02	0.130	5	1.18[a]	0.084	5

Urinalysis

Not performed.

Gross Pathology

Scheduled necropsy on Day 17 (3 full days following removal of last drug patch application). There were no apparent differences in gross necropsy observations between animals exposed to fresh and aged drug product.

Organ Weights

Organ weights as stipulated in the Sponsor's histopathology tissue inventory below were collected and recorded as absolute and relative values. No meaningful differences were observed between organ weights in animals exposed to fresh versus aged drug product.

Histopathology

Adequate Battery: According to the Sponsor's study protocol, an adequate battery of tissues was collected and preserved at necropsy (see Sponsor's tissue inventory

below). However, an inadequate fraction of these tissues was examined microscopically for histopathology.

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination
Adrenal glands	X	X	X
Aorta		X	
Bone with bone marrow, femur (process distal end with tibiofemoral joint only)		X	
Bone with bone marrow, femur		X	

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination
(proximal)			
Bone with bone marrow, sternum		X	
Bone marrow smear		X	
Brain	X	X	X
Epididymides		X	
Esophagus		X	
Eyes (with optic nerve)		X	
Gallbladder		X	
GALT (Gut-Associated Lymphoid Tissue)		X	
Gross lesions (including tissue masses)		X	X
Heart	X	X	X
Kidneys	X	X	X
Large intestine, cecum		X	
Large intestine, colon		X	
Large intestine, rectum		X	
Larynx		X	
Liver	X	X	X
Lung with bronchi		X	
Lymph node, mandibular		X	
Lymph node, mesenteric		X	
Mammary gland (process females only)		X	
Nerve, sciatic		X	
Ovaries	X	X	X
Oviducts		X	
Pancreas		X	
Pituitary gland		X	
Prostate gland		X	
Salivary gland, mandibular		X	
Salivary gland, parotid		X	
Seminal vesicles		X	
Skeletal muscle, biceps femoris		X	
Skin (treated)		X	X
Skin (untreated)		X	X
Small intestine, duodenum		X	

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination
Small intestine, ileum		X	
Small intestine, jejunum		X	
Spinal cord, cervical		X	
Spinal cord, lumbar		X	
Spinal cord, thoracic		X	
Spleen	X	X	X
Stomach, cardia		X	
Stomach, fundus		X	
Stomach, pylorus		X	
Testes	X	X	X
Thymus	X	X	X
Thyroid gland (with parathyroid)	X	X	
Tongue		X	
Trachea		X	
Ureters		X	
Urinary bladder		X	
Uterus with cervix		X	
Vagina		X	

Peer Review: Not performed.

Histological Findings: A signed and dated Study Pathologist's report was included in the submission. Microscopic observations are summarized in selected portions of the Sponsor's tables below. These data suggest some slights differences in the incidence of observations between animals exposed to fresh versus aged drug product. However, it is unclear to what extent, if any, the observed differences can be positively attributed to the differences in the impurity levels of the two test articles.

Summary of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	MTDID 25415 (Fresh) DOS	MTDID 25415 (Fresh) SNC	MTDID 25415 (Aged) DOS	MTDID 25415 (Aged) SNC
Number of Animals Examined		0	5	0	5
kidney, left		(0)	(5)	(0)	(5)
basophilic tubules	- minimal	0	1	0	1
infiltration, mononuclear cell, increased	- minimal	0	0	0	1
mineralization, tubular	- minimal	0	2	0	4
within normal limits		0	3	0	1
kidney, right		(0)	(5)	(0)	(5)
basophilic tubules	- minimal	0	2	0	1
infiltration, mononuclear cell, increased	- minimal	0	0	0	1
mineralization, tubular	- minimal	0	2	0	2
within normal limits		0	3	0	3
liver		(0)	(5)	(0)	(5)
infiltration/inflammation, mononuclear cell	- minimal	0	0	0	2
vacuolation, centrilobular	- mild	0	5	0	3

skin, treated		(0)	(5)	(0)	(5)
degeneration/necrosis	- mild	0	1	0	0
erosion/ulcer	- mild	0	1	0	0
hemorrhage	- minimal	0	2	0	0
hyperkeratosis	- minimal	0	5	0	5
hyperplasia, epidermal	- minimal	0	1	0	2
infiltration/inflammation, mixed cell		0	5	0	5
	- minimal	0	4	0	3
	- mild	0	1	0	2
skin, untreated		(0)	(5)	(0)	(5)
within normal limits		0	5	0	5
testes		(0)	(5)	(0)	(5)
dilation, seminiferous tubules, unilateral	- minimal	0	1	0	0
inflammation, subacute/chronic	- mild	0	0	0	1
thymus		(0)	(5)	(0)	(5)
anomaly, developmental	- no grade	0	1	0	0
decreased lymphocytes, generalized		0	5	0	5
	- minimal	0	2	0	1
	- mild	0	3	0	4

Summary of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	MTDID 25415 (Fresh) DOS	MTDID 25415 (Fresh) SNC	MTDID 25415 (Aged) DOS	MTDID 25415 (Aged) SNC
Number of Animals Examined		0	5	1	4
adrenal glands		(0)	(5)	(1)	(4)
infiltration, mononuclear cell, increased	- minimal	0	2	0	0
vacuolation, increased	- minimal	0	3	1	0
within normal limits		0	1	0	4
brain		(0)	(5)	(1)	(4)
increased adipocytes	- minimal	0	1	0	2
infiltration, mononuclear cell, perivascular	- minimal	0	1	0	0
within normal limits		0	4	1	2
kidney, left		(0)	(5)	(1)	(4)
basophilic tubules	- minimal	0	4	1	1
mineralization, tubular		0	2	1	0
	- minimal	0	1	1	0
	- mild	0	1	0	0
within normal limits		0	1	0	3
kidney, right		(0)	(5)	(1)	(4)
basophilic tubules	- minimal	0	2	0	1
mineralization, pelvic	- minimal	0	0	0	1
mineralization, tubular		0	3	1	1
	- minimal	0	2	1	1
	- mild	0	1	0	0
within normal limits		0	1	0	2
liver		(0)	(5)	(1)	(4)
infiltration/inflammation, mononuclear cell	- minimal	0	1	1	3
vacuolation, centrilobular		0	5	0	3
	- minimal	0	3	0	2
	- mild	0	1	0	1
	- moderate	0	1	0	0
ovaries		(0)	(5)	(1)	(4)
dilation, cystic bursal	- mild	0	0	0	1
hematocyst	- mild	0	0	1	0
mineralization	- minimal	0	1	1	2
within normal limits		0	4	0	1

skin, treated		(0)	(5)	(1)	(4)
exudate, epidermal surface	- minimal	0	1	0	0
hyperkeratosis		0	5	1	4
	- minimal	0	3	1	4
	- mild	0	2	0	0
hyperplasia, epidermal		0	4	1	1
	- minimal	0	3	1	1
	- mild	0	1	0	0
infiltration/inflammation, mixed cell		0	5	1	4
	- minimal	0	1	0	2
	- mild	0	4	1	2
skin, untreated		(0)	(5)	(1)	(4)
within normal limits		0	5	1	4
thymus		(0)	(5)	(1)	(4)
decreased lymphocytes, generalized		0	5	1	4
	- minimal	0	4	0	2
	- mild	0	1	1	2

*DOS = Died or euthanized on study; SNC = Scheduled necropsy

Special Evaluation

None

Toxicokinetics

Not performed.

Dosing Solution Analysis

Test articles were applied as received from the Sponsor without dilution or further characterization beyond that of Sponsor-provided CoA and other documentation (see below).

Test Article Characterization
MTDID 25415 (Aged and Fresh)

Was characterization performed under GLP?	X	Yes		No
Physical form (Size, shape, color, texture, etc):	**Green tinted uniform solution**			
Identity - Lot or Batch Number (3M Notebook number and page are acceptable):	**Fresh Solution:** PPE-05R-PROJ-05-129395-0080-0080 (CLIN-MFG-TKT-05-279611) **Aged Solution:** PPE-05R-PROJ-05-129395-0084-0084 (CLIN-MFG-TKT-05-280881)			
Strength of active ingredients (Chemical mixtures only):	**2% CHG / 70% IPA**			
Purity (% purity of each active ingredient):	**NA**			
Detailed Composition (attach additional pages, if needed)[1]:	**2% w/v CHG** **70% v/v IPA** **(b) (4)% w/w ATBC** **% w/w Polymer** (b) (4) **(b) (4)% w/w HEDTA** **Different Dye Levels for Aged and Fresh:** **Fresh:** (b) (4)% w/w Dye (FD&C Blue #1 and FD&C Yellow #5) **Aged:** (b) (4)% w/w Dye (FD&C Blue #1 and FD&C Yellow #5)			
Disclosed Composition (will be included in Protocol / Reports)[2]:	**2% CHG / 70% IPA**			
Stability/Expiration date (include on test article):	**TBD**			
Uniformity/Homogeneity (Chemical mixtures only):	**Uniform solution**			
Other Defining Characteristics:	**NA**			

Test Article Information – BU Requestor

pH (if applicable):	(b) (4)
Molecular Weight (if applicable):	**NA**
Vapor Pressure (if applicable):	**NA**
Density (if applicable):	(b) (4) g/mL
Absorption potential (if applicable):	**NA**

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay for MTDID 46013

Study no.:	16-077 (AE51ME.502ICH.(b) (4))
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	14 April 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MTDID 46013 ((b) (4) lot PPE-05R-PROJ-05-129395-0095-0095; purity 98.6% via UPLC

Key Study Findings

- Valid and negative mutagenicity assay

Methods

Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, and TA 1537; *Escherichia coli* WP2 *uvrA*
Concentrations in definitive study:	1.50, 5.00, 15.0, 50.0, 150, 500, and 1500 µg/plate
Basis of concentration selection:	Cytotoxicity
Negative control:	DMSO
Positive control:	See Sponsor's table below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Standard plate incorporation methodology employing Aroclor 1254-induced rat liver S9 exogenous activation; incubation 48-72 hr at 37 °C (triplicate plates); plates counted immediately or stored at 2-8 °C until counting was conducted.

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4) Purity 97.5%	1.0
TA100, TA1537			2.0
WP2 *uvr*A			15
TA98	None	2-nitrofluorene (b) (4) Purity 99.4%	1.0
TA100, TA1535		sodium azide (b) (4) Purity 99.6%	1.0
TA1537		9-aminoacridine (b) (4) Purity 99.5%	75
WP2 *uvr*A		methyl methanesulfonate (b) (4) Purity 100.0%	1,000

Study Validity

The study was considered valid based on all of the following criteria having been met: all appropriate tester strain gene mutations and/or deletions were confirmed; spontaneous revertant numbers in the presence of DMSO vehicle fell within historical ranges for all cultures; tester strain culture titers were at ≥ 0.3 x 10^9 cells/mL; positive control responses were sufficiently robust (≥ 3-fold that of vehicle control); and at least three non-toxic dose levels were available for evaluation in the definitive assay.

Results

Dosing formulations concentration analysis and stability assessment were confirmed by the Sponsor and were acceptable. A preliminary toxicity assay was conducted at dose levels ranging from 0.333 to 5000 µg/plate in DMSO. No precipitate was observed and toxicity was observed beginning at 66.7 to 1000 µg/plate. Based on these preliminary findings, dose levels for the mutagenicity assay were set at 1.50, 5.00, 15.0, 50.0, 150, 500, and 1500 µg/plate. Under the conditions of the assay, no evidence of a positive mutagenic response was observed with any tester strain either in the presence or absence of S9 activation (see Sponsor's summary table below). A second independent, confirmatory assay was not conducted given the clear negative findings of the definitive assay.

Metabolic Activation	Test Article	Dose Level (µg/plate)	Revertant Colony Counts (Mean ±SD)				
			TA98	TA100	TA1535	TA1537	WP2uvrA
Without Activation	DMSO	100 µL/plate	13 ± 4	85 ± 4	13 ± 5	7 ± 2	22 ± 6
	MTDID 46013	1.50	14 ± 4	81 ± 6	15 ± 3	9 ± 1	25 ± 1
		5.00	9 ± 2	87 ± 12	14 ± 3	7 ± 2	23 ± 8
		15.0	11 ± 5	92 ± 10	15 ± 3	11 ± 3	23 ± 6
		50.0	10 ± 3	75 ± 10	12 ± 3	8 ± 3	17 ± 1
		150	13 ± 2	66 ± 12	13 ± 3	7 ± 1	23 ± 3
		500	9 ± 1	0 ± 0	0 ± 0	6 ± 1	10 ± 1
		1500	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	2NF	1.0	354 ± 312				
	SA	1.0		759 ± 25	676 ± 75		
	9AAD	75				468 ± 136	
	MMS	1000					411 ± 43
With Activation	DMSO	100 µL/plate	19 ± 4	106 ± 8	15 ± 7	9 ± 2	38 ± 2
	MTDID 46013	1.50	16 ± 4	95 ± 11	13 ± 2	8 ± 2	42 ± 6
		5.00	19 ± 3	113 ± 10	15 ± 2	12 ± 4	34 ± 5
		15.0	19 ± 3	123 ± 17	14 ± 5	9 ± 1	40 ± 5
		50.0	22 ± 1	109 ± 10	11 ± 6	9 ± 2	34 ± 2
		150	20 ± 6	83 ± 8	11 ± 2	11 ± 3	28 ± 9
		500	14 ± 1	24 ± 7	10 ± 6	10 ± 1	12 ± 3
		1500	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	2AA	1.0	219 ± 23		80 ± 34		
	2AA	2.0		485 ± 114		78 ± 15	
	2AA	15					314 ± 95

Key to Positive Controls

SA	sodium azide
2AA	2-aminoanthracene
9AAD	9-Aminoacridine
2NF	2-nitrofluorene
MMS	methyl methanesulfonate

(b) (4) Study No. AE51ME.502ICH (b) (4) 64

Study title: Bacterial Reverse Mutation Assay for MTDID 46012

Study no.:	16-079 (AE51MD.502ICH (b) (4))
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	14 April 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MTDID 46012 (b) (4)), lot PPE-05R-PROJ-05-129395-0097-0097; purity 85.1% via UPLC

Key Study Findings

- Valid and negative mutagenicity assay

Methods

Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, and TA 1537; *Escherichia coli* WP2 *uvrA*
Concentrations in definitive study:	See Sponsor's table below under results
Basis of concentration selection:	Cytotoxicity and/or insolubility
Negative control:	DMSO
Positive control:	See Sponsor's table immediately below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Standard plate incorporation methodology employing Aroclor 1254-induced rat liver S9 exogenous activation; incubation 48-72 hr at 37 °C (triplicate plates); plates counted immediately or stored at 2-8 °C until counting was conducted.

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (Sigma Aldrich Chemical Co., Inc.)	1.0
TA100, TA1537		(b) (4)	2.0
WP2 *uvr*A		Purity 97.5%	15
TA98	None	2-nitrofluorene (b) (4) Purity 99.4%	1.0
TA100, TA1535		sodium azide (b) (4) Purity 99.6%	1.0
TA1537		9-aminoacridine (b) (4) Purity 99.5%	75
WP2 *uvr*A		methyl methanesulfonate (b) (4) Purity 100.0%	1,000

Study Validity

The study was considered valid based on all of the following criteria having been met: all appropriate tester strain gene mutations and/or deletions were confirmed; spontaneous revertant numbers in the presence of DMSO vehicle fell within historical

ranges for all cultures; tester strain culture titers were at ≥ 0.3 x 10^9 cells/mL; positive control responses were sufficiently robust (≥ 3-fold that of vehicle control); and at least three non-toxic dose levels were available for evaluation in the definitive assay.

Results

Dosing formulations concentration analysis and stability assessment were confirmed by the Sponsor and were acceptable. A preliminary toxicity assay was conducted at dose levels ranging from 0.333 to 5000 µg/plate in DMSO. Precipitate was observed beginning at 667 µg/plate and toxicity was observed beginning at 10.0 to 333 µg/plate. Based on these preliminary findings, dose levels for the mutagenicity assay were set at variable levels depending on the assay condition (see Sponsor's summary table below). No precipitate was observed in the definitive assay, but toxicity was apparent beginning at 15 to 500 µg/plate. Under the conditions of the assay, no evidence of a positive mutagenic response was observed with any tester strain either in the presence or absence of S9 activation. A second independent, confirmatory assay was not conducted given the clear negative findings of the definitive assay.

Metabolic Activation	Test Article	Dose Level (µg/plate)	Revertant Colony Counts (Mean ±SD)				
			TA98	TA100	TA1535	TA1537	WP2uvrA
Without Activation	DMSO	50.0 µL/plate	14 ± 6	87 ± 12	12 ± 4	9 ± 3	23 ± 4
	MTDID 46012	0.0500	10 ± 4	82 ± 10	11 ± 2	7 ± 2	
		0.150	9 ± 3	74 ± 16	10 ± 4	8 ± 2	
		0.500	12 ± 2	88 ± 10	10 ± 6	8 ± 2	23 ± 8
		1.50	11 ± 4	87 ± 5	8 ± 1	6 ± 1	23 ± 6
		5.00	11 ± 4	82 ± 5	11 ± 3	9 ± 1	21 ± 8
		15.0	15 ± 1	0 ± 0	0 ± 0	7 ± 1	26 ± 5
		50.0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	21 ± 4
		150					0 ± 0
		500					0 ± 0
	2NF	1.0	77 ± 10				
	SA	1.0		703 ± 48	687 ± 32		
	9AAD	75				352 ± 116	
	MMS	1000					376 ± 13
With Activation	DMSO	50.0 µL/plate	25 ± 5	82 ± 4	15 ± 2	9 ± 4	25 ± 8
	MTDID 46012	0.500	21 ± 6	81 ± 10	13 ± 4	8 ± 1	27 ± 5
		1.50	19 ± 4	76 ± 1	11 ± 6	9 ± 4	31 ± 4
		5.00	25 ± 13	87 ± 9	12 ± 2	11 ± 3	23 ± 5
		15.0	21 ± 3	91 ± 5	13 ± 3	8 ± 5	25 ± 3
		50.0	26 ± 3	88 ± 14	10 ± 2	8 ± 2	28 ± 5
		150	26 ± 2	0 ± 0	0 ± 0	13 ± 1	20 ± 4
		500	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	2AA	1.0	203 ± 14		81 ± 19		
	2AA	2.0		512 ± 260		53 ± 13	
	2AA	15					263 ± 4

Key to Positive Controls

SA	sodium azide
2AA	2-aminoanthracene
9AAD	9-Aminoacridine
2NF	2-nitrofluorene
MMS	methyl methanesulfonate

(b) (4) Study No. AE51MD.502ICH (b) (4) 68

7.2 *In Vitro* Assays in Mammalian Cells

Study title: In Vitro Mammalian Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes (HPBL) for MTDID 46012

Study no.:	16-078 (AE51MD.341ICH (b) (4))
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8 April 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MTDID 46012 (b) (4)), lot PPE-05R-PROJ-05-129395-0097-0097; purity 85.1% via UPLC

Key Study Findings

- Valid and negative clastogenicity assay

Methods

Cell line:	Human peripheral blood lymphocytes (HPBL) from a healthy, non-smoking male
Concentrations in definitive study:	See Sponsor's table below
Basis of concentration selection:	Cytotoxicity (reduction in mitotic index relative to the vehicle control) or insolubility in treatment medium
Negative control:	DMSO
Positive control:	Mitomycin C (-S9); cyclophosphamide (+S9)
Formulation/Vehicle:	DMSO (water for positive controls)
Incubation & sampling time:	Incubation at 37 °C for 4 hr ±S9 (Aroclor 1254-induced rat liver S9) and for 20 hr –S9; sampling at 20 hr. Colcemid (0.1 µg/mL) added 2 hr prior to sampling.

Treatment Condition	Treatment Time	Recovery Time	Doses (µg/mL)
Non-activated	4 hr	16 hr	0.5, 1.5, 5.0, 15, 20, 25, 30, 35, 40
	20 hr	0 hr	0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 10, 12.5, 15
S9-activated	4 hr	16 hr	5.0, 10, 15, 20, 25, 30, 35, 40, 45, 50

Study Validity

The study was considered to be valid based on all of the following criteria having been met: structural chromosomal aberration frequencies for vehicle controls fell within acceptable limits of historical control ranges; the responses for structural chromosomal aberration frequencies in positive controls were significantly greater ($p \leq 0.05$) than

concurrent vehicle controls and cytotoxicity was ≤ 60%; the test article was tested under all three assay conditions; and at least 300 metaphase spreads were analyzed from at least three appropriately selected test article concentrations.

Results

Dose concentrations for the definitive assay were set as summarized in the Sponsor's table above, based on results from a preliminary toxicity assay in which single HPBL cultures were exposed to nine different concentrations of test article at half-log increments. Dose selection was based on cytotoxicity as expressed by reduction in mitotic index or insolubility of test article in the medium. Cells were collected from all assay conditions (duplicate cultures) at 20 hr after treatment initiation and slides of metaphase chromosome spreads were prepared. Three dose levels were scored for each assay condition with the high dose selected based on an observed reduction in mitotic index of 50 ± 5% versus the vehicle control. A minimum of 300 metaphase spreads (2 x 150/treatment) were scored for chromosomal aberrations.

Dosing formulations concentration analysis and stability assessment were confirmed by the Sponsor and were acceptable. No precipitate was observed during the definitive assay under any assay condition. Hemolysis was observed at 40 µg/mL in the 4-hr exposure group (-S9) and at doses ≥ 40 µg/mL in the 4-hr (+S9) group. Mitotic inhibition at the highest doses scored was as follows: 48% at 15 µg/mL (4-hr, -S9); 50% at 10 µg/mL (20-hr, -S9); and 46% at 25 µg/mL (4-hr, +S9). Under the conditions of the assay, no evidence of a significant, dose-dependent increase in chromosomal aberrations (structural or numerical) was observed under any tested assay condition (see Sponsor's results summary below).

Metabolic Activation	Test Article	Dose µg/mL	Cytotoxicity [a] (% of Control)	Aberrant Cells		Aberrations per Cell [b, d] Mean ± SD [f]	Total Polyploid Cells (Mean %) [e]
				Structural (Mean %) [b]	Numerical (Mean %) [c]		
20-hr Continuous	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0
Treatment	MTDID 46012	1	5	0.0	0.0	0.000 ± 0.000	0.0
Without	MTDID 46012	4	24	0.0	0.0	0.000 ± 0.000	0.0
Activation	MTDID 46012	10	50	0.0	0.3	0.000 ± 0.000	0.3
	MMC	0.3	55	18.0**	0.0	0.213 ± 0.499	0.0
4-hr Treatment	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0
With 16 hr Recovery	MTDID 46012	1.5	5	0.0	0.0	0.000 ± 0.000	0.0
Without	MTDID 46012	5	15	0.0	0.0	0.000 ± 0.000	0.0
Activation	MTDID 46012	15	48	0.0	0.7	0.000 ± 0.000	0.7
4-hr Treatment	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0
With 16 hr Recovery	MTDID 46012	5	4	0.0	0.0	0.000 ± 0.000	0.0
With	MTDID 46012	10	24	0.0	0.3	0.000 ± 0.000	0.3
Activation	MTDID 46012	25	46	0.3	0.7	0.003 ± 0.058	0.7
	CP	2.5	54	14.0**	0.0	0.153 ± 0.397	0.0

DMSO: Dimethyl sulfoxide; MMC: Mitomycin C; CP: Cyclophosphamide; NA: Not Applicable; Fisher's Exact Test: ** p ≤ 0.01.

a. Based on mitotic inhibition relative to solvent control.
b. Does not include cells with only gaps.
c. Includes polyploid and endoreduplicated cells.
d. Severely damaged cells counted as 10 aberrations.
e. Does not include endoreduplicated cell.
f. SD = Standard Deviation.

Study title: In Vitro Mammalian Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes (HPBL) for MTDID 46013

Study no.:	16-080 (AE51ME.341ICH (b) (4))
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8 April 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MTDID 46013 ((b) (4)), lot PPE-05R-PROJ-05-129395-0095-0095; purity 98.6% via UPLC

Key Study Findings

- Valid and negative clastogenicity assay

Methods

Cell line:	Human peripheral blood lymphocytes (HPBL) from a healthy, non-smoking male
Concentrations in definitive study:	See Sponsor's table below
Basis of concentration selection:	Cytotoxicity (reduction in mitotic index relative to the vehicle control) or insolubility in treatment medium
Negative control:	DMSO
Positive control:	Mitomycin C (-S9); cyclophosphamide (+S9)
Formulation/Vehicle:	DMSO (water for positive controls)
Incubation & sampling time:	Incubation at 37 °C for 4 hr ±S9 (Aroclor 1254-induced rat liver S9) and for 20 hr –S9; sampling at 20 hr. Colcemid (0.1 µg/mL) added 2 hr prior to sampling.

Treatment Condition	Treatment Time	Recovery Time	Doses (µg/mL)
Non-activated	4 hr	16 hr	25, 50, 100, 200, 400, 450, 500
	20 hr	0 hr	10, 25, 50, 100, 140, 150, 160, 180, 200, 225, 250, 300
S9-activated	4 hr	16 hr	5, 10, 20, 40, 45, 50, 55, 60, 80, 100

Study Validity

The study was considered to be valid based on all of the following criteria having been met: structural chromosomal aberration frequencies for vehicle controls fell within acceptable limits of historical control ranges; the responses for structural chromosomal aberration frequencies in positive controls were significantly greater ($p \leq 0.05$) than concurrent vehicle controls and cytotoxicity was ≤ 60%; the test article was tested under

all three assay conditions; and at least 300 metaphase spreads were analyzed from at least three appropriately selected test article concentrations.

Results

Dose concentrations for the definitive assay were set as summarized in the Sponsor's table above, based on results from a preliminary toxicity assay in which single HPBL cultures were exposed to nine different concentrations of test article at half-log increments. Dose selection was based on cytotoxicity as expressed by reduction in mitotic index or insolubility of test article in the medium. Cells were collected from all assay conditions (duplicate cultures) at 20 hr after treatment initiation and slides of metaphase chromosome spreads were prepared. Three dose levels were scored for each assay condition with the high dose selected based on an observed reduction in mitotic index of 50 ± 5% versus the vehicle control, except for the 4-hr (-S9) assay where selection was driven by visible precipitate at the end of the treatment period. A minimum of 300 metaphase spreads (2 x 150/treatment) were scored for chromosomal aberrations.

Dosing formulations concentration analysis and stability assessment were confirmed by the Sponsor and were acceptable. Precipitate was observed during the definitive assay at the end of the treatment period in the 4-hr and 20-hr (-S9) assays at ≥ 200 µg/mL and in the 4-hr (+S9) assay at ≥ 80 µg/mL. Mitotic inhibition at the highest doses scored was as follows: -2% at 200 µg/mL (4-hr, -S9); 50% at 100 µg/mL (20-hr, -S9); and 46% at 40 µg/mL (4-hr, +S9). Under the conditions of the assay, no evidence of a significant, dose-dependent increase in chromosomal aberrations (structural or numerical) was observed under any tested assay condition (see Sponsor's results summary below).

Metabolic Activation	Test Article	Dose µg/mL	Cytotoxicity [a] (% of Control)	Aberrant Cells		Aberrations per Cell [b,d] Mean ± SD [f]	Total Polyploid Cells (Mean %) [e]
				Structural (Mean %) [b]	Numerical (Mean %) [c]		
20-hr Continuous	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0
Treatment	MTDID 46013	25	15	0.0	0.0	0.000 ± 0.000	0.0
Without	MTDID 46013	50	11	0.0	0.0	0.000 ± 0.000	0.0
Activation	MTDID 46013	100	50	0.0	0.0	0.000 ± 0.000	0.0
	MMC	0.3	53	17.3**	0.0	0.193 ± 0.444	0.0
4-hr Treatment	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0
With 16 hr Recovery	MTDID 46013	50	-10	0.0	0.0	0.000 ± 0.000	0.0
Without	MTDID 46013	100	-4	0.0	0.0	0.000 ± 0.000	0.0
Activation	MTDID 46013	200 p	-2	0.0	0.0	0.000 ± 0.000	0.0
4-hr Treatment	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0
With 16 hr Recovery	MTDID 46013	10	13	0.0	0.0	0.000 ± 0.000	0.0
With	MTDID 46013	20	16	0.0	0.0	0.000 ± 0.000	0.0
Activation	MTDID 46013	40	46	0.0	0.0	0.000 ± 0.000	0.0
	CP	2.5	48	10.7**	0.0	0.113 ± 0.339	0.0

DMSO: Dimethyl sulfoxide; MMC: Mitomycin C; CP: Cyclophosphamide; NA: Not Applicable; Fisher's Exact Test: ** $p \leq 0.01$.

a. Based on mitotic inhibition relative to solvent control.
b. Does not include cells with only gaps.
c. Includes polyploid and endoreduplicated cells.
d. Severely damaged cells counted as 10 aberrations.
e. Does not include endoreduplicated cell.
f. SD = Standard Deviation.
p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period

10 Special Toxicology Studies

Study title: ISO Skin Irritation Study in Rabbits

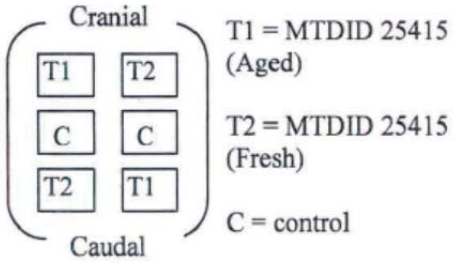
Study no.:	16-012
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	23 March 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MTDID 25415 (Aged)= PPE-05R-PROJ-05-129395-0084-0084, CLIN C and CLIN D pooled; MTDID 25415 (Fresh) = PPE-OSR-PROJ-05-129395-0080-0080, 42-0027-7331-7 (b) (4)

Key Study Findings

- Negligible skin irritation observed with either test article

Methods

Doses:	0.1 mL applied of each test article and control were applied to a 25 mm x 25 mm area of clipped dorsum of each animal, allowed to air dry for 5 minutes, and then covered with a similarly sized gauze pad and secured with nonreactive tape. Each treatment was applied twice to each animal, once to intact skin and once to abraded skin (see Sponsor's descriptive figure below). The trunk of each animal was then wrapped with an elastic binder.
Frequency of dosing:	Once for "23 hours and 6 minutes of exposure", after which wrap, tape, and patches were removed and the application sites gently wiped with a deionized water-moistened gauze sponge. The perimeter of each site was marked for scoring.
Route of administration:	Dermal topical, under semi-occlusive wrap
Dose volume:	0.1 mL
Control:	0.9% Sodium chloride
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	3 Males total
Age:	"Young adult"
Weight:	2.5-2.6 kg at selection
Satellite groups:	None
Unique study design:	Study guideline employed was ISO 10993-10, Biological Evaluation of Medical Devices, Part 10: Tests for irritation and skin sensitization. Each animal received buprenorphine (0.02 mg/kg SC) one hour prior to test article application.
Deviation from study protocol:	Not reported



Observations and Results

Following approximately 24 hours of occlusive dermal test article and control exposure as described above, the animals were returned to their cages and monitored for general health and dermal irritation scoring at 1, 24, 48, and 72 hours after patch removal.

Dermal scoring consisted of calculation of the Primary Irritation Index according to the classification scheme (for erythema and edema) outlined in the Sponsor's tables below.

Appendix 1 - Classification System For Skin Reaction

Reaction	Numerical Grading
Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Well-defined edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond exposure area)	4
Total possible score for irritation	8

NOTE: Other adverse changes at the skin sites shall be recorded and reported

Irritation Response Categories in the Rabbit

Response Category	Mean Score
Negligible	0.0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

Results indicate that "all animals were clinically normal throughout the study." Dermal irritation scores for the aged (T1) and fresh (T2) test articles are summarized below in the Sponsor's Table 3 and Table 4, respectively. The aged test article appeared to be slightly more irritating than was the fresh formulation, although both were categorized as "Negligible" overall. Importantly, while the CoA documentation included with the report characterizes each test article as to the percent of CHG (~2%), IPA (~72%), as well as total and individual impurities (b) (4)), a full finished product quantitative composition for each test article formulation is not provided with the report.

Table 3: Irritation Calculations for T1 (Aged)

Animal Number	Test Score Average	-	Control Score Average	Individual Primary Irritation Score	Combined Primary Irritation Score (CPIS)	Primary Irritation Index (CPIS ÷ 3)	Response Category
10607	0.5	-	0.0	0.5	1.3	0.4	Negligible
10608	0.5	-	0.0	0.5			
10610	0.3	-	0.0	0.3			

Table 4: Irritation Calculations for T2 (Fresh)

Animal Number	Test Score Average	-	Control Score Average	Individual Primary Irritation Score	Combined Primary Irritation Score (CPIS)	Primary Irritation Index (CPIS ÷ 3)	Response Category
10607	0.5	-	0.0	0.5	0.5	0.2	Negligible
10608	0.0	-	0.0	0.0			
10610	0.0	-	0.0	0.0			

Study title: Assessment of Skin Sensitization to MTDID 25415 (Aged) and MTDID 25415 (Fresh) in the Mouse (Local Lymph Node Assay)

Study no.: 16-013 (513006)
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: 27 April 2016
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: 207422/A: MTDID 25415 (Aged), batch PPE-05R-PROJ-05-129395-0084-0084, CLIN C and CLIN D pooled; 207422/B: MTDID 25415 (Fresh), batch PPE-05R-PROJ-05-129395-0080-0080, 42-0027-7331-7 (b) (4); (see summary table comparison of aged vs. fresh test articles below per CoA; however, complete drug product composition was not provided for either test article); Positive Control: (b) (4), batch MKBT2800V, purity 97.3%

Criteria	207422/B (fresh)	207422/A (aged)
CHG (%w/w)	2.0	1.8
IPA (%v/v)	72	71
(b) (4) (ppm)	(b) (4)	
Tot Imp (%w/w)		
(b) (4) %w/w)		
(%w/w)		

Key Study Findings

- Stimulation Index (SI) did not exceed or approach 3 for either fresh or aged drug product, thus indicating no evidence of a sensitization response.

Methods

Doses:	25 µL/ear (see Sponsor's table below)
Frequency of dosing:	Daily x 3 days (Days 1-3)
Route of administration:	Dorsal surface of each ear
Dose volume:	25 µL
Formulation/Vehicle:	Isopropanol (vehicle control); acetone/olive oil, 4:1 v/v (positive control)
Species/Strain:	Mouse/CBA/J
Number/Sex/Group:	5 Females/group
Age:	Approximately 10 weeks
Weight:	Not reported
Satellite groups:	None
Unique study design:	On Day 6, each animal was injected with ^{3}H-methyl thymidine via tail vein and then sacrificed 5 hours afterwards and draining auricular lymph nodes were harvested. Nodes from each animal were pooled and single cell suspensions were prepared, followed by DNA precipitation in 5% TCA. Liquid scintillation counting of the DNA pellets for radioactivity was performed on Day 7. A Stimulation Index (SI) was calculated for each group, as well as an estimate of the EC3 value (test article concentration estimated to yield a 3-fold increase in stimulation, SI = 3).
Deviation from study protocol:	None reported

Group[1]	animal numbers		Induction
1	01 - 05	Vehicle control (experimental groups)	Isopropanol
2	06 - 10	Experimental	100% 207422/A
3	11 - 15	Experimental	100% 207422/B
4	16 - 20	Vehicle control (positive control)	Acetone/Olive oil (4:1 v/v)
5	21 - 25	Positive control	(b) (4) in Acetone/Olive oil (4:1 v/v)

[1]. five females per group

Observations and Results

Results are summarized in the Sponsor's Figures 1 and 2 below. Under the conditions of the study, neither test article induced a Stimulation Index equal or greater than 3 (SI ≥ 3) and, thus, were not deemed to be skin sensitizers. In contrast, the (b) (4) positive control induced a sufficiently robust response and confirmed the sensitivity of the assay.

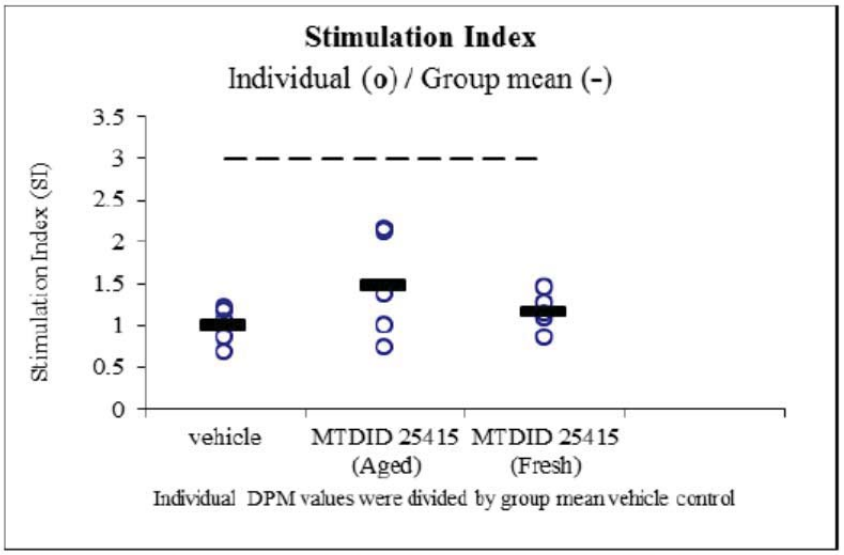


Figure 1: Dose-response Curve Experimental Groups

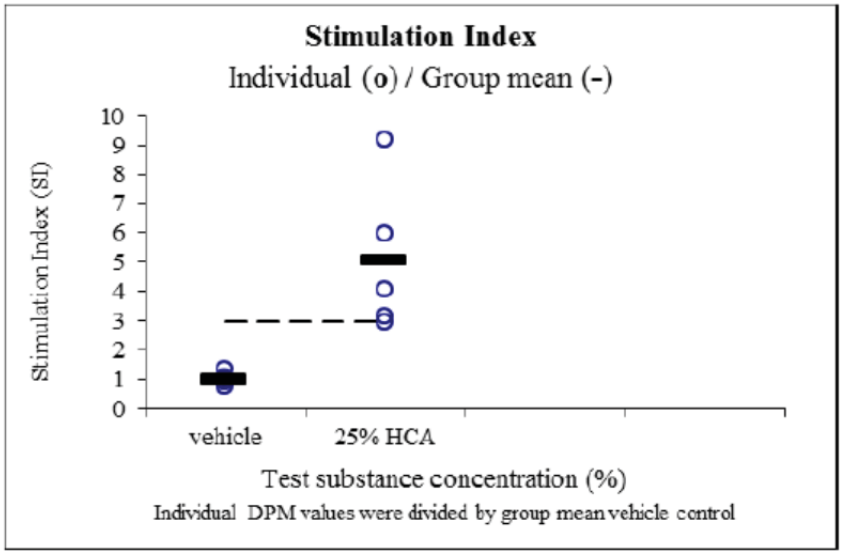


Figure 2: Dose-response Curve Positive Control Groups

11 Integrated Summary and Safety Evaluation

The 3M Health Care Business seeks market authorization for SoluPrep Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate & 70% v/v isopropyl alcohol), which would be the first sterile pre-surgical skin antiseptic product available to U.S. health care practitioners. However, during development, [redacted] resulted in drug product instability. That instability was a primary reason for DP degradant impurity specifications that exceeded the qualification threshold (≤ 1%) proscribed under ICH-Q3B(R2)[2] and was a key deficiency of NDA 208288 identified by FDA in the resulting CR action of May, 2016. The current submission constitutes the Sponsor's resubmission of the application following that CR action.

This submission contains new nonclinical data as recommended by FDA and ICH-Q3B(R2) to support safety qualification of the two identified impurities. These data were derived from genotoxicity (in silico QSAR and in vitro), local tolerance/toxicity, and general dermal toxicity studies (see Sponsor's study inventory in Appendix 1). Some of the data (genotoxicity) were generated with the individual purified impurities and the remainder (local tolerance and general dermal toxicity) with aged drug product containing elevated levels of these impurities. Based on these data, the Sponsor now proposes increased specifications for the two identified impurities (referred to as [redacted]') of ≤ [redacted]%, respectively.

The genotoxicity data generated by the Sponsor included in vitro assays (bacterial mutagenicity and chromosomal aberrations in mammalian cells) with each of the synthesized and purified DP impurities in isolation. These GLP-compliant data, in conjunction with FDA's own internal in silico QSAR assessment finding of negative mutagenic potential (see Appendix 2), are considered adequate and sufficient and support a determination of negligible risk of genotoxic activity for each impurity.

The Sponsor also conducted local tolerance toxicity studies with purportedly complete DP solution formulations that were either fresh or aged [redacted], the latter containing elevated levels of the two noted individual impurities and of total impurities. These GLP-compliant studies consisted of assessments of local skin irritation and skin sensitization potential in intact animals (rabbits and mice, respectively). The resulting data are considered adequate and confirm a lack of clinically relevant skin irritation or skin sensitization activity of either DP formulation, as well as a lack of difference in observed effects between the low and high impurity levels of the two test articles.

Finally, the Sponsor provided data from a pivotal, general dermal toxicity study conducted in rabbits that also evaluated the effects of the fresh versus aged DP solution formulations noted above. In this study, 3.7 mL of 2% CHG DP solution was applied to each animal with each application, which equates to approximately 74 mg CHG/animal/application. This, in turn, equates with an applied dose of approximately [redacted] mg/animal/day of the [redacted] and [redacted] mg/animal/day of the [redacted]

[2] Guidance for Industry: Q3B(R2) Impurities in New Drug Products, ICH, 2006.

impurity. Treatments were applied once per day, ≥ 23 hr/day under occlusion, on four separate days with four days between applications. Each dosing application was applied over an area of each animal's back of approximately 12 cm x 20 cm, or 240 cm^2. This equates to an applied CHG dose to the animals of approximately 0.308 mg/cm^2 (= 74 mg/240 cm^2).

The Sponsor's pivotal dermal study did not assess systemic absorption of impurities by animals, nor were clinical exposure data available. In the absence of such data, it is assumed that the impurities are 100% bioavailable after dermal exposure. Therefore, the applied doses noted above equate (in a ~3.5 kg rabbit) with systemic doses of approximately (b) (4) mg/kg for the (b) (4) impurities, respectively. Such systemic doses to a rabbit would equate to human equivalent doses (HED) of (b) (4) mg/kg, respectively, if normalized based on BSA.[3] These dose rates correspond, in turn, to total administered doses of each impurity of (b) (4) mg, respectively, in a reference 60-kg human.

By comparison, per the Sponsor's Table 3.2.P.5.5.1.1 below (as referenced in the previous nonclinical review, Dr. Wafa Harrouk, 23 March 2016), an estimated MDD of 1040 mg CHG will be applied under conditions of clinical use. According to the Sponsor's proposed professional product labeling, each 26-mL DP applicator will cover a maximum area of approximately 19.5 in x 19.5 in, or 380.25 in^2, which is approximately equivalent to 2453 cm^2. Thus, 2 x 26-mL applicators would cover a treated skin surface area of approximately 4906 cm^2 and, therefore, the applied CHG dose to humans would be approximately 0.212 mg/cm^2 (= 1040 mg/4906 cm^2). The resulting ratio of animal-to-human CHG exposures is 0.308 mg/cm^2 ÷ 0.212 mg/cm^2, or approximately 1.5. Of note, in the Sponsor's current submission (Pharmacokinetic Written Summary, 2.6.4.1.1. Absorption, pg. 11), it is stated that "In a single major surgery, such as a cardiovascular procedure, standard of care dictates that up to four 26-mL product applicators may be used which represents a maximal use circumstance." Presumably, however, the applied dose in such a situation would not change on a mg/cm^2 basis, as the amount applied and the surface area to which it is applied would both double (i.e., 2080 mg/9812 cm^2 = 0.212 mg/cm^2).

[3] Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, FDA/CDER, 2005.

Table 3.2.P.5.5.1.1 Maximum Daily Applied Amount for CHG

Product	CHG Concentration (%w/v)	Volume of Solution (mL)	Maximum Applied Dose (mg)	No. of Applications	Maximum Daily Applied Amount (mg)
10.5 mL Applicator	2.0	10.5	210	2	420
26 mL Applicator	2.0	26	520	2	1040

Table 3.2.P.5.5.1.2 Estimated Maximum Daily CHG Absorbed Amount

Product	CHG Concentration (%w/v)	Volume of Solution (mL)	Maximum Absorbed Dose (mg)	No. of Applications	Maximum Daily Absorbed Amount (mg)
10.5 mL Applicator	2.0	10.5	1.89	2	3.78
26 mL Applicator	2.0	26	4.68	2	9.36

From the perspective of comparing the amount of each impurity absorbed systemically, however, the greater the treated skin surface area, the greater the potential would be for systemic absorption of the impurities. At an applied human dose of 2 applicators as noted above, this would equate with 1040 mg of administered CHG, resulting in systemic impurity doses of (b) (4) mg/person of (b) (4) ((b) (4) mg/kg) and (b) (4) mg/person of (b) (4) ((b) (4) mg/kg). These assumed human systemic impurity doses resulting from the use of 2 applicators per person are, obviously, already greater than those evaluated in the rabbit safety qualification study. However, if one assumes a worst case scenario as suggested by the Sponsor of using 4 applicators per person, the negative animal-to-human exposure margin would be even less (i.e., (b) (4): (b) (4) mg/person, or (b) (4) mg/kg, and (b) (4) mg/person, or (b) (4) mg/kg, respectively) (see summary table below).

Animal vs. Human Impurity Exposure Comparison
(at current proposed specifications)

	Rabbits		Humans		Animal:Human Ratio	
	Impurity 1	Impurity 2	Impurity 1	Impurity 2	Impurity 1	Impurity 2
Surface Area (mg/cm^2)	(b) (4)					
Systemic Dose (mg/kg)[a]						

[a]Assuming 100% bioavailability; animal doses converted to HED based on BSA
[b]Based on MDD of 2 x 26-mL applicators
[c]Based on MDD of 3 x 26-mL applicators
[d]Based on MDD of 4 x 26-mL applicators

In addition, there are other aspects of the design and conduct of this study that raise concerns with respect to its adequacy to fully address the safety of the two impurities requiring qualification. Specifically, the animals were allowed to recover for a full 3-day non-dosing period between removal of the final drug patch application and terminal necropsy, which is not optimal. Further, the Sponsor performed microscopic examination on an inadequate number of organ tissues in their histopathology

evaluations, though they do indicate that an adequate battery of tissues was collected and preserved. In subsequent communications, the Sponsor has committed to submitting an amended study report containing results of microscopic observations on a full battery of organ tissues. Finally, no toxicokinetic analyses were performed as part of the study, so there are no data to address whether the impurities were systemically absorbed and, if so, to what extent.

These deficiencies—individually and in total—represent significant design flaws in a study that is intended to provide a full and complete assessment of the potential for these impurities to induce local and/or systemic toxicity. If the Sponsor designed the study as they did based on a determination that the impurities would not be absorbed into the systemic circulation, they should provide data supporting such a determination. Otherwise, the data provided are inadequate to establish the safety under proposed clinical use conditions of the two DP impurities, which, therefore, remain in need of qualification from a nonclinical perspective. Absent a Clinical Review Team finding that the benefit-risk assessment regarding the potential clinical utility of such a sterile drug product outweighs any potential safety risk due to the impurities, it is, thus, recommended that the dermal general toxicity study be repeated. In such case, it is recommended that a final study protocol be submitted for comment prior to study initiation.

Alternatively, consideration was given to the possibility that the Sponsor might agree to lower the proposed DP impurity specifications and how this might affect approvability from a nonclinical safety perspective. Such consideration is captured quantitatively in the summary table below, which reflect the underlying assumptions shown below. It will be a Clinical Review Team decision as to the appropriateness of discussing such product use and quality alternatives with the Sponsor.

- Both impurities are assumed to be 100% bioavailable in animals and humans.

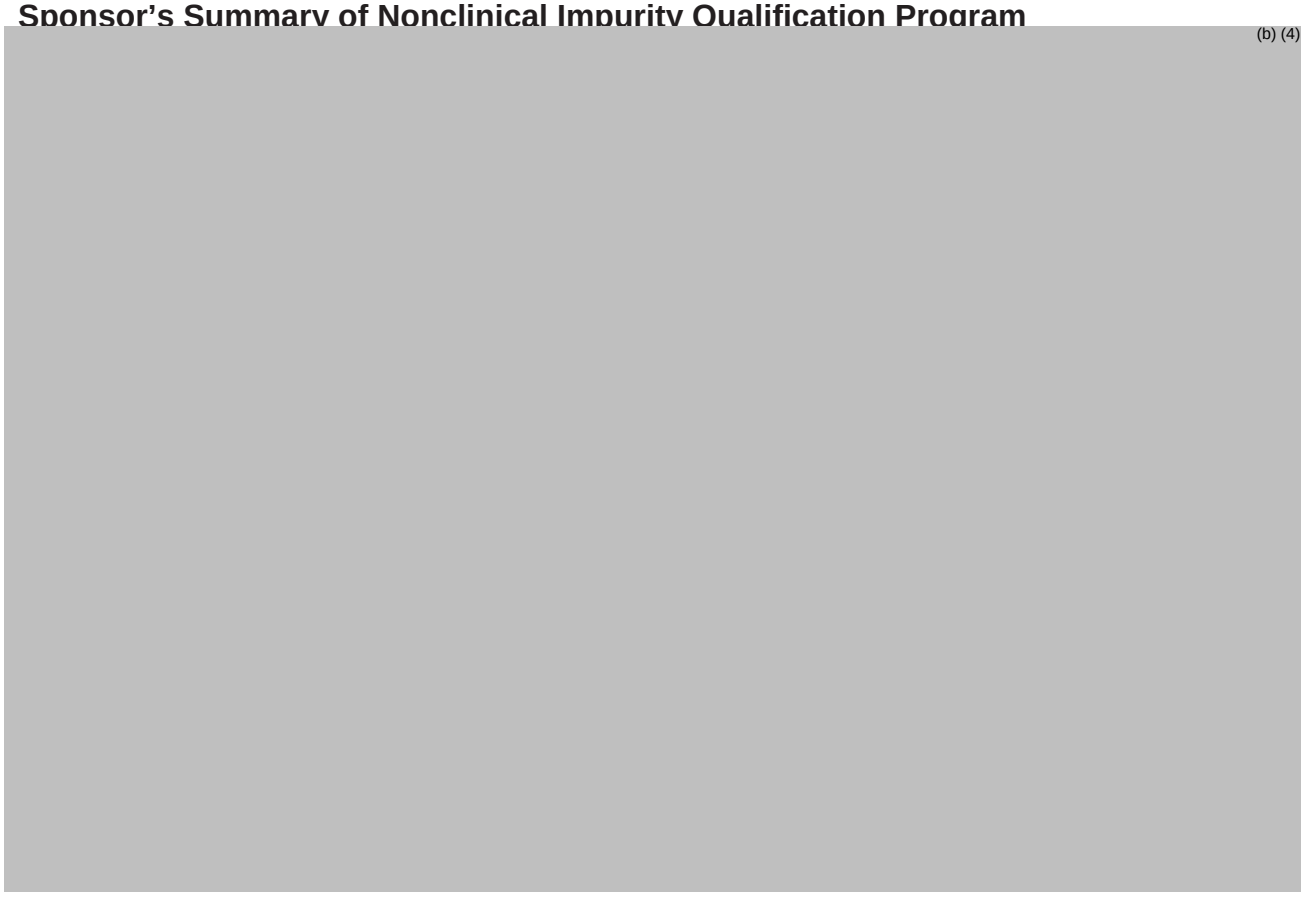
Anticipated Clinical Use		Maximal Supported Specification (%, NMT ???)	
Appl. No. & Size (CHG dose, mg)	Recommended Coverage Area (cm^2)*	Impurity 1	Impurity 2
1 x 26-mL (520)	2453	(b) (4)	
2 x 26-mL (1040)	4906		
3 x 26-mL (1560)	7359		
4 x 26-mL (2080)	9812		
1 x 10.5-mL (210)	1090		
2 x 10.5-mL (420)	2180		
3 x 10.5-mL (630)	3270		
4 x 10.5-mL (840)	4360		
5 x 10.5-mL (1050)	5450		

12 Appendix/Attachments

Appendix 1

Sponsor's Summary of Nonclinical Impurity Qualification Program

(b) (4)



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/s/

DONALD C THOMPSON
07/24/2017

JANE J SOHN
07/24/2017
I concur.

Division of Nonprescription Drug Products
Review

NDA: 208288
Document: SD-52
Date Received: June 21, 2017
Sponsor: 3M Health Care Business
Drug: SoluPrep™ Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate and 70°/o v/v isopropyl alcohol)

The following is a review of the Sponsor's submission in response to a nonclinical Information Request communicated via email on June 7, 2017. The submission provides justification for the Sponsor's nonclinical qualification program of impurities, conducted to date under this NDA. In addition, the Sponsor includes their version of Meeting Minutes for a teleconference with FDA on June 12, 2017, which was also in response to the Information Request sent on June 7, 2017. FDA does not agree with the Sponsor's minutes of the teleconference (refer to the internal Meeting Minutes in DARRTS, July 11, 2017). The teleconference was attended by RPM Tinya Sensie, Clinical Team Lead Francis Becker, and Pharm/tox Team Lead Jane Sohn. Drs. Becker and Sohn are the main authors of this review.

The Sponsor begins the submission by reproducing FDA's Information Request communicated via email on June 7, 2017. This is followed by the Sponsor's response, entitled "Summary of Discussion." The first paragraph of this section begins with the following justification for the Sponsor's nonclinical qualification of impurity (b) (4):

> "The plans for the Impurities Qualification Studies were discussed and accepted by the Agency following 3M submissions dated 12-17-15 (NDA Amendment 013), 1-8-2016 (NDA Amendment 014), 2-4-16 (NDA Amendment 016), and 4-26-16 (NDA Amendment 029) and in meetings with the Agency on January 12, 2016 and April 12, 2016. In FDA's General Advice response, dated 1-26-2016 (FDA Reference ID 3877594), FDA advised 3M to refer to ICH Q3B (R2) and ICH S2 (R1) for the qualification of impurities. A 16-day dermal toxicity study with local tolerance testing was selected based on Attachment 3 of ICH Q3B (R2), with the duration selected based on the acute / single use format of the drug product. 3M informed FDA that this study would replicate the pre-clinical work previously done in rabbits (NDA 208-288 eCTD Module 2.6.6.4.3 Study 11-399/Study EM-05-012174 Systemic Toxicity of Various Solutions of MTDID 25415 (Lot 3)) and in FDA's General Advice Letter dated 1-26-16 (FDA Reference ID 3877594), the Agency did not direct 3M to follow any specific guidance with respect to the conduct of this study which would proscribe the endpoints evaluated. During the June 12, 2017 teleconference with FDA, it was expressed by FDA that the Agency was surprised 3M did not pursue a pharmacokinetic strategy for the qualification of impurities. ICH Q3B (R2), which FDA advised 3M to follow, does not reference pharmacokinetic options for the qualification of impurities."

The Sponsor's comments reproduced above do not reflect the discussion during the teleconference on June 12, 2017. During the June 12, 2017 teleconference, the Sponsor stated several times that their main justification for the nonclinical impurities qualification program consisted of: 1) they had submitted the protocol for their submitted dermal toxicity study, and 2) FDA had approved the protocol for their submitted dermal toxicity study. The Sponsor now states in the current submission (SD-52) that FDA failed to raise concerns regarding the

adequacy of their 16-day dermal toxicity study. FDA maintains that no nonclinical protocol was approved under this NDA and stated this during the teleconference

The appendix to this review summarizes FDA's responses regarding nonclinical qualification of impurities in relation to the Sponsor's communications as cited in their first discussion summary paragraph excerpted above. Note that the Sponsor did not specifically cite these communications during the teleconference.

FDA has the following notes regarding subsequent paragraphs of the sponsor's summary that were not discussed during the teleconference on June 12, 2016:

- Paragraph 2: "This selection of target organs is supported by pathology recommendations of OECD 410 Repeat Dose Dermal Toxicity: 21/28-day Study." The sponsor did not cite this protocol during the teleconference.
- Paragraph 4: The publication by Lewis et al. was not discussed during the teleconference.
- Paragraph 7. The paragraph starting with, "Updates will be provided", reflects new information. The sponsor previously committed to providing draft data in mid-August during the teleconference.
- Paragraph 8: The paragraph starting with, "It is 3M's expectation", does not reflect that FDA stated several times during the teleconference that additional information submitted to the NDA may be considered a major amendment, resulting in an extension of the PDUFA goal data for this review cycle. The sponsor stated that they had disputed an issue in the previous review cycle, and had won. It was not clear if the sponsor was stating that they would dispute an issue in the current review cycle.

Appendix

- SD-13 (Received December 18, 2015; Sponsor referenced date December 17, 2015)
    - This submission was in response to a previous CMC IR (November 23, 2015). FDA did not provide a response to this submission that included an approval or acceptance of the Sponsor's proposed nonclinical impurity qualification program.

- SD-15 (Received January 11, 2016; Sponsor referenced date January 8, 2016)
    - The Sponsor's submission included questions about their nonclinical qualification program that were addressed at a teleconference on January 12, 2016. The meeting minutes (General Advice, January 26, 2016) show that FDA did not agree with the Sponsor's approach.

- SD-17 (Received February 5, 2016; Sponsor referenced date February 4, 2016)
    - The Sponsor stated that "3M will conduct a nonclinical qualification program for both impurities as documented on page 3 of the Agency Teleconference Meeting Minutes and as proposed in this submission and will also conduct genotoxicity testing (Ames Assay and Chromosomal Aberration) per ICH Q3B." (See General Advice, January 26, 2016).

- General Advice Letter (DARRTS April 18. 2016; Sponsor's cited minutes of meeting on April 12, 2016)
    - FDA did not agree to the Sponsor's nonclinical qualification program. The Sponsor outlined their proposed nonclinical qualification program, which was inconsistent with advice provided on January 12, 2016 (refer to meeting minutes conveyed under General Advice, January 26, 2016).

- SD-30 (Received April 29, 2016; Sponsor referenced date April 26, 2016)
    - This submission focused on specifications in communicating with the CMC team. FDA did not respond to this submission prior to taking a Complete Response action on May 6, 2016.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE J SOHN
07/19/2017

FRANCIS E BECKER
07/19/2017

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208-288
Supporting document/s:	S000
Applicant's letter date:	July 6, 2015
CDER stamp date:	July 6, 2015 (eCTD format)
Product:	SoluPrep Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate & 70% v/v isopropyl alcohol)
Indication:	Patient preoperation skin preparation
Applicant:	3M Health Care Business (3M)
Review Division:	Division of Nonprescription Drug Products
Primary Reviewer:	Wafa Harrouk, PhD
Secondary Reviewer:	Paul Brown, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Celia Peacock, RPM

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208-288 are owned by 3M for which the above mentioned applicant has obtained a written right of reference.
Any information or data necessary for approval of NDA 208-288 that the applicant does not own or have a written right to reference constitutes one of the following: (1) published literature or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are included for descriptive purposes only and are not relied upon for approval of NDA 208-288.

TABLE OF CONTENTS

1 Executive Summary

This fully electronic[1] New Drug Application (NDA 208-288) is a 505(b)(2) application which has been submitted by 3M to obtain marketing approval for the Over The Counter (OTC) use of a film forming sterile surgical solution for the preparation of the skin prior to surgery. The formulation contains two active ingredients, 2% w/v chlorhexidine gluconate (CHG), and 70% v/v isopropyl alcohol (IPA) and is referred to in the document as Soluprep Sterile Solution.

Soluprep Sterile Solution has been in development under IND 76,549 since 2006 where 3M has tested the effectiveness of various formulations containing CHG/IPA in reducing the bacterial count on human skin prior to surgery under a number of phase 2 clinical protocols. No nonclinical safety testing was conducted for the active ingredients, CHG and IPA as the applicant refers to non-product specific published literature for the general safety and efficacy of these ingredients. In the earlier phases of the drug development, the applicant proposed to use novel excipients whose safety profiles were not established for drug products, resulting in an IND clinical hold which was later removed after the applicant addressed the clinical hold issues. In the latest formulation, 3M has adjusted the formulation where inactive ingredients which have been used in previously approved drug products are used. No additional testing was needed to demonstrate the nonclinical safety profile of the formulation.

During the early developmental phases of this drug product, the applicant conducted some exploratory nonclinical studies to test the formulations which at the time were thought to contain a new polymer that had not been used in an approved drug product. These studies were not submitted to the NDA but the applicant refers to IND 76,549 for further details of these studies. The nonclinical studies were reviewed by the Agency at the time of their submission and will not be included in this review as they are irrelevant to the approval decision of this NDA (Reviews can be found in DARRTS under IND 76,549). The polymer was later considered by the Agency to be “highly similar” to the

[1] This NDA was submitted in accordance with the electronic Common Technical Document (eCTD)

polymer used in DuraPrep, another 3M approved product and thus was not considered to be a novel excipient. No further testing for the formulation was required.

The only nonclinical issue that will prevent pharmacology/toxicology (Pharm/Tox) from recommending an approval action for this NDA is the lack of an adequate qualification program for the impurities that were detected during the stability testing of the drug product. Namely, levels of two impurities, [redacted] (b) (4), were found to exceed the limits for impurities in the final drug product as allowed by the Agency's guidance on levels of impurities in drug products[2].

Recommendations

Approvability

Pharmacology/Toxicology recommends a "complete response" based on the inadequate qualification program for impurities detected during the stability testing of the final drug product.

Additional Non Clinical Recommendations

Comments to be conveyed to the applicant:

Your stability testing detected two impurities which exceed the allowed impurity threshold per FDA guidance and which have not been qualified. We refer you to the meeting minutes from the teleconference held on January 12, 2016 between representatives of your company and the FDA review staff.

To resolve this issue, you will need to follow the qualification program as stated in ICH Q3BR2 guidance which can be found on this link:

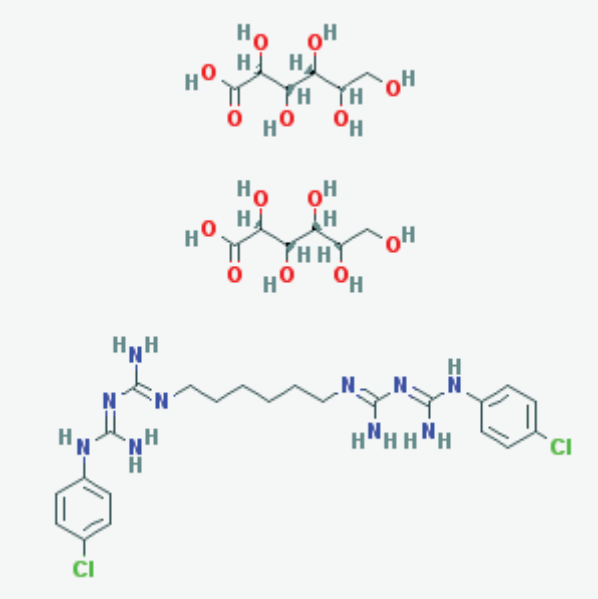
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf

[2] Impurities in new drug products Q3B(R2) guidance can be found on this link: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf

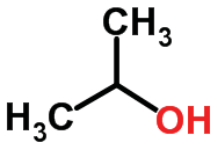
2 Drug Information

Trade name: SoluPrep Film-Forming Sterile Surgical Solution
Generic name: Chlorhexidine gluconate sterile solution with (2% CHG) and isopropanol (70% IPA)
Code name: None

CHG:
CAS registry number: 18472-51-0
Generic name: chlorhexidine gluconate
Chemical name: chlorhexidine gluconate
Molecular formula/molecular weight: C34-H54-Cl2-N10-O14 /897.8
Structure:



Isopropanol:
CAS#: 67-63-0
Generic name: 2-propanol
Chemical name: Isopropanol
Molecular formula/molecular weight: C3-H8-O/ 60.09502 g/mol
Structure:



Relevant INDs, NDAs, BLAs and DMFs

The original nonclinical summaries and reports referenced in the NDA are also included in IND 76,549 for Soluprep (same product; cross reference to the Nonclinical section).

Other antiseptic products available in the literature for CHG and IPA include:

- DuraPrep™ preoperative skin preparation (3M)
- ChloraPrep™ patient preoperative skin preparation (CareFusion)

Drug Formulation

The applicant, 3M, has used various formulations during the development of this product (see table below) to obtain a sterile solution in both tinted and colorless versions, using applicator sizes of 10.5 mL (colorless and tinted) and 26 mL (tinted only). The product is intended to be used by healthcare professionals as a single-use solution which becomes a film-forming adhesive upon topical application during surgical skin preparation. The film-forming attribute of the solution is due to the inclusion of 3M's proprietary acrylate copolymer as an inactive ingredient. The applicant is using the same acrylate copolymer that is used in their currently marketed product, DuraPrep™ surgical solution. The only difference between the two polymers is (b) (4) which was not deemed to be different from the polymer used in the previous 3M product by the CMC review team. The applicant conducted an abbreviated toxicology program for the polymer used in this product which was captured under IND 76,549 (Submission #11 dated July 20, 2012). The applicant cited a letter from the Agency dated June 7, 2012 regarding the acrylate co-polymer in the CHG/IPA formulation where the Agency determined that the new polymer was not a novel

excipient based on the high similarity between this polymer and the polymer complex used in the approved DuraPrep product. No further nonclinical testing was needed for the final formulation.

Table 3.2.P.1-1 Composition of Tinted and Non-tinted Drug Solution

Component	Function	Level in Tinted	Level in Non-tinted
Chlorhexidine Gluconate (b) (4) Chlorhexidine Gluconate Solution, USP, Ph.Eur.)	Active Drug Substance	2.0% w/v (2.3% w/w)	2.0% w/v (2.3% w/w)
Isopropyl Alcohol, USP	Active Drug Substance / (b) (4)	70% v/v (64.1% w/w)	70% v/v (64.1% w/w)
Purified Water, USP		(b) (4)	
Acetyltributyl citrate, NF			
3M Acrylate Copolymer: (b) (4)			
Yellow #5, FD&C			
Blue #1, FD&C			
Trisodium HEDTA*			
TOTAL		100%	100%

*HEDTA = hydroxylethyl ethylenediamine triacetic acid

The actual serial formulation changes are shown in detail below with changes marked in red.

Ingredient	Function	ORIGINAL SN008	SN016	SN021	SN039 and SN040
Chlorhexidine Gluconate	Drug substance	2.0% w/v (2.3% w/w)	2.0% w/v (2.3% w/w)	2.0% w/v (2.3% w/w)	2.0% w/v (2.3% w/w)
Isopropyl Alcohol	Drug substance	70% v/v (64.1% w/w)	70% v/v (64.1% w/w)	70% v/v (64.1% w/w)	70% v/v (64.1% w/w)
Water	(b) (4)	(b) (4)			
Acetyltributyl citrate					
3M poly (b) (4)					
FD&C Yellow #5					
FD&C Blue #1					
HEDTA					

3. INTRODUCTION AND DRUG HISTORY

Proposed Clinical Population and Dosing Regimen

The 3M CHG/IPA film-forming preoperative skin preparation is manufactured as a sterile solution contained in a sterile applicator and is intended for use in preparation of the patient's skin prior to surgery to help reduce the bacteria that can potentially cause skin infection. If approved, this will be the first FDA approved sterile preoperative solution. This product is intended to deliver a fast-acting, persistent, broad-spectrum activity required for this class of products and is delivered in a single-use, topically applied applicator by healthcare professionals. The product is available in 2 different forms, 10.5 mL and 26 mL applicators, containing a maximum applied amount of 420

mg and 1040 mg and resulting in a maximum human daily absorbed amount of CHG of 3.78 mg and 9.36 mg, respectively (see tables 3.2.P.5.1.1 & 3.2.P.5.1.2 below).

Table 3.2.P.5.5.1.1 Maximum Daily Applied Amount for CHG

Product	CHG Concentration (%w/v)	Volume of Solution (mL)	Maximum Applied Dose (mg)	No. of Applications	Maximum Daily Applied Amount (mg)
10.5 mL Applicator	2.0	10.5	210	2	420
26 mL Applicator	2.0	26	520	2	1040

Table 3.2.P.5.5.1.2 Estimated Maximum Daily CHG Absorbed Amount

Product	CHG Concentration (%w/v)	Volume of Solution (mL)	Maximum Absorbed Dose (mg)	No. of Applications	Maximum Daily Absorbed Amount (mg)
10.5 mL Applicator	2.0	10.5	1.89	2	3.78
26 mL Applicator	2.0	26	4.68	2	9.36

Regulatory Background

The applicant has filed this NDA under 505(b)(2) of the FDC Act whereby they intend to rely on non-product specific published literature for the general safety and efficacy of chlorhexidine gluconate and isopropyl alcohol, two antiseptic ingredients with a long history of clinical use. Several key literature articles were submitted under the NDA and its related IND (#76,549). The applicant also made a general reference to information available in the 1994 Tentative Final Monograph for Healthcare Antiseptic Drug Products, which includes isopropyl alcohol as an active ingredient (Federal Register Vol. 59, # 116, Friday June 17, 1994)[3]. Since the Health Care Antiseptics monograph is not finalized at this time, the sponsor cannot rely on the FDA's findings of safety for IPA by relying on this monograph. The sponsor did not rely on the safety findings of any specific drug product where the active ingredients, CHG and IPA, were used. It is important to note that the limited toxicology information provided in the articles would not be sufficient to allow for a fully independent review of all the nonclinical safety

[3] CHG is not included as an active ingredient in the Health Care Antiseptics monograph.

elements required for the approval of this product, if this were a new molecular entity. However, despite the absence of detailed data tabulations in the published literature, the nonclinical information may be sufficient to support the safety of the product for the indicated use (preoperative skin preparation) given the long history of clinical use of the active ingredients.

Studies Submitted

Various formulations were tested by the applicant (see table on page 8 above) including some short term toxicology studies intended to show a safe profile of the polymer used in this formulation. No toxicology studies were conducted with the final clinical formulation.

Previous Reviews Referenced

Refer to the following Pharm/Tox reviews in DARRTS:

- Under IND 76,549, see reviews dated 2/20/2008; 2/9/2011; 6/28/2012 and 7/23/2012
- Under NDA 208-288, see reviews dated 9/2/2015 and 1/22/2016

Comments on Novel Excipients

No novel inactive ingredients are used in the final formulation. The applicant had provided some toxicity studies for the film forming polymer which showed that the toxicity profile of the polymer used in this formulation did not show any concerns. Briefly, the toxicity testing for the polymer consisted of the following nonclinical safety toxicology studies:

- EM-05-012172 - Skin irritation study in rabbits
- EM-05-012173 - Murine Local Lymph Node Assay (LLNA) in mice
- EM-05-012174 - Systemic toxicity of various solutions of MTDID 25425 following repeated dermal application to the rabbit

- EM-05-012674 - Topical primary irritancy and phototoxicity of MTDID 25415 (tinted and untinted) in hairless mice

These studies demonstrated that the polymer had little or no skin irritation/sensitization and that no systemic toxicity was observed. The full review, dated June 20, 2012, can be found in DARRTS.

Comments on Impurities/Degradants of Concern

During the developmental stages of this sterile formulation, the applicant identified the (b) (4) the 3M™ CHG/IPA Film-Forming Patient Preoperative Skin Preparation solution. However, it was also discovered that (b) (4) the CHG/IPA solution resulted in a number of impurities which were detected during the stability testing under accelerated conditions. The applicant is expected to monitor and track individual and total impurities levels for all individual impurities at or above the reporting threshold of 0.1% w/w, in accordance with ICH Q3B guidelines. The applicant had initially committed to limiting the total Impurities to (b) (4) % w/w, which was later lowered to (b) (4) % w/w with respect to CHG label claim.

Stability testing of the formulation by 3M was within specification for all parameters and time-points up to 12 to 24 months at room temperature conditions. However, at accelerated conditions, a number of impurities were detected starting from month 3 and continued throughout the testing period of 24 months.

In term of individual impurities, the applicant identified (b) (4) as the primary impurity of concern. The applicant committed to specify and monitor (b) (4) in both the drug substance and the drug product. Stability testing showed this impurity to be well below the USP specification. Other drug-related impurities which were found during the stability testing for a proposed shelf-life of 24 months exceeded the maximum allowed impurities and included (b) (4) which were specified by the applicant as follows[4]: (b) (4) w/w with respect to CHG label claim and (b) (4) w/w with respect to CHG label claim

[4] For details, refer to NDA 208-288; edr section 3.2.P.5.6

Parameter	Proposed specification	3σ + 95% PI at 24 months 25°C/60%RH*	24 month results (CLIN A)	24 month results (CLIN B)	24 month results (CLIN C)	24 month results (CLIN D)
Total Impurities	(b) (4)					

Shelf life specification justification based on safety

The applicant suggests that a 24 month shelf life be granted to their CHG/IPA Sterile Skin Preparation Solution based on the following criteria: Positive outcomes of the safety and efficacy studies conducted to date, the Structure-Activity Relationship analysis of the impurities, including (b) (4), the normal usage of the 3M CHG/IPA Skin Preparation (1-2 times per life time), and the well-established safety profile of CHG. The applicant provided the formulas and structures of these two impurities (see table below).

Table 3.2.P.5.5.2.1: Species Projected to Meet the Qualification Threshold

Individual Impurity	Empirical Formula	Structure	Proposed Pathway of Formation
(b) (4)			

The CMC reviewer evaluated the submitted data and found that the acceptance criteria proposed by 3M for individual impurity/degradant, (b) (4), were inadequate (both of which exceeded the 1.0% limit per ICH Q3B by (b) (4) %). In addition,

the CMC reviewer found that the acceptance criterion set by the applicant for a total impurity limit of (b) (4)% also exceeds the limits set for similar approved products.
In response to the drug product information request, 3M proposed a shelf life specification of (b) (4)% for total impurity, (b) (4)% for impurity (b) (4), and (b) (4)% impurity (b) (4), based on their stability data.
Except for (b) (4), which is well below the USP specification, both (b) (4) degradants exceed the ICH Q3B guideline of < 1% when stored at 25°C/60% RH. These impuruities appear to be formed continuously and trend towards an increase with time starting at 3 months where (b) (4) (See CMC review for complete description of the stability testing program).
According to the applicant's proposed specifications, the total impurities/degradants is projected to reach up to (b) (4) mg (including (b) (4) mg of (b) (4) and (b) (4) mg of (b) (4)) when the solution is applied on the skin with a 10.5 mL applicator. For a 26-mL applicator, the amount of total impurity would reach up to (b) (4) mg (including (b) (4) mg (b) (4) and (b) (4) mg (b) (4)). 3M justified the lack of qualification program for these impurities citing factors such as (b) (4) However, the applicant did not provide any absorption data for these impurities to allow for an independent comparison between the parent compound, CHG, and the impurities/degradants.

The applicant also indicated that a QSAR analysis did not identify any potential concern for carcinogenic impurities for either of the 2 impurities. An independent QSAR analysis was conducted by the FDA and confirmed the applicant's conclusion.

A teleconference was held on January 12, 2016 between representatives of 3M and the FDA where 3M committed to initiating the proposed qualification studies as follows:

- Rabbit dermal toxicity study (16 days): 3M proposes testing at the shortest of the endpoints cited in ICH Q3B based on the acute use/single use format of this drug product as a patient preoperative skin preparation.

- Local tolerance testing (Primary Skin Irritation in rabbits and Sensitization by LLNA)

- No genotoxic testing was proposed in the qualification program for the 2 impurities as specified by ICH Q3B (R2). Instead, 3M argued that these studies are not appropriate for the following reasons:

    - No mutagenic potential is expected for (b) (4) based on the QSAR analysis.

    - Due to the antimicrobial and cytotoxic nature of CHG and its derivatives, these impurities are likely to cause point mutation or chromosomal aberration assays. Based on 3M's prior experience with CHG-containing medical devices, dilution of the impurities to less than 1% to enable testing in these assays is possible; however, the dilutions are not representative of proposed specification levels.

    - Since the impurities are not commercially available and synthesis would require significant time, especially in the case of (b) (4), the applicant argued that the technical challenges are significant and the stability of the impurity is unknown.

    - The intended use would typically be no more than 1 to 2 times in a patient's lifetime as a single-use preoperative skin preparation.

Furthermore, the applicant stated that final reports for these studies would not be available until after the deadline for the review cycle of the NDA (approximately June 2016) and committed to formally submitting the data (b) (4) as soon as they become available. 3M still asked for a 24 month expiry date based on their argument presented above.

The Pharm/Tox reviewer provided the following response to 3M:

- The shelf life for this product will have to be supported by the level of impurities and the results of the qualification program that you plan to conduct.

- The qualification program consisting of a rabbit dermal toxicity study (16 days) and local tolerance testing without any genotoxicity testing is not adequate. The reviewer referred the applicant to the qualification program as stated in ICH Q3BR2 guidance which can be found on this link: **http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf**). The genotoxicity testing aspect is needed for any qualification program even if the intended use of the product is for a single use. If the applicant finds that conducting an Ames Assay is not feasible for the proposed formulation, they were referred to S2 R2 guidance for alternative approaches to assess the genotoxicity potential of the detected impurities which can be found on this link: **http://www.fda.gov/downloads/Drugs/.../Guidances/ucm074931.pdf .**

- The final reports will have to be submitted during the NDA review cycle since the results of these reports will have a direct impact on the approvability of the NDA.

4 Pharmacology

No new studies were submitted. Chlorhexidine gluconate and isopropyl alcohol are skin antiseptics with a long history of use, and combination products of both compounds have been extensively used in many countries. CHG/IPA products are considered fast-acting antiseptics (due to a synergism between the two active components) with long-lasting activity (due to the residual chlorhexidine).

Since 1993, Solumed Inc. (acquired by 3M Healthcare in 2008) has been selling products containing 0.5% chlorhexidine/70% IPA in Canada. Beginning in 2005, the company introduced the 2% chlorhexidine/70% IPA- containing Solu-IV Swabs, Swabsticks and Maxi-Swabsticks to the Canadian market.

5 Pharmacokinetics/ADME/Toxicokinetics

No new studies were submitted.

6 General Toxicology

The applicant conducted some exploratory toxicology studies to test the safety of the polymer, [redacted] (b) (4) which was tested in formulation MTDID 25415. The applicant used MTDID 25415, lot #3 for the nonclinical testing which was the same lot that was used for the clinical testing.

The nonclinical testing of the polymer consisted of the following studies:

- EM-05-012172 - ISO Skin Irritation in Rabbits;
- EM-05-012173 - Murine Local Lymph Node Assay (LLNA) in Mice;
- EM-05-012174 - Systemic Toxicity of Various Solutions of MTDID 25425

Following the repeated Dermal Application to the Rabbit;

- EM-05-012674 - Topical Primary Irritancy and Phototoxicity of MTDID 25415 (tinted and untinted) in Hairless Mice.

The above cited nonclinical studies were reviewed under IND 75,549 and demonstrated that there was little or no skin irritation/sensitization and there was no systemic toxicity observed under the conditions of the studies. The polymer was later considered by the Agency to be “highly similar” to the polymer used in DuraPrep, another 3M approved product and thus was not considered to be a novel excipient. No further testing for the formulation was required.

No other general toxicity studies were conducted for this product.

7 Genetic Toxicology

No studies were submitted.

8 Carcinogenicity

No studies were submitted.

9 Reproductive and Developmental Toxicology

No studies were submitted.

10 Special Toxicology Studies

No studies were submitted.

11 Integrated Summary and Safety Evaluation

The applicant is relying on publicly available literature to support the safety of the two active ingredients, chlorhexidine and isopropyl alcohol. The final formulation did not contain new excipients and no testing was required. During the stability testing, the applicant identified two impurities which were found to exceed the allowable impurities according to ICH Q3B(R)(2) starting from month (b) (4) of the stability testing period. The applicant has suggested an abbreviated qualification program for the two impurities which was not found to be acceptable by the review team (Pharm/Tox & CMC) who had explained the FDA's position to the applicant via a teleconference in early January 2016. At the time of writing this review, the applicant has not submitted an acceptable qualification program or any data that would allow for a timely review of the two impurities, therefore the Pharm/Tox recommendation is to issue a complete response until the impurities are adequately qualified.

12 Appendix/Attachments

None

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/s/

WAFA HARROUK
03/23/2016

PAUL C BROWN
03/23/2016

Pharm/Tox Memorandum

NDA Number: NDA 208-288, Amendment #14

Drug name: SoluPrep Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate & 70% v/v isopropyl alcohol)

Sponsor: 3M HealthCare Business

Topic: Impurity qualification program for (b) (4)

Background:

3M has identified two impurities, (b) (4), in their chlorhexidine/isopropanol (CHG/IPA) Skin Preparation formulation at levels that exceed the allowable levels for drug impurities/degradants as specified by ICH Q3B(R2). The FDA requested from the sponsor that that they either lower the impurity levels or provide adequate qualification programs for these 2 impurities. In response, the sponsor proposed new limits that were still above the allowable limits per ICHQ3B(R2) and requested to have a teleconference with the review staff for further clarification (see timelines below).

Date	Correspondence	Subject
Nov. 12, 2015	FDA CMC Information Request #1	Q2: FDA requests 3M sets additional impurity limits
Nov. 30, 2015	3M Response to FDA's Nov. 12 Letter -- NDA A-010 submission (see Question 2)	3M proposes impurity limits and updates NDA section 3.2.P.5.6 Total Impurities (b) (4) % (b) (4)
Dec. 10, 2015	FDA e-mail response to 3M's Nov. 30 submission	FDA requests new proposed limits, numerical quantitative results for stability data, and justification
Dec. 17, 2015	3M Response to FDA's Dec. 10 e-mail – NDA A-013 submission	3M proposes revised limits, and requests a teleconference to discuss a qualification study plan and timing Total Impurities (b) (4) % (b) (4)
Dec. 17, 2015	FDA e-mail grants teleconference	Teleconference to be held January 12, 2016
January 8, 2016	Sponsor submits amendment #14 (see attachment below)	Teleconference held January 12, 2016

A QSAR analysis conducted by the FDA did not identify either of the 2 impurities to be of potential concern as mutagenic impurities.

At the teleconference held on January 12, 2016, the sponsor has proposed the following nonclinical qualification program for their two impurities:

- Rabbit dermal toxicity study (16 days): 3M proposes testing at the shortest of the endpoints cited in ICH Q3B based on the acute use/single use format of this drug product as a patient preoperative skin preparation.

- Local tolerance testing (Primary Skin Irritation in rabbits and Sensitization by LLNA)

- No genotoxic testing was included in the qualification program for the 2 impurities as specified by ICH Q3B(R2). Instead, 3M proposed that these studies are not appropriate and does not plan to conduct them for the following reasons:
    - No mutagenic potential is expected for (b) (4) based on the QSAR analysis.
    - Due to the antimicrobial and cytotoxic nature of CHG and its derivatives, these impurities are likely not to be suitable for point mutation or chromosomal aberration assays. Based on 3M's prior experience with CHG-containing medical devices, dilution of the impurities to less than 1% to enable testing in these assays is possible; however, the dilutions are not representative of proposed specification levels.
    - As stated above, the impurities are not commercially available and synthesis would require significant time, especially in the case of (b) (4). The technical challenges are significant and the stability of the impurity is unknown.
    - The intended use would typically be no more than 1 to 2 times in a patient's lifetime as a single-use preoperative skin preparation.

Specification justification based on stability data

The following numerical quantitative results (%) were provided for all the data points for the impurity stability figures submitted in Amendment 010 (Attachments 1 - 3).

Impurities Data Summary (full data tables are provided in Attachments 1-3)

(b) (4)

Shelf life specification justification based on safety
The sponsor suggests that a 24 month shelf life be granted to their CHG/IPA Skin Preparation product based on the following: Positive outcomes of the safety and efficacy studies conducted to date, the Structure-Activity Relationship analysis of the impurities, including (b) (4) (b) (4), the normal usage of the 3M CHG/IPA Skin Preparation (1-2 times per life time), and the well-established safety profile of CHG.

The following questions were raised by 3M prior to the meeting and were discussed at the teleconference held on January 12, 2016*:*

1) Does the Agency agree with 3M's approach to impurities qualification?

CMC response: *No. We do not agree. 3M's approach* (b) (4) (b) (4) *is not acceptable. The acceptance criterion should be derived from the 'average*

+ 3SD'; where average is the mean of the data points at your proposed shelf-life, which is 24 months, and SD is the standard deviation of the mean. In addition, each acceptance criterion should be set no higher than the qualification level of the given degradation product per ICH Q3B (R2). For qualification studies, see pharmacology and toxicology response below.

***3M response provided on Jan 12, 2016*:** 3M will re-calculate the acceptance criteria for Total Impurities, (b) (4) using 'average + 3SD', and propose a shorter shelf-life than 24 months. 3M stated that they could provide this information in one week.

2) Upon FDA agreement to question 1 above, 3M commits to initiating the proposed qualification studies as soon as possible. 3M will provide status updates and study outcomes prior to the May 2016 estimated NDA approval date, however, final reports for these studies would not be available until approximately June 2016, and would be formally submitted as a supplement to the approved NDA. Based on the safety demonstrated in all of the clinical studies on aged product, supported by the QSAR analyses and decades of safe use of CHG, 3M proposes that a 2 year shelf life be granted at the time of NDA approval. Does the Agency agree?

Pharm/Tox response:

- The shelf life for your product will have to be supported by the level of impurities and the results of the qualification program that you plan to conduct.

- Your proposal to conduct a rabbit dermal toxicity study (16 days) and local tolerance testing without any genotoxicity testing is not adequate. You will need to follow the qualification program as stated in ICH Q3BR2 guidance which can be found on this link: **http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf**). The genotoxicity testing aspect is needed for any qualification program even if the intended use of the product is for a single use. If you find that conducting an Ames Assay is not feasible for your formulation, refer to S2 R2 guidance for alternative approaches to assess the genotoxicity potential of the detected impurities which can be found on this link: **http://www.fda.gov/downloads/Drugs/.../Guidances/ucm074931.pdf.**

- The final reports will have to be submitted during the NDA review cycle since the results of these reports will have a direct impact on the approvability of your NDA.

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/s/

WAFA HARROUK
01/22/2016

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01/22/2016