CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208288Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 208288
Review # 2

Drug Name/Dosage Form	Chlorhexidine Gluconate (CHG) and Isopropyl Alcohol (IPA) Solution
Strength	2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
Route of Administration	Topical
Rx / OTC Dispensed	OTC
Applicant	3M Health Care (Infection Prevention Division) St Paul, MN 55144
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	03-Mar-2017	ONDP/OPF/FR
Response to quality IR	01-June-2017	ONDP/FR

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Erin Kim, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Maria Cruz-Fisher, Ph.D. Erika Pfeiler, Ph.D.	OPF/DPAII/BranchVI
Facility	Xiaohui (Sherry) Shen, Ph.D.	OPF/DIA/B3
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II	(b) (4)			Adequate	10/29/2014	None
	III			1	Adequate	5/14/11	None
	III			7	Adequate	N/A	(b) (4) glass
	III			1&4	Adequate	N/A	This is a medical device MF, same type of material is being used in approved products
	III			1&4	Adequate	12/23/15	None

C. [1] Action codes for DMF Table:
D. 1 – DMF Reviewed.
E. Other codes indicate why the DMF was not reviewed, as follows:
F. 2 –Type 1 DMF
G. 3 – Reviewed previously and no revision since last review
H. 4 – Sufficient information in application
I. 5 – Authority to reference not granted
J. 6 – DMF not available
K. 7 – Other (explain under "Comments")
L. [2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76,549	CHG/IPA Film-Forming Skin Preparation

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Office of Surveillance	NA			

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Executive Summary (NDA-208288)

I. Recommendations

–With respect to Chemistry Manufacturing and Controls, no recommendation can be made regarding approval at this time (see summary of quality assessment).

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the resubmitted application the drugsubstance, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application. The drug product has not been granted a shelf life due to pending resolution of specifications for specified impurities in the drug product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments:

The current application (NDA-208288) is a resubmission and a response to the CR letter dated May 6, 2016. The CR letter outlined deficiencies for clinical, clinical pharmacology, non-clinical, microbiology and chemistry. This review (executive summary) will summarize quality-related (microbiology and chemistry) CR responses to deficiencies. Microbiology issues have been resolved and drug product specifications for specified impurities are pending non-clinical review..

The complete response letter included 10 issues related to sterility assurance of the drug product. Microbiology review dated 14 June, 2017 indicates that all outstanding issues related to sterility issues are resolved. Regarding quality, CR letter included additional concerns on two impurities (b) (4) in the drug product which exceeded ICH Q3B (R2) limits (i.e., <1.0%) and increased during stability studies. As a result, no reasonable expiration date could be granted for the drug product. Nonclinical review required the applicant to conduct qualification studies for (b) (4) (see CR letter dated May 6, 2016). The non-clinical team determined that the qualification study for these impurities is not adequate based on non-clinical review dated 24 July, 2017. Thus, CMC drug product impurity specifications could not be finalized. A discipline review letter is planned to issue with the following quality comment.

"*The proposed drug product specifications for individual impurity* (b) (4) *of NMT* (b) (4) *%,* (b) (4) *of NMT* (b) (4) *%, and Total Impurities of NMT* (b) (4) *% have not been adequately justified. Refer to Nonclinical comments. However, based on levels of impurities in the product real time stability data, 3M may tighten limits for* (b) (4) *to*

NMT (b) (4)%, RRT (b) (4) to NMT (b) (4)%, and Total Impurities to NMT (b) (4)%. These limits would support a shelf-life of 2 years pending final non-clinical evaluation."

Facility review with "acceptable cGMP recommendation" was completed on 14 June, 2017.

A. Drug Product [SoluPrep Surgical Solution] Quality Summary

1. **Strength:** Chlorhexidine Gluconate (2% w/v) and Isopropyl Alcohol (70% v/v)

2. **Description/Commercial Image:**

The 3M™ CHG/IPA film-forming, sterile patient preoperative skin preparation (also referred to as "surgical solution") is formulated for use as either a tinted or untinted topical antiseptic drug solution.

The proposed sterile, topical antiseptic drug product will be supplied in single use applicators containing either 10.5 mL or 26 mL of solution. The finished drug product solution is filled into a (b) (4) sealed, (b) (4) glass ampoule that is housed in a single use (b) (4) plastic applicator. Each plastic applicator has a reticulated foam sponge at one end and is individually sealed in a (b) (4) pouch (b) (4) Each 26 mL applicator is provided with two cotton-tipped swabs inside the sealed pouch.

The proposed indication of the 3M CHG/IPA product is for use as a patient preoperative skin preparation; for the preparation of the patient's skin prior to surgery and to help reduce bacteria that potentially can cause skin infection.

3. **Summary of Product Design**

The New Drug Application describes? a dual-active antimicrobial hydroalcoholic solution comprising 2% (w/v) chlorhexidine gluconate and 70 % (v/v) isopropyl alcohol and (b) (4) inactive ingredients (b) (4). The inactive ingredients used were a film forming organic polymer (b) (4) and a colorant mixture to obtain a single phase,

isotropic, topical antiseptic solution. The polymer used in the 3M CHG / IPA prep is the same polymer used in the FDA approved DuraPrep solution (NDA 21-586), but with a (b) (4).
The manufacturing process involves (b) (4)

The formulation remains in contact with glass only until at the time of application, when the ampoule is broken, the solution flows through the reticulated foam sponge and applied to the skin.

4. List of Excipients:

Poly (b) (4) Acetyl tributyl citrate, FD&C blue #1, FD&C Yellow #5 and Trisodium HEDTA (Hydroxylethyl ethylenediamine triacetic acid).

5. Process Selection (Unit Operations Summary)

(b) (4)

6. **Container Closure**:

3M CHG/IPA Film-forming Preoperative Skin Preparation is packaged in (b) (4) sealed 10.5 mL and 26 mL primary container. The primary container closure system is made of (b) (4) glass. Each sealed ampoule is housed in a plastic applicator, and sealed in a (b) (4) pouch. Two cotton-tipped swabs are provided with each 26 mL applicator.

7. Expiration Date & Storage Conditions

Expiration date of the drug product is not assigned at this time due to pending resolution of the impurity specifications of the drug product. However, quality review included a

comment in the "discipline review letter" indicating 2-year product shelf life based on real time stability data: (NMT (b) (4)% total impurity, NMT (b) (4)% of (b) (4) and NMT (b) (4)% of (b) (4)).
The storage statement will be written as "Store between 15°C – 30°C (59°F - 86°F); avoid freezing and excessive heat above 40°C (104°F). This reflects the numerical value of the controlled room temperature [stored at 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F)].

8. List of co-packaged components: None

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	SoluPrep Surgical Solution
Non Proprietary Name of the Drug Product	2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
Non Proprietary Name of the Drug Substance	chlorhexidine gluconate; isopropyl alcohol
Proposed Indication(s) including Intended Patient Population	Patient preoperative skin preparation, for the preparation of the skin prior to surgery and to help reduce bacteria that can potentially cause skin infection
Duration of Treatment	Single use topical application: 10.5 mL applicator (Clear/Tint) • Solution volume 10.5 ml / 0.36 fl. oz. • Coverage area 13 in. x 13 in. (178.8 in2). 26 mL applicator (Tint) • Solution volume 26 mL / 0.9 fl. oz. • Coverage area 19.5 in. x 19.5 in. (387.5 in2).
Maximum Daily Dose	N/A
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I.
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: No
   - PK studies: Yes
   - IVIVC: No

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations
None

F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	4	3	2	24	Similar assay method as approved for capsule dosage form. Impurities are monitored (not finalized)
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on limited data provided.
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	3	2	3	12	(b) (4)
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Controlled with specifications.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Outstanding issues:

- The application is approvable pending resolution of the impurities specifications of the drug product.
- Based on finalized drug product specification, shelf life of the product needs to be assigned.

Application Technical Lead Signature:

Swapan K. De -S

Digitally signed by Swapan K De -S
DN: c=US o=U.S. Government ou=HHS ou=FDA ou=People cn=Swapan K De -S 0.9.2342.19200300.100.1.1=1300132497
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Xiaohui (Sherry) Shen

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B.J. Ryan

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Date: 6/14/2017 02:15:48PM
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Product Quality Microbiology Review

May 22, 2017

NDA: 208288

Drug Product Name
Proprietary: SoluPrep Surgical Solution
Non-proprietary: Chlorhexidine Gluconate (CHG) and Isopropyl Alcohol Solution (IPA)

Review Number: #2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
3/3/2017	3/3/2017	N/A	3/6/2017

Submission History (for 2nd Reviews or higher)

Submit	Microbiology Review #	Review Date (s)
7/6/2015	1	3/18/16
8/3/2015	1	3/18/16
8/12/2015	1	3/18/16
11/5/2015	1	3/18/16
12/4/2015	1	3/18/16
12/17/2016	1	3/18/16
1/15/2016	1	3/18/16
2/9/2016	1	3/18/16
3/9/16	1	3/18/16

Applicant/Applicant
Name: 3M Health Care
Address: 3M Center, Building 275-5 W-06
St. Paul MN 55144-1000

Representative: Dianne Gibbs, Regulatory Affairs Dr., IPD Division
Telephone: 651-737-9117
Fax: 651-737-5320

Name of Reviewer: Maria I. Cruz-Fisher, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Complete Response – Original NDA

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product

3. MANUFACTURING SITE:

DP (b) (4)
3M Cordova Plant
3M Company
22614 Route 84 North
Cordova, IL 61242

Filling, sterilization, sealing and release
3M Columbia
5400 Route B
Columbia MO 65202-9348

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile topical solution, 2% solution packaged as a 10.5 mL and 26 mL fill in a single use glass ampule.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Patient preoperative skin preparation, for the preparation of skin prior to surgery.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: This is an eCTD submission.

Some of the tables are copied directly from the application.

A CR letter (dated 5/6/2016) was sent to the firm with a list of the microbiology deficiencies. The applicant's responses (dated 3/3/2017) are included in the review.

The applicant requested a teleconference to clarify some of the deficiencies included in the CR letter dated 5/6/16. The main discussion points were the new CCIT validation data, requalification of (b) (4), bioburden and sterility testing methods (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016).

Filename: N208288MR02R.doc
Template version: OGD modified_TS_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission **is recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

(b) (4)

B. Brief Description of Microbiology Deficiencies –

None identified.

C. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment – N/A

B. Final Risk Assessment -

No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/Maria I. Cruz-Fisher, Ph.D.
Microbiology Secondary Reviewer /Erika Pfeiler, Ph.D.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

The subject ANDA amendment is in response to the microbiology deficiencies conveyed to the Applicant in the Agency's Complete Response letter dated 5/6/2016. The original deficiencies are italicized. The applicant's responses (dated 3/3/2017) have been included in the review.

Microbiology Deficiencies:

1. The container closure integrity test (CCIT) validation data provided in the submission dated 3/10/16 demonstrate that the proposed headspace oxygen analysis method has a detection rate of approximately 33% or less for defects that are 50 µm or larger in 10.5 mL drug product (DP) filled ampules. Moreover, you did not detect defects of any size in the 26 ml DP filled ampules. Further, the information presented indicates that your selected test method is only capable of detecting holes of 50 µm or greater, which, per the USP 1207.1 you previously provided, corresponds to an air leak rate of > 0.360 sccs. Kirsch, et. al. (also referenced in the Parenteral Drug Association's Technical Report 27) demonstrates that a leakage rate that correlates with microbial ingress is approximately 10^{-5} sccs, which is considerably lower than what your results demonstrate. With the low detection rate demonstrated by positive controls, and without further information to correlate your proposed method with the potential for microbial ingress, the method that you propose is not acceptable as a container closure integrity test method. Provide CCIT results from a validated testing method capable of detecting microbial ingress in order to demonstrate the integrity of the proposed container closure system (glass ampules) for the DP.

CR Response (3/7/17): The applicant proposes to use the High Voltage Leak Detection-microcurrent (HVLD-mc) as the new CCIT method. Previous CCIT methods evaluated were not capable of detecting defects due to the film forming aspect of the drug product (DP). Briefly, the HVLD-mc method consists of applying a high voltage to a hermetically sealed container made of non-conductive material. If a pinhole or crack is present on the package, the discharge current flows into the package through the pinhole or crack. The defective package is detected by the differential of the current flow as measured in the intact package. The product inside the package must be conductive for this technology to function correctly. A high voltage reading indicates defect, caused by voltage passing through the package barrier. The firm provided a copy of the CCIT test method protocol (TM-05-295444) and the validation report (TM-VAL-DRUG-RPT-05-295446) for both ampoules sizes. This information is reviewed below.

CCIT testing method validation

Study: HVLD-mc Container Closure Integrity Validation Report for Filled SoluPrep Film Forming Prep 10.5 and 26 mL Ampoules, for TM-05-295444 in Columbia, MO

Report # and date: TM-VAL-DRUG-RPT-05-295446, dated 3/1/2017

The proposed HVLD-mc test method (TM-05-295444) was validated for the 10.5 mL and 26 mL empty glass ampules using a HVLD-mc E-scan ([redacted] (b) (4) equipment ID: Equip-ID-05-301675) per protocol TM-VAL-DRUG-PRO-05-2954458.

Summary: The pass/fail criterion used by the instrument is the voltage output. If the voltage output obtained from a test sample is greater than the maximum voltage output of a negative control, then the system has detected a defect and the instrument will report a failing result. If the voltage output obtained is between the minimum and maximum range set for the method of a test sample, then the instrument will report a passing result (i.e., no defect has been detected for the sample).

Negative Controls: DP ampules with no known defects.

Positive Controls: DP ampules with 2 μm, 5 μm, 10 μm and 20 μm laser drilled defects.

Results:

Method precision: Negative and positive controls were tested three times over the course of three days. The method precision was defined as the standard deviation of ten test voltage (VDC) measurements taken on an individual negative control sample. The test voltage ranged from 6.02 – 6.65 V (0.2 V standard deviation) for the 10.5 mL ampules and from 6.37 – 6.83 V (0.2 V standard deviation) for the 26 mL ampules.

The validation study included evaluation of the method's maximum reference point, repeatability, precision, accuracy, specificity and limit of detection. See Table 1 for a summary of the results.

Table 1 - Summary of validation results

Validation Parameter	Validation Acceptance Criteria (b) (4)	Results	Pass / Fail
Repeatability		**10.5 mL:** 0.2 V **26 mL:** 0.2 V	Pass
Intermediate Precision		**10.5 mL:** 0.2 V **26 mL:** 0.3 V	Pass
Maximum Reference Set Point (VDC)		**10.5 mL:** 7.10 V **26 mL:** 7.42 V	Pass
Method LOD		**10.5 mL:** 5 µm **26 mL:** 5 µm	Pass
Intermediate Precision Accuracy/ specificity		**10.5 mL:** All negative controls tested over three days have passing results and 90% of the positive controls at or above the Method LOD (5 µm) have failing results on day 2 and day 3 **26 mL:** All negative controls tested over three days have passing results and 95-100% of the positive controls at or above the Method LOD (5 µm) have failing results on day 2 and day 3	Pass Pass

Limit of detection (LOD) – voltage output: Results from 90 negative controls were used to determine the average voltage output and standard deviation. The maximum voltage output for the test method is defined as the average plus 3 standard deviations. This maximum voltage is considered the instrument LOD in detecting a defect. However, since negative control results fell outside 3 standard deviations from the mean, the number of standard deviations was increased to four such that no false positives are identified. The overall voltage reading obtained for the 10.5 mL ampules was 6.07 V and the maximum set point was 6.29 V. For the 26 ml ampules, overall voltage reading obtained was 7.10 V and the maximum set point was 7.42 V.

LOD – defect size: The method LOD is defined as the lowest defect size where 100% of the positive samples tested are detected as "fail" according to the instrument output on day 1. The 10.5 mL ampules were detected 100% at 5 µm on day 1, whereas the 26 ml ampoules were detected 90% at 5 µm on day 1 (see table 2). A 100 % detection was obtained in both ampule sized for 10 µm defects.

Table 2 – Method limit of detection

Defect size	% detected – 10.5 mL ampules (n=10)			% detected – 26.0 ml ampules (n=22)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
2 µm	80 %	50 %	60 %	76 %	76 %	76 %
5 µm	100 %	90 %	90 %	91 %	100 %	95 %
10 µm	100 %	100 %	100	100	100	100
20 µm	100 %	100 %	100	100	100	100

All negative controls tested over the three days have passing results (i.e., no defect detected) for both ampules sizes. 100% of the 10.5 mL ampule positive controls at or above 5 µm have failing results (i.e., defect detected) on day 1 and at least 90% failing results on day 2 and day 3. The positive controls results for the 26.0 mL ampule showed at least 91% failing results at or above 5 µm with 100 % for 10 µm defect size at day 1.

Note to Reviewer: The firm claims that the HVLD-mc test method is capable of reliably detecting 100% defects as small as 5 µm in the 10.5 ml ampoule. It was noted that the report concluded that the LOD of the test method is 5 µm although this defect size was detected 90% in the 26 mL ampules. However, the results demonstrated a 100 % detection rate in both 10.5 mL and 26 mL ampules for the 10 µm defect size. Moreover, the firm claims that this method has been proven to be capable of detecting defects as many as 67 days after filling, sealing, and inverting of the ampoules, a timeframe already demonstrated as sufficient to plug a 50 µm hole. To further assess the risk of microbial ingress, the applicant completed a literature-based comparison of defect size and leak rates to microbial ingress. This comparison demonstrated that the HVLD- mc methodology, with a LOD of 10 µm, compares favorably to published microbial ingress methods, demonstrating that the risk of microbial ingress is very low. This approach was discussed with the firm during the teleconference of October 27, 2016.

Reviewer's Assessment: The adhesive and antimicrobial properties of the DP make it impractical to use traditional CCIT methods such as microbial ingress, dye ingress and helium leak testing methods to test the integrity of the DP ampules. Therefore, the original submission evaluated the headspace oxygen analysis as an alternate CCIT method. Unfortunately, this method was not able to detect defects in the DP filled ampules due to the ability of the DP to 'self-seal' the laser drilled defects. This concern was discussed during the October 27th, 2017 teleconference (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016). The applicant was informed that while results from the literature can be used to perform a comprehensive comparison of their method with microbial ingress, validation data is necessary to support the use of their proposed CCIT for the DP.

The CR response dated 3/7/17 included data from a study using their proposed HVLD-mc test method which demonstrate that this method is capable of reliably detecting 100% defects as small as 10 µm in the both size ampoules. While a direct comparison of their proposed method with a microbial ingress testing method cannot be performed, the results from the data provided by the applicant demonstrated a more sensitive LOD compared to the results obtained from other studies in the literature. For example, the results from the PDA TR 27, USP <1207>, specifically, the Kirsch, *et. al*. work on leak detection using the microbial ingress test method, showed a detection rate of 96.55 % on defect sizes of 8 µm. The data provided by the applicant

showed that their method is more sensitive than microbial ingress study performed by Kirsch, *et al.* since it is capable of detecting 100% of the 5 µm defects in the 10.5 mL ampules and 100% of the 10 µm defects of the 26.0 mL ampules. The applicant also made reference to two additional studies (Burrell LS, *et al.*, and Morrical BD, *et al*.) that also used the microbial ingress method. These two referenced studies were able to demonstrate 100 % detection of microbial ingress in defect sizes of 20 µm or larger, which is lower than the LOD provided by the applicant. In addition, Moll *et al.* (PDA J Pharm Sci and Tech 1998, 52 215-227) stated that microbial penetration through small leaks (< 5 µm) is only possible under strong influences such as a very high challenge concentration ($\geq 10^8$ cfu/ml), long contact time and high pressure differentials. Moreover, Moll *et al.* states that under ''specific'' conditions, microbial penetration through pinholes <10 µm may not take place. The sensitivity of a CCIT method is dependent on many factors, including the sensitivity of the detection system, the test conditions, the package, and the nature of the product itself. Therefore, the Agency does not have a required minimum LOD to be demonstrated for a given CCIT method. However, a CCIT method can be considered adequate if test data is provided to demonstrate a method LOD of at least 20 µm from breached positive controls. The applicant provided data to show that the HVLD-mc test method can detect 100% of the 10 µm defects, which is more sensitive than other traditional CCIT methods. No additional clarification is requested.

Adequate

2. Provide CCIT results for the (b) (4) *pouch used to package the DP applicator. Provide a description of methods (and applicable validation information), a description of controls, and a summary of results.*

CR Response (3/7/17): Relevant CCIT information and results for the 3M DuraPrep™ Surgical Solution (NDA 21-586) pouch have been determined to be representative and supportive of the SoluPrep film forming prep pouch container closure integrity through end of shelf life. The secondary sterile barrier (b) (4) pouch for the CHG film-forming prep, the process by which the applicators are pouched and the pouching equipment are the same as for 3M's currently marketed product, DuraPrep™ Surgical Solution. The DuraPrep™ process validation lots were placed on stability, which demonstrated that the secondary sterile barrier remained intact, based on closure integrity testing, through 24 months. Relevant CCIT information and results for the DuraPrep™ pouch were discussed during the Oct 27th, 2017 Type C meeting briefing package and the information have been added to the NDA in Module 3.2.P.7.

Note to Reviewer: The firm summarized the testing methods (ISO 11607:2009 A1:2014) performed in DuraPrep, which are the same proposed methods to be used the subject DP of this submission. The required elements of strength and integrity testing of the secondary (b) (4) pouch packaging include Seal Strength, Dye Penetration and Bubble leak. Seal Strength will be conducted (b) (4) at release, and on stability to demonstrate the seal strength at the periphery of the pouch is sufficient to maintain a sterile barrier. Dye Penetration will be conducted (b) (4) on stability to demonstrate there are no channels in the seals. Finally, the Bubble

Leak method will be conducted on stability at the end of shelf life to demonstrate whole package integrity. The Bubble Leak method will also be used (b) (4) . Each of the three methods has been validated to its ASTM equivalent: Seal Strength (TM-05-176747) validated per ASTM F88/F88M-09 (TSV-05-000026) Dye Penetration (TS-10034) validated per ASTM F1929 (TM-VAL-05-306542) Bubble leak (TM-05-301034) validated per ASTM F2096 (TM-VAL-05-305362). In addition, the firm commits to place the first three validation lots for SoluPrep film-forming prep on stability and container closure integrity will be evaluated per the stability protocol in Module 3.2.P.8.2 using the SoluPrep film forming product/shipper combination. Performance testing will be conducted during the course of process validation.

Reviewer's Assessment: Although the CR response dated 3/7/17 does not provide additional validation data for these testing methods, the same testing methods have been approved for use in DuraPrep (NDA 21-586), which uses the same secondary packaging pouch system. (b) (4)

Adequate

3. Regarding (b) (4) *monitoring during production, the December 9th 2015 response (under section Q5) stated that* (b) (4) *" Please clarify if* (b) (4) *for the 26.0 mL ampules is the same for the 10.5 mL ampule* (b) (4) *during commercial production.*

CR Response (3/7/17): (b) (4)

Reviewer's Assessment: (b) (4)

(b) (4)

Adequate

4. The information provided for the requalification (RQ) schedule for the Low (b) (4)
is acknowledged. However, (b) (4)

This is not acceptable, (b) (4)
Please revise your SOP to provide (b) (4)

CR Response (3/7/17): (b) (4)

Reviewer's Assessment: (b) (4)

Adequate

5. The 12/9/15 submission stated that two samples from the 46 samples were tested for bioburden, (b) (4) whereas the other 44 samples were taken from ampules that were placed in the stability program. Please identify the source of each sample (lot numbers) and please clarify if the 44 samples that were taken from the stability programs were (b) (4)

CR Response (3/7/17): All samples subjected to bioburden testing (DP sealed ampules) that were taken from the stability program were (b) (4). Module 3.2.P.5.4 Batch Analysis has been updated with a tabular summary that clarifies the source of each sample, with lot numbers, and bioburden results. For clarification, 40 of the 46 samples were sealed ampules and the other 6 samples were collected from (b) (4).

Reviewer's Assessment: In the original submission, the applicant only provided a summary of the bioburden results for the 46 samples. However, none of the samples were clearly identified. This concern was discussed during October 27, 2016 Type C meeting (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016). In the CR response dated 3/7/16, the applicant provided a table that identifies each sample tested and provides the bioburden results for each lot. The bioburden results for each lot were reported in average CFU/1.0 mL, 2.0 mL or 5.0 mL. For all lots, the results were <1 CFU, thus, no organisms were detected in the sample. Validation data for the bioburden testing method was provided in response in the CR response dated 3/7/17 (see Reviewer's assessment for deficiency #6). No additional clarification is requested

Adequate

6. In regard to the bioburden testing per (b) (4) testing method STP00036, please address the following concerns:
a. Please clarify the name of the microorganisms that are used as positive monitors for aerobic bacteria and fungi organisms.

CR Response (3/7/17): The applicant stated that *Bacillus atrophaeus* will be used as a positive monitor for aerobic bacteria. In addition, *Aspergillus brasiliensis* has been implemented as the mold positive monitor and *Candida albicans* has been implemented as the yeast positive monitor. *Clostridium sporogenes* is an anaerobic positive monitor and *Pseudomonas aeruginosa* is an anaerobic negative monitor.

Acceptable

b. Please clarify any additional rinsing steps (rinse fluid and volume) or neutralization buffers that are used to neutralize the antimicrobial activity of the DP against aerobic bacteria and fungi.

CR Response (3/7/17): The applicant stated the rinsing steps and neutralization steps used to neutralize the DP against aerobic bacteria are the same steps used for fungi. The steps are listed below:
• Drug Product transferred to 40 mL of 70% IPA. This becomes the test sample.
• Pre-wet filter funnel with 20 mL sterile 70% IPA
• Filter test sample.
• Rinse filtered test sample one time with each of the following:
i. 10 mL sterile 70% IPA
ii. 100 mL Dey Engley Neutralizer
iii. 100 mL sterile water

Reviewer's Assessment: The CR response dated 3/7/17 provided a detailed description of the bioburden testing method. Moreover, the validation data provided demonstrates that the rinsing and neutralization steps described allows for the proper recovery of bioburden from samples (see CR response and the reviewer's assessment to comment "6-c" below). No additional clarification is requested.

Acceptable

c. Please provide validation testing data to demonstrate that the STP00036 is capable or recovering aerobic bacteria, fungi, anaerobic bacteria and spores.

CR Response (3/7/17): Due to the antimicrobial and hydroalcoholic nature of our DP solution, bioburden testing is performed per AAMI/ANSI/ISO 11737-1 (which includes spore-formers) rather than testing per USP <61/62>. The bioburden test protocol, 3M SoluPrep Film Forming: (b) (4) CHG/IPA Solution Bioburden Test, has been updated to include additional positive monitors for fungi organisms and a clarification of the rinsing steps. A section for bioburden of the solution has been added to Module 3.2.P.5.3 Validation of Analytical Methods that includes the updated test protocol and a validation discussion that includes (b) (4) test report 940904-S01 with all of the positive and negative monitors. Of note, 3M's internal test method reference is CS-05-307266 to which (b) (4) protocol STP0036 and the current Customer Specification Sheet (CSS) 201604733 are attached. The CS document is intended to capture the agreement between 3M and (b) (4) and to manage change. (b) (4) uses both the STP and CSS to fully execute the bioburden evaluation. Protocol reference STP0036 has not changed over the course of the NDA review. The working documents have been revised; CSS 201604733 is current and has replaced Sample Detail Sheet (SDS) 201310195.

Bioburden Validation:
Bioburden Final Report # 940904-S01 (purchase order # (b) (4))

Study received date: 19 Jan 2017
Test protocol: STP0036 Rev 12
CSS#: 201604773 Rev 01

Summary: Bioburden testing was performed in one test article (identified as "SV 11.15"). The results for this test article are reported as <1 CFU per 5 mL for aerobic, anaerobic and for fungal and < 5 CFU per 1 mL for spores. The report stated that for this test article, sample positive testing was performed using *B. atrophaeus, C. albicans* and *A. brasilliensis*. The test article was found not to be inhibitory (data not shown). In addition, the report provided the results (see table 3 below) obtained for the additional inhibition screening. The product CFU should be 50 % of the positive monitors (positive and negative controls).

Table 3 – Bioburden Control Organisms Results*

Organisms	Positive Monitor / Titer	Test Article Count	Result
Aspergillus brasiliensis	47	67	>99.9%
Candida albicans	63	77	>99.9%
Bacillus atrophaeus	69	73	95%
Clostridium sporogenes	N/A	N/A	Positive
Pseudomonas aeruginosa	N/A	N/A	Negative

*reported as CFU/5 mL

Note to Reviewer: The applicant proposed to perform bioburden testing per AAMI/ANSI/ISO 11737-1 instead of per USP <61/62>. Moreover, the applicant stated that the bioburden of the DP is "validated" every time the test is conducted. That is, positive and negative controls must meet their acceptance criteria at the time of testing in order for the test to be considered valid. Further, the applicant provided the final version of the general bioburden test method used by (b) (4) (STP00036) and the current CSS #201604733, which basically specifies which steps from STP00036 are unique to the DP. The CSS #201604733 specifies the positive and negative organisms to be tested each time, volume of DP to use, the media and rinsing steps, incubation conditions (aerobic/anaerobic conditions: 3-7 days at 30-35C; fungi: 3-7 days at 20-25C) and the specific instructions for spore-forming bacteria (each step as stated above, CR response #6a - 6b). Finally, the applicant provided a copy of Bioburden Final Report # 940904-S01, which includes the results of the test article evaluated and the results for the protocol positive and negative controls. The report indicates all test method acceptance criteria were met and that the test article was not inhibitory using this test method.

Reviewer's Assessment: The original submission did not include validation data to support the proposed bioburden testing method. This concern was discussed during the October 27th, 2017 teleconference (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016). Given the antimicrobial nature of the DP, the applicant proposed to perform bioburden testing per AAMI/ANSI/ISO 11737-1 instead of per USP <61/62>. The proposed bioburden testing method per ISO 11737-1 requires the recovery of aerobic (*B. atropaeus*), anaerobic (*C. sporogenes*), yeast (*C. albicans*) and mold (*A. brasiliensis*) microorganisms each time a sample is evaluated in order to consider the test results valid. This additional evaluation for each sample prevents the reporting of false negatives due to the

antimicrobial nature of the DP. Finally, the CR response dated 3/7/17 provided validation data that demonstrate that the rinsing and neutralization steps of the proposed bioburden method allows for the proper recover the positive control organisms. No additional clarification is requested.

Adequate

7. The information provided in the submission dated 8/12/15 and 11/6/15 included validation data for (b) (4) *lack clarity, and the report appears to contain discrepancies. Please address the following points:*
a. The significance of the (b) (4) *procedures described in protocol 201404182 is unclear; further, it is unclear if these were utilized in testing to support the conclusion that the method is validated.*

CR response (3/7/17): (b) (4)

Reviewer's Assessment: The description provided in the original submission lacks clarification (b) (4) This concern was discussed during the October 27th, 2017 teleconference (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016). The CR response dated 3/7/17 clarified these two terms, (b) (4) No additional clarification is requested.

Acceptable

b. The Phase 1 Validation report (745554.1) was performed according to protocol 201401236. A description of this method was not provided, and it is unclear how this relates to the proposed method intended for product testing ((b) (4) *testing method #201404182).*

CR response (3/7/17): (b) (4)

Reviewer's Assessment: The original submission used different protocol numbers for validation than the protocols proposed for routine testing. This concern was discussed during the October 27th, 2017 teleconference (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016). In the CR response dated 3/7/17, the applicant clarified that although the protocol numbers are different; the methods are basically the same. The discrepancy in protocol numbers is due to changes made to the test method during validation, which triggered a new protocol number. Specifically, protocol sections 13.2 and 16.2 were added to (b) (4) 201404182 to include validation and testing of the (b) (4) in addition to the drug solution. An updated copy of the final version of protocol (b) (4) 201404182 was included in the CR response. No additional clarification is requested.

Acceptable

c. Eight samples were utilized for Phase 2 testing (786924); however, results were only reported for three samples. No explanation was provided to indicate why the other 5 samples were discarded.

CR Response (3/7/17): Phase 2 validation testing was conducted per protocol # (b) (4) 201404182 and reported in (b) (4) report 786924. Eight (8) samples were submitted for testing to ensure an adequate quantity of samples in the event of breakage or process errors. Three (3) samples were utilized during the initial round of testing (a minimum of three is required); however, the inoculum exceeded the 100 CFU maximum required by the protocol, therefore three (3)

additional samples were then tested and correctly inoculated with ≤ 100 CFUs. The remaining two (2) samples were discarded. TM-VAL-05-275152 was updated with this clarification.

The NDA has been updated as follows:
• Module 3.2.P.5.2 Analytical Procedures has been updated with a description of the (b) (4) testing protocol, CHG/IPA Prep: (b) (4) Spore Challenge Test for Chemical Antiseptic (CS-SF-05-261224).
• Module 3.2.P.5.3 Validation of Analytical Procedures has been updated to include a revision to the TM-VAL-05-275152 and the new TM-VAL-05-306997. The TM-VAL-05-275152 has been revised to clarify all points highlighted by the Agency. The supplemental validation TMVAL-05-306997 using (b) (4) has been completed demonstrating the method is suitably validated.

Note to Reviewer: The proposed CR responses to deficiencies #7a – 7c were discussed during the teleconference of October 27, 2016 (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016) and the applicant's clarifications provided above were deemed adequate.

Reviewer's Assessment: The applicant provided clarification on the proposed (b) (4) testing method (see Reviewer's assessment to comment #7a - b). In addition, per the Agency's request, the applicant also performed a final validation study (TM-VAL-05-306997; see document "tm-val-05306997.pdf," pages 30-32 of 40) to demonstrate neutralization of the drug solution and recovery of spores using (b) (4) of the method, (b) (4) (b) (4) (using current (b) (4) protocol #201605555). The study was performed with three samples and three controls. (b) (4) dequate neutralization was demonstrated and acceptance criteria were met in both Phases of testing. No additional clarification is requested.

Acceptable

8. In regard to the sterility testing requirement for release of the DP, please address the following concerns:
a. *The possibility of testing the (b) (4) instead of performing sterility testing for DP release was discussed in the December 1st 2015 teleconference. As discussed, (b) (4) is dependent on the validation data for the testing method ((b) (4) testing method # 201404182) of the (b) (4). Please revise the DP specifications to include a sterility testing method that has been fully validated.*

CR response (3/7/17): Per response to Question 7, the (b) (4) testing method, CHG/IPA Prep: (b) (4) Spore Challenge Test for Chemical Antiseptic (CS-SF-05-261224, formerly (b) (4) protocol #201404182), is fully validated and suitable (b) (4)

(b) (4). Refer to Module 3.2.P.5.3 for full validation reports, including a supplemental validation in which Phase 1 and 2 validations were completed with (b) (4) as per the Agency's request. As noted in response to Question 7, CS-SF-05-261224 is the internal 3M reference for the (b) (4) protocol for (b) (4) testing.

Reviewer's Assessment: The original submission proposed to use the (b) (4) protocol #201404182 for the sterility testing of the DP. However, the original submission did not provide a clear description of the method and validation data to demonstrate that this method is suitable for use for the DP. This concern was discussed during the October 27th, 2017 teleconference (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016). As recommended by the Agency, the validation data for this method was also provided was reviewed and deemed adequate as part of the applicant's CR response to comment #7 (see Reviewer's assessment to comment #7). Therefore, since the applicant provided data to demonstrate that the (b) (4) testing method has been validated, the method can be added to the DP release specifications. No additional clarification is requested.

Acceptable

b. *It was noted that the 12/9/15 submission stated that "additional sterility testing will only be conducted as part of release only if* (b) (4) *Please note that a backup method for sterility testing cannot be utilized for DP release in instances where the primary sterility testing method fails or in instances where an in-process control fails. This represents a testing-into-compliance mentality, and increases the chances of acceptance of false negative results. Please clearly state the sterility testing method for the DP release, noting that inclusion of a backup testing method is not acceptable.*

CR Response (3/7/17): USP <71> sterility testing was removed from all release testing within the NDA and the scenario described in the September 27th, 2016 Type C meeting request package will not occur. As stated in response to #7, 3M has conducted a final supplemental validation study as requested by the Agency, demonstrating the (b) (4) test method per CHG/IPA Prep: (b) (4) Spore Challenge Test for Chemical Antiseptic (CS-SF-05-261224, formerly (b) (4) protocol #201404182) has been suitably validated and will be used as part of the sterile release process of the DP solution.

Reviewer's Assessment: In the original submission, the applicant proposed to perform sterility testing per USP <71> if (b) (4) This concern was discussed during the October 27th, 2017 teleconference (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016), in which the applicant was informed that this conditional testing approach is not acceptable. The applicant agreed with FDA's recommendation regarding the use of (b) (4) protocol for the release of the DP of all lots

instead of USP <71> if the method has been suitably validated. The validation data for this method was also provided was reviewed and deemed adequate as part of the applicant's CR response to comment #7 (see Reviewer's assessment to comment #7). Further, the applicant stated that no additional conditional sterility testing for the solution will be completed as a part of DP release. Finally, Specifications and Justification of Specifications (Modules 3.2.P.5.1 and 3.2.P.5.6) were updated to reflect the final specification for sterile solution, and Modules 3.2.P.5.2 and 3.2.P.5.3 were revised to include the analytical procedures and validations with a description of the methodology and the full validation reports.

Adequate

9. *Your proposal to utilize CCIT in lieu of sterility testing for filled ampoules in the stability program is acceptable. Please provide a stability specification which includes a validated CCIT method.*

CR Response (3/7/17): Validation for CCIT of the glass ampoule by High Voltage Leak Detection – microcurrent (HVLD-mc) has been completed and added to Validation of Analytical Procedures, Module 3.2.P.5.3. In addition, this CCIT method has been added to the post approval stability commitment in Module 3.2.P.8.2. The analytical test method has been added to Analytical Procedures, Module 3.2.P.5.2.

Note to Reviewer: The updated stability protocol has been updated and the testing regimen (see Tables 4 and 5 below) includes the High Voltage Leak Detection – microcurrent (HVLD-mc) as the CCIT for the ampules.

Table 4 – Stability Protocol

Protocol Parameter	Description
Storage conditions	25°C ± 2°C / 60% RH ± 5%
Testing Frequency (months)	0, 3, 6, 9, 12, 18, 24, 36
Number of Batches	1 batch of each size (10.5 , 26 mL) annually
Container closure system	Refer to Section 3.2.P.7 of this submission
Tests and criteria	Refer to Table 3.2.P.8.2.2 below

Table 5 – Stability Testing Regimen

Test description	Test method #	Specifications
CCIT: HVLD-mc (glass ampoule)*	TM-05-295444	No defects detected
CCIT: Bubble Leak (pouch)*	TM-05-301034	No leaks detected
CCIT: Dye Penetration (pouch)	TS-10034	No leaks observed
CCIT: Seal Integrity (pouch)	Visual	• No open / cut seals that affect seal integrity. No inserts in seals • Pouch seal must be smooth without wrinkles, ripples, or other flaws that affects seal integrity around the entire seal formation.
CCIT: Seal Width (pouch)	Measurement	(b) (4) mm

* Container closure integrity testing is conducted in lieu of sterility testing on stability

Reviewer's Assessment: The original submission did not include a validated CCIT method in the stability program. This concern was discussed during the October 27th, 2017 teleconference (NDA # 208288; Meeting date: 27 October 2016; Meeting minutes drafted by T. Vu, DARRTS date: 14 November 2016). The CR response dated 3/7/17 included the High Voltage Leak Detection – microcurrent (HVLD-mc) method as the proposed validated CCIT method for the stability program instead of sterility testing of the DP. The validation data for this method was also provided was reviewed and deemed adequate as part of the applicant's CR response to comment #1 (see Reviewer's assessment to comment #1). No additional clarification is requested.

Adequate

10. *Please incorporate a specification for sterility testing for the drug product applicator, or container closure integrity testing for the* (b) (4) *pouch into the stability program.*

CR Response (3/7/17): The applicant stated that the CCIT for the (b) (4) pouch by the methods listed above (see Table 5) have been added to the post approval stability commitment in Module 3.2.P.8.2.

Reviewer's Assessment: The original submission did not include CCIT or sterility testing of the DP applicator. However, the CR response dated 3/7/17 included a revised specification for the CCIT of the DP applicator pouch. Accordingly, the applicator will be subjected to Bubble leak, dye penetration, seal integrity and seal width testing. No additional clarification is requested.

Adequate

Maria Cruz-Fisher

Digitally signed by Maria Cruz-Fisher
Date: 5/22/2017 12:55:25PM
GUID: 534c15db00067ee34b9c0732d53497ed

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 6/14/2017 02:10:00PM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

Swapan De

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Date: 8/10/2017 01:43:28PM
GUID: 508da7220002a114329c9e07775b6e02

NDA 208288
Review # 1

Drug Name/Dosage Form	SoluPrep Surgical Solution
Strength	2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
Route of Administration	Topical
Rx / OTC Dispensed	OTC
Applicant	3M Health Care (Health Care Infection Prevention Division) 3M Center Bldg 275 5W 06 St Paul, MN 55144
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	07-June-2015	OPQ
Amendment	03-Aug-2015	OPF
Amendment	06-Nov-2015	ONDP/OPF.
Amendment	O2-Dec-2015	ONDP
Amendment	09-Dec-2015	ONDP/OPF
Amendment	12-Dec-2015	OPF
Amendment	18-Dec-2015	OPF
Amendment	19-Jan-2016	OPF
Amendment	05-Feb-2016	ONDP
Amendment	10-Feb-2016	OPF
Amendment	10-Mar-2016	OPF

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erika Englund , Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Erin M Kim, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Maria I. Cruz-Fisher, Ph.D.	OPF/DPAII/BranchVI
Facility	Vipulchandra Dholakia, Ph.D.	OPF/DIA/B3
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

B. Supplement to drug product review.

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II	(b) (4)			Adequate	10/29/2014	None
	III			1	Adequate	5/14/11	None
	III			7	Adequate	N/A	(b) (4) glass
	III			1&4	Adequate	N/A	This is a medical device MF, same type of material is being used in approved products
	III			1&4	Adequate	12/23/15	None

C. [1] Action codes for DMF Table:

D. 1 – DMF Reviewed.

E. Other codes indicate why the DMF was not reviewed, as follows:

F. 2 –Type 1 DMF

G. 3 – Reviewed previously and no revision since last review

H. 4 – Sufficient information in application

I. 5 – Authority to reference not granted

J. 6 – DMF not available

K. 7 – Other (explain under "Comments")

L. [2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

M. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76,549	CHG/IPA Film-forming Skin Preparation

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Office of Surveillance/OPQ	NA			

Table of Contents

Executive Summary (NDA-208288)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may not be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the application the drug substance, drug product, microbiology, process and facility sections are reviewed. Drug product and microbiology section of the application are inadequate to support the approval of the application. The drug product impurities, stability of the drug product and sterility assurance of the finished product were found to have significant issues and thus, the application is not recommended for approval. Following comments should be included in the action letter.

Drug product:

1. Your proposed limits for two related impurities (b) (4) in the drug product at (b) (4)% exceed ICH Q3B (R2) limits (≤ 1%) and are not acceptable. Based on your quantitative stability data, (b) (4) will reach 1.0% at (b) (4) months, and (b) (4) will exceed 1.0% at (b) (4) months. These degradants continue to rise and accumulate in the drug product throughout the shelf-life. Even though you have proposed to shorten the shelf-life from 24 months to (b) (4) months, we cannot grant it without additional justifications.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES:

1. You will need to conduct qualification studies for (b) (4) and (b) (4). Refer to pharmacology and toxicology comments.

2. (a) Your proposal of an Interim Specification for the drug product shelf-life of (b) (4) months has not been adequately justified. Since stability data of 13 Lots are available at the (b) (4) months period, you should use all 13 stability Lots (i.e. CLIN A, B, C, D, E, G, H, J, L, M, P, and Q) in the calculation of this Interim Specification.

(b) 3M's approach of using the upper limit the regression line and 3σ to derive the acceptance criteria for Total Impurities, (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, 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). We have discussed this in great detail in the 01/12/16 teleconference between 3M and FDA.

(c) Your Amendment-16 dated 02/05/16 introduced a response factor of (b) (4) in the calculations of the true level of impurity (b) (4) with the goal to derive a new shelf-life specification for this impurity. When recalculating the original stability data using this factor, the impurity level become worse, your product fails instantaneously at (b) (4) month, because the true level is equal to the uncorrected level divided (not multiplied) by this factor.

Microbiology Deficiencies:

1. The container closure integrity test (CCIT) validation data provided in the submission dated 3/10/16 demonstrate that the proposed headspace oxygen analysis method has a detection rate of approximately 33% or less for defects that are 50 µm or larger in 10.5 mL drug product (DP) filled ampules. Moreover, you did not detect defects of any size in the 26 mL DP filled ampules. Furthermore, the information presented indicates that your selected test method is only capable of detecting holes of 50 µm or greater, which, per the USP 1207.1 you previously provided, corresponds to an air leak rate of > 0.360 sccs. Kirsch, et. al. (also referenced in the Parenteral Drug Association's Technical Report 27) demonstrates that a leakage rate that correlates with microbial ingress is approximately 10^{-5} sccs, which is considerably lower than what your results demonstrate. With the low detection rate demonstrated by positive controls, and without further information to correlate your proposed method with the potential for microbial ingress, the method that you propose is not acceptable as a container closure integrity test method. Provide CCIT results from a validated testing method capable of detecting microbial ingress in order to demonstrate the integrity of the proposed container closure system (glass ampules) for the DP.

2. Provide CCIT results for the (b) (4) pouch used to package the DP applicator. Provide a description of methods (and applicable validation information), a description of controls, and a summary of results.

3. Regarding (b) (4) monitoring during production, the December 9, 2015 response (under section Q5) stated that (b) (4) Clarify if (b) (4) for the 26.0 mL ampules is the same for the 10.5 mL ampule (b) (4) during commercial production.

4. The information provided for the requalification (RQ) schedule for the (b) (4) is acknowledged. However, (b) (4) This is not acceptable, (b) (4) Revise your SOP to provide a (b) (4)

5. The 12/9/15 submission stated that two samples from the 46 samples were tested for bioburden, (b) (4) whereas the other 44 samples were taken from ampules that were placed in the stability program. Identify the source of each sample (lot numbers) and clarify if the 44 samples that were

taken from the stability programs were [redacted] (b) (4)

6. In regard to the bioburden testing per [redacted] (b) (4) testing method STP00036, please address the following concerns:

a. Clarify the name of the microorganisms that are used as positive monitors for aerobic bacteria and fungi organisms.

b. Clarify any additional rinsing steps (rinse fluid and volume) or neutralization buffers that are used to neutralize the antimicrobial activity of the DP against aerobic bacteria and fungi.

c. Provide validation testing data to demonstrate that the STP00036 is capable or recovering aerobic bacteria, fungi, anaerobic bacteria and spores.

7. The information provided in the submission dated 8/12/15 and 11/6/15 included validation data for [redacted] (b) (4) lack clarity, and the report appears to contain discrepancies. Please address the following points:

a. The significance of the [redacted] (b) (4) " procedures described in protocol 201404182 is unclear; further, it is unclear if these were utilized in testing to support the conclusion that the method is validated.

b. The Phase 1 Validation report (745554.1) was performed according to protocol 201401236. A description of this method was not provided, and it is unclear how this relates to the proposed method intended for product testing ([redacted] (b) (4) esting method #201404182).

c. Eight samples were utilized for Phase 2 testing (786924); however, results were only reported for three samples. No explanation was provided to indicate why the other 5 samples were discarded.

8. In regard to the sterility testing requirement for release of the DP, please address the following concerns:

a. The possibility of testing the [redacted] (b) (4) instead of performing sterility testing for DP release was discussed in the teleconference dated December 1, 2015. As discussed, [redacted] (b) (4) is dependent on the validation data for the testing method ([redacted] (b) (4) testing method # 201404182) of the [redacted] (b) (4). Revise the DP specifications to include a sterility testing method that has been fully validated.

b. It was noted that the 12/9/15 submission stated that "additional sterility testing will only be conducted as part of release only if [redacted] (b) (4) Note that a backup method for sterility testing cannot be utilized for

DP release in instances where the primary sterility testing method fails or in instances where an in-process control fails. This represents a testing-into-compliance mentality, and increases the chances of acceptance of false negative results. Clearly state the sterility testing method for the DP release, noting that inclusion of a backup testing method is not acceptable.

9. Your proposal to utilize CCIT in lieu of sterility testing for filled ampoules in the stability program is acceptable. Provide a stability specification which includes a validated CCIT method.
10. Incorporate a specification for sterility testing for the drug product applicator, or container closure integrity testing for the (b) (4) pouch into the stability program.

A. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Quality Assessments;

The drug product contains two drug substances, Chlorhexidine gluconate solution (b) (4) USP and Isopropanol USP.

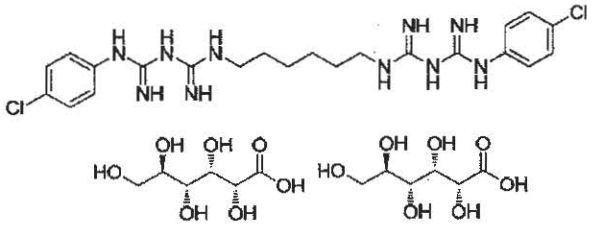
1. Drug Substance [USAN Name] Quality Summary

Chlorhexidine gluconate solution (b) (4) USP (CHG) information is referred to DMF (b) (4) This DMF was last reviewed on 29-OCT-2014 and is found adequate. There have been no quality amendments to the DMF since that last review. This DMF is adequate to support this NDA.
Isopropanol is a well-characterized molecule. It has a USP monograph and is found in numerous approved drug products as either an active ingredient or an excipient. It is one of the active ingredients in Duraprep (iodine povacrylex and isopropanol alcohol) which is also produced by 3M. The submitted description of isopropanol is adequate.

Some basic information for CHG and isopropanol are shown below.

Chlorhexidine gluconate solution (b) (4) USP:

Molecular structure and formula:



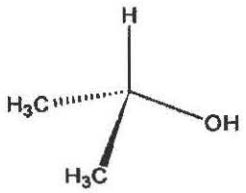
Molecular Formula:
$C_{34}H_{54}Cl_2N_{10}O_{14}$

Chemical name: 1,1'-(hexane-1,6-diyl)bis[5-(4-chlorophenyl)biguanide] di- D-gluconate

Molecular Weight: 898 g/mol
CAS: 18472-51-0
The drug substance is manufactured by [redacted] (b) (4) and described in DMF [redacted] (b) (4). The specifications of CHG is provided in the application and it is deemed adequate (see page DS-4). The re-test period of the [redacted] (b) (4) CHG Solution is [redacted] (b) (4)

Isopropanol:

Molecular structure, formula and weight:



Molecular Formula: C_3H_8O

Molecular Weight: 60.10 g/mol

Trivial name: Isopropyl alcohol
Synonyms: Isopropanol, dimethyl carbinol, IPA, sec-propyl alcohol, 2-propanol, petrohol
CAS: 67-63-0
Appearance: Colorless liquid.
Flash Point- Closed Cup: 12°C (54°F)
Flammable Limits in Air: Lower: 2.0% (V) Upper: 12.0% (V)
Autoignition Temperature: 399°C (750°F)
Boiling Point: 82.3°C (180°F)
Vapor Pressure: 33 hPa @ 20°C
Vapor Density (air = 1): 2.1
Solubility Profile: water, alcohol, and ether.
Specific Gravity: 0.785 at 20°C
Freezing Point: -89°C (-128°F)
Dynamic Viscosity: 2.4 mPa.s @ 20°C

Isopropanol is identified by IR and GC retention time in the USP monograph. It is also tested for specific gravity, refractive index, and the purity must be NLT 99.8% by assay. [redacted] (b) (4) The overall information provided is found adequate to support this NDA.

Drug Product [Established Name] Quality Summary

1. **Strength:** 2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol

2. **Description/Commercial Image:**

The 3M™ CHG/IPA Film-forming Patient Preoperative Skin Preparation Solution (also referred to as "surgical solution") is formulated for use in a tinted and nontinted solution. The primary container closure for the finished drug product solution is a (b) (4) sealed glass ampoule containing either 10.5 ml (tinted and non-tinted) or 26 ml (tinted only) of active drug solution. Each unit dose (b) (4) sealed glass ampule of solution is housed in a (b) (4) plastic applicator, with a (b) (4) sponge at the end through which the solution is dispensed for topical application to a patient's skin prior to surgery. Each applicator is sealed in a rectangular (b) (4) pouch with a peelable top (one unit per pouch).

1. **Summary of Product Design**

The New Drug Application focused a dual-active antimicrobial hydroalcoholic solution comprising 2% (w/v) chlorhexidine gluconate and 70 % (v/v) isopropyl alcohol and (b) (4) inactive ingredients (b) (4). The inactive ingredients used were a film forming organic polymer (b) (4) and a colorant mixture to obtain a single phase, isotropic, topical antiseptic solution. The polymer used in the 3M CHG / IPA prep is the same polymer used in FDA approved DuraPrep solution (NDA 21-586), but with a (b) (4)

The manufacturing process involves (b) (4)

1. **List of Excipients:**

Poly (b) (4) Acetyl tributyl citrate, FD&C blue #1, FD&C Yellow #5 and Trisodium HEDTA (Hydroxylethyl ethylenediamine triacetic acid).

2. **Process Selection (Unit Operations Summary)**

(b) (4)

3. **Container Closure**:

3M CHG/IPA Film-forming Preoperative Skin Preparation is packaged in (b) (4) sealed 10.5 mL and 26 mL primary container. The primary container closure system is made of (b) (4) glass. Each sealed ampoule is housed in a plastic applicator, and sealed in a (b) (4) pouch. Two cotton-tipped swabs are provided with each 26 mL applicator.

4. **Expiration Date & Storage Conditions**

Proposed expiration date of the drug product of 24 months is found **not acceptable** and **not supported** by the real time stability data obtained from 24-month study at long-term storage conditions (25°C/60% RH) and 6-month study at accelerated conditions (40°C/75% RH). Stability data shows higher amounts of impurities ((b) (4) and total impurities). The applicant 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. The impurities are above the limits specified in ICH Q3B(R2). The CMC review team and Pharm/tox review team decided that qualification of such impurities will

be necessary and that should be done before approval since the product will be approved as an OTC product.

The storage statement will be written as "Store between 15°C – 30°C (59°F - 86°F); avoid freezing and excessive heat above 40°C (104°F). This reflects the numerical value of the controlled room temperature [stored at 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F)].

5. **List of co-packaged components: None**

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	SoluPrep Surgical Solution
Non Proprietary Name of the Drug Product	2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
Non Proprietary Name of the Drug Substance	chlorhexidine gluconate; isopropyl alcohol
Proposed Indication(s) including Intended Patient Population	Patient preoperative skin preparation, for the preparation of the skin prior to surgery and to help reduce bacteria that can potentially cause skin infection
Duration of Treatment	Single use topical application: 10.5 mL applicator (Clear/Tint) • Solution volume 10.5 ml / 0.36 fl. oz. • Coverage area 13 in. x 13 in. (178.8 in2). 26 mL applicator (Tint) • Solution volume 26 mL / 0.9 fl. oz. • Coverage area 19.5 in. x 19.5 in. (387.5 in2).
Maximum Daily Dose	N/A
Alternative Methods of Administration	None

B. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I.
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: No
   - PK studies: Yes
   - IVIVC: No

C. Novel Approaches

D. Any Special Product Quality Labeling Recommendations
None

E. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	4	2	3	24	Stability data shows high levels of impurities.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on provided data provided.
Sterility	• Formulation • Container closure • Process parameters (b) (4) • Scale/equipments • Site	6	5	5	(b) (4)	bioburden testing and sterility testing are not properly validated.
Viscosity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	2	2	8	Monitored as an additional parameter during release

RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Swapan K. De -S

Digitally signed by Swapan K. De -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Swapan K. De -S, 0.9.2342.19200300.100.1.1=1300132497
Date: 2016.03.25 10:07:27 -04'00'

APPEARS THIS WAY ON ORIGINAL

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

Drug Product Review Addendum-2

Date: May 3, 2016

From: Elise Luong, Ph.D.
Product Quality Chemistry Reviewer
CDER/OPQ/ONDP/DNDP II/Branch VI

Through: Danae Christodoulou, Ph.D.
Acting Branch Chief, CDER/OPQ/ONDP/DNDP II/Branch VI

Subject: **Revised CR comments, NDA 208288; SoluPrep Film-Forming Sterile Surgical Solution (2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol)**

The original CR comments in the Drug Product Review had been revised as following to be included in the Action Letter:

"Your proposed limits for two related impurities (b) (4) in the drug product at (b) (4) % exceed ICH Q3B (R2) limits (< 1%) and are not acceptable. Based on your quantitative stability data, (b) (4) will reach 1.0% at (b) (4) months, and (b) (4) will exceed 1.0% at (b) (4) months. These degradants continue to rise and accumulate in the drug product throughout the shelf-life. Even though you have proposed interim specifications for (b) (4) at (b) (4) % to shorten the shelf life to (b) (4) months, impurity (b) (4) still exceeds the ICH limit of < 1.0%. Therefore, at this time no expiration date can be granted for the drug product.

Conduct qualification studies for (b) (4). Refer to non-clinical comments."

The above revision occurred after the 04/12/16 T-CON discussion with the applicant (3M), refer to T-CON memo submitted to DARRTS on 04/15/16.

As advised by FDA during the 04/12/16 T-CON, 3M recalculated the limit for impurity (b) (4) for the proposed interim shelf-life of (b) (4) months (refer to 3M's email communications to PM Celia Peacock on 04/12/16 and PM Thao Vu on 04/27/16). Pharmacology Toxicology (PT) did not accept this limit. The PT team determined that (b) (4) % for (b) (4) is unsafe and requires qualification. Therefore, CMC cannot grant a viable expiry for the drug product.

Elise T. Luong -S (Affiliate)
Digitally signed by Elise T. Luong -S (Affiliate)
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=001030159, cn=Elise T. Luong -S (Affiliate)
Date: 2016.05.03 13:09:53 -04'00'

Danae D. Christodoulou -S
Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.05.03 13:24:06 -04'00'

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

/s/

ELISE T LUONG
05/03/2016

Reference ID: 4309409

NDA 208288
Review # 3

Drug Name/Dosage Form	SoluPrep™ Film-Forming Sterile Surgical Solution
Strength	2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
Route of Administration	Topical
Rx / OTC Dispensed	OTC
Applicant	3M Health Care (Infection Prevention Division) St Paul, MN 55144
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (Seq #44-47; #50)	03-Mar-2017 28-Mar-2017 17-May-2017 1-Jun-2017	ONDP/OPF/FR
Resubmission (Seq. #59)	09-Feb-2018	ONDP/DP/FR

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance[1]	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process[1]	Erin Kim, Ph.D.	OPF/DPAII/BranchVI
Microbiology[1]	Maria Cruz-Fisher, Ph.D. Erika Pfeiler, Ph.D.	OPF/DPAII/BranchVI
Facility	Xiaohui (Sherry) Shen, Ph.D.	OPF/DIA/B3
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Teshara Bouie	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)[1]	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

[1]No review needed for Resubmission (Seq. #59) and drug substance remains adequate regarding Quality (see review #2)

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II	(b) (4)			Adequate	10/29/2014	None
	III			1	Adequate	5/14/11	None
	III			7	Adequate	N/A	(b) (4) glass
	III			1&4	Adequate	N/A	This is a medical device MF, same type of material is being used in approved products
	III			1&4	Adequate	12/23/15	None

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76,549	CHG/IPA Film-Forming Skin Preparation

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Office of Surveillance	NA			

Table of Contents

Executive Summary (NDA-208288)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the resubmitted application the drug product and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 24 months under controlled room temperature (ICH) storage conditions.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments:

Current application (NDA-208288) is a resubmission and a response of the CR letter dated September 9, 2017. The CR letter outlined deficiencies for non-clinical and clinical safety. The CR letter included a statement regarding specifications of impurities as stated below.

"We acknowledge that you have accepted the Agency's recommendation for the drug product impurity levels and updated specifications (dated 21 August, 2017). Since the qualification of impurities is still inadequate, updated specifications for the drug product will remain as tentative specifications."

Since 3M accepted the Agency's recommendation for drug product impurities and tightened the limit for (b) (4) to NMT (b) (4)%, (b) (4) to NMT (b) (4)% and Total Impurities to (b) (4)% at the end of previous review cycle, no new CMC information is submitted in this third review cycle.

Nonclinical review (dated 6/29/2018) confirmed that the proposed impurity limit of (b) (4) (NMT (b) (4)%) and (b) (4) NMT (b) (4)%) are acceptable based on MuST study performed by the applicant (see Clinical Pharmacology review dated 27th June, 2018). Thus, regarding CMC, drug product specification is no longer tentative and it is the final regulatory specification (see regulatory specifications of the drug product in DP review pages DP3-4).

Facility review with "acceptable cGMP recommendation" was completed on 7 June, 2018.

A. Drug Product [SoluPrep Surgical Solution] Quality Summary

1. **Strength:** Chlorhexidine Gluconate (2% w/v) and Isopropyl Alcohol (70% v/v)

2. **Description/Commercial Image:** No new information (See Executive Summary #2)

3. **Summary of Product Design**

No new information (See Executive Summary #2)

4. **List of Excipients:**

Poly (b) (4) , Acetyl tributyl citrate, FD&C blue #1, FD&C Yellow #5 and Trisodium HEDTA (Hydroxylethyl ethylenediamine triacetic acid).

5. **Regulatory Specifications of the drug product:**

6. **Container Closure:**

3M CHG/IPA Film-forming Preoperative Skin Preparation is packaged in (b) (4) sealed 10.5 mL and 26 mL primary container. The primary container closure system is made (b) (4) glass. Each sealed ampoule is housed in a plastic applicator, and sealed in a (b) (4) pouch. Two cotton-tipped swabs are provided with each 26 mL applicator.

7. **Expiration Date & Storage Conditions**

The drug product has been granted a shelf life of 24 months under controlled room temperature storage conditions.
The storage statement will be written as "Store between 15°C – 30°C (59°F - 86°F); avoid freezing and excessive heat above 40°C (104°F). This reflects the numerical value of the controlled room temperature [stored at 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F)].

8. **List of co-packaged components: None**

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	SoluPrep Surgical Solution
Non Proprietary Name of the Drug Product	2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol
Non Proprietary Name of the Drug Substance	chlorhexidine gluconate; isopropyl alcohol
Proposed Indication(s) including Intended Patient Population	Patient preoperative skin preparation, for the preparation of the skin prior to surgery and to help reduce bacteria that can potentially cause skin infection
Duration of Treatment	Single use topical application: 10.5 mL applicator (Clear/Tint) • Solution volume 10.5 ml / 0.36 fl. oz. • Coverage area 13 in. x 13 in. (178.8 in2).

	26 mL applicator (Tint) • Solution volume 26 mL / 0.9 fl. oz. • Coverage area 19.5 in. x 19.5 in. (387.5 in2).
Maximum Daily Dose	N/A
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I.
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: No
   - PK studies: Yes
   - IVIVC: No

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations
None

F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	4	3	2	24	Similar assay method as approved for capsule dosage form. Impurities are monitored (not finalized)
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on limited data provided.

Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	3	2	3	12	(b) (4)
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Controlled with specifications.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Regarding Chemistry Manufacturing and Controls, the application may be approved.

Application Technical Lead Signature:

81 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page