CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-586

CHEMISTRY REVIEW(S)

NDA 21-586

DuraPrep™ Surgical Solution

3M Medical Division

Milton J. Sloan, Ph. D.
Division of Anti-Infective Drug Products (HFD-520)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-586

2. REVIEW #: 2

3. REVIEW DATE: August 19, 2004

4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	24-OCT-2004
Amendment (BL)	09-MAR-2004
Amendment (BC)	16-MAR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	24-OCT-2004
Amendment (BC)	12-AUG-2004
Amendment (BC)	19-AUG-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	3M Medical Division.
Address:	3M Center Bldg. 275-5W-06 St. Paul, MN 55144-1000
Representative:	Diane Gibbs, RAC Regulatory Affairs Manager
Telephone:	(651) 733-1110 (651) 737-5320 (Fax)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: DuraPrep™ Surgical Solution

b) Non-Proprietary Name (USAN): see Review
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 New Formulation
- Submission Priority: S Standard Review, Substantially equivalent

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antimicrobial

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.7 % available Iodine, 74 % Isopropyl alcohol

13. ROUTE OF ADMINISTRATION: Topical

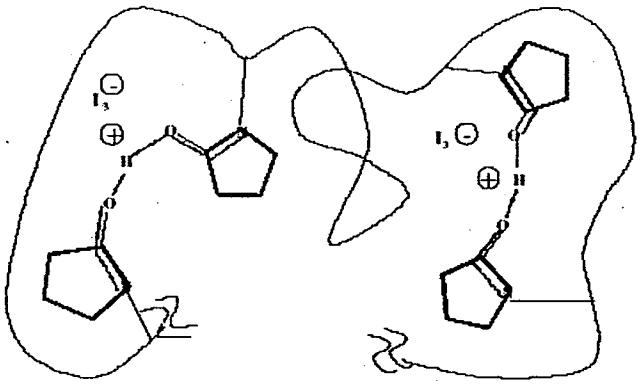
14. Rx/OTC DISPENSED: __Rx √ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula:
$(I_3^-)_n (C_6H_9O_2)_{n1} (C_4H_8O_2)_{n2} (C_{10}H_{20}O_2)_{n3}$

Molecular Weight:
Approximately 5.2×10^5 daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate	N/A	None
					Adequate	N/A	None
					Adequate	N/A	None
					Adequate	N/A	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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION/Status
IND	49,411	Duraprep Surgical Solution

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Acceptable	08-Jul-2004	C. Cruz
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	Unacceptable proposal for non-proprietary name	16-Aug-2004	David Lewis/Yana Mille
Methods Validation	Package not sent to District Laboratory	N/A	N/A
OPDRA (DMETS)	No objections to proprietary name	18-Jun-2004	Charles Hoppes, Alina Mahmud, Carol Holquist
EA	Categorical exclusion claimed-Adequate	N/A	N/A
Microbiology	N/A	N/A	N/a

19. ORDER OF REVIEW (OGD Only) N/A

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 50-586

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval (AP) from the Chemistry, Manufacturing and Control perspective pending an official name with respect to 21 CFR 299.4. A concern stated in Review #1 for the lack of a non-proprietary name (established name) is still an unresolved matter. Although the Agency does not approve drug products without an official name, this drug product for some time now has been on the OTC market. The lack of an established name may be considered a deficiency.

Iodine is technically the drug substance. The "Iodine Acrylate Copolymer" is a [redacted]. The rate of release is controlled by the equations given below and in Section 3 (S.3) of this review. The uniqueness of this drug product from the standpoint of chemistry is the copolymer/iodine complex. The povidone-iodine complex is an assigned USAN. Although the complexation is similar, this drug product is not described under the monograph for povidone-iodine. The applicant has been encouraged to apply for a USAN(United States Adopted Name). The applicant has amended the NDA with another set of proposed established names.

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

3M has committed to providing and acceptable established name by completion of the USAN application and to provide a copy of the completed, submitted application to the Agency.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

3M DuraPrep™ Surgical Solution is a broad-spectrum antimicrobial agent indicated for use as a patient preoperative skin preparation. The DuraPrep formulation is comprised of a combination of two active drug substances; 0.7% available iodine as a copolymer/iodine complex and 74% weight/weight (w/w) isopropyl alcohol (IPA). Both iodine and IPA are well-known, well-characterized, active raw materials. The iodine and IPA used for DuraPrep solution are manufactured according to USP specifications.

Executive Summary Section

The starting materials include the [redacted] The novel starting material, [redacted] was developed specifically for isopropyl alcohol solubility and iodine compatibility. Iodine is [redacted] that is composed of [redacted] to form the active iodine acrylate copolymer in solution with isopropyl alcohol.

The DuraPrep solution copolymer/iodine complex has been characterized by infrared spectroscopy, molecular weight, nuclear magnetic resonance (NMR), ultraviolet spectroscopy (UV), and x-ray scattering techniques of thin films. As a non-surfactant polymer complex of iodine, DuraPrep solution is similar to povidone-iodine in that both [redacted] The appearance of an isopropyl alcohol/water solution of the copolymer-iodine complex is a red-brown clear solution.

The presence of I_2 can be determined by titration which is the compendial assay method specified for Povidone-iodine. The addition of reagent, during titration, shifts the equilibrium the right so that all I_2 that was associated with the complex is assayed. Since titration is able to measure all the available I_2 and historically has been the method of assay for iodophors, titration is the proposed method for monitoring iodine concentration to demonstrate product stability.

DuraPrep™ Surgical Solution is batch formulated in [redacted] key phases. [redacted]

Finished drug product stability studies submitted for the sealed glass ampules fully support a two-year expiration date. A one-year expiration date is proposed and is supported by studies for the DuraPrep™ Surgical Solution stored in [redacted] The proposed expiration periods are both acceptable.

B. Description of How the Drug Product is Intended to be Used

The indication for use is as a patient preoperative skin preparation. It is intended for use as a topical agent only. The actual dose will vary according to the area of the skin that requires disinfection. DuraPrep solution is to be marketed in sealed glass ampules containing either 6 ml (DuraPrep Catalog No. [redacted]) or 26 ml (DuraPrep Catalog No. [redacted]) of active drug substance solution. Each unit dose ampule is housed in a [redacted] plastic applicator, with a [redacted] sponge at the end through which the solution is dispensed for topical application to a patient's skin prior to surgery. The user "activates" the device by pumping the housing lever [redacted] or by pressing down on the end-cap [redacted], thereby crushing the enclosed ampule, and allowing the solution to flow out of the applicator housing into the applicator foam sponge for delivery onto the patient's skin. The copolymer/iodine complex is soluble in alcohol and remains in solution until DuraPrep solution is applied dermally. Note there are no chemical reactions taking place on the skin, only the evaporation of the volatile compounds (alcohol and water) that deposits the copolymer film containing iodine onto the surface of the skin. Following use, DuraPrep solution can be removed from the skin using water, IPA, or 3M™ Remover Lotion.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has satisfactorily demonstrated via CMC data submitted in the application that this new formulation is stable throughout the two year shelf life of the drug product. The manufacturing sites have been found acceptable with the Office of Compliance. The proposed specifications have been found adequate and suitable for a quality drug product. However as mentioned above, this application is recommended for approval (AP) pending an official name with respect to 21 CFR 299.4. The lack of a non-proprietary name (established name) is still an unresolved matter. The applicant was made aware of the unsuitability of the proposed established name.

The amendment dated August 12, 2004 serves to document a phone conversation with Ms. Dianne Gibbs of 3M. During the conversation, the Reviewer gave clarity to comments communicated from initial CMC review of the NDA and requested 3M to provide a suitable established name. The amendment submitted by 3M proposed as names the following two options: [redacted] or "[redacted]". These two name proposals were submitted for expedited consult to the LNC. Subsequently, each name was found unacceptable. The applicant has been encouraged to apply for a USAN(United States Adopted Name) as an outcome to the LNC consult. The lack of an established name may be considered a deficiency,

however, the applicant has amended the NDA with another set of proposed established names.

The amendment dated August 19, 2004 serves to document our teleconference requesting 3M to contact the USAN Council. 3M contacted USAN and commits to completing a USAN application and then faxing a copy to the NDA prior to the pdufa date. The applicant provided the proposed names, [redacted] and "Iodine-povacrylex". Although "Iodine-povacrylex" appears the most descriptive, the reviewer will defer to LNC for consult. An expedited consult to the LNC for these choices has been submitted and is expected to result in a preferred name to USAN.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name: Milton J. Sloan, Ph. D. Date: August 19, 2004
Chemistry Team Leader Name: James D. Vidra, Ph. D. Date:

C. CC Block

HFD-520/Archival
HFD-520/DillonParker/PM
HFD-520/Bostwick/MO
HFD-520/Sloan/CHM
HFD-520/Peters/PhmTox
HFD-520/Coderre/Micro
HFD-520/Jiang/Stat
HFD-520/Vidra/TLCHM
HFD-830/Lin/ActingDivDir

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Milton Sloan
8/23/04 11:38:11 AM
CHEMIST

Jim Vidra
8/24/04 11:07:07 AM
CHEMIST

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NDA 21-586

DuraPrep™ Surgical Solution

3M Medical Division

Milton J. Sloan, Ph. D.
Division of Anti-Infective Drug Products (HFD-520)

Appears This Way
On Original

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Original	24-OCT-2004
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Representative:	
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This application is recommended for approval (AP) from the Chemistry, Manufacturing and Control perspective. Some pending concerns remain but are not approvable issues.

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None

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III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name: Milton J. Sloan, Ph. D. Date: July 30, 2004
Chemistry Team Leader Name: James D. Vidra, Ph. D. Date:

C. CC Block

HFD-520/Archival
HFD-520/DillonParker/PM
HFD-520/Bostwick/MO
HFD-520/Sloan/CHM
HFD-520/Peters/PhmTox
HFD-520/Coderre/Micro
HFD-520/Jiang/Stat
HFD-520/Vidra/TLCHM
HFD-830/Lin/ActingDivDir

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Milton Sloan
8/4/04 04:20:40 PM
CHEMIST
Comments are to be communicated to the Applicant.

Jim Vidra
8/4/04 04:29:06 PM
CHEMIST

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