III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton labeling, information for the health care practitioner (training video and training poster), and sample DuraPrep™ devices and packaging proposed for DuraPrep™, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL LABELING COMMENTS

1. Please note that the statement of identity for over-the-counter products requires that an accurate statement of the general pharmacological category of the drug or the principal intended action appears in conjunction with the established name. Please revise to include this information on the principal display panel of outer packaging and container labels. We refer you to 21 CFR 201.60 for guidance.

2. We encourage use of a brighter color of red for the flame pictorial appearing on labels and labeling.

B. CONTAINER, APPLICATOR (6 mL and 26 mL)

1. We encourage the use of colors or other means to differentiate the 6 mL size of DuraPrep™ from the 26 mL size.

2. Revise the following text appearing as the second step on the instruction, ——— , **DO NOT SCRUB.**

C. OUTER PACKAGING

See GENERAL COMMENT and comment under CONTAINER above.

D. DURAPREP TRAINING POSTER

1. Increase the prominence of the following statement appearing in the Boxed Warning: "Warning: ——— In addition, revise the word, "Warning" to appear in all capital letters in bold face, red print.

2. DMETS recommends that this poster cite the DuraPrep™ area of the 3M web site, for further information. In addition, DMETS believes that this information should be made available via a link on the web site entitled: "3M™ DuraPrep™ Surgical Solution"[1], in addition to other web pages.

[1] Web Reference:
http://products3.3m.com/catalog/us/en001/healthcare/professional/node_GSF83Z3YYXbe/root_GST1T4S9TCgv/vroot_GS2PVC6H4Dge/gvel_GS627RKQ1Jgl/theme_us_professional_3_0/command_AbcPageHandler/output_html

E. DURAPREP TRAINING VIDEO

1. We note that this video recommends the use of 3M surgical drapes when using DuraPrep Surgical Solution. Please ensure that warning statements appear on the labeling for surgical drapes that when DuraPrep™ is used, the drapes should not be used until dry.

2. We note that outer packaging for DuraPrep™ states, "3M recommends all users participate in product in-service training prior to use. In-servicing is available on video, from your 3M sales representative, on at the 3M website. A link to the video should also be placed on the web site entitled: "3M™ DuraPrep™ Surgical Solution"[2], in addition to other web pages.

IV. RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions and safety recommendations outlined in Section III of this review that might lead to safer use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

[2] Web Reference:
http://products3.3m.com/catalog/us/en001/healthcare/professional/node_GSF83Z3YYXbe/root_GST1T4S9TCgv/vroot_GS2PVC6H4Dge/gvel_GS627RKQ1Jgl/theme_us_professional_3_0/command_AbcPageHandler/output_html

Appendix A. Reports Relating to Safe Use of DuraPrep™

AERS/DQRS REPORT #	DATE	TYPE OF ERROR	ABBREVIATED NARRATIVE
DuraPrep™ Ignition			
3922480-8-00	[redacted]	Actual Error	In the operating room, immediately prior to the procedures, the patient was prepped with DuraPrep. During the procedures the patient sustained 2nd and 3rd degree burns to right neck, clavicle, shoulder and cheek. The patient was transferred to a Burn Unit in stable condition.
127722	April 23, 1999	Potential Error	Concern for inconspicous FLAMMABLE LABELING. There is no Flammable label on the outer package. The flammable label on the final product is the same color as other labeling information and is difficult to identify-74% Isopropyl Alcohol-the flammable label should be in Larger Red Letters to make it easy to see and read.
3116787-4	[redacted]	Actual Error	Male undergoing surgical procedure in O.R. bilateral subacute subdural hematomas. "MAC" anesthesia used, not general, due to poor cardiac status. O^2 on at 5 L. First Burr Hole completed without complications. Second Burr Hold site prepped with DuraPrep surgical solution. Drapes applied, incision made and electrocautery device used after solution dried on skin. Immediately a "Popp" sound heard. Discovered patient's face on fire. Patient sustained severe burns on face, neck, shoulders, and mouth. There was no obvious arc or spark from the electrocautery device and no alarms. There were no burns near or at the ground pad site.
851772	[redacted]	Actual Error	Duraprep used to Prep skin for OR oper. using cautery. Flames engulfed patient's neck and chest. 1st and 2nd degree burns noted on chest, neck.
912081	[redacted]	Actual Error	Prep was applied to an undraped area on the torso just prior to use of electrocautery. [redacted] area ignited, but was quickly extinguished without damage to the sterile field. Surgeon was new and inexperienced in use of DuraPrep. Hospital reportedly has done 21,000 cases with DuraPrep since 11/88 without incident. Brochure discussing proper use and published studies was forwarded.
912080	[redacted]	Actual Error	Doctor wasn't used to using DuraPrep. Flames on patient – caused redness, patient is doing fine. (Happened a week ago, but didn't call until now.) Did not dry, used electrocautery on chest, extinguished immediately…will inservice.
807471	[redacted]	Actual Error	Intraoperative Fire- Patient prepped for Right Carotid Endoarterectomy, prep soln. Dried for 5 to 6 minutes. After right neck incision cautery applied to bleeders and small blue flame flashed followed immediately by smoke from under drapes over left side of neck. Water dumped through drape and drape pulled off. Patient's hair on left neck singed and second degree burns on right neck.
D 001493	[redacted]	Actual Error	A patient was having a surgical procedure done in main O.R. Patient had been prepped with Duraprep and draped, the surgical incision made, cautery utilized and the patient was burned.

913338	[redacted]	Actual Error	Alleged fire incident in OR reported....DuraPrep solution was used to prep the patient....patient experienced a second degree burn and is doing fine.
913337	[redacted]	Actual Error	Hospital reported a flammability incident in OR while using electrocautery on patient prepped with DuraPrep. The incident occurred this morning....The patient had multiple lesions on front, back, arm and axilla areas of his body. DuraPrep was used to prep the area and squared off with linen towels. A Bovie was used to remove the lesions....A blue flame occurred and the patient's skin turned into a red patch. The patient was under local anaesthesia. According to the doctor, it was a first degree burn.
912082	[redacted]	Actual Error	...The surgery went fine. They also decided to remove skin tags in the axillary region with electrocautery; one side had been prepped earlier with DuraPrep and the cauterization of the skin tags went fine. The surgeon decided to also do the other side and prepped at that time with Duraprep. He did not allow the prep to dry and immediately used the electrocautery on [redacted] Duraprep. The alcohol ignited and a flash fire occurred. The patient received a few quarter sized second degree burns and had his chest hair singed. The burns were treated with Sulfadine and the patient is now discharged.
DuraPrep™ Allergy			
3603589-5	[redacted]	Actual Error	Duraprep applied to patient. Iodine based solution. Patient developed multiple raised welts. Patient given Benadryl – symptoms subsided. Iodine added to allergy list.

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/s/

Charles Hoppes
7/9/04 01:06:01 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/9/04 02:45:59 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **ODS//DMETS/OPaSS**

FROM: Maureen Dillon-Parker, Project Manager, HFD-520
David C. Bostwick, Clinical Reviewer, HFD-520

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 2, 2004	49,411	21-586	In-service/Training Materials	May 11, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
DURAPREP	High	Topical Antiseptic	July 16, 2004

NAME OF FIRM: 3M Health Care

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ✓ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Request for Medication Error Safety Review for Duraprep, Topical Antiseptic, pending NDA 21-586.

Please return materials with review.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ✓ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Maureen Dillon-Parker
6/2/04 12:39:21 PM
NDA 21-586 - DuraPrep

David Bostwick
6/2/04 12:41:58 PM

Jean Mulinde
6/2/04 12:46:07 PM

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CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:**
May 28, 2004	June 30, 2004	03-0230-1

TO: Janice Soreth, M.D.
Director, Division of Anti-Infective Drug Products
HFD-520

THROUGH: Maureen Dillon-Parker
Project Manager, Division of Anti-Infective Drug Products
HFD-520

PRODUCT NAME:	**NDA SPONSOR:** 3M Health Care Markets
Duraprep™ Surgical Solution [Iodophor (0.7% available iodine) and Isopropyl Alcohol (74% w/w) Topical Solution]	

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions and safety recommendations outlined in Section III of this review that might lead to safer use of the product.

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Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

LABELING REVIEW

DATE OF REVIEW: June 3, 2004

NDA# 21-586

NAME OF DRUG: **Duraprep™ Surgical Solution** [Iodophor (0.7% available iodine) and Isopropyl Alcohol (74% w/w) Topical Solution]

NDA HOLDER: 3M Health Care Markets

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective Drug Products (HFD-520), for review of the container labels, carton labeling, information for the health care practitioner (training video and training poster), and sample DuraPrep™ devices and packaging. Comments on the proprietary name were forwarded in ODS Consult #04-0129.

DuraPrep™, an over-the-counter product, has been available in the marketplace since 1988, under IND 49,411. DuraPrep™ has had a history of product safety problems related to the ignition of flammable ingredients upon use. However, the sponsor has made significant improvements in product safety, including labeling changes, information for healthcare providers, and monitoring. On August 7, 2003, the sponsor submitted a risk/benefit assessment for DurPrep™ which included safety studies, surgeon testimonials, product complaints summary and proposed labeling changes. In order to comply with the tentative final monograph for topical antiseptic products once it is finalized, the sponsor has filed a new drug application, NDA 21-586 (October 24, 2003, submission). In this latest submission, safety changes are summarized by the sponsor in the statement below:

> 3M has been proactive in monitoring complaints and improving labeling. Extensive work has been performed on the DuraPrep solution label over the last 5 years. 3M has also improved and added training tools to further alert customers to the importance of using the product correctly (i.e. per labeling instructions) as well as the dangers of using the product incorrectly. Key changes to the label include specific instructions for application to avoid pooling (with methods stated to correct pooling), allow a wait time of ——————until the preparation is dry, and avoid the use of cautery of laser until the preparation is dry. These instructions are enhanced by international symbols....3M has also been working closely with the FDA, making them aware of improvements in labeling and training tools. The FDA has indicated its satisfaction with and approval of 3M's initiatives in this regard.

PRODUCT INFORMATION

DuraPrep™ is the proposed proprietary name for Iodophor (0.7% available iodine) and Isopropyl Alcohol (74% w/w) Topical Solution. DuraPrep™ is a film-forming iodophor complex for preparation of the skin prior to surgery. It helps reduce bacteria that potentially can cause skin infection. DuraPrep™ is available over-the-counter in a sterile 6 mL or 26 mL applicator with a urethane sponge tip.

II. RISK ASSESSMENT:

In order to assess DuraPrep™ product safety, the FDA's Adverse Event Reporting System (AERS) and Drug Quality Reporting System (DQRS) databases were searched and medication error reports were reviewed to determine error causality (see Appendix A). DuraPrep™ has been available in the marketplace since 1988. Thus, DMETS conducted searches of the FDA Adverse Event Reporting System (AERS) and Drug Quality Reporting System DQRS). The MedDRA Preferred Terms (PTs), "Medication Error", "Accidental Overdose", "Overdose", "Pharmaceutical Product Complaint", and "Treatment Non-Compliance", and the drug names, "Dura prep%", "Duraprep%", and "Dura-prep%", were used to perform the search in AERS. This search strategy yielded no reports from AERS. Ten reports of actual accidents involving the ignition, primarily during cautery, of DuraPrep™, and one report of the potential for this to happen, citing inconspicuous warning statements in the product labeling were identified in DQRS (see Appendix A). In two of the actual cases, causation was attributed to "pooled" or "wet" DuraPrep™. In the past five years only one instance of DuraPrep™ ignition was identified from AERS and DQRS (Report 3922480-8; dated May 24, 2002). In addition, concerns expressed in the potential error (see excerpt below), citing inconspicuous warning statements, have since been addressed by revised labeling.

> Concern for inconspicous FLAMMABLE LABELING. There is no Flammable label on the outer package. The flammable label on the final product is the same color as other labeling information and is difficult to identify-74% Isopropyl Alcohol-the flammable label should be in Larger Red Letters to make it easy to see and read.

There have been relatively few errors due to DuraPrep ignition in the past five years. DMETS error assessment analysis is consistent with that reported by the sponsor in the risk/benefit data package forwarded on August 7, 2003. The sponsor reports:

> The incidence of DuraPrep solution flammability complaints has been extremely low. Since 1988 through 4/30/03, there have been a total of 80 incidents, with an incidence rate of 0.0000015. The annual incidence rate per million units sold has been <2 since 1993. All but one incident was associated with the 26-mL applicator (the 26-mL applicator alone has an incidence rate of 0.0000019). The three most prevalent characteristics associated with flammability incidents were preparation not dried (38.8%), pooling of preparation (30.0), and use of oxygen (16.3%). The head and neck was the most frequent known body region (46.3%) involved in flammability incidents, followed by axillary (6.3%0, and hand regions (5.0%).

Current product labeling bears prominent and detailed warning statements regarding the potential for product ignition. The labeling submitted is in accordance with the Drug Facts regulations with regard to warnings for flammable products [21 CFR 201,66(c)(5)(ii)(C)]. Warnings are also present in healthcare provider information which comprehensively explain the risk of fires and how to prevent them (Application Instructions and Video entitled, DuraPrep™ Surgical Solution: A Unique One-step Prepping System).

DMETS considers the 3M safety information for the healthcare practitioner to be very useful. DMETS recommends that the information be more readily accessible to providers via the www.3M.com web site. Since the sponsor recommends the use of their surgical drape products with DuraPrep™, warnings regarding the flammable nature of these products should also appear on surgical drape products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton labeling, information for the health care practitioner (training video and training poster), and sample DuraPrep™ devices and packaging proposed for DuraPrep™, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL LABELING COMMENTS

1. Please note that the statement of identity for over-the-counter products requires that an accurate statement of the general pharmacological category of the drug or the principal intended action appears in conjunction with the established name. Please revise to include this information on the principal display panel of outer packaging and container labels. We refer you to 21 CFR 201.60 for guidance.

2. We encourage use of a brighter color of red for the flame pictorial appearing on labels and labeling.

B. CONTAINER, APPLICATOR (6 mL and 26 mL)

1. We encourage the use of colors or other means to differentiate the 6 mL size of DuraPrep™ from the 26 mL size.

2. Revise the following text appearing as the second step on the instruction, ——, **DO NOT SCRUB.**

C. OUTER PACKAGING

See GENERAL COMMENT and comment under CONTAINER above.

D. DURAPREP TRAINING POSTER

1. Increase the prominence of the following statement appearing in the Boxed Warning: "Warning: ——. In addition, revise the word, "Warning" to appear in all capital letters in bold face, red print.

2. DMETS recommends that this poster cite the DuraPrep™ area of the 3M web site, for further information. In addition, DMETS believes that this information should be made available via a link on the web site entitled: "3M™ DuraPrep™ Surgical Solution"[1], in addition to other web pages.

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E. DURAPREP TRAINING VIDEO

1. We note that this video recommends the use of 3M surgical drapes when using DuraPrep Surgical Solution. Please ensure that warning statements appear on the labeling for surgical drapes that when DuraPrep™ is used, the drapes should not be used until dry [redacted] on skin).

2. We note that outer packaging for DuraPrep™ states, "3M recommends all users participate in product in-service training prior to use. In-servicing is available on video, from your 3M sales representative, on at the 3M website. [redacted] A link to the video should also be placed on the web site entitled: "3M™ DuraPrep™ Surgical Solution"[2], in addition to other web pages.

IV. RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions and safety recommendations outlined in Section III of this review that might lead to safer use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
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807471	[redacted]	Actual Error	Intraoperative Fire- Patient prepped for Right Carotid Endoarterectomy, prep soln. Dried for 5 to 6 minutes. After right neck incision cautery applied to bleeders and small blue flame flashed followed immediately by smoke from under drapes over left side of neck. Water dumped through drape and drape pulled off. Patient's hair on left neck singed and second degree burns on right neck.
D 001493	[redacted]	Actual Error	A patient was having a surgical procedure done in main O.R. Patient had been prepped with Duraprep and draped, the surgical incision made, cautery utilized and the patient was burned.

913338	[redacted]	Actual Error	Alleged fire incident in OR reported....DuraPrep solution was used to prep the patient....patient experienced a second degree burn and is doing fine.
913337	[redacted]	Actual Error	Hospital reported a flammability incident in OR while using electrocautery on patient prepped with DuraPrep. The incident occurred this morning....The patient had multiple lesions on front, back, arm and axilla areas of his body. DuraPrep was used to prep the area and squared off with linen towels. A Bovie was used to remove the lesions....A blue flame occurred and the patient's skin turned into a red patch. The patient was under local anaesthesia. According to the doctor, it was a first degree burn.
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/s/

Charles Hoppes
7/9/04 01:06:01 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/9/04 02:45:59 PM
DRUG SAFETY OFFICE REVIEWER

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OTC DRUG LABELING REVIEW

Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

SUBMISSION DATES: October 24, 2003 March 9, 2004	**REVIEW DATE**: April 26, 2004
NDA:	21-586
SUBMISSION TYPE:	Original (N-000) N-000/BL
SPONSOR:	3M Health Care 3M Center 275-5W-06 St. Paul, MN 55144-1000
CONTACT:	Dianne L. Gibbs, RAC Regulatory Affairs Manager (651) 737-9117
DRUG PRODUCT:	DuraPrep™ Surgical Solution
ACTIVE INGREDIENT:	Povidone-Iodine [redacted] (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w) Solution
PHARMACOLOGICAL CATEGORY:	Healthcare Antiseptic: Patient Preoperative Skin Preparation
LABELING SUBMITTED:	• Labeling for individual applicator packet - 6-mL and 26-mL immediate container - 6-mL and 26-mL *Drug Facts* - 6-mL and 26-mL PDP • Labeling for shipping carton - 6 mL (50 applicator packets per case) - 26 mL (20 applicator packets per case) • Package insert
PROJECT MANAGER:	Maureen Dillion-Parker
REVIEWER:	Michelle M. Jackson, Ph.D.

Background: On October 24, 2003, the sponsor submitted labeling for an NDA for an iodophor isopropyl alcohol combination antiseptic solution (DuraPrep™ Surgical Solution) in 6- and 26-mL applicators for use as a patient preoperative skin preparation. The iodophor active ingredient, povidone-iodine [redacted] solution, [redacted] The proposed labeling submitted in the submission included color draft labeling of the Principle Display Panel (PDP), ***Drug Facts***, applicator handle labeling, shipping labeling for the 6-mL and 26-mL applicators, and a package insert containing product performance information.

On January 9, 2004, the Agency submitted a filing review letter to the sponsor that included a request for specifications for ***Drug Facts*** labeling. On March 9, 2004, the sponsor submitted an amendment (N-000/BL) that provided the graphic specifications for the DuraPrep™ ***Drug Facts*** labeling and proposed marketed package labeling for the 6- and 26-mL applicators. The review of the ***Drug Facts***, PDP, and applicator handle labeling is based on the March 9, 2004 amendment. The review of the shipping carton label is based on the October 24, 2003, original submission.

Reviewer's comments on the labeling: This review will only cover the ***Drug Facts***, PDP, applicator handle label, and shipping carton label. The package insert is part of the submission and will be covered later in a separate review. The Agency needs to ask the sponsor, if there is any outer carton for the 6- and 26-mL drug product.

A. Principle Display Panel (PDP):

1. The June 17, 1994, tentative final monograph (TFM) for OTC Healthcare Antiseptic Drug Products (59 FR 31402) proposes the following as acceptable statements of the pharmacologic category for OTC use patient preoperative skin preparations: "antiseptic" or "patient preoperative skin preparation." The pharmacologic category "patient preoperative skin preparation" appears more appropriate to the product, given its indication for use. See 59 FR 31402 at 31443.

2. The portion of the established name of the drug "Iodophor (0.7% Available Iodine)" will need to be revised. The term "Iodophor" describes an entire class of antiseptic drug products and is not appropriate for use as the established name. The sponsor submitted a citizen petition to the OTC drug monograph for review and described the product as a povidone-iodine [redacted] However, the sponsor will still need to provide an appropriate established name.

3. 21 CFR 201.61(a) and (b) requires that the PDP of a product include a statement of identity consisting of the established name of the drug "established name of the iodophor to be determined" (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w) solution), followed by the general pharmacological category of the drug

4. (Patient Preoperative Skin Preparation). Both statements must appear in direct conjunction with the most prominent display of the proprietary name (DuraPrep™ Surgical Solution). The immediate container needs to include the appropriate established name. Revise the PDP to read as follows: (See prototype of PDP attached.)

DuraPrep™
Surgical Solution
"established name to be determined" (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w) Solution
Patient Preoperative Skin Preparation

4. The font of the established name ("established name to be determined" (0.7% Available Iodine and Isopropyl Alcohol (74% w/w) solution) and the pharmacological category (Patient Preoperative Skin Preparation) should be bolded and be in a size reasonably related to the most prominent display of the trade name, i.e., half the size of the tradename (DuraPrep™ Surgical Solution). See 21 CFR 201.61(c).

5. The statement "[redacted] is hard to read and is not very prominent. The sponsor may increase the prominence or change the statement to read "[redacted] for consistency with other approvals in this class. This should also be applied to the immediate container.

6. The term "flammable vapors" appears to be light orange in color and does not give sufficient prominence to this warning. This reviewer recommends that the term "flammable vapors" on the PDP and immediate container handle be made more prominent by appearing in bold and red in color.

7. On the PDP and immediate container the net weight "0.9 fl. oz" and "0.2 fl. oz" should be revised to read "0.9 fl oz" and "0.2 fl oz."

8. Include the expiration date on the immediate package container label as required by 21 CFR 201.17. According to 21 CFR 201.17, expiration dating of this product must appear on the immediate container and also the outer package, if any, unless it is easily legible through such outer package.

9. Include the lot number information on the labeling as required by 21 CFR 201.18. According to 21 CFR 201.18, the lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. An incorrect lot number may be regarded as causing the article to be misbranded.

B. *Drug Facts* Labeling:

1. The Agency recommends that the ***Drug Facts*** labeling be presented using the graphic specifications set forth in 21 CFR 201 Appendix A. We recommend revision as follows:

    a) ***Drug Facts*** box or enclosure barline containing all information should be a 2.5-point type size, not a 2-point type size on the 6- and 26-mL size applicators.

    b) The horizontal barline separating the headings should be a 2.5-point type size, not a 2-point type size on the 6- and 26-mL size applicators.

    c) The horizontal hairlines between the warning subheadings, should be a 0.5-point type size, not a 1-point type size on the 6- and 26-mL size applicators.

2. The hairline below the ***Drug Facts*** title should be shortened to extend within two spaces of either side of the ***Drug Facts*** box as described in 21 CFR 201.66(d)(8). (See ***Drug Facts*** prototype attached.)

3. The subheader **Stop use and ask a doctor if** and the statement **Keep out of reach of children** on the 6-mL size applicator is 7-point type size. All the other subheaders are 6-point type sizes. For consistency and uniformity of the label, revise the subheader **Stop use and ask a doctor if** and **Keep out of reach of children** to have consistent font sizes throughout. (See 21 CFR 201.66(d)(2).)

4. The headers ***Other information***, ***Inactive ingredients***, and ***Questions*** on the 26-mL size applicator is 10-point type size. All the other headers are a 9-point type size. For consistency and uniformity of the label, revise the headers ***Other information***, ***Inactive ingredients*** and ***Questions*** to have consistent font sizes throughout.

5. The header ***Active ingredient*** should be revised to read ***Active ingredients***. This should be plural because more than one active ingredient is listed under this header.

6. The ingredient "Isopropyl Alcohol 74% w/w", needs to be revised to read "Isopropyl alcohol, 74% w/w", under ***Active ingredients***. The letter "a" in the word alcohol should be lower case and a comma should be placed after the word alcohol.

7. Under ***Uses***, labeling is recommended to be consistent with the specific labeling requirements for the product's intended use as stated in the Healthcare Antiseptic TFM. This reviewer recommends including the heading "patient preoperative skin preparation" under ***Uses***. The statement under ***Uses*** should be revised as follows: (See ***Drug Facts*** prototype attached.)

patient preoperative skin preparation:
- for preparation of the skin prior to surgery
- helps reduce bacteria that potentially can cause skin infection

8. Under ***Uses***, ***Warnings***, ***Directions***, and ***Other information***, the first letter of the first word in each bulleted statement should be lower case and not capitalized. No periods should follow after each statement unless the bulleted statement contains more than one sentence. (See ***Drug Facts*** prototype attached.)

9. The tradename "DuraPrep" will need to be removed from the ***Drug Facts*** enclosure. The OTC Labeling Requirements final rule published March 17, 1999 (64 FR 13254 at 13271), states that brand names may not appear in the ***Drug Facts*** enclosure, but may appear anywhere else on the labeling outside of the boxed area.

10. The term "prep" and "solution" has been used interchangeably throughout the label. This reviewer finds the term "prep" has been used inappropriately to refer to the solution throughout the label and has proposed revisions to some labeling statements. For example, see 12(f) and (h) below. Other labeling statements have been revised to emphasize that the prep needs to dry completely. (See ***Drug Facts*** prototype attached.)

11. The Agency will allow the use of pictograms to improve visibility and prominence to decrease the incidence of fires in operating rooms. The Agency has concerns of reports of burns which have been connected with the use of the product. On November 5, 2001, the Agency requested that the sponsor improve the labeling to address the issue of flammability and the pooling of the product solution. The pictogram of the flame under ***Warnings*** and the no pooling sign under ***Directions*** are acceptable. However, the pictogram of the handling the applicator and electrocautery will need to be removed from the ***Directions***, but may appear elsewhere in labeling.

12. Under ***Warnings***, this reviewer recognizes the need for additional warning statements, but there are numerous warning statements and the impact of all these warning statements on the label will be reduced. Most of the statements are repeated under ***Directions***, and do not belong under ***Warnings***. The Agency has concluded that warning statements required are those that are scientifically and clinically documented and important for safe use of the product. Revise the ***Warnings*** section for the 6- and 26-mL size applicator as follows: (See ***Drug Facts*** prototype attached.)

a) The external use warning statement "[redacted] should be revised to read "**external use only**" in accordance with 21 CFR 201.66(c)(5)(i). The use on intact skin is described under ***Directions***. The external use and flammability warning should be moved to one line with the external use warning appearing first. The statements need to be revised to read "[redacted] **external use only. Flammable: keep away from fire or flame.**" These warning statements should not be bulleted and just below the ***Warnings*** header. (See ***Drug Facts*** prototype attached.)

b) Bullet and unbold the statement "[redacted] solution contains alcohol and gives off flammable vapors while drying" and place it immediately under warnings For external use only and Flammable: keep away from fire or flame.

c) The term "flammable vapors" should be emphasized to communicate the importance of this information. DAIDP-HFD-520 recommended this phrase be made prominent and to be also included in the warning box located on the immediate applicator container handle. However, for ***Drug Facts***, according to 21 CFR 201.66(d)(3) requires the use of a single dark print. The sponsor can, however, use color as recommended elsewhere in the labeling. Change the contrasting term "flammable vapors" to a single dark print and bold the term to increase its size and prominence.

d) Remove the statement "[redacted] This statement has been repeated in ***Warnings***.

e) Revise the statement "[redacted] to read "[redacted]

f) Revise the bulleted statement "• Do not drape or use ignition source (e.g., cautery, laser) [redacted] to read "• [redacted]

g) Remove the following statements:

These statements are redundant and appear under ***Directions***. They are also not considered warnings.

h) Revise the bulleted statement "• ..." to read "• do not allow solution to pool" and "• ... to read "• remove solution- ... materials from prep area."

i) Remove the statement "• follow all directions for use" and place it under ***Directions*** as the first bulleted statement.

j) Thus, revise and up-date ***Warnings*** section under the external use and flammability warnings to read as follows:

> ***Warnings***
> **For external use only. Flammable: Keep away from fire or flame.**
> **To help prevent fire:**
> - solution contains alcohol and gives off **flammable vapors**
> - do not drape or use ignition source (e.g., ...cautery, laser) until solution is completely dry
> - do not allow solution to pool
> - remove solution- ... material from prep area

13. The subheader **Do not use** is followed by all contradications for use with the product. These contradications are absolute and are intended for situations in which the product should not be used on the patient unless a prior diagnosis has been established by a doctor or for situations in which the healthcare professional should not use the product under any circumstances regardless of whether a doctor is consulted. See 21 CFR 201.66(c)(5)(G)(iii). To be consistent with other OTC approved labeling for this drug product category, this reviewer suggests the following revisions under the **Do not use** subheader:

a) The subheader **Do not use** should be placed on a separate line.

b)

c) The statement "... should be revised to read "on patients with known allergies to iodine or any other ingredients in this product."

d) The statement " [redacted] should be revised to read "● [redacted]

e) Thus, revise and up-date **Do not use** section to read as follows:

Do not use
• on patients with known allergies to iodine or any other ingredients in this product
• [redacted]

14. The subheader **When using this product** is followed by the side effects that the patient may experience, and substances or activities to avoid while using the product. See 21 CFR 201.66(c)(5)(G)(vi). To be consistent with other OTC approved labeling drug product category, this reviewer suggests the following revisions under the **When using this product** subheader: (See ***Drug Facts*** prototype attached.)

a) The bulleted statement "● [redacted] is not appropriate for the **When using this product** section. This statement belongs in the ***Directions*** section under the subheader **Getting patient ready for solution**, as the third bulleted statement.

b) The following statements "● [redacted] and "● [redacted] are not appropriate for the **When using this product** section. The first statement belongs under the header ***Directions*** and the second statement belongs under the header ***Other information***.

c) Revise the statement ' [redacted] under the subheader **Do not use** to read " [redacted] include this statement under the subheader **When using this product**.

15. To be consistent with other approved labeling for this drug product category, this reviewer recommends that the statement " [redacted] ." under the subheader **Stop use and ask a doctor if** be revised to read " [redacted] (See ***Drug Facts*** prototype attached.)

16. Under the header ***Directions*** on the 26-mL size applicator labeling, remove the barline above the subheader about **after applying the solution**. The regulation requires the use of horizontal barlines extending to each side of the ***Drug Facts*** box to provide separation between headings. See 21 CFR 201.66(d)(8). These requirements contribute to the overall organization of the ***Drug Facts*** information which provides the user with easy and consistent access to required information.

17. Under the header ***Directions***, revise the numbered statements under the subheader about **activating the applicator** and **when applying the solution** to bulleted statements. Section 201.66(d)(4) specifies the style and format for using bullet points to introduce and highlight information. The bullet style is limited to solid squares or solid circles of 5-point type size and must be presented in the same shape and color throughout the labeling. This format provides a valuable visual cue for introducing each required "chunk" of information, without unnecessarily distracting or confusing the reader.

18. The phrase "**do not scrub**" under the subheader about **when applying the solution**, in the third bulleted statement on the 6-mL size applicator and the fourth bulleted statement on the 26-mL size applicator is bolded and is acceptable. DAIDP-HFD-520 recommended this phrase be made prominent and to be also included in the warning box located on the immediate applicator container handle.

19. Under the header ***Directions***, the directions for use as a patient preoperative skin preparation should be revised to include separate directions for dry surgical sites and moist surgical sites. This would also include application drying time and an estimate of the cm^2 area that is covered by a unit dose for both directions sites. This will be deferred to DAIDP-HFD-520 to decide whether or not additional directions will be required.

20. Under the header ***Directions***, several directions statements should be revised to remove excess verbiage and focus on the most important messages:

    a) Under the subheader about **getting the patient ready for the solution** for the 6- and 26-mL size applicator, revise the bulleted statement "● [redacted] to read "● [redacted] This should appear as the fourth bulleted statement. Revise the bulleted statement "● [redacted] to read "● apply to clean, dry, residue-free, intact skin". This should appear as the third bulleted statement. Revise the bulleted statement "● [redacted] to read "● do not microwave or heat the solution applicator". This should appear as the

second bulleted statement. The bulleted statements were reordered according to the most important concepts first and should be, revised as follows:

Getting patient ready for solution:
- use in a well-ventilated area
- do not microwave or heat the solution applicator
- apply to clean, completely dry, residue-free, intact skin
- If a wet shave is used, thoroughly remove all soap residues.

b) Under the subheader about **activating the applicator** for the 6-mL size applicator, revise the bulleted statement "• to read "• Revise as follows:

Activating the applicator:
•
•

c) Under the subheader about **when applying the solution** for the 6- and 26-mL size applicator, revise the bulleted statement "• to read "• Revise the bulleted statement "• to read "• . Revise the bulleted statement "• to read "• do not allow solution to pool. Use sponge applicator to absorb excess solution and continue to apply a uniform coating. Revise the bulleted statement "• to read "• when prepping skin folds, toes, or fingers, use a sterile-gloved hand to hold skin apart until dry. Otherwise, skin may adhere to itself." Revise the bulleted statement "• to read "• The bulleted

statements were rearranged by grouping instructions on body parts together and instructions on pooling together. Revise as follows:

When applying solution:

- when prepping skin folds, toes, or fingers, use a sterile-gloved hand to hold skin apart until dry. Otherwise, skin may adhere to itself.
- do not allow solution to pool. Use sponge applicator to absorb excess solution and continue to apply a uniform coating

d) Under the subheader about what to do **after applying the solution** for the 6- and 26-mL size applicator, revise the first two sentences "

to read "●

' Revise the last three sentences '

" to read "●

Revise as follows:

After applying solution:

d) The subheader about what to do

should be revised to read "**While waiting for the solution to completely dry**" for the 6- and 26-mL size applicator. Revise the second bulleted statement "● '

' to read "●

Remove the first bulleted statement "● Do not drape or use ignition source (e.g. cautery, laser)." This statement is redundant and has been repeated under the subheader about **after the solution is dry**. Revise the third bulleted statement "●

to read

"• remove solution- materials. Replace if necessary." Revise as follows:

While waiting for solution to completely dry: • check for pooled solution. Do not blot. • remove solution- materials. Replace if necessary.

f) Under the subheader about what to do should be revised to read "**After the solution is completely dry**" for the 6- and 26-mL size applicator. Revise the first bulleted statement to read " . Revise the second bulleted statement "If incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove film." to read "if incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove film." Remove the bulleted statements "• and "• These statements are not considered directions and do not belong under this section. These statements are included on the Patient Take Home Instructions.

After solution is completely dry: • • If incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove film. • apply dressing following standard practices

21. This reviewer recommends including the statement "• avoid excessive heat above 40 °C (104°F)" under the header ***Other information***.

22. Under "***Questions?***" it is recommended that the days of the week and the times when someone is available to respond to questions be included. A website address is recommended if available. The first letter in the word "call" should be in lower case. (See ***Drug Facts*** prototype attached.)

23. Under ***Questions***," the toll free telephone number must be bolded (6 point bold type) in accordance with 21 CFR 201.66(c)(9).

C. Immediate Container Label

1. The warning box containing the following statement "• [redacted] solution contains alcohol and gives off flammable vapors [redacted] • [redacted] Do not drape or use [redacted] until [redacted] is dry [redacted] • Pooled solution or solution soaked materials can lead to fire. • Use: See Drug Facts." was added to the applicator label. On March 11, 1999, the Division of Anti-Infectives Drug Products (DAIDP) informed the sponsor in a telecon that the red boxed Warnings section need to include the statement "[redacted] and appear as the first bulleted statement in the warning box. This statement needs to be in all uppercase letters so that the statement can be made prominent on the label. Revise the statement "[redacted] to read "[redacted] These statement need to be included in the red boxed Warnings section on the 6- and 26-mL applicator handle label. Revised as follows:

WARNING
• [redacted], DO NOT SCRUB [redacted]
• DuraPrep™ solution contains alcohol and gives off **flammable vapors** while drying.
• [redacted] Do not drape or use [redacted] until [redacted] is dry [redacted]
• [redacted]
• Use: See *Drug Facts*.

D. Shipping Carton Label

1. The sponsor will need to add the revised established name of the product to their shipping carton label.

RECOMMENDATIONS TO THE SPONSOR:

Required Changes

A. Principle Display Panel (PDP):

1. The June 17, 1994, tentative final monograph (TFM) for OTC Healthcare Antiseptic Drug Products (59 FR 31402) proposes the following as acceptable statements of the pharmacologic category for OTC patient preoperative skin preparation: "antiseptic" or "patient preoperative skin preparation." The pharmacologic category "patient preoperative skin preparation" appears more

appropriate to the product, given its indication for use. See 59 FR 31402 at 31443.

2. Revise the portion of the established name of the drug '[redacted]. The term '[redacted]' describes an entire category of antiseptic drug products and is not appropriate for use as the established name.

3. 21 CFR 201.61(a) and (b) requires that the PDP of a product include a statement of identity consisting of the established name of the drug "portion of the established name of the iodophor to be determined" (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w) solution, followed by the general pharmacological category of the drug (Patient Preoperative Skin Preparation). Both statements must appear in direct conjunction with the most prominent display of the proprietary name (DuraPrep™ Surgical Solution). The immediate container needs to include the appropriate established name. Revise the PDP read as follows (See prototype of PDP attached.):

DuraPrep™
Surgical Solution
"established name of the iodophor to be determined"(0.7% Available Iodine) and Isopropyl Alcohol (74% w/w) Solution
Patient Preoperative Skin Preparation

4. Bold and increase the size of established name ("portion of established name to be determined" (0.7% Available Iodine and Isopropyl Alcohol (74% w/w) solution) and the pharmacological category (Patient Preoperative Skin Preparation) to be half the size of the most prominent display of the tradename (DuraPrep™ Surgical Solution). See 21 CFR 201.61(c).

5. Increase the prominence of the statement '[redacted] or change the statement to read "Single Use" for consistency with other approvals in this class. This should also be applied to the immediate container.

6. The term "'[redacted] is light orange in color and does not give sufficient prominence to this warning. The Agency recommends that the term "[redacted] in the warnings box on the PDP and immediate container handle be prominent appearing in bold and red in color.

7. Revise the net weight "0.9 fl. oz" and "0.2 fl. oz" should be revised to read "0.9 fl oz" and "0.2 fl oz" on the PDP and immediate container.

8. Include the expiration date on the immediate package container label as required by 21 CFR 201.17. According to 21 CFR 201.17, expiration dating of this product must appear on the immediate container and also the outer package, if any, unless it is easily legible through such outer package.

9. Include the lot number information on the labeling as required by 21 CFR 201.18. According to 21 CFR 201.18, the lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. An incorrect lot number may be regarded as causing the article to be misbranded.

B. *Drug Facts* Labeling:

10. The subheader **Stop use and ask a doctor if** and the statement **Keep out of reach of children** on the 6-mL size applicator is 7-point type size. All the other subheaders are 6-point type sizes. For consistency and uniformity of the label, revise the subheader **Stop use and ask a doctor if** and the statement **Keep out of reach of children** to have consistent font sizes throughout. (See 21 CFR 201.66(d)(2)).

11. The headers ***Other information***, ***Inactive ingredients***, and ***Questions*** on the 26-mL size applicator is 10-point type size. All the other headers are a 9-point type size. For consistency and uniformity of the label, revise the headers ***Other information***, ***Inactive ingredients*** and ***Questions*** to have consistent font sizes throughout.

12. Shorten the hairline below the ***Drug Facts*** title to extend within two spaces of either side of the ***Drug Facts*** box as described in 21 CFR 201.66(d)(8). (See ***Drug Facts*** prototype attached.)

13. Revise the header ***Active ingredient*** to read ***Active ingredients***. This should be plural because more than one active ingredient is listed under this header.

14. Revise the ingredient "Isopropyl Alcohol 74% w/w" to read "Isopropyl alcohol, 74% w/w," under ***Active ingredients***. The letter "a" in the word alcohol should be lower case and a comma should be placed after the word alcohol.

15. Revise the first letter of the first word in each bulleted statement under ***Uses***, ***Warnings***, ***Directions***, and ***Other information*** to be lower case. No periods should follow after each statement unless the bulleted statement contains more than one sentence. (See ***Drug Facts*** prototype attached.)

16. Remove the tradename "——— from the ***Drug Facts*** enclosure. The OTC Labeling Requirements final rule published March 17, 1999 (64 FR 13254 at 13271), states that brand names may not appear in the ***Drug Facts*** enclosure, but may appear anywhere else on the labeling outside of the boxed area.

17. The term '—— and "solution" has been used interchangeably throughout the label. The Agency finds the term '— has been used inappropriately to refer to the solution throughout the label and has proposed revisions to some labeling statements. Other labeling statements have been revised to emphasize that the

prep needs to dry completely. See prototype of ***Drug Facts*** attached for recommended revisions.

18.

19. Under ***Warnings***, the Agency recognizes the need for additional warning statements, but there are numerous warning statements and the impact of all these warning statements on the label will be reduced. Most of the statements are repeated under ***Directions*** and do not belong under ***Warnings***. The Agency has concluded that warning statements required are those that are scientifically and clinically documented and important for safe use of the product. Revise the ***Warnings*** section for the 6- and 26-mL size applicator as follows: (See ***Drug Facts*** prototype attached.)

a) Revise the external use warning statement '———— ————' to read "**For external use only**" in accordance with 21 CFR 201.66(c)(5)(i). The use on intact skin is mentioned under ***Directions***. The external use and flammability warning should be moved to one line with the external use warning appearing first. Revise the statements to read "**For external use only. Flammable: Keep away from fire or flame.**" These warning statements should not be bulleted and just below the ***Warnings*** header.

b) Bullet and unbold the statement '———— solution contains alcohol and gives off flammable vapors' ———— and place it immediately under the warnings **For external use only** — **Flammable: keep away from fire or flame.**

c) Change the contrasting term ' ———— to a single dark print and bold the term to increase its size and prominence. (See 21 CFR 201.66(d)(3).)

d) Remove the statement ———— ————.' This statement is repeated in ***Warnings***.

e) Revise the statement ' ———— to read "———

f) Revise the bulleted statement "• Do not drape or use ignition source (e.g., cautery, laser) until [illegible] is dry [illegible] to read "• do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry [illegible]"

g) Remove the following statements:

These statements are redundant and appear under ***Directions***. They are also not considered warnings.

h) Revise the bulleted statement "• [illegible] " to read "• do not allow solution to pool" and "• [illegible] to read "• remove solution- [illegible] materials from prep area."

i) Remove the statement "• [illegible] and place it under ***Directions*** as the first bulleted statement. This statement is redundant and is not needed under ***Warnings***.

j) Thus, revise and up-date ***Warnings*** section under the external use and flammability warnings to read as follows:

> ***Warnings***
> **For external use only. Flammable: Keep away from fire or flame.**
>
> - solution contains alcohol and gives off **flammable vapors**
> - do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry
> - do not allow solution to pool
> - remove solution- material from prep area

20. The subheader **Do not use** is followed by all contradications for use with the product. These contradications are absolute and are intended for situations in which the product should not be used on the patient unless a prior diagnosis has been established by a doctor or for situations in which the healthcare professional should not use the product under any circumstances regardless of whether a

doctor is consulted. See 21 CFR 201.66(c)(5)(G)(iii). To be consistent with other OTC approved labeling for this drug product category, the following revisions under the **Do not use** subheader are needed:

a) Place the subheader **Do not use** on a separate line.

b) The statement [redacted] belongs under the subheader [redacted].

c) Revise the statement [redacted] to read "• on patients with known allergies to iodine or any other ingredients in this product."

d) Revise the statement "[redacted] to read "• [redacted] infants less than 2 months old due to risk of [redacted]

e) Thus, revise and up-date **Do not use** section to read as follows:

Do not use
- on patients with known allergies to iodine or any other ingredients in this product
- [redacted] infants less than 2 months old due to risk of [redacted]

21. The subheader [redacted] is followed by the side effects that the patient may experience, and substances or activities to avoid while using the product. See 21 CFR 201.66(c)(5)(G)(vi). To be consistent with other OTC approved labeling drug product category, the following revisions under the [redacted] subheader (See ***Drug Facts*** prototype attached.) are needed:

a) The bulleted statement "• [redacted] " is not appropriate for the **When using this product** section. This statement belongs in the ***Directions*** section under the subheader **Getting patient ready for solution**, as the first bulleted statement.

b) The following statements "• [redacted] ' and "• [redacted] are not appropriate for the [redacted] section. The first statement belongs under the header ***Directions*** and the second statement belongs under the header ***Other information***.

c) Revise the statement [redacted] Under the subheader **Do not use** to read " keep out of eyes, ears, mouth, [redacted] If contact occurs, [redacted] with cold water right away and contact a doctor." Include this statement under the subheader **When using this product**.

22. To be consistent with other approved labeling for this drug product category, the statement "[redacted] irritation, sensitization or other allergic reactions occurs." under the subheader **Stop use and ask a doctor if** should be revised to read "irritation, sensitization or [redacted] allergic reactions occurs. These may be signs of a serious condition." (See ***Drug Facts*** prototype attached.)

23. Remove the barline above the subheader about **after applying solution**, under the header ***Directions*** on the 26-mL size applicator labeling. The regulation requires the use of horizontal barlines extending to each side of the ***Drug Facts*** box to provide separation between headings. See 21 CFR 201.66(d)(8). These requirements contribute to the overall organization of the ***Drug Facts*** information which provides the user with easy and consistent access to required information.

24. Revise the numbered statements under the subheader about **activating the applicator** and **when applying solution** to bulleted statements under the header ***Directions***. Section 201.66(d)(4) specifies the style and format for using bullet points to introduce and highlight statements of information. The bullet style is limited to solid squares or solid circles of 5-point type size and must be presented in the same shape and color throughout the labeling. This format provides a valuable visual cue for introducing each required "chunk" of information, without unnecessarily distracting or confusing the reader.

25. Revise the directions for use as a patient preoperative skin preparation to include separate directions for dry surgical sites and moist surgical sites under the header ***Directions***. Also include application drying time and an estimate of the cm^2 area that is covered by a unit dose for both directions sites. This will be deferred to DAIDP-HFD-520 to decide whether or not additional directions will be required.

26. Revise several directions statements under the header ***Directions*** to remove excess verbiage and focus on the most important messages:

a) Under the subheader about **getting [redacted] patient ready for [redacted] solution** for the 6- and 26-mL size applicator, revise the bulleted statement "● When hair removal is necessary [redacted] use a surgical clipper on the morning of the surgery. If a wet shave is used, [redacted] thoroughly remove all soap residues." to read "● [redacted] . If a wet shave is used, thoroughly remove all soap residues." This should appear as the

fourth bulleted statement. Revise the bulleted statement "● [redacted] to read "● apply to clean, completely dry, residue-free, intact skin." This should appear as the third bulleted statement. Revise the bulleted statement "● [redacted] to read "● do not microwave or heat the solution applicator." This should appear as the second bulleted statement. The bulleted statements were reordered according to the most important concepts first, revise as follows:

Getting patient ready for solution:
- use in a well-ventilated area
- do not microwave or heat the solution applicator
- apply solution to clean, dry, residue-free, intact skin
- [redacted] If a wet shave is used, thoroughly remove all soap residues

b) Under the subheader about **activating the applicator** for the 6-mL size applicator, revise the bulleted statement "● [redacted] to read "● [redacted] Revise as follows:

Activating the applicator:
- [redacted]
- [redacted]

c) Under the subheader about **when applying [redacted] solution** for the 6- and 26-mL size applicator, revise the bulleted statement "● [redacted] to read "● tuck prep towels under both sides of the neck to absorb excess solution." Revise the bulleted statement "● [redacted] to read "● avoid getting solution into [redacted]. Revise the bulleted statement "● [redacted] to read "● do not allow solution to pool. Use sponge applicator to absorb excess solution and continue to apply a uniform coating. [redacted], remove excess with gauze." Revise the bulleted statement "● when prepping skin folds, toes, or fingers, use a sterile-gloved hand to hold skin apart until dry. Otherwise, [redacted] skin may adhere to itself." to read "● When prepping skin folds, toes, or fingers, use a sterile-gloved hand to hold

skin apart until completely dry. Otherwise, skin may adhere to itself." Revise the bulleted statement "• Paint a single, uniform application and do not [redacted] to read "• paint a single, uniform application [redacted] The bulleted statements were rearranged by grouping instructions on body parts together and instructions on pooling together. Revise as follows:

When applying solution:

- [redacted]
- tuck prep towels under both sides of the neck to absorb excess solution. Remove towels before draping.
- when prepping skin folds, toes, or fingers, use a sterile-gloved hand to hold skin apart until completely dry. Otherwise, skin may adhere to itself.
- avoid getting solution into hair
- paint a single, uniform application [redacted]
- do not allow solution to pool. Use sponge applicator to absorb excess solution and continue to apply a uniform coating. [redacted] remove excess with gauze.

d) Under the subheader about what to do **after applying [redacted] solution** for the 6- and 26-mL size applicator, revise the first two sentences [redacted] to read "• [redacted] Solution will turn from a shiny to a dull appearance on skin alerting the user that the solution is completely dry and no longer flammable." Revise the last three sentences "[redacted] to read "• [redacted] Revise as follows:

After applying solution:

- [redacted] Solution will turn from a shiny to a dull appearance on skin alerting the user that the solution is completely dry and no longer flammable.
- [redacted]

e) The subheader about what to do [redacted] should be revised to read **"While waiting for [redacted] solution to completely dry"** for the 6- and 26-mL size applicator. Revise the second bulleted statement "• check for pooled [redacted] Do not blot because it may remove [redacted] from skin." to read "• check for pooled solution. [redacted] Do not blot." Remove the first bulleted statement "• Do not drape or use

ignition source (e.g. cautery, laser)." This statement is redundant and has been repeated under the subheader about **after the solution is dry**. Revise the third bulleted statement "• remove solution- materials. Replace if necessary." to read "• remove solution- materials. Replace if necessary." Revise as follows:

While waiting for solution to completely dry:
• check for pooled solution. Do not blot.
• remove solution- materials. Replace if necessary.

f) Under the subheader about what to do , should be revised to read "**After solution is completely dry**" for the 6- and 26-mL size applicator. Revise the first bulleted statement , begin draping and/or using cautery only after is dry and all solution- materials are removed." to read " begin draping and/or using cautery only after solution . Revise the second bulleted statement "If incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove film." to read "if incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove film." Remove the bulleted statements "• and "• These statements are not considered directions and do not belong under this section. These statements are included on the Patient Take Home Instructions.

After solution is completely dry:
• begin draping and/or using cautery only after solution is completely dry and all solution- materials are removed
• if incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove film.
• apply dressing following standard practices

27. Under ***Questions***," the toll free telephone number must be bolded (a minimum 6 point type bold type) in accordance with 21 CFR 201.66(c)(9).

Immediate Container Label

28. The warning box containing the following statement "• solution contains alcohol and gives off flammable vapor • Do not drape or use . • Use: See Drug Facts." was added to the applicator label. On March 11, 1999, the Division of Anti-Infectives Drug Products (DAIDP) informed the sponsor in a telecon that the red

boxed Warnings section need to include the statement "• [redacted] **DO NOT SCRUB** [redacted]" and appear as the first bulleted statement in the warning box. This statement needs to be in all uppercase letters so that the statement can be made prominent on the label. Revise the statement "[redacted] Do not drape or use [redacted]" to read "[redacted] Do not drape or use [redacted] These statement needs to be included in the red boxed Warnings section on the 6- and 26-mL applicator handle label. Revised as follows:

WARNING
• [redacted] **DO NOT SCRUB** [redacted]
• [redacted] solution contains alcohol and gives off **flammable vapors** [redacted]
• [redacted] Do not drape or use [redacted]
• [redacted]
• Use: See *Drug Facts*.

Shipping Carton Label

29. Include the revised established name of the product to their shipping carton label.

Recommend Changes

Drug Facts

30. The submitted font size specifications for the 6- and 26-mL size applicator labeling do not meet the Agency's recommended specifications. The Agency recommends that the ***Drug Facts*** labeling be presented using the graphic specifications set forth in 21 CFR 201 Appendix A. We recommend revision as follows:

a) ***Drug Facts*** box or enclosure barline containing all information should be a 2.5-point type size, not a 2-point type size as on the 6- and 26-mL size applicators.

b) The horizontal barline separating the headings should be a 2.5-point type size, not a 2-point type size as on the 6- and 26-mL size applicators.

c) The horizontal hairlines between the warning subheadings, should be a 0.5-point type size, not a 1-point type size as on the 6- and 26-mL size applicators.

31. Under ***Uses***, the labeling is recommended to be consistent with the specific labeling requirements for the product's intended use as stated in the Healthcare Antiseptic TFM. The Agency recommends including the heading "patient preoperative skin preparation" under ***Uses***. The statement under ***Uses*** should be revised as follows (See prototype of ***Drug Facts*** attached.):

    patient preoperative skin preparation:
    - for preparation of the skin prior to surgery
    - helps reduce bacteria that potentially can cause skin infection

32. The Agency recommend including the statement "• avoid excessive heat above 40 °C (104°F)" under the header ***Other information***.

33. Under "***Questions?***" it is recommended that the days of the week and the times when someone is available to respond to questions be included. A website address is recommended if available. The first letter in the word "call" should be in lower case. (See prototype of ***Drug Facts*** attached.)

The changes requested will make the labeling consistent with recently approved healthcare topical antiseptic OTC drug Products. The sponsor should be provided with a draft of the prototype of Drug Facts labeling and the PDP. The prototype does not reflect true specifications (i.e., fonts, typeface and size) that are required in the OTC labeling requirements final rule. This labeling is subject to further modification during the ongoing review of this NDA.

Michelle M. Jackson, Ph.D.
IDS Reviewer

Concurrence
Debbie L. Lumpkins, Team Leader

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Michelle Jackson
6/23/04 09:01:53 AM
INTERDISCIPLINARY

Debbie Lumpkins
6/24/04 08:25:12 AM
INTERDISCIPLINARY

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE:	May 18, 2004
TO:	Maureen Parker-Dillon, Regulatory Project Manager David Bostwick, M.D., Medical Officer, Clinical Reviewer Jean Mulinde, M.D., Medical Team Leader Division of Anti-Infective Drug Products, HFD-520
THROUGH:	Leslie K. Ball, M.D., Chief Good Clinical Practice Branch II, HFD-47 Division of Scientific Investigations
FROM:	Brenda R. Friend, R.Ph., J.D. Good Clinical Practice Branch II, HFD-47 Division of Scientific Investigations
SUBJECT:	Evaluation of Clinical Inspections
NDA:	21-586
APPLICANT:	3M Health Care.
DRUG:	DuraPrep™ Surgical Solution [Iodophor (0.7% available iodine) and Isopropyl Alcohol (74% w/w) Solution]
CHEMICAL CLASSIFICATION:	Type 4
THERAPEUTIC CLASSIFICATION:	Standard Review
INDICATIONS:	Patient pre-operative skin preparation
CONSULTATION REQUEST DATE:	January 8, 2004
GOAL DATE TO PROVIDE INSPECTION SUMMARY REPORT:	May 15, 2004
ACTION GOAL DATE:	June 15, 2004

I. BACKGROUND

Prior to surgery or other invasive procedures, the skin is treated with topical antimicrobial products to reduce the risk of nosocomial infections by reducing the number of microorganisms on the skin. DuraPrep solution is a topical antimicrobial skin-prepping agent. When the solution is applied to the skin, it dries to form a water-insoluble film; this anti-microbial film makes DuraPrep solution unique from other skin prepping agents. The sponsor, 3M Health Care, has requested the use of DuraPrep solution as a patient preoperative skin preparation. The NDA was supported by the pivotal protocol: LIMS 8918 entitled "Pivotal Study to Assess the Antimicrobial Effectiveness of 3M™ DuraPrep™ Surgical Solution Against Resident Human Skin Flora on Abdomen and Groin Regions (Study 2)."

The Review Division was concerned about discrepancies found at the [redacted] site (Clinical Investigator [redacted] The positive control did not meet the log reductions, whereas other sites did not report this finding. In addition, there were a disproportionate number of exclusions (contaminations) than at other sites.

II. RESULTS (by site):

NAME	CITY, STATE	ASSIGNED DATE	EIR RECEIVED DATE	CLASSIFICATION
[redacted]	[redacted]	2-6-04	Pending	Pending

Protocol LIMS 8918

The study was a randomized, partially blinded, paired-comparisons design study conducted in healthy volunteers 18 years of age or older. The study comprised of a 14-day pretreatment phase during which standardized antimicrobial soaps, shampoos and deodorants were used, a one-day screening phase, and a two-day treatment phase of DuraPrep and either Hibiclens® Antiseptic Skin Cleanser (Hibiclens cleanser) or Betadine® Surgical Scrub and Betadine® Solution (Betadine combination) to the groin or abdomen site.

The primary efficacy endpoint was the $\log_{10}$ reduction of skin flora at each body site following application. Microbiological samples were to be collected at the time points specified in the 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) criteria for log reduction with a few exceptions.

A total of 357 subjects were enrolled with 100 subjects completing the study. A total of 257 subjects were either screened out or withdrew for various reasons.

1. Site Inspected ([redacted]): Data Acceptable

a. What was inspected: The study records of 30 of 100 subjects completing the study were reviewed including the log baseline requirements for entry into the test phase of the study.

b. Limitations of the inspection: None.

c. General observations/commentary

The sponsor monitored this site from off-site; no on-site visits were performed. During the inspection and at the close of the inspection, the following observations were discussed with the clinical investigator. A 3-item 483 was issued.

1) Record availability: All subjects' records were available.
2) Protocol Deviations: No significant issues found.
3) Subject eligibility: No significant issues found.
4) Subject withdrawals: No significant issues found.
5) Adverse events: No significant issues found.
6) Informed consent/IRBs/protocol amendments: All subjects signed and dated consent forms prior to enrollment. However, there was no documentation that each subject was given a signed copy of the informed consent. In addition, a complete copy of each subject's informed consent was not maintained at the study site.
7) Record Keeping: There is no documentation for any of the 100 subjects completing the study that a visual skin assessment of the test area was performed at the pretreatment and the screening phase to ensure no injury or dermatoses, as required by protocol.
8) Drug accountability: No significant issues found.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, the inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, and adequately reported adverse events.

The data submitted in support of this NDA appear acceptable.

Follow-up action: None needed.

[**Note:** This Clinical Inspection Summary was based on a draft EIR, without exhibits, received from the FDA inspector. Should the final review of EIR and exhibits contain information that would significantly affect the classification or have an impact on the approval process, I will inform the Review Division.]

Brenda R. Friend, R.Ph., J.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D., Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-586
HFD-45/Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Ball/Friend
HFD-47/Lackner GCPB2 Files

rd:BRF:5/7/04:5/10/04:5/18/04

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/s/

Brenda Friend
5/19/04 11:40:38 AM
CSO

Leslie Ball
5/19/04 04:27:52 PM
MEDICAL OFFICER

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 5, 2004

To: Dianne Gibbs Regulatory Affairs	Maureen Dillon-Parker **From:** Project Manager
Company: 3M	FDA - Division of Division of Anti-Infective Drug Products
Fax number: 651-737-5320	**Fax number:** 301-827-2325
Phone number: 651-737-9117	**Phone number:** 301-827-2125

Subject: Request for information from the Microbiology reviewer on NDA 21-586

Total no. of pages including cover: 2

Comments: Please see attached.

Document to be mailed: • YES ☑ NO

Application: NDA 21-586

Drug: 3M™DuraPrep™ Surgical Solution

The Microbiology reviewer comments are as follows:

1. The Applicant supplied MBC data for most of the organisms listed in the Tentative Final Monograph. However, MBC data for one organism, *Klebsiella pneumoniae*, was not provided. It is unclear whether this MBC data was supplied within the MBC data for *Klebsiella* sp. or was omitted. The Applicant should clarify and if necessary, rectify this discrepancy by providing the MBC data for *K. pneumoniae*.

2. There are two deficiencies in the presentation of the time-kill studies. First, $\log_{10}$ reductions for each of the organisms listed in the TFM list must be provided. Second, the Applicant must supply enumerations at 0, 3, 6, 9, 12, 15, 20 and 30 minutes for these organisms. These time frames are of greatest interest for patient preoperative skin preparations and should be reflected in the *in vitro* time-kill studies.

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/s/

Maureen Dillon-Parker
4/26/04 06:09:07 PM
CSO
NDA 21-586; Facsimile sent 2-5-04 - Microbiologist Request for Information

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2004

To: Dianne L. Gibbs	**From:** Maureen Dillon-Parker
Company: 3M Health Care	Division of Division of Anti-Infective Drug Products
Fax number: 651-737-5320	**Fax number:** 301-827-2325
Phone number: 651-737-9117	**Phone number:** 301-827-2125

Subject: Reviewer Request for Information on NDA 21-586.

Total no. of pages including cover: 2

Comments: See attached comments.

Document to be mailed: ☐ YES ☑ NO

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RE: DURAPREP (NDA 21-586)

Biopharmaceutical Reviewer's Request:

Please submit the complete analytical validation data (accuracy, precision, specificity, and stability) for Study LIMS 1621 (Study of transdermal absorption of two iodine solutions: DuraPrep surgical solution (alcohol solution) versus Betadine (aqueous solution), after single cutaneous application in twelve normal healthy volunteers).

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/s/

Maureen Dillon-Parker
4/26/04 05:38:47 PM
CSO
NDA 21-586; Facsimile sent 3-15-04 @ 5:30pm

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE : **February 3, 2004**

FROM: Dr. Peter Coderre, Microbiology Reviewer, Division of Anti-Infective Drug Products

THROUGH: Dr. Albert Sheldon, Microbiology Team Leader, Division of Anti-Infective Drug Products (HFD-520)

SUBJECT: DuraPrep pre-operative prep, NDA 21-586

TO : Maureen Dillon-Parker

At this stage in the review of this NDA, this Reviewer has detected the following deficiencies that require the Applicant's attention.

1. The Applicant supplied MBC data for most of the organisms listed in the Tentative Final Monograph. However, MBC data for one organism, *Klebsiella pneumoniae*, was not provided. It is unclear whether this MBC data was supplied within the MBC data for *Klebsiella* sp. or was omitted. The Applicant should clarify and if necessary, rectify this discrepancy by providing the MBC data for *K. pneumoniae*.

2. There are two deficiencies in the presentation of the time-kill studies. First, $\log_{10}$ reductions for each of the organisms listed in the TFM list must be provided. Second, the Applicant must supply enumerations at 0, 3, 6, 9, 12, 15, 20 and 30 minutes for these organisms. These time frames are of greatest interest for patient preoperative skin preparations and should be reflected in the *in vitro* time-kill studies.

Peter Coderre, Microbiology Reviewer
Division of Anti-Infective Drug Products

Albert Sheldon, Microbiology Team Leader
Division of Anti-Infective Drug Products

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/s/

Peter Coderre
2/4/04 04:05:22 PM
MICROBIOLOGIST

Albert Sheldon
2/4/04 04:16:23 PM
MICROBIOLOGIST
Recommendatiions to be provided to company.

Lillian Gavrilovich
2/9/04 03:37:35 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-586

JAN 9 2004

3M Health Care Markets
Attention: Suzanne M. Danielson, RAC
Director of Regulatory Affairs and Quality
3M Center, Building 275-5W-06
St. Paul, MN 55144-1000

Dear Ms. Danielson:

Please refer to your October 27, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DuraPrep™ Surgical Solution (Iodophor [0.7% available iodine] and Isopropyl Alcohol [74% w/w/] Solution).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 26, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

MICROBIOLOGY

1. Spectrum of Activity:

   - Submit minimum bacteria concentrations (MBC) data for MBC-50s and MBC-90s. We note that MBC ranges were submitted previously.
   - Supply the number of isolates from these studies. Please place all data in tables.

2. Resistance Studies:

   - Please identify the pertinent articles from the literature review of antiseptic resistance studies performed by 3M and provide the results of the review.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

CLINICAL

In the summary of DuraPrep Solution Clinical Complaints (Table 2.7.4.22 in Module 2 of the submission), the Skin irritation complaints include "chemical burn, blistering, skin removal". Please provide the adverse event reports for these occurrences, as well as any other information concerning them that may be relevant.

LABELING

Please submit the graphic specifications for your Drug Facts Labeling, in accordance with 21 CFR 201.66(d). Specify the font type and size for the title, headings, subheadings, text, barlines, hairlines, etc., and also font type and size for bullets.

Drug Facts contents and formatting issues have also been identified. A complete set of comments from the review of the proposed labeling will be provided later in the review cycle.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Maureen Dillon-Parker, Regulatory Project Manager, at (301) 301-827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Janice Soreth
1/9/04 01:27:48 PM

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DSI CONSULT: Request for Clinical Inspections

Date: January 5, 2004

To: Antoine N. El-Hage, Ph.D., Associate Director for Good Clinical Practice/ Branch Chief GCP2/HFD-47
Brenda Friend, Consumer Safety Officer/GCPBII/HFD-47

From: Jean Mulinde, M.D., Clinical Team Leader, Division of Anti-Infective Drug Products (DAIDP)/HFD-520
Maureen Dillon-Parker, Project Manager, DAIDP/HFD-520

Subject: **Request for Clinical Inspections**
NDA 21-586- 3M Health Care - DuraPrep™ Surgical Solution

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
1. Patient Pre-Op (pivotal efficacy)	LIMS (NDA 21-586)		
(safety)	LIMS (NDA 21-586)	same	
2. Patient Pre-Op (pivotal efficacy)			

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **May 15, 2004**. We intend to issue an action letter on this application by (action goal date) **June 15, 2004**.

Should you require any additional information, please contact Maureen Dillon-Parker #301-827-2125 or Jean Mulinde #301-827-2120.

Concurrence: (if necessary)
Jean Mulinde, Medical Team Leader
Peter Kim/David Bostwick, Medical Reviewer

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/s/

Maureen Dillon-Parker
1/7/04 04:24:21 PM
NDA 21-586 DuraPrep and NDA 21-669 Sage 2% CHG
- DSI Inspection Request

Jean Mulinde
1/7/04 04:26:56 PM

Janice Soreth
1/8/04 10:55:11 AM

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45 DAY MEETING CHECKLIST FOR NDA 21,586

MICROBIOLOGY FILEABILITY

On initial overview of the NDA application:	YES	NO
1. Is the microbiologic section of the NDA organized in a manner to allow substantive review to begin?	√	
2. Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin?	√	
3. Is the microbiology section and other microbiologically pertinent sections of the NDA legible so that substantive review can begin?	√	
HAS THE APPLICANT SUBMITTED:		
4. *In vitro* data in necessary quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories *to* meet current Divisional standards for approvability of the product based on the submitted draft labeling?	√	
5. Any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	NA	
6. Draft breakpoints and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	NA	
7. All special studies/data requested by the Division during pre-submission discussions?	NA	
8. Draft labeling consistent with 201.56 and 201.57, current Divisional policy, and the design of the development package?		
9. FROM A MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.**	YES	

_____
Reviewing Microbiology Officer

_____
Supervisory Microbiology Officer

December 5, 2003

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/s/

Peter Coderre
12/11/03 02:57:12 PM
MICROBIOLOGIST

Albert Sheldon
12/15/03 10:18:05 AM
MICROBIOLOGIST

Lillian Gavrilovich
12/15/03 04:56:57 PM
MEDICAL OFFICER

NDA FILEABILITY CHECKLIST

NDA Number: 21-586 **Applicant:** 3M Medical Division. **Stamp Date:** 24-Oct-2003

Drug Name: 3M™ DuraPrep™ Surgical Solution

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) YES

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	✓		The CMC section of the NDA is organized in a manner to allow substantive
2	Is the section indexed and paginated adequately?	✓		
3	On its face, is the section legible?	✓		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	✓		Addendum I to FDA 356h form has all the establishment information.
5	Is a statement provided that all facilities are ready for GMP inspection?	✓		They are all ready for inspection.
6	Has an environmental assessment report or categorical exclusion been provided?	✓		A claim for categorical exclusion has been made and the EIC has calculated to be below 1 ppb
7	Does the section contain controls for the drug substance?	✓		
8	Does the section contain controls for the drug product?	✓		
9	Has stability data and analysis been provided to support the requested expiration date?	✓		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		
11	Have draft container labels been provided?	✓		
12	Has the draft package insert been provided?	✓		
13	Has an investigational formulations section been provided?	✓		A pharmaceutical development report has been included (3.2.P.2)
14	Is there a Methods Validation package?	✓		A hard copy has been requested for District Laboratory.
15	Is a separate microbiological section included?	✓		

If the NDA is not fileable from a manufacturing and controls perspective, state why it is not.

Review Chemist: Date:

Team Leader: Date:

cc:
Original NDA 21-586
HFD-520/Division File
HFD-520/Chem/Sloan
HFD-520/PM/DillionParker
HFD-830/DivDir/Chen

Have all DMF References been identified?

DMF Number	Holder	Description	LOA Included	Status
[redacted]	[redacted]	[redacted]	Yes	No Records (Never reviewed)
[redacted]	[redacted]	[redacted]	Yes	Adequate
[redacted]	[redacted]	[redacted]	Yes	Adequate
[redacted]	[redacted]	[redacted]	Yes	Adequate

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/s/

Milton Sloan
12/5/03 01:41:49 PM
CHEMIST

Jim Vidra
12/5/03 01:45:02 PM
CHEMIST

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-586

NOV 6 2003

3M Health Care
Attention: Suzanne M. Danielson, RAC
Director of Regulatory Affairs and Quality
3M Center, Building 275-5W-06
St. Paul, MN 55144-1000

Dear Ms. Danielson:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: DuraPrep™ Surgical Solution
Iodophor (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w) Solution

Review Priority Classification: Standard (S)

Date of Application: October 24, 2003

Date of Receipt: October 27, 2003

Our Reference Number: NDA 21-586

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 26, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 27, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Ms. Maureen Dillon-Parker, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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On Original

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

/s/

Frances LeSane
11/6/03 02:26:48 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
3M Health Care
3M Center, Building 275-5W-06
St. Paul, MN 55144-1000

2. TELEPHONE NUMBER *(Include Area Code)*
(651) 737-9117

3. PRODUCT NAME
DuraPrep Surgical Solution (Iodophor (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w) Solution)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 21-586

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4612

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Suzanne M. Danielson	Director of Regulatory Affairs and Quality	10/02/2003

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-1090 EF

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