Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 19, 2006

To: Dianne Gibbs	**From:** Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: 3M	Division of Nonprescription Regulatory Evaluation
Fax number: 651-737-5320	**Fax number:** (301) 796-9899
Phone number: 651-737-9117	**Phone number:** (301) 796-0994
Subject: TPI Comments	
Total no. of pages including cover: 3	

Document to be mailed: ☐ YES ☑ NO

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7. Provide an explanation of how the level of color retention on the skin at 6 hours post-prep contributes to the safe and effective use of DuraPrep solution.

8. Revise the summary of the results for the 21-Day Human Cumulative Irritation Potential Test to include study results obtained when the product is patched wet as follows:

   In a 21-Day Human Cumulative Irritation Potential Test involving 32 subjects, DuraPrep solution's Base 10 cumulative Irritation Score when patched wet under occlusive conditions (the standard procedure for testing of this type) was 453.7 (Class 4: experiment cumulative irritant). When DuraPrep solution was allowed to dry on the skin prior to patch application, reflecting intended use, the Base 10 cumulative irritation score was 307.7 (Class 3: possibly mild in normal use).

9. Update the following sections to be consistent with FDA's comments of September 15, 2006 on Drug Facts: Indications and Usage, Contraindications, and Warnings.

10. [redacted]

    Also, revise the last sentence in the first paragraph under the heading "Postmarketing Complaints" to reflect that all but one flammability incident were associated with the 26 mL applicator. The revised paragraph should read as follows:

    All DuraPrep solution clinical complaints from 1988 through November 30, 2005 based on total units sold are presented in Table 4. The most frequent overall complaint was skin irritation ([redacted] reports). Reports of infection or infection rate were the second most common with 109 reports. Flammability incidents were the third most prevalent complaint (a total of 97 flammability complaints since 1988, all but one of these was associated with use of the 26 mL solution). Based on sales per million per year, the annual incidence rate [redacted] has been < 2.0 since 1993.

11. [redacted]

12. Update the coverage area stated for the 26-mL and 6-mL size applicators in the "How Supplied" section to be consistent with FDA's comments on this in Drug Facts.

13. Add storage conditions to the "How Supplied" section.

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

/s/

Laura Shay
9/19/2006 02:15:53 PM

OTC LABELING REVIEW

Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products

NDA 21-586

Sponsor Package Submission: March 28, 2006
Received by CDER White Oak: March 30, 2006
Review Completed: September 13, 2006

REVIEWER: Debbie Lumpkins
Team Leader, Team 3

PROJECT MANAGER: Laura Shay, R.N., M.S.

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

CONTACT PERSON
Dianne L. Gibbs, RAC
Regulatory Affairs Manager
(651) 737-9117

DRUG PRODUCT NAMES:
Proprietary Name: DuraPrep™ Surgical Solution
Established Name: Iodine Povacrylex (0.7% available iodine) and Isopropyl Alcohol (74% w/w) Solution

INDICATION: Patient preoperative skin preparation

PHARMACOLOGICAL CATEGORY: Healthcare Antiseptic

DOSAGE FORM: Topical Solution

MATERIAL REVIEWED: Targeted Product Information

Executive Summary

On March 28, 2004, the sponsor submitted an amendment (N-000/AZ) to the original submission that included a pivotal study and draft labeling. Among the labeling included in the submission is a target product information sheet (TPI) containing product safety and performance information that has been commented on by a number of reviewers (Joel Schiffenbauer, M.D, Dr. Steve Osborne, M.D., Colleen Rogers, Ph.D., and Michelle Jackson, Ph.D.) The purpose of this review is the development of cohesive comments for the sponsor.

Comments for the Sponsor:

1. Remove the statement " [redacted] Data demonstrating a clinical benefit of these product attributes have not been provided.

2. [redacted]

3. As currently proposed, the discussion of the patient preoperative skin prepping studies does not include the criteria for a demonstration of effectiveness. In order to allow an accurate assessment of the information presented by the reader add the following statement:

   > "FDA currently requires that patient preoperative skin preparations meet the following effectiveness criteria: a 2-log reduction on the abdomen in 10 minutes, a 3-log reduction on the groin in 10 minutes, and counts not exceeding baseline values at 6 hours post-application. A correlation between these effectiveness criteria and clinical outcomes has not been established."

   The statement should be added as the second sentence of the paragraph entitled "Patient Preoperative Prep Studies."

4. [redacted]

5. The text of the discussion of the clinical studies needs to match the information in the figures. Do not present data averaged from separate study arms in the text when this information is not provided in the figures.

6. [redacted]

7. Please provide an explanation of how the level of color retention on the skin at 6 hours post-prep contributes to the safe and effective use of DuraPrep solution.

8. Revise the summary of the results for the 21-Day Human Cumulative Irritation Potential Test to include study results obtained when the product is patched wet as follows:

   In a 21-Day Human Cumulative Irritation Potential Test involving 32 subjects, DuraPrep solution's Base 10 cumulative Irritation Score when patched wet under occlusive conditions (the standard procedure for testing of this type) was 453.7 (Class 4: experiment cumulative irritant). When DuraPrep solution was allowed to dry on the skin prior to patch application, reflecting intended use, the Base 10 cumulative irritation score was 307.7 (Class 3: possibly mild in normal use).

9. Update the following sections to be consistent with FDA's comments of September 15, 2006 on Drug Facts: Indications and Usage, Contraindications, and Warnings.

10. [redacted]

    Also, revise the last sentence in the first paragraph under the heading "Postmarketing Complaints" to reflect that all but one flammability incident were associated with the 26 mL applicator. The revised paragraph should read as follows:

    All DuraPrep solution clinical complaints from 1988 through November 30, 2005 based on total units sold are presented in Table 4. The most frequent overall complaint was skin irritation ([redacted] reports). Reports of infection or infection rate were the second most common with 109 reports. Flammability incidents were the third most prevalent complaint (a total of 97 flammability complaints since 1988, all but one of these was associated with use of the 26 mL solution). Based on sales per million per year, the annual incidence rate [redacted] has been < 2.0 since 1993.

11. [redacted]

12. Update the coverage area stated for the 26-mL and 6-mL size applicators in the "How Supplied" section to be consistent with FDA's comments on this in Drug Facts.

13. Add storage conditions to the "How Supplied" section.

Background:
On October 24, 2003, the sponsor submitted draft labeling for DuraPrep™ Surgical Solution that included a TPI. On August 17, 2004, FDA provided a revised TPI to the sponsor by facsimile. 3M never responded to this guidance.

On August 27, 2004, an approvable letter was sent to the sponsor. The action was based on the product's failure to attain a 3-log reduction in the resident bacteria at the groin site as required for approval as a patient preoperative skin preparation. The response to FDA's action dated March 28, 2004 (N-000/AZ) included a pivotal study and a revised TPI that responds to the August 17, 2004 facsimile.

Reviewer's comments on the labeling:

Product Title

1. The revised TPI provided by FDA on August 17, 2006 noted that the established name of the drug product was yet to be determined. In the agency's approvable letter FDA recommended that the sponsor use "iodine povacrylex" until the United States Adopted Name (USAN) Council determined an acceptable established name for the product. On March 30, 2005, the name "iodine povacrylex" was adopted by USAN as the established name for DuraPrep. The Product Title section of the labeling has been updated to include the established name. The section has also been updated to include the pharmacological category of the product, i.e., patient preoperative skin preparation.

   Reviewer's comment: Per Dr. Jackson's review, this is acceptable.

Description

2. The following statement has been added to the end of the first paragraph under the heading "Descriptions:"

   "....and helps reduce bacteria that can potentially cause skin infection."

   Reviewer's comment: ***Per Dr. Jackson's review, this statement is part of indications in Drug Facts and is acceptable.***

3. The following statement has been added under the heading "Description:"

Reviewers' comments:

Clinical Pharmacology

4. In the August 17, 2005 facsimile, the sponsor was advised to either omit MDR (multidrug resistant) after Enterococcus faecalis or more fully define MDR in the legend by listing the specific antibiotic resistances of this strain. This aspect of the TPI was not revised.

Reviewer's comment:

Dr. Rogers, in her review dated July 20, 2006, recommends only that they define antibiotic resistances for the organism. Given that there is no reason to change our previous recommendation, the sponsor should be reminded of FDA's previous comments on this aspect of the TPI.

Clinical studies

5. In the August 17, 2006, facsimile, FDA advised the sponsor to remove the section that discusses the results of the pivotal studies. In the current submission the sponsor disagrees and has included a discussion of the three pivotal clinical trials in the draft TPI..

Reviewers' comments:

In order for the discussion of the pivotal trials to remain in the TPI a number of revisions should be required. Dr. Rogers has recommended that a statement be added to the beginning of the discussion of the clinical studies denoting the unknown clinical significance of the surrogate testing results. However, her review does not provide any suggested wording for the statement. Given the extensive discussion centering on the lack of a correlation between the results of clinical simulation studies and hospital infection rates at the March 23, 2005 NDAC meeting a statement should be added to this section.

In her evaluation of the discussion of the studies, Dr. Rogers also noted that the specific effectiveness criteria in the TFM are not included in the discussion of the clinical studies. This is misleading because in two of the three studies presented both DuraPrep and the active comparator fail to attain the required 3-log$_{10}$ reduction in resident bacteria in the groin. Dr. Rogers recommended the following statement be added to this section:

However, this statement should be modified to state:

> ***"FDA currently requires that patient preoperative skin preparations meet the following effectiveness criteria: a 2-log reduction on the abdomen in 10 minutes, a 3-log reduction on the groin in 10 minutes, and counts not exceeding baseline values at 6 hours post-application. A correlation between these effectiveness criteria and clinical outcomes has not been established."***

Dr. Schiffenbauer has commented that the presentation of the results of the active comparator in each study implies that the studies were designed to compare products, rather than to assess the effectiveness of DuraPrep. The studies were not designed to provide robust comparative data.

Dr. Rogers has recommended that the results of the 2-minute assessments be removed from the text discussion and figures representing the results of Study 2 Study 3. This

recommendation is based on the fact that this measurement is not available for all treatment groups, i.e., this information is available only for the groin. However, an argument can be made to allow the sponsor to include this information in the figures because the groin is considered the most stringent test of a patient preoperative skin preparation, and the results are consistent between the two studies. Therefore, the inclusion of the 2-minute log reductions should be allowed.

6. [redacted]

Reviewer's comment:

[redacted]

14. [redacted]

Reviewer's comment:

[redacted]

Safety Studies

Dermal irritation study

15. In the current submission the sponsor indicates that it is unclear to them what FDA's revisions to the discussion of the results of the 21-Day Cumulative Irritation Potential

Test. In response to FDA's comments the sponsor removed the results of test when the product was patched wet.

***Reviewer's comment*:**

Dr. Osborne noted the removal and recommends that the sponsor revise the summary to include the result when the product is patched wet as follows:

> In a 21-Day Human Cumulative Irritation Potential Test involving 32 subjects, DuraPrep solution's Base 10 cumulative Irritation Score when patched wet under occlusive conditions (the standard procedure for testing of this type) was 453.7 (Class 4: experiment cumulative irritant). When DuraPrep solution was allowed to dry on the skin prior to patch application, reflecting intended use, the Base 10 cumulative irritation score was 307.7 (Class 3: possibly mild in normal use).

Indications and Usage, Contraindications, and Warnings

16. These sections contain information that is consistent with the sponsor's draft **Drug Facts**.

***Reviewer's comment*:**

The labeling in these sections needs to be updated to be consistent with FDA's comments on the draft Drug Facts.

Postmarketing Complaints:

17. In previous version of the TPI the sponsor included a table of the clinical complaints for DuraPrep that is the same as the one in the currently proposed TPI. FDA did not comment on the table.

***Reviewers' comment*:**

Dr. Osborne has proposed a revision to the first paragraph under this heading to clarify that the flammability reports except one were associated with the 26-mL applicator. He recommends the following revision to the last sentence of the paragraph:

> Flammability incidents were the third most prevalent complaint [redacted] Based on sales per million per year, the annual incidence rate [redacted] has been < 2.0 since 1993.

Dr. Schiffenbauer also recommends that the information contained in the box at the bottom of the Table 4 be separated from the table so that the information is more clearly presented. He further recommends that this information be placed below the table in a regular font and size to increase its prominence.

How Supplied

18. The sponsor revised the statement "As a 26 mL filled glass ampule in a sponge applicator (covers an area of approximately 12"x36") and as a 6 mL filled glass ampule in a sponge applicator (covers an area of approximately 8"x10" area)." to read as follows:

    DuraPrep Surgical Solution 8630 applicator contains 0.9 fl.oz. (26 ml) of solution which covers an approximate area from shoulder to groin, 15"x30".

    For procedures requiring less coverage (i.e., neck, foot, hand), a smaller applicator is available. DuraPrep Surgical Solution 8635 application contains 0.2 fl.oz. (6 ml) of solution which covers an approximate 8"x10" area.

    Reviewer's comments:
    Per Dr. Jackson's review the sponsor will need to revise the coverage area stated for the 26-mL and 6-mL size applicators to be consistent with FDA's comments on this in Drug Facts. The sponsor will also need to include the storage temperature.

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/s/
Debbie Lumpkins
9/18/2006 06:20:36 PM
INTERDISCIPLINARY

Joel Schiffenbauer
9/19/2006 07:42:06 AM
MEDICAL OFFICER
I concur except under number 5, I recommend that

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 15, 2006

To: Dianne Gibb	**From:** Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: 3M	Division of Nonprescription Regulatory Evaluation
Fax number: 651-737-5320	**Fax number:** (301) 796-9899
Phone number: 651-737-9117	**Phone number:** (301) 796-0994

Subject: Labeling Comments

Total no. of pages including cover: 12

Document to be mailed: ☐ YES ☑ NO

Please refer to your March 28, 2006 resubmission to your new drug application for DuraPrep™ Surgical (iodine povacrylex (0.7% available iodine) and 74% w/w isopropyl alcohol) Solution.

Below are label changes requested by the reviewer. Please submit draft labeling for the 6-mL and 26-mL products with the following changes as an amendment to your NDA as soon as possible so that the reviewer can complete the review. If you have any questions you may call Laura Shay, regulatory project manager, at (301) 796-0994.

Principal Display Panel (PDP)

1. Revise the labeling to meet the requirements of 21 CFR 201.61. [redacted] The statement of identity that consists of the established name of the drug followed by the statement of general pharmacological category of the drug must be directly under the most prominent display of the tradename. The [redacted] statements may be placed directly after the general pharmacological category of the drug. Increase the prominence of theses statements by bolding and enlarging the font size. (See below and PDP prototype attached.)

DuraPrep Surgical Solution
Iodine Povacrylex (0.7% Available Iodine) and Isopropyl Alcohol (74% w/w)
Patient Preoperative Skin Preparation
for large prep areas below the neck

2. The term "flammable vapors" still appears in a light orange color. The contrast of the light orange print against the white background is poor. This makes the words harder to read and does not give them sufficient prominence. Revise the font used for the term "flammable vapors" in the warnings box on the PDP and immediate container handle so that it appears in bold-face type and in red print in order to increase its prominence.

3. FDA has revaluated its previous requirements for the labeling of this product and has concluded that additional information is needed to help users manage the product's flammability risk. Revise the boxed warnings found on the PDP and the applicator barrels as follows:

   a) Incorporate the following statement on the 26-mL applicator PDP, "Do not use on an area smaller than 8 in. x 10 in." as the second bulleted statement followed by the statement " [redacted]

   b) Revise the statement "[redacted] to read "Solution contains alcohol and gives off flammable vapor".

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

d) Include the bulleted statement "Avoid getting solution into hairy areas. Solution may take much longer to dry or may not dry completely." to come after the bulleted statement "Do not drape or use ignition source (e.g., cautery, laser) until solution is completely dry".

e) Revise the statement "Remove solution-[redacted]material from prep area" to read [redacted]

Thus, the boxed warnings for the 26-mL applicator should be revised as follows:

[redacted]

Keep away from fire or flame.
To reduce the risk of fire:

- Do not use 26-mL applicator for head and neck surgery
- [redacted]
- Solution contains alcohol and gives off **flammable vapors**
- Do not drape or use ignition source (e.g. cautery, laser) until solution is completely dry
- [redacted]
- Do not allow solution to pool
- [redacted]

The boxed warnings for the 6-mL applicator should be revised as follows:

[redacted]

Keep away from fire or flame.
To reduce the risk of 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
- [redacted]
- Do not allow solution to pool
- [redacted]

4. Revise the coverage area on the PDP of the 26-mL applicator from inches to feet.

5. Revise the statement "For procedures requiring less coverage [redacted] a smaller applicator is available (8635). It contains 0.2 fl oz (6mL) of solution which covers an approximate 8"x10" area" on the 26-mL PDP to:

   - [redacted]
   - Include the abbreviation for inches
   - Add the statement "Do not use more than required for the area"

   The revised statement should read as follows:

   - "For procedures requiring less coverage, a smaller applicator is available (8635). It contains 0.2 fl oz (6mL) of solution which covers an approximate 8 in. x 10 in. area."

6. Indicate the location of the expiration date as required by 21 CFR 201.17.

7. Indicate the location of the lot number information on the labeling as required by 21 CFR 201.18.

Drug Facts

8. The use of pictograms to improve the visibility and prominence of information relevant to the risk management of the product is acceptable. [redacted]

9. Provide ***Drug Facts*** specifications for the revised 26-mL and 6-mL size applicator labels.

10. Italicize and bold type all of the headers (***Drug Facts, Active ingredients, Purpose, Uses, Warnings, Directions, Other information, Inactive ingredients, Questions?***) as described in 21 CFR 201.66(d)(3) for the 26-mL size applicator. (See ***Drug Facts*** prototype attached.)

11. 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).

12. Revise the first letter of the second word in the active ingredients to be lower case.

13. Place a comma after the word alcohol, under ***Active ingredients***.

14. Change the contrasting term "flammable vapors" to red print and bold the phrase to increase its size and prominence.

15. Revise the bulleted statements under ***Warnings*** for the 26-mL and 6-mL applicator to appear the same as the warnings described for the PDP warnings. (See ***Drug Facts*** prototype attached.)

16. Additional labeling is needed to address the potential for iodine toxicity and the possibility of hypothyroidism in children. Add the following warning as the second bullet under the **Do not use** subheader:

17. Revise the bulleted statement "on infants less than 2 months of age due to risk of ' to read under the **Do not use** subheader.

18. Revise the directions for use to be consistent with the revised warnings as follows:

    - Revise the fifth bulleted statement under the subheader "When applying solution" by adding "Solution may take much longer to dry or may not dry completely."

    - Revise the statement " to read ' under the subheaders "While waiting for solution to completely dry" and "After solution is completely dry." (See ***Drug Facts*** prototype attached.)

19. Remove the period at the first bulleted statement, under the subheader about after solution is completely dry for the 26-mL size applicator. No periods should follow after each statement unless the bulleted statement contains more than one sentence.

Immediate Container Applicator Handle

20. Revise the bulleted statements in the warning box for the 26-mL and 6-mL applicator to appear the same as the warnings described for the PDP boxed warnings (See Immediate Container Applicator Handle prototype attached).

Targeted Product Information (TPI)

21. Revise the coverage area " " and ' " to read "1.25 ft. x 2.50 ft." and "8 in. x 10 in." for the 26-mL and 6-mL applicators on page 12. Also include the storage temperature.

22. Additional comments on the TPI to follow.

Canadian Labeling

23. FDA recommends that the sponsor consider incorporating the storage temperature to read [redacted] and the newly revised warnings on their Canadian labels.

6 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Laura Shay
9/15/2006 02:36:51 PM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21-586	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: DuraPrep™ Surgical Solution Established Name: (iodine povacrylex (0.7% available iodine) and 74% w/w isopropyl alcohol Dosage Form: Topical Solution		Applicant: 3M	
RPM: Laura Shay		Division: DNCE	Phone # 301-796-0994

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	August 27, 2004 September 29, 2006
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE August 27, 2004
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

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❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 4020400 (4S)

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☒ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Depty Div. Dir: Oct. 5, 2006 Deputy Div. Dir: Sept. 20, 2006 OND Dir: August 26, 2004 Office Dir: August 26, 2004 Office Dir: August 25, 2004 Div. Dir: August 23, 2004 Div. Dir: August 5, 2004
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	NA
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	9/28/06
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS June 17, 2004 and July 9, 2004 ☐ DSRCS ☐ DDMAC ☐ SEALD ☐ Other reviews OTC label Review: 9/26/06, September 13, 2006 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	January 9, 2004
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	AP letter
• Incoming submission documenting commitment	September 25, 2006
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	11/26/03, 1/9/04, 9/22/06, 9/22/06, 9/19/06, 9/19/06, 9/19/06, 9/15/06, 8/19/04, 5/16/06, 8/4/04, 7/20/04, 3/15/04, 2/5/04
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	4/26/04
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	8/4/04; 8/24/04
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☒ No
❖ Environmental Assessment (check one) (original and supplemental applications)	

• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC Review 8/4/04
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: DMF summary 8/23/04 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4/1/04
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	7/31/06; 8/5/04; 7/21/04
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	8/3/04
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None Peds 7/21/06
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☐ Not needed 7/20/06; 8/5/06
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	7/20/06 MO review; 7/9/04
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	7/9/04 Office of Drug Saftey Consult
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	10/2/06; 9/29/06
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 8/3/04; 7/28/06
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/6/04

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS
Attention: Yoo Jung Chang

FROM: Laura Shay, PM
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 10, 2006		21-586	New NDA-resubmission	March 29, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
DuraPrep (iodine povacrylex 0.7% and isopropyl alcohol 74%)			August 10, 2006

NAME OF FIRM: 3M

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ 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
- X CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- X REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- X SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

X CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

DuraPrep (iodine povacrylex 0.7% and isopropyl alcohol 74%), has been on the market for many years not under an NDA. It is currently under review for approval under NDA 21-586 for a patient preoperative skin preparation. There have been reports of flammable incidents to patients in the operating room when this product has been used causing significant burns. ODS conducted a safety review of DuraPrep in 2003 and 2004. A low incidence of fires associated with DuraPrep was found. The company reported in their NDA submission 80 fires related to their product and are proposing to enhance the warning on the label to address this safety issue. We are concerned that the combination of iodine povacrylex and isopropyl alcohol in the DuraPrep product may cause a greater problem associated with flammability as compared to other similar pre-operative antiseptic products on the market that also contain high concentrations of alcohol. These products are ChloraPrep (NDA 20-832, NDA 21-555) and ChloraScrub (NDA 21-524). Both contain Chlorhexadine gluconate with 70% isopropyl alcohol. We request a review of the Adverse Events for all of these products (DuraPrep, ChloraPrep, and ChloraSrub) looking specifically for the incidence of flammability and patient burns in order to determine approvability and/or appropriate labeling.

SIGNATURE OF REQUESTER Susan Johnson, PhD Acting Deputy Director, Office of Nonprescription Products	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Susan Johnson
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NDA 21-586

06/20/06
Page 1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 20, 2006

To: Dianne Gibb	**From:** Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: 3M	Division of Nonprescription Regulatory Evaluation
Fax number: 651-737-5320	**Fax number:** (301) 796-9899
Phone number: 651-737-9117	**Phone number:** (301) 796-0994

Subject: Request for information

Total no. of pages including cover: 2

Document to be mailed: ☐ YES ☑ NO

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In order to ensure a timely action for this new drug application, we request that you respond to the issue listed below as soon as possible. If you have any questions, contact Laura Shay, Regulatory Project Manager at (301) 796-0994.

Provide the neutralizer validation for the following two studies: No. 12MS 05-010214 (pivotal) and No. 12MS 05-010346 (pilot).

Provide the neutralization plate counts for each sample, average CFU/mL, and log10 CFU/mL, as well as the average log10 CFU/mL and log10 difference for each study.

Provide the data in a table format similar to what you submitted for study LIMS 8918

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/s/

Laura Shay
6/20/2006 12:28:34 PM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Lisa Mathis, MD, Division Director
Pediatric & Maternal Health Team
Office of New Drugs

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Laura Shay, Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonpresciption Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/22/06		21-586	New NDA	03/29/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
DuraPrep			07/15/06

NAME OF FIRM: 3M

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 2a MEETING
- ☐ END-OF-PHASE 2 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

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 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
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DuraPrep Surgical solution is iodine polacrylex (0.7% available iodine) and isopropyl alcohol (74%w/w). 3M has submitted a response to an approvable letter (sent August 27, 2004) for this product. In their original NDA submission (October 27, 2003) 3M requested a full pediatric waiver. We did not formally respond to their request during the first review cycle. In a meeting held between FDA and 3M prior to their NDA submission (July 8, 2001), we stated "if 3M agreed to inclusion of contraindication for use in children less than 2 months of age, then as study in pediatrics would not be required." The division feels that we can extraploate the efficacy data in adults to the pediatric population, however we have questions regarding the safety of this product and the age cut off that was stated in the july 2001 meeting. Although below 2 months of age is the standard cut off for other healthcare antisptic products, we want to be sure this is the appropriate cut off since this is an iodine-containing product. In addition, we would like to know if there is any additional labeling that your team would consider to be appropriate to address the potential for iodine toxicity and the possibility of hypothroidism in children.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Andrea Segal
5/25/2006 12:07:37 PM

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DSI CONSULT: Request for Clinical Inspections

Date: May 16, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: Laura Shay, Regulatory Project Manager, HFD-560
Division of Nonprescription Clinical Evaluation

Subject: **Request for Clinical Site Inspections**
NDA 21-586
Sponsor: 3M Health Care
DuraPrep™ Surgical (iodine povacrylex (0.7% available iodine) and 74% w/w isopropyl alcohol) 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.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Sponsor: 3M Health Care Medical Division 3M Center, Bldg. 270-4N-01 St. Paul, MN 55144-1000 **Study Monitor:** Julie Stahl 3M Health Care Medical Division 3M Center, Bldg. 270-4N-01 St. Paul, MN 55144-1000 **Data Management, Biostatistics, and Report Preparation:** [redacted] **Clinical Supply Packaging:** 3M Pharmaceuticals Division Clinical Support Group 3M Center, Bldg. 260-4N-12 St Paul, MN 55144-1000 **Statistician:** [redacted]	12MS 10214	66 62 (completers)	Patient Preoperative Skin Preparation

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) August 29, 2006. We intend to issue an action letter on this application by (division action goal date) September 29, 2006. The PDUFA due date for this application is September 29, 2006.

Should you require any additional information, please contact Laura Shay at 301-796-0994.

NAME, Division Director (for foreign inspection requests only)

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/s/

Laura Shay
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-586

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

Dear Ms Danielson:

We acknowledge receipt on March 29, 2006 of your March 28, 2006 resubmission to your new drug application for DuraPrep™ Surgical (iodine povacrylex (0.7% available iodine) and 74% w/w isopropyl alcohol) Solution.

We consider this a complete, class 2 response to our August 27, 2004 action letter. Therefore, the user fee goal date is September 29, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 796-0994.

Sincerely yours,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-586

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

Dear Ms. Danielson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duraprep (iodine povacrylex and isopropyl alcohol solution).

We also refer to the meeting between representatives of your firm and the FDA on January 10, 2005. The purpose of the meeting was to discuss NDA deficiencies described in our August 27, 2004, approvable (AE) letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

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FDA MEETING MINUTES

NDA 21-586
End of Review Conference

Meeting Date: January 10, 2005
Between: the Office of New Drugs, Center for Drug Evaluation and Research
And
3M Health Care

Attendees:

Center for Drug Evaluation and Research Attendees

Dr. John Jenkins	Director, Office of New Drugs (OND)
Dr. Ed Cox	Deputy Director, Office of Drug Evaluation IV (ODE IV)
Mr. David Roeder	Associate Director for Regulatory Affairs, ODE IV
Dr. Jonca Bull	Director, Office of Drug Evaluation V (ODE V)
Mr. David Hilfiker	Acting Associate Director for Regulatory Affairs, ODE V; Chief, Project Management Staff, Division of Over The Counter Drug Products (DOTCDP)
Dr. Janice Soreth	Director, Division of Anti-Infective Drug Products (DAIDP)
Dr. Charles Ganley	Director, DOTCDP
Dr. Susan Johnson	Associate Director, DOTCDP
Ms. Tia Frazier	Project Manager, DOTCDP
Dr. Jean Mulinde	Clinical Team Leader, DAIDP
Dr. Peter Coderre	Clinical Microbiology, DAIDP
Dr. Thamban Valappil	Biostatistician, DAIDP
Ms. Maureen Dillon-Parker	Chief, Project Management Staff, DAIDP
Dr. Robert Temple	Director, Office of Medical Policy
Mr. Robert Heller	Office of Compliance
Mr. Warren Rumble	Office of the Ombudsman

3M Attendees

Ms. Sue Danielson	Director of Regulatory Affairs and Quality
Ms. Dianne Gibbs	Regulatory Affairs Manager
Dr. Karen Riddles	Clinical Lead
Mr. Eugene Pfeifer	King & Spaulding LLP

Background

Duraprep (povidone/iodine polymer and isopropyl alcohol) was first marketed as a presurgical preparative solution in 1988 without an NDA with the support of an existing Tentative Final Monograph (TFM) for Topical Antimicrobial Drug Products (43 FR 1210; January 6, 1978). In 1994, representatives of 3M Health Care (3M) met with the FDA and were informed that FDA considered Duraprep to be a new drug that did not meet the conditions of the TFM. Following that meeting, the CDER Office of Compliance issued a warning letter to 3M informing them that Duraprep is considered a new drug being marketed without an approved NDA and is considered misbranded. The decision of the CDER director was to allow 3M a finite period of time to develop an NDA while continuing to market the product. 3M met with FDA for a pre-IND discussion in October 1995 and filed IND 49,411 in December 1995. An End of Phase 2 meeting was held in October 2000 and a pre-NDA meeting in August 2003. 3M filed NDA 21-586 on October 24, 2003. Following the review, FDA issued an approvable (AE) letter to 3M on August 27, 2004. 3M submitted a meeting request on October 18, 2004, to discuss the deficiencies.

Meeting Discussion

FDA began the meeting with clarification that the meeting is considered an "End of Review" conference [per 21 CFR 314.102(d)] and not a means for dispute resolution. FDA intended to clarify the basis for the approvable (AE) action and provide advice for future steps for this NDA. The sponsor was advised that they may choose to submit a formal dispute resolution request, which would be referred to the Office of the Center Director for resolution, or they may resubmit the application with new data or analyses to address the stated deficiencies.

3M provided information on the clinical attributes of the product, the regulatory history of the product, and their two major concerns with the AE action (see attached slides). The two areas of concern were the regulatory procedures leading to the AE action and the validity of the current effectiveness standards (two $\log_{10}$ microbial reduction on the abdomen; three $\log_{10}$ reduction on the groin) and totality of data submitted in the application to support approval.

1. Regulatory Procedures

In the October 18 submission, 3M noted conversations with DAIDP just prior to the NDA action that informed them of the concerns raised by DOTCDP in supporting effectiveness and the decisional responsibility shifting to the Office of New Drugs. 3M disputed DOTCDP's authority in matters of clinical effectiveness as a matter of regulatory policy.

FDA referred to the current Manual of Policies and Procedures for the review of new OTC drugs (MaPP 6020.5). According to this MaPP, all new OTC NDAs are jointly reviewed by the DOTCDP and any other review division in OND that regulate similar prescription products. Under this review procedure, DOTCDP and DAIDP shared the review of this NDA and must agree on the ultimate decision. Since DOTCDP and DAIDP could not reach agreement on the decision, the respective Offices overseeing these divisions (ODE IV and ODE V) assumed the responsibility for the decision. Since ODE IV and ODE V could not reach agreement on the ultimate decision, the Director of OND assumed responsibility for the final decision. This procedure has been in place and has been used consistently for all decisions on NDAs for OTC drugs, and validates the role of DOTCDP in this decision.

2. Current effectiveness standards and substantial evidence for approval

3M raised the following concerns with the methods used to develop the current 2-$\log_{10}$ (abdomen)/3-$\log_{10}$ (groin) standards for these products.

- The original methods were developed in the late 1970's during the FDA review of an NDA for Hibiclens (chlorhexidine gluconate) and the FDA development of a Tentative Final Monograph for OTC Topical Antimicrobial Products (43 FR 1210; January 6, 1978). The methods used at this time did not include neutralization[1] of the sample, and this lack of neutralization led to a higher kill rate for products such as Hibiclens. FDA adopted these standards using the old method.
- FDA published revised testing recommendations in a 1994 Tentative Final Monograph (59 FR 31402; June 17, 1994). At this time, conventional methods had evolved to include neutralization as part of the standard procedure. The timing of neutralization can effect the log reduction. When neutralizer is added at the time of sample collection, reduction of bacterial counts is generally less pronounced then when neutralization is delayed. Although the timing of neutralization was variable, there was a mean decrease in efficacy results because of neutralization.
- Hibiclens routinely fails to meet the effectiveness criteria that it was originally approved on because the 2-$\log_{10}$/3-$\log_{10}$ standards were based on outdated methods that did not include neutralization.

[1] A neutralizing agent is added to the sampling medium to stop the antimicrobial activity of the test agent.

and that further demonstration of the role of the two active ingredients in the effectiveness of Duraprep were not required for approval.

3M wanted assurance that the NDA would be approved if, in the additional study, Duraprep met the 3-$\log_{10}$ reduction in the groin but the active control did not meet the 3-$\log_{10}$ reduction in the groin. FDA was not able to provide such assurance in advance of review of the resubmitted application; however, FDA noted that the primary goal of the study was to demonstrate the appropriate log reduction in bacteria for Duraprep. Should the data from the study show the expected log reduction for Duraprep and not the active control, the FDA will carefully review the data to understand whether the failure of the active control to meet the expected log reduction adversely impacts on a conclusion that Duraprep is effective. The review will include the methodology used in the study, an audit of the conduct of the study, and an assessment of the variability observed in the study results.

FDA recommended that 3M submit their protocol well in advance of initiating the study to ensure that FDA can provide feedback on the appropriateness of the study design.

Conclusions

FDA reiterated their conclusions as stated in the AE letter that Duraprep failed to meet the predetermined primary endpoint in each of the two pivotal trials, and failed to provide other information that would constitute substantial evidence of effectiveness for approval.

Recommendations

FDA recommended that 3M consider one of three options to proceed:

- Conduct the study outlined in the AE letter and further discussed today.
- Explore ways to demonstrate the clinical benefits of Duraprep, rather than continuing to rely on a surrogate marker for effectiveness.
- Pursue formal dispute resolution by contacting Kim Colangelo in the Office of New Drugs.

FDA reminded 3M that Duraprep has been marketed for 16 years without a conclusive demonstration of effectiveness and urged them to proceed expeditiously with further studies to resolve this matter.

Attachments

3M Slides

16 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

John Jenkins
2/2/05 02:33:26 PM

Appears This Way
On Original

MEMORANDUM OF TELECONFERENCE

DATE: August 19, 2004

Time: 09:20AM-09:50AM

APPLICATION NUMBER: NDA 21-586, DuraPrep™ Surgical Solution

BETWEEN:

Name: Dianne Gibbs, RAC, Regulatory Affairs Specialist
John Dell, Ph.D., Senior Research Specialist
Phone: 651-737-9117
Representing: 3M

AND

Name: Tia Frazier, R.N., M.S., Project Manager
David Lin, Ph.D., Acting Division Director, Division of New Drug Chemistry III
James Vidra, Ph.D., Chemistry Team Leader (attended by teleconference)
Milton Sloan, Ph.D., Chemistry Reviewer
Terri Rumble, R.N., Associate Director of Regulatory Affairs, ODE V
Center for Drug Evaluation and Research

SUBJECT: Selecting an established name for DuraPrep™ Surgical Solution

3M informed FDA that they had consulted the FDA regulations found at 21 CFR 299.4, and viewed the U.S. Adopted Names Council (USAN) website for initial direction prior to this meeting. 3M informed FDA that they found the USAN guidance more directed at new chemical entities, rather than for products like this particular iodine copolymers.

FDA informed 3M that the terms "iodine" and "copolymer" do not refer to any specific chemical entities. Further, FDA reiterated its position that "iodophor" is not an acceptable established name for this product for the same reason stated above.

- FDA clarified that it was for these reasons that the Office of New Drug Chemistry decided that the two nonproprietary names (iodophor copolymer and povidone-iodine copolymer) proposed by 3M on 8/12/04 were unsuitable.

- FDA reiterated its advice to submit an application for a nonproprietary name to the USAN prior to August 27, 2004. We proposed that 3M formally commit to contacting USAN by August 27, 2004, and to adopting the established name that USAN recommends.

3M voiced concern about the length of time required for a USAN review and recommendation.

3M voiced concern that they would not be able to obtain a CAS (chemical abstract service) number which they report is required in order to obtain a nonproprietary name from USAN.

3M inquired why the chemical "povidone acrylate copolymer" was considered by FDA to be an inactive ingredient, and is thus required to be listed in under ***Inactive ingredients*** in ***Drug Facts***. 3M also asked FDA whether " _____ could be referenced as an active ingredient in the labeling, and yet also appear under ***Inactive ingredients*** in ***Drug Facts***.

- FDA committed to discussing these questions internally, and providing feedback on the issue after this meeting.

FDA requested that 3M submit alternate nonproprietary names to FDA and to USAN as soon as possible.

3M voiced their plans to submit additional suggestions for nonproprietary names to FDA by the close of this business day. 3M submitted three additional proposed established names to the FDA on April 19, 2004, via facsimile.

FDA committed to work with 3M to try to review and agree on an acceptable established name for use before USAN's recommendation is available.

_____
Tia Frazier, R.N., M.S.
Regulatory Project Manager
Division of Over-the-Counter Drug Products

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

/s/

Tia Frazier
8/26/04 04:35:26 PM
CSO

On Original

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 17, 2004

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

Subject: Microbiology and Labeling Comments Fax

Total no. of pages including cover:

Comments: Please see attached.

Document to be mailed: ☐ YES ☑ NO

DuraPrep 8630 Solution – 26 ml applicator insert [Principle Display Panel (PDP)] (ATTACHMENT 2)		
Label Change	**Justification/Discussion**	**FDA COMMENTS**
1. The international symbols for EO sterilization, latex-free, do not reuse and Warning, will continue to be incorporated. Symbols have been bolded and enlarged.	Per 8/5 Agency agreement.	• This is acceptable.
2. Generic product descriptor changed per FDA comment.	Established name for [redacted] to be determined by FDA	FDA is still in the process of considering the established names you proposed on 8/12. We will provide guidance on this issue in the near future.
3. Boxed Warning has been revised to: • Incorporate "FLAMMABLE" as a separate header • Delete first bullet, [redacted] • Incorporate as the first bullet the statement "Do not use 26-ml applicator…" (Exact wording of this statement to be determined based on panel considerations.)	Per 8/5 Agency agreement, the statements "For external use [redacted] and "[redacted] have been removed from the Warning Box. Although not addressed in the 8/5 telecon discussion, upon review of the revised labeling mock-ups, 3M realized the negative impact of removing as the first bullet in the Warnings Box (on both the product insert and applicator handle label) "[redacted]. The effectiveness of the remaining warning statements is greatly reduced by not fully explaining why the remaining warnings are important in preventing flammability related events. Therefore, it is 3M's opinion that incorporating the concept, "Do not use 26-ml applicator…" into the product description (see ATTACHMENTS 12-15) provides a better alternative to incorporation into	• We agree with you that the most important issues concerning flammability should be included in the Warnings. However, it is unnecessarily confusing to present different warnings in different sections of the product labeling. The inclusion of the statement about the 26 mL applicator is critical because 46% of the reported burn incidents involved use of the 26 mL applicator at the head/neck, and 10 of 14 third degree burns were at the head/neck. • The statement concerning flammability is mandated by regulation (Refer to 21CFR 201(c)(5)(ii)(c) for clarification.) • Therefore, the warnings at all places in all product labeling for the 26-mL size should read as follows: --- **WARNING**

	the Warning section of the labeling, as it allows the existing warning statements on both the product insert and applicator label to remain unchanged. Per 8/5 telecon discussion • It is 3M's position, that to maintain label effectiveness, the front panel Warning box include only the most important pieces of information with respect to flammability, and to direct the user to follow Drug Facts and Warnings on applicator (see bullet 2 of Warning box). Complete product Warnings as suggested in the Agency's July 20 comments are reflected in the Drug Facts box, but not repeated on the applicator insert. • It is 3M's position that the phrase, "keep away from fire or flame" is inappropriate to highlight in the Warning Box. Fire and/or flame is not present in the operating room environment, and misdirects the clinician as to the potential fire source. Additionally, it is not DuraPrep solution that should be kept away from fire or flame, but rather sources of heat (i.e., electrocautery, laser) that should be kept away from DuraPrep solution until solution is dry.	**FLAMMABLE** **Keep away from fire or flame. To fire:** Do not use 26-mL applicator for head and neck surgery. 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-soaked material from prep area. --- The 6-mL warning should be identical with the exception of the omission of the statement concerning the 26-mL applicator. We will allow you to use pictograms in the Warnings section of the PDPs for the 26-mL and 6-mL package sizes. • The term "flammable vapors" appears in a light orange color and does not give sufficient prominence to this warning. Revise the font used for the term "flammable vapors" in the warnings box on the PDP and immediate container handle so that it appears in bold-face type and in a red-colored print in order to increase its prominence.

Label Change	Justification/Discussion	FDA COMMENTS
4. The statement "DuraPrep Surgical Solution is a film-forming iodophor complex" has been expanded upon to add, " [redacted]	Based on LIMS 8198 and SRFE 1246, DuraPrep solution is a film former that resists removal by a blood/saline challenge. This is a key product differentiator from aqueous Iodophor paint/scrub products and requires inclusion in the product description statement.	• [redacted]
5. The coverage area was changed from ".. [redacted] to read, " [redacted]	In the Agency's 7/20/04 comments, a coverage area of 12" x 36" was recommended. However, since a descriptive body area provides a more meaningful and well understood coverage area to the clinician, this area is being represented as "shoulder to groin". Note that the word [redacted] was replaced with shoulder to coincide with the Warning not to use the 26-ml applicator on head and neck procedures.	• The coverage area may be modified to read, "Each unit dose applicator contains 0.9 fl oz (26 mL) [redacted] area (approximately from shoulder to groin in an average size adult)." This is necessary because specific patient body areas differ significantly by weight and height.
6. The statement " [redacted] Has been deleted. The 3M password is incorporated in its' place.	Based on DMETS August 4, 2004 fax communication of recommendations, the inservice video is being made available on the 3M website without a required password for access.	• No comment.

DuraPrep 8630 Solution – 26 ml *Drug Facts* (ATTACHMENT 3)		
Label Change	**Justification/Discussion**	**FDA COMMENTS**
7. Active ingredient name for Iodophor TBD.	Established name for [redacted] to be determined by FDA	Issue still under discussion at FDA.
8. *Uses* section has been revised to include "patient preoperative skin preparation in bold.	Per FDA 7/20 comment	• Include a colon after the statement patient preoperative skin preparation.
9. ***Warnings*** have been revised as follows: • The term [redacted]" has been replaced with "solution"; per FDA comment. (NOTE: - This change has been made throughout the labeling.) • All ranges of [redacted] have been revised to 3 minutes. (NOTE: - This change has been made throughout the labeling.) • The Warning, "Do not use the 26 ml applicator for head and neck..." has been added as the first bullet, per Agency comment. • To coincide with the warning not to use this product for head and neck procedures, the statement, [redacted] has been deleted from the 4th bulleted warning	Per 8/5 Agency agreement, the statement "[redacted], DO NOT SCRUB" has not been incorporated into the Warning section. Per the FDA 7/20 comments, the Agency recommended that the statement, "Solution contains alcohol and gives off flammable vapors [redacted] be moved down in the Warning section as the second bullet. It is 3M's position that since this statement expands and more fully clarifies the bolded "Flammable, keep away from fire or flame" statement, that it remain as the second sentence of the bolded flammability warning. Further, 3M believes that the statement [redacted] is also an important part of this flammability warning. This sentence has not been deleted, and remains as originally worded, as the third sentence of the bolded flammability warning. The opening statement [redacted], remains as originally worded, as opposed to incorporating the word "help" (i.e., [redacted]), since it is the intent of these warnings and instructions to prevent the occurrence of flammability-related events.	• 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: (Also, refer to attached ***Drug Facts*** prototype.) • Revise the external use warning statement "[redacted] 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 should be located just below the heading ***Warnings***.

	statement, and revised to read, "Tuck prep towels as needed [redacted] Remove towels before draping." • The last bullet. [redacted] has been deleted per the Agency's 7/20 comments.	Per 8/5 telecon discussion, it is 3M's position that to maintain label effectiveness and value to the user, that warnings specific to instances of product misuse that have led to flammability-related events, as documented in our 15-year complaint database, be included in the Warning section. Therefore, the Warnings, "[redacted] followed by the three-bullet point examples have not been deleted, and remain as originally worded. Per the FDA 7/20 comments, the Agency recommended that the statement to avoid getting product into hair be removed from the Warning statement, and only included in the Directions for Use. It is 3M's position however that this is an important piece of information with respect to the safe use of DuraPrep solution, and should remain in the Warning section. This statement has been revised, and is reworded per the Agency's 7/20 comments.	• Relocate and remove the bolding from the statement "solution contains alcohol and gives off flammable vapors [redacted], and place it under the warnings **For external use only and Flammable: keep away from fire or flame** so that it becomes the second bulleted statement. (Refer to 21CFR 201(c)(5)(ii)(c) for clarification.) • Change the contrasting term "flammable vapors" to be a single dark print and bold the term to increase its size and prominence. (See 21 CFR 201.66(d)(3).) • Revise the statement [redacted] to read [redacted] or **"To reduce the risk of fire:"**. • Remove the following statements: FDA finds these statements redundant, and does not consider them to be warnings.. We also note that they are repeated under ***Directions***.

		• The statement "• [redacted] is described under the ***Directions***. Revise this bulleted statement to read "• remove solution-[redacted] materials from prep area." as the fifth bulleted statement under the ***Warnings***.
10. The **Do Not Use** section has been revised per the Agency's 7/20 comments with the exception that 3M has deleted "...and excessive skin irritation." from the end of the second bullet point statement.	3M is unaware of any data to suggest that excessive skin irritation has been associated with the use of DuraPrep solution on infants less than 2 months of age.	• This statement should not be revised. The recommendation is based on the submitted irritancy study, which establishes that DuraPrep is 3-4 times more irritating than the positive control (SLS) when tested by standard methodology. This statement is standard labeling for products with this irritation potential. • No periods should follow after each statement unless the bulleted statement contains more than one sentence.
11. The **When using the product** section has been revised per the Agency's 7/20 comments with the exception that the word. '[redacted] has been replaced with "flush" (i.e., "flush with cold water..."). Also, a fourth sentence has been added to this sentence that reads, [redacted]	3M believes that the term "flush" is more appropriate and better describes the action required should DuraPrep solution gets into the eyes. [redacted]	• Remove the tradename "DuraPrep" 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.
12. The **Stop use and ask a doctor if...** section of the labeling has been reworded per the Agency's 7/20 comments, except that per our	Based on the 15-year complaint database, 3M has received 19 complaints of skin blistering on 33 patients (several complaints reported blistering on more than one patient), out of [redacted] units of	•Revise the statement '[redacted]...." to read "On rare occasions, ..."

8/5 telecon discussion, the rate description for skin blistering has been revised to describe this type of occurrence as rare, as opposed to occasional.	DuraPrep solution sold through Dec 31, 2003. This supports the fact that skin blistering is a rare occurrence.	
13. ***Directions*** section has been revised as follows: a. The phrase, "(follow all directions for use)" has been incorporated, per the Agency's 7/20 comments.	In the Agency's 7/20 comments, it was recommended that the following sentences be added as a bullet immediately after the ***Directions*** heading: "discard any portion of the solution which is not required to cover [redacted] area. It is not necessary to use the entire amount available." 3M has no information based on 15 years of product use that clinicians are under the assumption that all solution must be used in a surgical prep. Further, by including this statement as the first direction for use, it can mislead the clinician to think that they should somehow discard excess solution before they begin the prep, and to somehow estimate how much solution they will need before the prep begins. It is 3M's position that this statement adds no value to the clinician, and is misleading and therefore has not been incorporated into the revised labeling. For the clinician's ease in following product directions, 3M has retained numbering as opposed to the use of bullet points in the sections, **Activating the applicator** and **When applying solution.**	• Retain the recommended revisions, as communicated in our July 20, 2004, facsimile to you, in this labeling section. The statement is intended to minimize the possibility of overapplication of the product. Such overapplication is demonstrated by the reported flammability incidents. Since the clinician will now have additional information in the form of an estimated area of coverage, it might well be useful to estimate how much solution will be needed to cover the area to be prepped. It is not clear to us how this statement is misleading. Please provide alternative language for our consideration. • Revise the numbered statements under the subheaders **Activating the Applicator** and **When Applying Solution** to bulleted statements under the heading ***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.
14. The **Getting patient ready for solution:** section of the ***Directions***	The 3M wording for the direction for hair removal is based on the CDC guideline for preoperative	• Revise the statement "When hair removal is

has been revised per the Agency's 7/20 comments with the exception of wording for the direction regarding hair removal. Placement of this direction of use is per the Agency's 7/20 comments, but the Agency's suggested wording has not been adopted.	hair removal. This guideline includes two important points that are not included in the Agency's suggested wording including the fact that; 1) hair should only be removed when necessary , and 2) that the preferred method is to use a surgical clipper the morning of surgery. These important points were not reflected in the Agency's revised wording, and therefore this direction remains as worded in 3M's original draft labeling.	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 "when hair removal is necessary, use a surgical clipper on the morning of the surgery. If a wet shave is used, thoroughly remove all soap residues." This statement was revised to remove excess verbiage and focus on the most important message.
15. The **When applying solution** section of the ***Directions*** has been revised as follows: • To coincide with the warning not to use this product for head and neck procedures, the statement, [redacted] has been deleted from the 4th bulleted warning statement, and revised to read, "[redacted] Remove towels before draping." • 3M has incorporated the Agency's 7/20 suggested rewording of the bullet regarding "Do not scrub". However, the phrase, [redacted] prefaces the "Do not scrub" direction, to inform the clinician why this is important, and the potential outcome. The words "Do not scrub" are in bold font, but are not all in capital letters as	Per the Agency's 7/20 comments, the bullet point directions under the **When applying solution heading** were reordered. This reordering took each direction statement out of the correct sequence that a clinician would need to follow for safe and proper product usage. Therefore, the original order of these statements has been retained. It is 3M's position that the original wording for the direction on how to clean the umbilicus be retained. In the Agency's 7/20 labeling comments, the rewording might suggest that the swabs are pre-moistened, which they are not (i.e., clean umbilicus with moistened swabs, when applicable.). Per the Agency's 7/20 comments, the full direction regarding "Avoid getting solution into [redacted] was moved from the ***Warnings*** into the **When applying solution** section of the ***Directions***. As stated above, it is 3M's position that this statement, based on the potential consequences, more appropriately belongs in the ***Warnings*** sections. The simple form of the statement, "Avoid getting solution [redacted] , remains as originally worded in this section of the ***Directions***. Per the Agency's 7/20 comments, suggested	• The agency's request to put the DO NOT SCRUB statement first should be retained, especially since it has been removed from the Warnings. This is an important factor in minimizing pooling and should be emphasized. It is noted that a similar statement is prominent on the applicator. • The statement concerning avoidance of getting solution into the hair should be extended to include the Agency's wording, since it will no longer be in the warnings section. • Revise the numbered statements under the subheading **When Applying Solution** to bulleted statements under the header ***Directions***. (Section 201.66(d)(4)). • Revise the statement "[redacted] Remove towels before draping." to read "tuck prep towels as needed under both sides of the neck to absorb excess solution. Remove towels before draping." As the fourth bulleted statement.

suggested by the Agency. 3M has no data that would support why this particular direction of use should appear as the most prominent and/or important piece of information on the label.	rewording was provided for the statement regarding, "Do not allow solution to pool. Use sponge applicator… remove excess with gauze." It is 3M's position that the original proposed wording for this statement is more clinically accurate, in that, for example, it reflects the need for immediacy when absorbing excess solution. Therefore, the Agency's suggested rewording for this statement has not been incorporated into the revised draft labeling.	• Relocate the bulleted statement "**do not allow solution to pool.** Use sponge applicator to absorb excess solution and continue to apply a uniform coating. If solution accidentally get outside of prep area, remove excess with gauze." so that it becomes the next bulleted statement after "DO NOT SCRUB". Also bold the phrase "**do not allow solution to pool.**"
16. The **After applying solution** section of the ***Directions*** has been revised per the Agency's 7/20 comments with the exception that the words " preface the first bullet point statement, "wait until solution is completely dry…"		• Revise the statement " to read " or "**To reduce the risk of fire:**".
17. The **While waiting for solution to completely dry:** section of the ***Directions*** has been revised per the Agency's 7/20 comments with the exception that 3M has retained the first bullet in this section from the original draft labeling which reads, "Do not drape or use ignition source (e.g., cautery, laser).	The first bullet from the original labeling is critical to remind the clinician that although the prep is complete, they cannot begin draping or using any ignition source before allowing the solution to completely dry.	• Revise the second bulleted statement "T ' to read "Use gauze to soak up pooled solution." • No periods should follow after each statement unless the bulleted statement contains more than one sentence.

18. The **After solution is completely dry:** section of the ***Directions*** has been revised per the Agency's 7/20 comments with the exception that 3M has retained, "[redacted] as the preface to the first bullet point statement, "begin draping and/or using cautery only after solution is completely dry…"	The preface "[redacted] is an important reminder as to the relevance and critical importance of following this direction for use.	• Remove the tradename "DuraPrep" 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. • Revise the statement "[redacted] to read "[redacted]." or "**To reduce the risk of fire:**". • Revise the first word in the statement "apply dressing following standard practices" to be lower case and no period after this statement.
19. The ***Other Information*** section has been revised per the Agency's 7/20 comments.		• Revise the first word in the statement "store 20-25°C (68-77 °F)" to be lower case.
20. The ***Questions*** section has been revised per the Agency's 7/20 comments, but revised to correctly state the 3M help line's hours of operation (Monday to Friday 7AM – 6 PM CST).		• Bold the telephone number.

DuraPrep 8630 Solution – 26 ml Immediate Container Applicator Handle (ATTACHMENT 4)		
Label Change	**Justification/Discussion**	**FDA COMMENTS**
21. Boxed Warning has been revised to: • Incorporate "FLAMMABLE" as a separate header • Delete first bullet, "[redacted] solution contains alcohol and gives off flammable vapors [redacted]." • Incorporate as the first bullet the statement "Do not use 26-ml applicator…" • Italicize *Drug Facts* in Use: See *Drug Facts*	Per 8/5 Agency agreement, the statements "For external use on intact skin only" and "[redacted] DO NOT SCRUB" have not been incorporated into the Warning Box. Per 8/5 telecon discussion • It is 3M's position, that to maintain label effectiveness, the Warning box on the applicator handle include only the most important pieces of information with respect to flammability, and to direct the user to see Drug Facts for use instructions. Complete product Warnings as suggested in the Agency's July 20 comments are reflected in the Drug Facts box, but not repeated on the applicator handle labeling. • It is 3M's position that the phrase, "keep away from fire or flame" is inappropriate to highlight in the Warning Box. Fire and/or flame is not present in the operating room environment, and misdirects the clinician as to the potential fire source. Additionally, it is not DuraPrep solution that should be kept away from fire or flame, but rather sources of heat (i.e., electrocautery, laser) that should be kept away from DuraPrep solution until solution is dry.	• See comments above concerning Warnings section. • 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).

22. Per the agency's 7/20 comments, the generic product name is pending regarding Agency decision on established name for [redacted] The word "solution" has been revised to incorporate the product indication, "patient preoperative skin preparation."	Per 8/5 Agency agreement, the statements "For external use on intact skin only" and "[redacted], DO NOT SCRUB" have not been incorporated into the Warning Box. Per 8/5 telecon discussion • It is 3M's position, that to maintain label effectiveness, the Warning box on the applicator handle include only the most important pieces of information with respect to flammability, and to direct the user to see Drug Facts for use instructions. Complete product Warnings as suggested in the Agency's July 20 comments are reflected in the Drug Facts box, but not repeated on the applicator handle labeling. • It is 3M's position that the phrase, "keep away from fire or flame" is inappropriate to highlight in the Warning Box. Fire and/or flame is not present in the operating room environment, and misdirects the clinician as to the potential fire source. Additionally, it is not DuraPrep solution that should be kept away from fire or flame, but rather sources of heat (i.e., electrocautery, laser) that should be kept away from DuraPrep solution until solution is dry.	• No comment.

Principle Display Panel

23. 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.

24. 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.

25. 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.

Drug Facts

26. 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). (Refer to attached ***Drug Facts*** prototype.)

27. Under ***Active ingredients,*** a comma should be placed after the word alcohol.

28. ***Drug Facts*** specifications should be provided to the revised the 26-mL and 6-mL labels.

30. FDA will allow the use of pictograms to improve visibility and prominence to decrease the incidence of fires in operating rooms. FDA is concerned about reports of burns that have been connected with the use of the product. The pictograms of the flame under ***Warnings***, the no pooling pictogram, and electrocautery pictogram under ***Directions*** are acceptable. However, we request that you use a standard or internationally-recognized pictogram or symbol to communicate flammability risk under ***Warnings*** in ***Drug Facts***. Remove the pictogram of the applicator in ***Drug Facts*** for the 26-mL and 6-mL labeling. To emphasize the risk of pooling, FDA recommends instead that you bold the bulleted statement "**• do not allow solution to pool**" under ***Directions*** (2nd bulleted statement under the subheader, **When Applying Solution**).

Immediate Container labels

31. We find the content and layout of the Warnings section that appears in Attachments 8 and 10 of your August 11, 2004 submission to be the most acceptable for the 26-mL and 6-mL applicator sizes.

32. Revise the statement "Made in Usa for 3M Health Care..etc" located on the 6-mL applicator label should be relocated to another area on the label. This will permit enlargement of the type size in the Warnings statement.

Shipping Carton Label

33. Include the revised established name of the product to your shipping carton label.

TPI comment

34. Table 1 and 2 , Two options: 1. Omit ' —— after "Enterococcus faecalis" or 2. ——————————

35. Table 1 and Table 3, place an ——————————— wherever it occurs in the TPI labeling..

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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Tia Frazier
8/17/04 11:35:36 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 5, 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: Chemistry Request for Concurrence on CMC portion-DuraPrep NDA 21-586.

Total no. of pages including cover: 2

Comments: Please see attached.

Document to be mailed: ☐ YES ☑ NO

NDA 21-586 – DuraPrep™ Surgical Solution
CMC Request

The proposal for the changes listed below in the Comparability Protocol is adequate for reporting in the Annual Report.

a) Change to comparable USP Type 1 [redacted]
b) Change to comparable [redacted] in applicator components.
c) Change in manufacturer or manufacturing site of the [redacted] or [redacted] components – no change in component composition.

Accordingly, supporting data that would be described in the annual report would be expected to establish equivalency to the approved container/closure following the protocol. However, if the resin formulations in (b) differ, then further extraction studies would be needed and the change would need to be filed as a supplement.

Written confirmation of your concurrence with this agreement would be appreciated.

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 4, 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: Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) Review Comments on NDA 21-586 – DuraPrep Surgical Solution

Total no. of pages including cover: 2

Comments: Please see attached.

Document to be mailed: ☐ YES ☑ NO

DURAPREP TRAINING POSTER

1. Increase the prominence of the following statement appearing in the Boxed Warning: "Warning: [redacted]". 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.

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 (2-3 minutes 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.

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/s/

Maureen Dillon-Parker
8/4/04 06:39:07 PM
CSO
N21-586 DMETS Training Video/Training Poster comments to 3M - facsimile 8 4 04

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 20, 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: Draft PDP and TPI for DuraPrep.

Total no. of pages including cover: 20

Comments: Please see attached.

Document to be mailed: • YES ☑ NO

Hi Dianne,

Attached please find the **revised draft** TPI and PDP for DuraPrep Surgical Solution.

Please note that the following issues are still under discussion:

1. The use of the "icons" in Drug Facts. (PDP)
2. The Microbiology section in the TPI.

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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Maureen Dillon-Parker
7/28/04 05:01:59 PM
CSO
NDA 21-586; DuraPrep PDP and TPI draft labeling comments

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 [redacted] 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.