(negative control) and 70% isopropyl alcohol. All test subjects received all test medications and served as his or her own control. Forty-one subjects began the study and 32 completed it. Both the test subject and the person doing the scoring were blinded to the identity of the test materials.

2. Inclusion criteria: The following is taken directly from p. 19 of the study report:

   1) Able to read, understand and willing to sign the consent form
   2) Males or females, ages 18-70 (inclusive). No more than 20% of the study population were older than 65
   3) Fitzpatrick skin type I, II, III or IV
   4) Female subjects were surgically sterile, post-menopausal for at least 1 year or using an acceptable method of birth control (abstinence, oral contraceptives, hormonal implant devices, Depo-Provera, condom with spermicidal, diaphragm with contraceptive cream or foam or intrauterine device) while participating in the study
   5) Willingness to avoid direct sun exposure of the test sites and avoid the use of tanning beds, swimming pools, whirlpools, etc. for the duration of the study
   6) Willingness to meet study requirements and to report any adverse symptoms immediately.

3. Exclusion criteria: The following is taken directly from p. 20 of the study report:

   1) Individuals with active psoriasis, allergic skin responses or eczema as recorded on the medical history form
   2) Individuals with diabetes, hyperthyroidism, hypothyroidism or any other condition that the Investigator believes may increase risk to the subject or interfere with the evaluation of the data
   3) Individuals who have had a mastectomy for cancer involving removal of lymph nodes recorded on the medical history form
   4) Individuals receiving routine administration of antihistamines and/or steroids or corticosteroids (except birth control methods, hormone replacement for post-menopausal symptoms, eye drops and nasal sprays containing steroids or intermittent use of antihistamines)
   5) Individuals currently receiving any anticancer, immunosuppressive treatments/ medications and/or radiation as recorded on the concomitant medication form
   6) Women known to be pregnant, nursing or planning to become pregnant within the next six months
   7) Use of topical steroids and/or drugs at the test sites as recorded on the concomitant medication form
   8) Individuals with allergy or hypersensitivity to any of the components of the patch system (i.e., adhesive dressing, medical tape, bandages), iodine (i.e., shellfish allergies), isopropyl alcohol or acrylates
   9) Individuals with uncontrolled metabolic diseases, such as hypertension
   10) Individuals who have had less than a four-week rest period since completion of any previous patch test on the back or upper arms
   11) Planned strenuous exercise during the study period
   12) Individuals who have responded adversely in any previous patch test as recorded on the medical history form
   13) Individuals with active or untreated skin cancer or active hepatitis as recorded on the medical history form
   14) Current routine or frequent use of high doses of anti-inflammatory drugs for a defined medical condition as determined by the concomitant medication form. Aspirin use should not exceed two tablets (650 mg/tablet) per day

15) Use of oral antibiotics within two weeks of study initiation or during the study
16) Individuals with any irritation, sunburn, acne, abrasions, scar tissue, or tattoos on the test site or diseases of the skin that might interfere with the evaluations made in this study or that expose study participants to unacceptable risks

4. Dosage and duration of therapy: Approximately 0.12 mL of the test products were applied to one sq. in. test sites on the back and deltoid region of the arm. Sodium lauryl sulfate, sodium chloride and 70% isopropyl alcohol were applied to the occlusive patch and then applied immediately to the back (this is the standard method of application for tests of this type). DuraPrep, DuraPrep vehicle and Betadine were tested in two different ways. In the first case, they were applied to the back, allowed to dry, and then patched. In the second, they were applied to the deltoid region, and patched immediately. The patches were left in place for 24 hours, at which time they were removed and graded for irritation. This process was repeated daily for 3 weeks (21 days).

5. Scoring scales: Irritation responses were graded on the following scale:

0 No evidence of irritation
1 Minimal erythema, barely perceptible
2 Moderate erythema, readily visible; or minimal edema; or minimal papular response
3 Strong erythema; or erythema and papules
4 Definite edema
5 Erythema, edema and papules
6 Vesicular eruption
7 Strong reaction spreading beyond test site

Effects on superficial layers of the skin were recorded as follows:

A Slight glazed appearance
B Marked glazing
C Glazing with peeling and cracking
F Glazing with fissures
G Film of dried serous exudates covering all or portion of the patch site
H Small petechial erosions and/or scabs

The simplest way to compare irritation potential between test products is to sum the results for all subjects to all readings. There are a number of (similar) classification systems for evaluating cumulative irritancy using total scores. The following was used in this study:

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Table 1. Classification of irritancy reactions

Class	Base 10 Score	Indications from Text	Description of Observed Responses
1	0–49	Mild article – no experimental irritation	Essentially no evidence of cumulative irritation under conditions of test (i.e., continuous reapplication and occlusion at concentration specified).
2	50-199	Probably mild in normal use	Evidence of a slight potential for very mild cumulative irritation under conditions of test.
3	200-449	Possibly mild in normal use	Evidence of a moderate potential for mild cumulative irritation under conditions at test.
4	450-580	Experimental cumulative irritant	Evidence of a strong potential for mild to moderate cumulative irritation under conditions of test.
5	581-630	Experimental primary irritant	Evidence of potential for primary irritant irritation under conditions of test.

Results:

1. Withdrawals: Nine subjects withdrew from the study. Two of these were due to adverse events which will be discussed below. Two others withdrew because they "did not like wearing patches". From the data listings, it appears that these patients were never evaluated. Two other subjects withdrew because of conflicting schedules. Three subjects withdrew because they "decided that it is in his/her best interest". Only one of these patients (no. 37) received the test materials and was evaluated. This patient left the study after the eleventh day following scores of 2B and 1C (see scoring scale above) for DuraPrep patched wet. This subject may have discontinued due to an adverse event, though this is not certain.

2. Demographics: The subjects in this study were all Caucasian. This is typical in studies of this type in that irritation reactions are more apparent in lighter skinned test subjects. The population who entered the study was predominantly (85%) female. The mean age of the subjects was 47 years.

3. Irritation: The following table, which is taken directly from p. 5 of the study report, summarizes the irritation scores.

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Table 2. Cumulative irritancy Totals

Treatment	Base 10 Score	Classification
A (DuraPrep Surgical Solution [applied to skin-patched dry])	307.7	Class 3 (possibly mild in normal use)
B (DuraPrep Surgical Solution [applied to Skin-patched wet])	453.7	Class 4 (experimental cumulative irritant)
C (Betadine Solution [applied to skin-patched dry])	345.3	Class 3 (possibly mild in normal use)
D (Betadine Solution [applied to skin-patched wet])	333.2	Class 3 (possibly mild in normal use)
E (DuraPrep w/o iodine [applied to skin-patched dry])	8.8	Class 1 (mild article-no experimental irritation)
F (DuraPrep w/o iodine [applied to skin-Patched wet])	18.4	Class 1 (mild article-no experimental irritation)
G (Sodium lauryl sulfate [applied to patch-patch applied to skin])	92.6	Class 2 (probably mild in normal use)
H (Sodium chloride [applied to patch-patch applied wet to skin])	3.0	Class 1 (mild article-no experimental irritation)
I (Isopropyl Alcohol [applied to patch-patch applied wet to skin])	16.6	Class 1 (mild article-no experimental irritation)

4. Adverse reactions: The sponsor has adopted a conservative approach to reporting of adverse events in that pruritus, burning, irritation, etc. at the test sites have been classified as adverse events. In most studies of this type, these events are considered to be necessary results of the testing process: that is, if there were no such events, the test would be considered a failure in that the goal of the protocol is to produce extreme conditions which will produce these events.

   With this in mind, the following table, taken directly from p. 7 of the study report, gives the percentage of subjects (N=40) who had adverse events considered to be possibly or probably related to treatment. These events were all mild in severity.

Table 3. % of patients with adverse events possibly or probably related to treatment.

	Percentage of subjects					
Treatment	Pruritus	Burning	Irritation	Pain	Swelling	Tenderness
A (DuraPrep Surgical Solution [applied to skin-patched dry])	50	10	3	5	3	0
B (DuraPrep Surgical Solution [applied to skin-patched wet])	25	8	0	5	0	3
C (Betadine Solution [applied to skin-patched dry])	45	8	3	5	0	0
D (Betadine Solution [applied to skin-patched wet])	25	3	0	0	0	0

E (DuraPrep w/o iodine [applied to skin-patched dry])	38	5	3	0	0	0
F (DuraPrep w/o iodine [applied to skin-patched wet])	23	3	0	0	0	0
G (Sodium lauryl sulfate [applied to patch-patch applied to skin])	40	3	3	0	3	3
H (Sodium chloride [applied to patch-patch applied to skin])	38	3	3	0	0	0
I (Isopropyl Alcohol [applied to patch-patch applied to skin])	38	5	3	0	0	0

There were two serious adverse events resulting in subject withdrawal during the study. One subject was admitted to the hospital for depression, and the other was diagnosed with thyroid cancer. Both of these subjects were discontinued from the study. These events were not related to drug administration.

Reviewer's Comment: This study establishes that DuraPrep, whether allowed to dry prior to occlusion or patched while wet, is quite irritating. This would be a serious problem if the product were proposed for repeated use. However, DuraPrep is intended only for single time usage. No repeat usage (unless such use is separated by a considerable period of time) is expected. It is interesting that both DuraPrep and Betadine produced more frequent pruritus in subjects who had the product patched after it was dry than those who had the product patched wet.

B. Contact Sensitization Study

Study Title: A Study to Evaluate the Contact Sensitization Potential of Topically Applied 3M DuraPrep Surgical Solution (Protocol No. 02-109762-111-LIMS 7296).

Investigator: [redacted]

Study Dates: June 10-August 16, 2002

Study Objectives: The following is taken directly from p. 16 of the study report:

> The objective of this study was to assess the contact sensitization potential of DuraPrep solution compared to that of DuraPrep w/o I_2, Betadine solution and 70% isopropyl alcohol. The primary objective was the assessment of skin inflammatory response during the challenge phase.

Method:

1. Study design: This was a paired comparison of DuraPrep, 70% IPA, the DuraPrep vehicle, and Betadine Solution. All test subjects received all test medications and served as his or her own control. Two hundred forty-seven subjects began the study and 204 completed it. Both the test subject and the person who did the scoring were blinded to the identity of the test materials.

2. Inclusion criteria: These were the same as for the irritation study described above.

3. Exclusion criteria: These were the same as for the irritation study above.

4. Dosage and duration of therapy: Approximately 0.02 mL of the test products were applied to one sq. in. test sites on the deltoid region of the arm. All products were allowed to dry, followed by placement of occlusive patches. The patches were left in place for 48 hours (72 hours on weekends) for 3 weeks. Thus, a total of 9 applications were made during the induction phase of the study. The test sites were evaluated for irritation at each patch change. If excessive irritation was noted, the protocol permitted moving the induction patches for that product to a new site. A rest period of 10-14 days followed the induction phase (no test articles were applied).

   During the final (challenge) phase, the subjects received another 0.02 mL application of the test materials at the original site and a new, previously untreated site on the other arm. The patches were left on for 48 hours, and readings for sensitization were made upon patch removal and 48 hours later.

5. Scoring scales: Inflammatory responses were graded on the following scale:

   0 No visible reaction
   + Slight, confluent or patchy edema
   1 Mild erythema (pink)
   2 Moderate erythema (definite redness)
   3 Strong erythema (very intense redness)

   Definition of letter grades appended to a numerical grade:

   E Edema-swelling, spongy feeling when palpated
   P Papule- red, solid, pinpoint elevation
   V Vesicle- small elevation containing fluid
   B Bulla reaction- fluid-filled lesion (blister)
   S Spreading- evidence of the reaction beyond the pad area
   W Weeping- result of a vesicular or bulla reaction- serous exudates
   I Induration- solid, elevated, hardened, thickened skin
   * Residual reaction to earlier application after absence

Results:

1. Withdrawals: 247 subjects were enrolled, and 204 completed the study. Of the 43 withdrawals, 9 were due to adverse events which will be discussed below. There were also 10 protocol violations and 22 patients "decided it was in his/her best interest to

withdraw." One other subject was withdrawn by the investigator, and one withdrawal is only identified as "other." This patient was apparently excluded because of antibiotic use during the challenge phase.

Of the subjects who withdrew themselves or were withdrawn by the investigator, 13/23 never received any test materials. The other 10 had 2 to 4 evaluations before dropping out. None of them had displayed any irritation at the time of leaving the study.

2. Demographics: The subjects in the study were predominantly (96%) Caucasian. There were also 3 African-Americans, 2 Hispanic and single Asian and "other" subjects. Subjects were 76.5% female and the average age of the subjects was 47 years.

3. Sensitization reactions: The following table, which is taken directly from p. 31 of the study report, outlines the response of the subjects at the challenge application.

Table 1. Inflammatory Response at Challenge

		48 Hours		96 Hours	
Test material	**Grade**	**Original Site**	**Naïve Adjacent Site**	**Original Site**	**Naïve Adjacent Site**
A DuraPrep solution	0	199	203	204	205
	+	2	2	0	0
	1	5	1	1	0
	2	0	0	0	0
	3	0	0	0	0
B Betadine solution	0	197	202	202	203
	+	1	0	0	0
	1	7	4	3	2
	2	1	0	0	0
	3	0	0	0	0
C DuraPrep w/o Iodine	0	206	206	205	205
	+	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
D 70% Isopropyl Alcohol	0	206	204	205	204
	+	0	1	0	0
	1	0	1	0	0
	2	0	0	0	0
	3	0	0	0	0

4. Adverse reactions: The following table is adapted from the table on p. 36 of the study report and presents those adverse events which were judged to be probably or possibly related to treatment. There were also single reports of mild paraesthesia related to Dura Prep and mild tenderness related to Betadine which are not represented in the table.

Table 2. Adverse events probably or possibly related to treatment

Treatment Group	Severity			Occurrences	Total Number of Subjects (%)
	Mild	Moderate	Severe		
Application Site Pruritus					
A DuraPrep Surgical Solution	9	1	0	10	10 (4.05%)
B Betadine Solution	4	2	0	6	6 (2.43%)
C DuraPrep w/o Iodine	3	1	0	4	4 (1.62%)
D 70% Isopropyl Alcohol	4	1	0	5	5 (2.02%)
Not associated with specific treatment site	2	1	0	3	3 (1.21%)
Application Site Burning					
A DuraPrep Surgical Solution	7	0	0	7	7 (2.83%)
B Betadine Solution	4	0	0	4	4 (1.62%)
C DuraPrep w/o Iodine	2	0	0	2	2 (0.81%)
D 70% Isopropyl Alcohol	3	0	0	3	2 (0.81%)
Not associated with specific treatment site	1	0	0	1	1 (0.40%)
Application Site Pain					
A DuraPrep Surgical Solution	5	0	0	5	5 (2.02%)
B Betadine Solution	2	0	0	2	2 (0.81%)
C DuraPrep w/o Iodine	1	0	0	1	1 (0.40%)
D 70% Isopropyl Alcohol	2	0	0	2	1 (0.81%)
Not associated with specific treatment site	0	0	0	0	0 (0%)

There were 9 adverse events in subjects who withdrew from the study. These included 4 which were not related to therapy (possible heart attack, injured in fall, influenza, tooth extraction), and 5 others probably or possibly related to therapy, all of which were burning or itching (or both) at the application site.

Reviewer's Comment: The most commonly accepted means of evaluating sensitization potential is by reactions seen at the naïve (previously untested) site at challenge. By this standard, none of the test medications exhibits potential to cause sensitization in normal use. The protocol used in the study is a standard one which is useful in predicting sensitization potential.

C. Flammability/Vapor Dissipation Studies

Study Title: Quantification of DuraPrep Surgical Solution Isopropyl Alcohol Vapors in an Operating Room Setting (Study No. 05-009834).

Investigator: John Dell
3M Company
St. Paul, MN

Study Objectives: The following is taken directly from p. 1 of the study report:

> In response to questions from the FDA regarding the relationship between the time after application of applied DuraPrep™ surgical solution and the concentration of isopropyl alcohol vapors on or near a patient, [redacted] and 3M measured the following:
>
> 1. The concentration of isopropyl alcohol vapors during the time that the surgical solution is drying on a patient in an operating room setting.
> 2. The concentration of isopropyl alcohol vapors near the operative site at a time when the surgical solution appears to be dry.
>
> The goal of these measurements was to determine if:
>
> - the instruction in the DuraPrep™ solution Directions for Use to wait until dry is appropriate and
> - the dry time specified (2 to 3 minutes) is appropriate

Method:

1. Study design: This study is better classified as an engineering study than as a clinical study. The concentration of IPA vapors evaporating from freshly applied DuraPrep was measured in healthy volunteers. Four test scenarios were studied, with 3 subjects being used in 3 scenarios and one subject in the fourth. All tests were run in an operating room environment.

2. Inclusion – exclusion criteria: Healthy adult males were enrolled.

3. Testing parameters: In the first test, DuraPrep was allowed to dry after application to a 15 x 17 inch section of the back. Drying time was visually judged by 3 nurses who frequently use the product. IPA vapor levels were measured from time of visual drying until levels had decreased to near zero.

   In the second test, DuraPrep was applied to a 13 x 14 inch section of the back. immediately (within 5 seconds) IPA vapor levels were measured and measurements continued until they were 10% of the lower flammability limit. (The flammability limits, according to a document produced by NIOSH and included with the submission, are [redacted] or [redacted] ppm by volume).

   In the third test, DuraPrep was applied to a 14 x 16.5 inch section of the back. IPA vapor levels were measured at 4 areas (left and right shoulder blades, center of the

back in the thoracic and lumbar areas) at 4 time intervals, beginning 30 seconds after application.

In the fourth test (using only one subject), the IPA vapor concentration was measured near the back and neck (the measuring device was placed on the operating table, but not on the skin) after application of DuraPrep and time for drying. In a second portion of the study, the subject was prepped and then the area was immediately covered with a plastic covering (to simulate misuse) and the IPA levels under the drape were measured.

4. Results:

   i. Test one (measurement following observed drying by nurses). The three nurses had varying estimates of the time necessary for drying (44-102 seconds). The highest IPA level was observed for the shortest drying time (1.24% at 44 seconds).

   ii. Test two (measurement while wet to 10% of lower flammability limit).
   In this test, the IPA levels were above the ___ flammability limit initially, averaging about 3.8%. By 1 minute 45 seconds, all levels were 0.1% or lower.

   iii. Test three (measurement at different areas at different times). At the initial (30 second) measurement, levels averaged about 3.8%. By 1 minute 45 seconds, all levels were 0.1% or lower.

   iv. Test four (measurement near treated skin and under extreme conditions).
   The maximum concentration of IPA when the measuring device was placed near treated skin was about 0.05%, while under the draped area it was about 0.4%. It is not clear exactly what space under the drape was measured.

Reviewer's Comment: It is clear that DuraPrep vapors are flammable when the product is newly applied. The vapor levels drop sharply, and under all circumstances are below flammability levels at 2 minutes from application. It is interesting that even experienced observers had a two fold discrepancy in their perceptions of when the product is completely dry (see also the following study).

D. Drying Time Study

Study Title: Nurse Panel for DuraPrep Solution Dry Time (Study No. 05-009855).

Investigator: Karen Rittle
3M Company
St. Paul, MN

Study Objective: The following is taken directly from p. 1 of the study report:

> The objective of the study was to have local nurses perform simulated patient preps and evaluate the dry time of 3M DuraPrep Surgical Solution.

Method:

1. Study Design: Six practicing nurses were asked to apply DuraPrep to a specific body area according to directions. Then each nurse visually determined the dry time for his or her own prep (the product is considered to be dry when it is no longer shiny on the skin). Two of the nurses were not consistent users of DuraPrep.

2. Inclusion – exclusion criteria: The study used 12 healthy adults of either sex as test subjects. Exclusions were those:

    1. with a history of psoriasis, any active dermatitis or skin reactions
    2. who have a sunburn or skin infection on the area to be prepped
    3. who have sensitivities to alcohol or any iodine-containing product or sensitivities to thiosulfates
    4. who have an existing thyroid condition
    5. who have a history of skin allergies
    6. who are pregnant or nursing
    7. who have participated in a DuraPrep solution study in the past weeks
    8. who have used lotions on the site(s) to be used in the last 24 hours
    9. in addition, the Investigator may exclude those not compliant with the requirements of the study or anyone else the Investigator believes is unsuitable for inclusion in this study

3. Testing parameters: Each of the six nurses prepped 2 subjects: on the first subject the back was prepped, and on the second, the neck, leg and shoulder were done. The nurse then visually estimated the drying time following the prep.

4. Results: The following table, which is taken from p. 5 of the study report, summarizes the results.

Table 1: Dry Time by Body Area

	Dry Time (Min)					
	N	**Mean**	**Median**	**Std**	**Min**	**Max**
Body Area						
Back	6	1.89	1.90	0.72	1.02	2.88
Leg	6	1.38	1.35	0.29	1.02	1.87
Neck	6	1.65	1.48	0.55	1.20	2.67
Shoulder	6	1.21	1.18	0.32	0.77	1.60
All	24	1.53	1.37	0.54	0.77	2.88

Reviewer's Comment: Again, the spread of estimated drying times is striking. This may have to do with the amount applied, since all preps were applied under the same conditions. Also, the DuraPrep may actually have been dry relatively much sooner than detected by some of the nurses. In any event, the results of this study and the previous one indicate that a labeling recommendation for a drying time of 3 to 4 minutes would provide an adequate safety margin.

E. Skin coverage study

Reviewer's Note: This study was performed at the request of the Division and was not part of the NDA submission. It was included as part of the October 4, 2001 submission to IND 49,411.

Study Title and Investigator: Not given. The study was performed by 3M personnel.

Method:

1. Study design: This study was intended to establish a) the area covered by the presently marketed 26 mL applicator when used as directed and b) to determine the area covered by 20 mL of the product when applied from the same type of applicator. A single nurse was used for all applications. A total of 6 applicators of each size were used on 12 volunteers (6 male, 6 female). This was because an applicator typically covers more than one adult back, which was the chosen application area.

2. Testing parameters: Each applicator was weighed, then used to coat the backs of the test subjects and weighed again. The applicator was judged to the "empty" when it could no longer deliver a uniform coating to the skin.

   In order to compare this test procedure to an actual usage in the OR, observations of surgical procedures were done at a St. Paul hospital. Five cardiac artery bypass graft procedures, which require a large area of skin preparation, were used. The same observations as were made in the in-house study were performed, except the target area was the chest area (chin to groin).

3. Results: The following are average values obtained in the study.

Table 1. Volumes used and areas of coverage

	Volume used (mL)	Area covered (sq. in./sq. ft.)
26 mL	12	471 / 3.27
20 mL	8.4	370 / 2.57
26 mL (OR)	14	652 / 4.53

Reviewer's Comment: This is interesting, though limited, information. The 5 patients observed in the OR were large, with an average weight of 226 lbs. (range 181-282 lbs.). Admittedly, the OR staff use was not as carefully controlled as during the in-house study, and it was probably difficult to do precise area measurements under the circumstances.

However, it appears that the OR staff was able to cover a much (28%) larger area than the in-house nurse, and to utilize more (2mL), of the material in the 26 mL applicator.

This may be due to a number of reasons, but it seems most likely that the OR staff simply pressed harder. Another possibility, though not stated in the study report, is that a second applicator was used in some or most persons.

In any event, the more closely controlled data will be used to evaluate the situation. It appears that one 26 mL applicator, used as directed, would not be sufficient to provide coverage of the neck to groin area for the larger patient, which was the case in the OR patients. Two 20 mL applicators would be sufficient. This still leaves a similar problem for the smaller patient. That is, a patient of medium size could well require one 20 mL applicator and only a small part of a second one, still leaving a relatively large amount for spillage. The only certainty is that virtually no ignition incidents are seen with the smaller (6mL) container. As a matter of instinct, it would seem reasonable to limit the size of the container as much as possible, but it is not practical to restrict sale of the product to the smaller size only.

Therefore, the reviewers recommend that the amount of product in the container be allowed to remain at 26 mL. The labeling should include a statement to the effect that any amount not required to cover the recommended area be discarded.

F. Adverse Event Reports

1. Reports during clinical testing

Please see sections 1.4.A. and 1.4.B. above for description of adverse events seen during the irritancy and sensitization studies.

There were 5 pivotal efficacy subjects (297 subjects) and 10 pilot efficacy studies (87 subjects). A total of 380 subjects were exposed to DuraPrep during these studies. There were 5 adverse effects reported in these patients, as follows:

A. Study 8918 – pivotal patient preoperative skin preparation study. One patient experienced discomfort NOS (not otherwise specified) and withdrew from the study. The report did not name a specific treatment associated with the discomfort.
B. Study 9302 – pivotal bacterial challenge study. One patient developed papules at the DuraPrep test site. The investigator felt that the reaction was not treatment related, though it seems at least possible that it was.
C. Study 8061 – this was a small (5 subject) development study to evaluate the test methodology which applied the drug, washed the test area with autologous blood and saline, and then applied a challenge organism. The reactions reported were: one erythema at the Betadine site (not evaluated as treatment related), one erythema at the DuraPrep site (evaluated as treatment related), and one skin injury NOS at the DuraPrep site (not evaluated as related).

<u>Reviewer's Comment:</u> The small number of reports seen here is not unexpected, given that the studies provided for one time use of the products on relatively small areas of skin.

2. Spontaneous reports

DuraPrep has been marketed since 1988. Through December, 2002, about [redacted] units of the product were sold. The following table is adapted from Table 2.7.4.2.2 on p. 2-133 of Module 2 of the NDA. It presents the adverse events seen until December, 2002, with the exception of "flammability", which is presented through April 30, 2003.

Table 1. Spontaneous DuraPrep Adverse Event Reports

Complaint	**Total**
Skin irritation*	291
Infection or rate increase	108
Flammability	80
Skin laceration/cut	29
Flaking/rolling/falling into wound	21
Allergy	7
Eye irritation/damage	3
Staff headache/watery eyes/dizziness	7
Skin staining	4
DuraPrep squirted on face	6
Bowel placed on DuraPrep	1
Elevated temperature	1
Film/color gone	1
Cellulitis	1
Wound dehiscence	1
* Includes redness, itching, rash, chemical burn, blistering, skin removal.	

Reviewer's Note: There are three types of reaction which are (relatively) numerous and/or of special concern. The "infection or rate increase" category might also be classified as complaint of lack of drug effectiveness and will not be further mentioned. The other two categories, "skin irritation" and "flammability" require further discussion. The skin irritation complaints were not sufficiently categorized in the initial submission, so the applicant was asked to provide more specific information in the safety update. This was received February 27, 2004. The data reviewed under b. Skin irritation, below are from the safety update. The following discussion concerns the flammability reports up to April 30, 2003. Additional flammability reports received after that time are reviewed under section 1.8. Safety Update, below.

a. Flammability

There have been 80 occurrences of DuraPrep catching fire during a surgical preparation in 15 years. These incidents have been almost exclusively associated with the 26 mL size. Only one incident was reported for the 6 mL size, and there was only one incident reported until 1991. Since then, reports have varied between 2 and 11 per year. There were 11 reports in 2002. It should be noted that sales for the product have increased over the years [redacted] in 2002) making the incidence fairly steady at around [redacted] units sold. These incidents were

most commonly associated with failure to let the preparation dry (33), pooling of the preparation (24) and use with oxygen (14). Severity of the burns was as follows:

Table 2. Burn Severity Totals

Burn Severity*	**Total**
1st	15
2nd	33
3rd	14
None or unknown	18

*If more than one severity was reported, the most severe is reported.

The following table, which is adapted from Table 2.7.4.25 on p. 2-140 of Module 2 of the NDA, provides analysis of the burns by the person doing the prep and body site affected.

Table 3. Persons Applying Prep and Body Site Affected
(N=80)

Person applying:	N (%)
Surgeon	15 (18.8)
Anesthesiologist	1 (1.3)
Staff	22 (27.5)
Unknown	42 (52.5)
Body site:	
Head and neck	37 (46.3)
Other	43 (53.8)
Site unknown	9 (11.3)
Axillary	5 (6.3)
Hand	4 (5.0)
No injury*	4 (5.0)
Shoulder/upper back	3 (3.8)
Abdomen	3 (3.8)
Thigh	3 (3.8)
Pubic area	3 (3.8)
Armpit	2 (2.5)
Back	2 (2.5)
Arm	1 (1.3)
Breast	1 (1.3)
Chest	1 (1.3)
Abdomen/pelvis	1 (1.3)
Nose	1 (1.3)

* For these 4 complaints, no injury occurred to the patient though flames and/or smoke were reported.

As nearly as can be determined, all these incidents were associated with the introduction of a spark (usually electrocautery) into the surgical field of a patient who had prepped with the product.

Reviewer's Comment:

Most adverse events are the result of allergy, overdose, associated drug toxicity, etc. These reports are unique in that they have nothing to do with the intended action of the drug . Also, reports of burns appear to have been completely preventable in that introduction of a spark was necessary for their occurrence. The Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products classifies isopropyl alcohol 70-91.3% as safe and effective as a patient preop. However, the TFM states that labeling for such products should contain the following warning: "Do not use with electrocautery procedures".

This matter has been discussed internally, and it has been determined that such a warning would prevent most usage of the product, since modern surgery commonly requires the use of electrocautery. The sponsor has revised the labeling at least twice in recent years to emphasize warnings against allowing the product to pool, to emphasize drying time, etc. These changes do not appear to have greatly affected the incidence rate of flammability reports. The following comments are offered:

1. **The volume of material available is the primary determinant of whether ignition takes place. The 6 mL container has been associated with only one of the flammability incidents. All others took place while the 26 mL size was in use.**

2. **Nearly half (46%) of the burn incidents were at the head and neck. The 26 mL applicator label references the smaller (6 mL) applicator for procedures in this area. It is also notable that of the 14 third-degree burns, 10 were associated with head/neck surgery.**

3. **Some labeling revisions are necessary to further minimize the risk of flammability. Among them are:**

   a. [redacted]
   b. **Contraindicating the 26 mL container in head and neck surgery.**
   c. [redacted]

Please see the Labeling Safety Issues section below for complete comments.

b. Skin irritation

The safety update contained more detailed information on the skin irritation complaints received during the marketing of the product. The following table, which is adapted from Table 1.2.4.2 in the safety update submission, lists the types of disorders which were grouped under skin irritation.

Table 4. DuraPrep Skin Irritation Complaints

Complaint	Total
Skin irritation- all	339
Subcategories	
Blistering	159
Rash, hives, itching, burning, irritation	72
Chemical burn	35
Skin stripping	33
Allergy	12
Redness	11
Dehiscence of wound	5
Abrasion	2
Bruise	4
Contact dermatitis	4
Skin breakdown	2

The reactions of most concern are blistering, chemical burn and skin stripping, due to their relative frequency and/or seriousness. The individual adverse event reports for these reactions were examined. The reports are somewhat interchangeable in that a report of blistering might also include skin stripping. It was also seen that some reports contain multiple examples of the same type of reaction. An extreme (but not isolated) example is a report from one hospital concerning 13 cases of blistering. This report counts as 1 in the above table.

The blistering reports were classified by the sponsor in some cases as "tension blisters". These are defined as blisters caused by too-tight application of tape and/or dressing, which, when incorrectly removed, causes blisters to rise. Most of the reports concern blisters which do not meet this definition. Some of the more severe cases resulted in skin loss (and in a few cases) subsequent infection. The blistering cases occurred in a wide range of ages, from infants to the elderly. Some of the reports had common patterns. These include:

- blistering in skin folds (possibly the product did not dry completely)
- blistering in surgeries requiring use of elastic bandages, even though the elastic did not touch the skin (knee replacement, etc.)
- blisters in patients who were draped with Ioban (which also contains iodine).

The skin stripping reports were typically in elderly patients who had DuraPrep applied but not removed after surgery. The wounds were then dressed, and when the dressings were removed, the skin (or portions of it) came off with the dressing. This type of damage is not uncommon in elderly patients with fragile skin.

The chemical burn reports are apparently the result of irritation, with many of them occurring in infants. Almost all of these cases were in those who had DuraPrep applied and not subsequently removed once the surgery was finished.

Reviewer's Comment: These reports are infrequent, given the wide use of the product. Even so, the labeling should refer to the possibility of blistering and skin loss. Please see the Labeling Safety Issues section below for complete comments.

1.5. Miscellaneous Studies

None

1.6. Literature Review for Safety

The sponsor has submitted a number of references concerning the efficacy and safety of iodine and iodine/alcohol products. The following are relevant to safety:

A. Jeng, et al. Neonatal thyroid function is unaffected by single treatment with different preparations of povidone-iodine on a wide skin surface. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1997 Jan-Feb; 38(1): 28-31.

In this paper, 48 healthy newborns were split into four equal groups: 10% tincture povidone-iodine; 10% aqueous povidone-iodine; 10% tincture povidone-iodine followed with 75% alcohol; and control (no treatment). The babies required central line insertions and were randomized to one of the above groups for skin preparation for this procedure. The entire arm was treated (fingers to shoulder). The investigators then measured the thyroid function of the children, and found no significant differences between the groups.

B. Emergency Case Research Institute. Fire hazard created by the misuse of DuraPrep solution. (Hazard Report). Health Devices 1998 Nov 27; 11:400-2.

This and the following reference concern a single incident in which a flash fireball erupted as a surgeon used an electrode at the surgical site. In this case, the prep was overapplied and some pooled in the surgical linens. The patient was draped with the wet solution still present. This document also mentions that the same group has investigated other fires associated with DuraPrep use, including one in which improperly applied prep was channeled through a fold in the incise drape to the surgical site. The paper notes that if the solution is allowed to soak into hair, bandages, etc. a drying time of at least 10 minutes is necessary. Apparently as a result of this incident, 3M revised the labeling for the product in 1997.

C. Emergency Care Research Institute. DuraPrep solution fire hazard. Health Care Hazard Materials Management 1999 Mar; 12(7): 5-6.

This is a restatement of the article above, with the added information that third-degree burns were discovered away from the surgical site when the

surgical drapes were removed. It appears that after the original fireball was extinguished, the pooled liquid continued to burn underneath the patient until exhausted.

D. Barker and Polson, Fire in the operating room: A case report and laboratory study. Anesth Analg 2001 Oct 93: 960-5.

This and the following references concern a single incident in 1998 in which a man was burned on the face, neck and shoulders during surgery. An oxygen mask had been strapped to his face, and the surgical site (head) prepped with DuraPrep. The surgical site was draped. When an electrosurgical tool was activated, smoke appeared from under the drapes. When the drapes were removed, the head was "engulfed in a ball of flame". The patient's burns were second degree, but he spent 2 months in the ICU due to inhalation injury.

The authors attempted to recreate the incident, using a noninflammable manikin. The conclusion drawn after a number of experiments was that DuraPrep had provided the fuel for the fire, ignited by an electrical surgical instrument. Two other pieces of information are notable:

a. Based on anecdotal information, the authors estimate that there are 20-30 surgical patient fires per year in the US, most of which are unreported. (This does not imply that DuraPrep is associated with a specific number of them).
b. Because head-neck surgery often involves mask anesthesia, extra care is necessary.

E. Bentzen (3M Market Development Manager) - unpublished letter to the authors of the reference just above.

This letter points out a series of possible flaws in the methodology used by Barker and Polson to recreate the fire described in D. above. Principally, the letter states that the hospital's consulting fire expert found that fuel for the fire was provided by very fine hair next to the patient's scalp, rather than by DuraPrep.

F. Anesth Analg 2002; 95:1,464-5. Letter to the editor of Anesthesia and Analgesia, written by Bruley, concerning the Barker and Polson paper, and a response to Bruley by Barker.

The Bruley letter is from ECRI, the same organization which published references B and C above. In this letter, it is theorized that the oxygen mask provided an atmosphere in which the electrosurgical tool ignited the surgical linen or gauze sponge in the surgical field. Barker rejects this theory on the ground that the surgical towels at the actual fire did not burn, nor did they in his recreation of the event.

1.7. Postmarketing Surveillance

This product is presently marketed, and surveillance is ongoing.

1.8. Safety Update

In addition to the skin irritation information reviewed in section 1.4.F.2.b above, the safety update contains reports of four more fire ignition reports associated with DuraPrep use from April 30 to December 31, 2003. This brings the total of flammability reports for 2003 to 7. Two of the incidents concerned face/neck surgery, one concerned hand surgery, and the site for the other was unspecified. In one of the reports, no injury was seen, and in a second the severity of the injury was not specified. The other 2 incidents resulted in first and/or second degree burns. This information does not change the conclusions previously reached regarding flammability of the product.

1.9. Drug Withdrawal, Abuse, and Overdose Experience

None. Since the product will typically be used only once, overdose is not a concern.

1.10. Adequacy of Safety Testing

The drug has been adequately tested for safety. Please see section 1.1 for synopses of the relevant data.

1.11. Labeling Safety Issues and Postmarketing Commitments

The following DuraPrep labeling pieces have been submitted:

A. The immediate container labels. These are the labels that are directly attached to the 6 and 26 mL dispensers.
B. The "inserts". This is actually the front and back sides of the label which is inserted in the plastic carton with the dispenser.
C. Bulk case labels.
D. The Target Product Information leaflet.

The labeling pieces will be commented on individually.

A. Immediate container labels

These labels are necessarily small because they are applied to a round applicator with relatively small surface area. Aside from drug identifying information, the following safety-related material is present:

i. Information on how to start the product flowing through the dispenser and an admonition to paint, rather than scrub with the product. This

information is acceptable.

ii. A Warning section concerning flammability, the necessity to let the product dry, and warning against letting the product pool. There are also two illustrations in this section.

Comments: The recommended drying time should be extended to 3-4 minutes and the larger size should be contraindicated in head/neck surgery. Therefore, it is recommended that the immediate container labels be revised as follows:

i. For the larger size, the WARNING should read as follows:

WARNING

- Do not use the 26 ml for head/neck surgery.
- Do not drape or use ignition source until the is completely dry
- Do not allow to pool. . Remove solution-soaked materials

*

ii.

iii. For both containers, the "no pooling" and flame-cautery symbols should be reconsidered. The primary objective should be to make the printed material as large and readable as possible. It seems likely that the symbols could remain on the larger container, which is the one which poses the greatest ignition danger. The smaller container may not have sufficient space available for the required text and the symbols.

B. "Inserts"

Comments:

i. For the larger size:

a. The WARNING on the front panel (with the picture of the applicator) should be revised to read identically to the recommendation above for the immediate container label,

with the exception that the phrase, "For external use on intact skin only" should be retained.

b. The WARNING on the back panel (titled "Drug Facts") should read as described above for this size. If the sponsor wishes to retain the section which begins, " [redacted], it may be moved to the Directions section.

c. The "Do not use" section should read as follows:

- in [redacted] less than 2 months of age [redacted]
- on patients with known allergies to iodine or [redacted]
- on open wounds, on mucous membranes or as a general skin cleanser.

d. The "When using this product" section should read as follows:

- keep out of eyes, ears and mouth. May cause serious injury if permitted to enter and remain. If contact occurs, [redacted] with cold water right away and contact a physician.
- [redacted]
- [redacted]

e. The "Stop use and ask a doctor" section should read as follows:

Stop use and ask a doctor if irritation, sensitization or [redacted] allergic reactions occur. These may be signs of a serious condition. [redacted] use has been associated with [redacted] skin blistering [redacted]

f. In the "Directions" section, "When Applying [redacted] Solution" subsection:

- the first bullet should be (in bold font):
  [redacted] DO NOT SCRUB
- [redacted]

g. In the "Directions" section, "After applying [redacted] Solution" subsection:

- [redacted]
- [redacted]

ii. For the 6 mL size:

a. [redacted]

b. The "Do not use" section should read as recommended for the larger size.

c. The "When using this product" section should read as recommended for the larger size.

d. The "Stop use and ask a doctor" section should be revised as recommended for the larger size.

e. In the "Directions" section, "When Applying DuraPrep Solution" subsection, the first bullet should read (in bold font): [redacted], DO NOT SCRUB.

f. In the "Directions" section, "After applying DuraPrep Solution" subsection, the drying time should b[redacted] (in two places).

C. There are no comments on the bulk case labels.

D. Target Product Information Label

Comment: In the "Safety Studies" section, the second paragraph, concerning the cumulative irritation test, should read as follows:

> In a 21-Day Human Cumulative Irritation Potential Test (LIMS 7294) involving 32 subjects, DuraPrep solution Base 10 cumulative irritation score when patched wet under occlusive conditions (the standard procedure for testing of this type) was 453.7 (Class 4: experimental 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).

1. Dosing, Regimen, and Administration Issues

[redacted]

[redacted]

[redacted] Please see the addendum to this review for integrated labeling recommendations from a safety perspective.

David C. Bostwick

Appendix: Recommended
Safety Labeling Changes

Jean Mulinde, MD

Appears This Way
On Original

Appendix: Recommended Safety Labeling Changes

A. Immediate container labels

i. 26 mL size

a. The primary objective should be to make the printed material as large and readable as possible. It may be necessary to reduce the sizes of the flame illustration and the "no pooling" symbol to facilitate this. Use of contrasting and colored inks to highlight important points is encouraged

b. The WARNING section should read as follows:

WARNING-

- Do not drape or use ignition source until the is completely dry
- Do not allow to pool. Remove solution material

*

ii. 6 mL size

a. The primary objective is to make the printed material as large and readable as possible. It may be necessary to reduce the sizes of the flame illustration and the "no pooling" symbol, or to eliminate one or both entirely, to facilitate this. Use of contrasting and colored inks to highlight important points is encouraged.

b. The WARNING section should read as follows:

- Do not drape or use ignition source until the is completely dry
- Do not allow to pool. . Remove solution material

*

c. A statement recommending this size for smaller surgeries may be added if space permits.

B. Inserts

i. 26 mL size (front)

a. The WARNING section should read as above for the immediate container label, with the exception that the phrase, "For external use only" should be retained.

b. [redacted]

ii. 26 mL size (back) (Drug Facts)

a. The WARNING section should read as above for the immediate container labels. If the sponsor wishes to retain the material which begins " [redacted] ', it may be moved to the Directions section.

b. The "Do not use" section should read as follows:

- in [redacted] less than 2 months of age [redacted]
- on patients with known allergies to iodine or [redacted]
- on open wounds, on mucous membranes or as a general skin cleanser.

c. The "When using this product" section should read as follows:

- keep out of eyes, ears and mouth. May cause serious injury if permitted to enter and remain. If contact occurs, [redacted] with cold water right away and contact a physician.
- [redacted]
- [redacted]

d. The "Stop use and ask a doctor" section should read as follows:

Stop use and ask a doctor if irritation, sensitization or other allergic reactions occur. These may be signs of a serious condition. [redacted] use has been associated with [redacted] skin blistering [redacted]

e. In the "Directions" section, "When Applying DuraPrep Solution" subsection:
- the first bullet should be (in bold font): [redacted] DO NOT SCRUB

f. In the "Directions" section, "After applying DuraPrep Solution" subsection:

iii. 6 mL size (front)

The WARNING should read as recommended for the larger size except the first statement concerning head/neck surgery should be omitted. It may be replaced by a statement recommending this size for smaller surgeries if desired.

iv. 6 mL size (back)

a. The "Do not use" section should read as recommended for the larger size.

b. The "When using this product" section should read as recommended for the larger size.

c. The "Stop use and ask a doctor" section should be revised as recommended for the larger size.

d. In the "Directions" section, "When Applying DuraPrep Solution" subsection, the first bullet should read (in bold font): , DO NOT SCRUB.

e. In the "Directions" section, "After applying DuraPrep Solution" subsection, the drying time should be (in two places).

C. Target Product Information Label

In the "Safety Studies" section, the second paragraph, concerning the cumulative irritation test, should read as follows:

In a 21-Day Human Cumulative Irritation Potential Test (LIMS 7294) involving 32 subjects, DuraPrep solution Base 10 cumulative irritation score when patched wet under occlusive conditions (the standard procedure for testing of this type) was 453.7 (Class 4: experimental 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).

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/s/

David Bostwick
8/5/04 11:10:28 AM
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Medical Officer's Review

NDA: 21-586/N-000
Product Name: DuraPrep Solution
Use: Patient Preoperative Skin preparation
Type of Document: Label Comprehension Study
Date Submitted: June 25, , 2004
Date Reviewed: July 19, 2004
Reviewer: Steven Osborne, M.D.

Table of Contents:

Purpose

The purpose of this review is to evaluate the Sponsor's applicator label and package insert comprehension study for DuraPrep solution, 26 ml, conducted in 2001.

Background

DuraPrep Surgical Solution is currently marketed as a patient preoperative skin preparation with professional labeling by 3M (the Sponsor). The product is an antiseptic with 74% isopropyl alcohol and 0.7% available iodine. The labeling has undergone changes since a 1998 meeting between FDA and the Sponsor. FDA recommended strengthening the warnings regarding flammability, following reports of fires in the operating room that occurred when drapes or material wetted with isopropyl alcohol caught fire. In 2001 the Sponsor performed a three-phase label comprehension study (the LC study), as part of the IND process, in support of their proposed labeling. The Sponsor forwarded a copy of the LC study to FDA in June 2004 as part of a package of information summarizing the major labeling revisions to DuraPrep Solution since the 1998 FDA meeting. This package of information submitted to the NDA for DuraPrep is currently under review by FDA.

Review

The LC study was performed in three phases with 10 nurses as participants in Phase 1, 11 nurses in Phase 2, and 7 physicians in Phase 3. After each evaluation phase, modifications were made to the applicator label and package insert based on comments from the participants and discussion between the participants and the Sponsor. 3M employees from hospital facilities in the [redacted] selected all participants. In general, the participants were familiar with DuraPrep solution. The nurses all regularly applied the product. The surgeons did not apply DuraPrep solution, but regularly performed surgery after someone else applied DuraPrep solution. The Sponsor did not seek to include novice users as they judged it unlikely that, under normal surgery prep conditions, a nurse or physician would use DuraPrep solution without any form of guidance, oversight, or instruction.

Phase 1 Evaluation

Ten nurses participated in the Phase 1 evaluation of the applicator label and package insert for DuraPrep solution. The nurses were interviewed at two hospitals in the [redacted] area on May 29th and May 30th, 2001. Seven of the participants were from [redacted] and three were from the [redacted] in [redacted].

All ten participants were female registered staff nurses who worked in operating rooms. Their ages ranged from 30 to 57 years old, with an average age of 45.7 years. Two participants were in orthopedic surgery; one participant in neurosurgery; one participant in cardiovascular surgery; and six were in general surgery.

All participants said that the circulating nurse usually applied DuraPrep solution. Five participants said that a surgeon or physician might apply DuraPrep solution on a less frequent basis. One participant said that the scrub nurse might apply DuraPrep solution on a less frequent basis. All ten participants were experienced users of DuraPrep solution and they estimated having used DuraPrep solution "hundreds of times". All participants had either used DuraPrep solution a few hours or a few days before being interviewed. All of the participants reported that they received their training in the use of DuraPrep solution through an in-service training.

Phase 2 Evaluation

Eleven nurses participated in the Phase 2 evaluation of the applicator label and package insert for DuraPrep solution. Participants were interviewed at [redacted] on June 18th and June 19th, 2001.

All eleven participants were female registered staff nurses who worked in operating rooms. One of the participants recently became a surgical educator, but had past

experience as a registered nurse. Their ages ranged from 38 to 57 years old, with an average age of 47.5 years. Two participants were in neurosurgery; two were in spine surgery; two were in neural-spine surgery; two were in ear, nose, and throat surgery; one was in orthopedic surgery; one was in cardiovascular; and one was in general surgery.

All participants said that the circulating nurse usually applied DuraPrep solution. Ten participants said that a surgeon or physician might apply DuraPrep solution on a less frequent basis. Of these ten participants, two said that a scrub nurse might also apply DuraPrep solution on a less frequent basis. One participant said that only the scrub nurse might apply DuraPrep solution on a less frequent basis. All eleven participants were experienced users of DuraPrep solution. Nine of the participants had used DuraPrep solution a few hours or a few days before being interviewed. Two of the participants had used DuraPrep solution a few weeks before being interviewed.

Phase 3 Evaluation

Seven surgeons participated in the Phase 3 evaluation of the applicator label and package insert for DuraPrep solution. The participants all used DuraPrep solution at hospitals in the [redacted]. The Phase 3 evaluation was conducted on July 30th, August 1st, 2nd, 9th, 15th, and 16th, 2001.

All seven participants were male surgeons who worked in operating rooms. Their ages ranged from 33 to 58 years old, with an average age of 46.9 years. Three participants were in cardiovascular surgery; two were in orthopedic surgery; and two were in general surgery. All participants said that the circulating nurse usually applied DuraPrep solution. Three participants said that a surgeon or physician might apply DuraPrep solution on a less frequent basis, such as in an emergency situation or when extending a prep area. Six of the seven participants said that they do not apply DuraPrep solution to a patient themselves. One of the six participants said that it had been years since he personally applied DuraPrep solution to a patient. One participant said that he personally uses it on a daily basis. Three of the participants reported that they learned to use the product through instructions from an operating room nurse. Two participants learned through their residency training. Another received training through an in-service.

Comments:

1. The Sponsor did not make it clear how it recruited participants. There are no listed inclusion criteria other than working in the selected hospitals in the [redacted] area. There are no listed exclusion criteria.

2. Highly trained surgical nurses and surgeon-physicians who already used the DuraPrep Solution product might be expected to understand the label graphics and text. Their selection as participants is a bias in this study.

3. Selection of non-surgical nurses instead of surgical nurses and medical students instead of surgeon-physicians might have provided a better assessment of label comprehension.

4. It is not clear why only physicians were tested in Phase 3 and why only nurses were tested in Phases 1 and 2, instead of a mixture of health care professionals in all Phases.

4. There is no apparent randomization in the selection of participants from a larger pool of potential participants. Conceivably, the selected pool could have indicated a familiarity with the DuraPrep Solution, leading to bias.

Questionnaire Methodology

The Phase 1 and 2 evaluations consisted of face-to-face interviews, while the Phase 3 evaluation consisted of telephone interviews conducted individually with each participant. The length of these interviews was typically 25-35 minutes. The participants were told that they were participating in a study that would gather their impressions of product information provided with the DuraPrep Surgical Solution. None of the participants that were asked to participate in the interview declined to participate. Each participant received either a $25 gift certificate or a 3M gift box as a result of their participation.

The interviews were facilitated using a questionnaire and supplemented by discussion prompted by participant comments. The Sponsor mailed the study materials to the participants in Phase 3. In all three phases the questionnaire was divided into three parts:

Part 1 – Comprehension of the Illustrations on the Label
Part 2 – Ease of Reading and Comprehension of Label Text
Part 3 – Ease of Reading and Comprehension of Package Insert Text

Part 1 – Comprehension of the Illustrations on the Label

The participants were provided with the prototype applicator label and asked to read the section on the label entitled, "Warning". When the participant had finished reading the label, the applicator label was taken from the participant. At this time, the participant was provided with a version of the label that either did not have text or covered the text in order to show only the illustrations (this depended on whether or not it was a face-to-face interview or a telephone interview). The subsequent panels of the label were covered to only expose one illustration at a time. The participants were asked what each of the illustrations meant to them.

For each illustration, the questionnaire contained a table with specific concepts or interpretations of the illustration. If a participant reported a concept, the interviewer would place a "4" in the box next to that concept. If the participant reported additional concepts that were not in the table of concepts, the interviewer would record these concepts in the "Other/Comments" section on the questionnaire.

Comments:

1. The Sponsor does not state whether or not the table was visible to the participants.

2. The Sponsor does not state whether or not any of the "Other/Comments" by the participant were recorded verbatim or paraphrased by the interviewer.

3. The Sponsor does not explain how they verified that participants in Phase 3, the telephone interviewees, removed or covered up the applicator label.

Part 2 - Ease of Reading and Comprehension of Label Text

The participants were provided with the applicator label with the "Warning" panel faced towards them. Each panel was covered sequentially and the participant was asked if there were any words or phrases that were difficult to read or understand. If the respondent reported any words or phrases, the interviewer would circle these on the label provided in the questionnaire. The comments that the participant reported would either be recorded near the label provided in the questionnaire or recorded in the Other-Comments section. If the participant did not report any words or phrases, a checkmark was placed to the right of the label provided in the questionnaire.

In Phases 2 and 3, the participants were then asked to report what the label was telling them to do (or not to do) in order to prevent fire. In Phase 1, they were asked to explain to a new user what conditions might lead to a fire and how fire should be prevented. *In all phases, the applicator label was either taken away from the participant or covered up and removed from sight.*

Comments:

1. The Sponsor does not state how long the participants were permitted to view the label before it was covered up.

2. The Sponsor does not explain how they verified that participants in Phase 3, the telephone interviewees, removed or covered up the applicator label.

3. Removal of the applicator label from the participant's sight helps to avoid a potential bias in this LC study (in that study participants might review the labeling more than actual users).

In Phase 1, the questions were asked to elicit a "free response" from the participant while the interviewer would record the responses on the questionnaire. However, in Phases 2 and 3, the questionnaire contained a table with specific "main responses" and three columns next to the specific "main responses": Reported, RAFP (Reported after Follow-up Prompt) and RAD (Recognition after Discussion).

Main Response	Reported	RAFP	RAD
Do not drape until dry			
Do not use cautery until dry			
Do not allow solution to pool			

Beside each "main response" (e.g., Do not drape until dry) were columns into which the interviewer would place marks. If, after asking the question, the respondent reported with something like "Always wait before the prep is dry before draping", the interviewer would place a "4" in the column labeled "Reported". This meant that the participant "reported" this "main response" in response to the question without any further probing or other intervention on the part of the interviewer.

After the participant provided an initial response to the question, the interviewer would examine the list of "main responses" to determine if they had all been reported. If there was one or more "main responses" that the participant did not report freely, the interviewer would follow up with a non-leading probe, such as "Anything else?", "What do you mean by...." or "Could you be more specific as to what you meant by...". If any of the "main responses" were accurately reported after this follow-up prompt a checkmark was placed in the column labeled RAFP.

If, after this non-leading follow-up probe, there were still "main responses" that were not reported by the participant, a more detailed question would be asked to determine if the participant failed to clearly describe components of the messages. The purpose of this final step was to determine if participants really misunderstood the meaning being conveyed or whether they simply failed to report a particular "main response". For example, if they simply forgot to state a certain point in the midst of their lengthy description of other "main responses", they may have thought that their previous answer presumed another component of the messages, etc.

The detailed follow-up question involved having the interviewer provide the participant with the intended meaning of the "main response" in a form such as "Is it your understanding that you should not drape until the prep is dry?" If respondent responded affirmatively to the follow-up question, a checkmark was placed in the column labeled RAD. A check in this column indicates that, while the participant did not report it freely, they still understood that the label was providing that information and that they understood it as intended. If participants responded negatively, then an "X' was placed in the RAD. column, indicating that they did *not* properly understand this component of the label. The interviewer recorded any additional responses that were not listed in the "main responses" either in the "Other/Comments" section or below the table on the questionnaire.

Comments:

1. *It is not clear whether or not the interviewers used scripted follow-up questions.*

2. *The leading question "Is it your understanding that you should not drape until the prep is dry?" contributes a bias.*

Part 3 - Ease of Reading and Comprehension of Package Insert Text

In all three phases of evaluation, the participants were provided with the package insert and asked to familiarize themselves with the text. The interviewer then asked the participants about particular sections within the insert (e.g., 'Warning box', 'When Applying DuraPrep Solution', 'After Applying DuraPrep Solution', 'After DuraPrep Solution is Dry'). Each of these sections was divided into subsections.

For each of these subsections the participants were asked two questions. The first question asked the participant to report any words or phrases that they found difficult to read or understand. If the participant reported any words or phrases, the interviewer circled these on the insert provided in the questionnaire. The comments that the participant reported would either be recorded near the insert provided in the questionnaire or recorded in the "Comments" section.

The second question asked the participant to rate their understanding of the message in the subsection using the following scale:

1. understand completely
2. understand mostly
3. understand some
4. understand a little
5. don't understand at all

The interviewer recorded the reported scale rating and any comments in the table provided in the questionnaire. If a scale rating lower than a "1" rating was reported, the interviewer would discuss the subsection with the participant in order to increase their understanding. However, after this discussion, the initial scale rating that the participant reported remained on the questionnaire.

The participants were also asked several "Background Questions" about their experiences with DuraPrep Surgical Solution. If time permitted in the interview, they were also asked if they thought there were any messages or concepts that should either be removed from or added to the applicator label. They were also asked to describe how they typically activate the applicator and how they hold it while prepping the patient.

Comment:

1. Participants who said that they understood mostly or completely did not undergo testing to prove their understanding. A scenario question might have helped to verify their understanding.

Summary of Results and Modifications to Labeling After Evaluation Phases

After each evaluation phase, modifications were made to the applicator label and package insert based on comments from the participants and discussions with the Sponsor. Below is a brief discussion of the modifications that were made to the labeling from Phase 1 through Phase 3.

Applicator Label

In all phases of the evaluation, the participants found the text and illustrations on the label easy to read and fully understand. None of the responses indicated a lack of comprehension or significant difficulty reading or understanding any element of the label. One illustration that was intended to illustrate the concept of "Wait" was not as reliably understood and appeared to have the potential for conveying the opposite meaning. As such it was discarded and replaced with the text, "[redacted] in capital, bold letters.

The majority of the participants said that there were no messages or concepts that they would add to the label. There were three participants that suggested adding to or expanding upon concepts in the label. One participant suggested that phrases should be added to the label which addresses that drapes should not be applied over wet prep because vapors could collect underneath the drapes. A second participant commented that the concept of '[redacted]' should be added to the label. A third participant commented that [redacted] should be added to the label. In addition, there were other comments regarding how the text and illustrations could be clarified or rearranged on the label. These comments were taken into consideration when modifications were made to the label.

With the exception of one participant, no other participants said any message that should be removed from the label. The one participant suggested that "[redacted] Solution contains alcohol and gives off flammable vapors" should be removed because it is an obvious concept.

One response suggested that the user be instructed to hold the applicator in a manner that does not obstruct the view of the proposed label.

Throughout the discussions with the participants, there were a number of comments and suggestions that led to minor labeling modifications. Some examples of the modifications include the following:

1. using the word "cautery" instead of "[redacted]" to account for any battery-powered cautery in the operating room
2. adding text to the cautery instrument in the 'cautery and flame' illustration in order to clarify the type of instrument that may cause a fire
3. re-arrangement of text associated with the 'cautery and flame' illustration
4. highlighting the phrases "flammable vapors" and "Do not drape or use [redacted]"

Comments:

1. The Sponsor highlighted the phrase "flammable vapors" in the proposed label, but apparently did not highlight the phrase "Do not drape or use [redacted]' in the proposed label.

2. The Sponsor did not provide actual data showing the checkmarks in the boxes of the questionnaire for Phases 2 and 3, or all of the free responses for Phase 1.

Package Insert

The following sections provide an overview of the results of the ease of reading and comprehension evaluation related to the package insert. Minor modifications were made to the text throughout the phases based upon the participants' comments. Examples of the modifications to the various subsections of the package insert are also discussed in each section below. For consistency, the modifications that were made to the illustrations and text on the applicator label throughout the evaluation phases were also made to the insert after each phase.

•Warning Box Text

All of the participants found most of the messages in the 'Warning Box' subsection to be easily read and fully understood. A few participants who said something other than "understand completely" made comments related to the following:

A. Suggested addition of information or replacement of words or phrases to further clarify the concept and more accurately portray the usage in their particular facility, such as:

1. the time needed for prep to dry in hair
2. [redacted]
3. clarification of statements that describe additional situations in which to wait for prep to dry

B. Re-read the text to understand its meaning (e.g., waiting for prep to dry in somewhat unusual situations)

C. Compared text in other subsections and noted what appeared to be conflicting information (e.g., blot the hair, do not blot the skin).

The comments that were received from the participants were considered when modifying the insert. Below are some examples of modifications to the 'Warning Box' subsection:

1. format of the three statements: (a) the prep area to be extended, (b) prep for an additional procedure, and (c) re-application of prep, was changed to an indented list of bullets to enhance ease of processing.

2. word "laser" was included in addition to the word "cautery" as a source of ignition that might be used in the operating room.

3. text related to the drying of prep that accidentally gets in the hair was modified in response to participants' comments and discussions amongst 3M team members.

4. text related to the removal of prep if it accidentally gets in the hair.

•When Applying [redacted] Solution

All of the participants found most of the numbered steps in the 'When Applying [redacted] Solution' subsection to be easily read and fully understood. A few participants that indicated something other than complete understanding of the words and/or phrases made comments related to:

1. the location of cotton swab
2. the use of a substitute for gauze
3. the method for applying prep (going back over areas already prepped, or scrubbing prep on skin)
4. the use of the sponge applicator to absorb excess solution
5. the phrasing of how skin will adhere to skin.

The comments that were received from the participants were considered when modifying the insert throughout the evaluation phases. Below are some examples of modifications to the 'When Applying [redacted] Solution' subsection:

1. the text related to removing prep if it extends past the prep area and if it pools on or around the patient was clarified
2. the text related to the location of the cotton swab
3. the text related to not scrubbing the prep on the skin was highlighted in bold text
4. the text related to the potential for skin to adhere to skin was clarified

Comment:

1. The applicator label mentions that two cotton swabs are contained in the package. The package insert does not mention cotton swabs.

•After Applying [redacted] Solution

All of the participants found most of the messages in the 'After Applying [redacted] Solution' subsection to be easily read and fully understood. A few participants that said something other than "understand completely" made comments related to the concept of 'blotting' and noted possible inconsistencies with the text that describes this concept within the insert.

The comments that were received from the participants were considered when modifying the insert throughout the evaluation phases. Below are some examples of modifications to the 'After Applying DuraPrep Solution' subsection:

1. word "laser" was included in addition to the word "cautery" as a source of ignition that might be used in the operating room
2. text related to the drying of prep that accidentally gets in the hair was modified in response to participants' comments and discussions amongst 3M team members
3. text related to the removal of prep if it accidentally gets in the hair
4. the text was clarified for how to remove prep if it pools on or around the patient.

•After [redacted] Solution is Dry

For the queried text in the subsection, 'After [redacted] Solution is Dry', all of the participants said that they "understood completely" all of the words and/or phrases.

Comment:

1. The Sponsor summarized the results of the evaluation phases and provided samples of comments from the participants, but did not provide the raw data.

Summary

The Sponsor performed a three-phase LC study with surgical nurses and surgeons to ensure that users of the DuraPrep Solution could properly interpret the symbols and text on the proposed label. In particular, users needed to understand the warning symbols and text regarding potential flammability of the product in the operating room where cautery, spark, or flame could ignite the isopropyl alcohol in the product. The Sponsor provided a detailed protocol and methods but the results were in a summary format, without raw data.

The study has many flaws. However, providing that the raw data validates the Sponsor's summary of the results, then the Sponsor's LC study supports that surgical nurses and surgeon-physicians, with prior DuraPrep experience, can comprehend the Sponsor's

proposed applicator label for DuraPrep Solution. By comparison, the method of questioning about the package insert was so flawed that the resulting data is not useful. The Sponsor did not include other healthcare workers who might use the product, such as non-surgical nurses and medical students, in the LC study. The sponsor did not assess whether the illustrations added to, decreased, or had any effect on participants' understanding of the label.

Conclusions

The Sponsor's LC study, although very small, supports that surgical nurses and surgeon-physicians, with prior DuraPrep experience and training, can comprehend the Sponsor's proposed applicator label for DuraPrep Solution. The LC study does not show that other healthcare workers who might use the product, such as non-surgical nurses and medical students, can comprehend the Sponsor's proposed applicator label or insert for DuraPrep Solution. The applicator label and package insert tested are not identical to the Sponsor's proposed label for the NDA product. This LC study showed that participants understood the illustrations per se, but the Sponsor did not study what contribution, if any, that the illustrations added to the participant's understanding of the applicator label or package insert.

Recommendations

1. The study results suggest that the labeling use the word *cautery* instead of

2. Additional modifications are probably not needed to enhance comprehension of the proposed applicator label by a sophisticated healthcare worker.

3. No meaningful recommendation can be made about the package insert.

4. This study does not permit a meaningful recommendation about a contribution of the illustrations to a user's comprehension of the package insert or applicator label.

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