CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-586

MEDICAL REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Nonprescription Clinical Evaluation
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
301.796.2280

MEMORANDUM

Date: **October 5, 2006**

From: **Joel Schiffenbauer, M.D.**
Deputy Director, DNCE

Subject: **NDA 21-586**

Sponsor: **3M**

This document serves as an addendum to my previous review of NDA 21-586 dated September 20, 2006. DSI conducted their inspection for this NDA on July 17-18, 2006. I received 2 items from DSI, after the action on this application was taken on September 29, 2006, the PDUFA date. The first item was dated September 29, 2006 (5:17 PM) and the second dated October 2, 2006. The first item is a copy of a letter sent to [redacted], the investigator for study #05-010214, in regards to protocol violations in which four subjects had bacterial counts completed by non-blinded study staff. Specifically the letter states the following:

The protocol specified that study staff performing the bacterial enumeration not be involved in the investigational material application or the collection of samples. According to our investigation, four subjects #009, 013, 015, and 026 had bacterial enumeration performed by study staff who were not blinded to the test materials.

The conclusion by the DSI reviewer was that this deviation was unlikely to affect the overall data integrity and reliability of the study.

The second item is a copy of the reviewer's actual review which supports this conclusion. The reviewer also comments that the study appears to have been well conducted.

I agree with the conclusion that the protocol deviation is unlikely to affect the overall data integrity and reliability of the study, as bacterial counts are an objective measure of efficacy and are not likely to be subject to bias. No further action is warranted.

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Joel Schiffenbauer
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Toxicology: **No new data submitted.**

Clinical Pharmacology: **No new data submitted.**

Chemistry: **No new data submitted.**

Efficacy:

The single efficacy study submitted entitled "Study to assess the antimicrobial effectiveness of 3M DuraPrep surgical solution against resident human skin flora on the groin area" was reviewed in detail by Dr. Rogers. Please see her review for study design details.

A total of 80 subjects were enrolled. The sponsor's analysis included data from 66 subjects for the 10 minute evaluation, excluded data from 15 subjects who either had at least one side of the groin area baseline log value not reaching 5, or who did not have paired data available at the time point of interest.

In this study both DuraPrep and Hibiclens met the TFM criteria of a 3 log reduction in bacterial counts at 10 minutes post application (see Table, below). Counts also remained below baseline at 6 hours and at 24 hours post application. DuraPrep also met the 3 log reduction using the 95% confidence interval approach (95% CI was 3.09 to 3.55 at 10 minutes; see also Tables 1 and 2 in Dr. Rogers' review). In addition, 61% of subjects treated with DuraPrep met the TFM criteria compared to 68% of subjects treated with Hibiclens.

As Dr. Lin points out, even subjects who did not start with a 5 log bacterial count could still have a 3 log reduction in counts, and so could have been included in the ITT analysis. Dr. Lin re-analyzed the data including all 80 subjects and at the 10 minute time point, the results of this analysis are not significantly different from those of the sponsor's analysis of 66 subjects, which is reassuring.

However, Dr. Lin also points out a number of design issues that might have an impact on the outcome of the study. First, this was a single center study and was not conducted at a center where a previously negative result was obtained. Second, the only group that is truly blinded are those individuals performing bacterial counts. The application phase is not blinded because differences in the treatments (application technique, color) does not allow for this. However even considering these issues, Dr. Lin's conclusion is that it is likely that the study showed a mean reduction in microbial counts in the groin of 3 logs.

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Safety:

Dr. S. Osborne reviewed the safety data submitted. This included safety data from 5 new clinical studies, an overall analysis of safety from previous studies, post-marketing data, FDA AERs data, and a literature search. Safety data is provided for 795 subjects enrolled in a total of 20 clinical trials. In general DuraPrep was well tolerated. There were no significant safety risks identified in clinical studies. There were no serious AEs related to DuraPrep solution. There was an increase in the number of subjects with any treatment emergent AE with Duraprep compared to Betadine, for example (15% vs 10.5%; see Table 1 in Dr. Osborne's review). There was an increase in application site burning with Duraprep compared to Betadine (4.5% vs 2.4%; see Table 2 in Dr. Osborne's review). In an analysis of post-marketing reported AEs, the 3 most commonly reported events were skin irritation (382 events), infection (109 events), and flammability (97 events) out of 79 million units sold. Of these, flammability appears to be an AE that can be further addressed with appropriate labeling warnings (see below). A concern with the use of this product is that excess fluid either pools or gets into hairy areas, and does not dry adequately, resulting in the potential for fire with the use of electrocautery. Of note, the 6 ml applicator has been associated with only one case of flammability and the remainder of the cases are associated with use of the 26 ml applicator, reinforcing the idea that excess fluid may result in inadequate drying and the potential for fire hazard. However, I do not believe that the 26 ml applicator product should be contraindicated, at least in part because it is likely that multiple 6 ml products would be used in its place, which will ultimately deliver a comparable volume of product.

Skin irritation was also further evaluated and a breakdown of AEs subsumed under this heading provided (see Table 9). Terms such as blistering, chemical burn are reported with DuraPrep. I agree with Dr. Osborne's comment that since some of these events are severe, and further that these events should be described in the TPI (a breakdown of skin irritation events has been added to the TPI).

Pediatrics:

The Division consulted the Pediatric and Maternal Health Team in regards to the use of Duraprep in the pediatric population. Current draft labeling reads:

The PMT agreed that the age cutoff of 2 months is appropriate for Duraprep. In addition they made labeling recommendations as follows:

requires further discussion. When electrocautery is used in the situation where DuraPrep has not adequately dried, fire may occur. There are 2 instances where this situation may occur. First, when the liquid pools, and second, in the case where the liquid gets onto a hairy area of the body and does not adequately dry. I believe it unlikely that contraindicating the 26 ml applicator would resolve this problem as one could still use multiple 6 ml applicators. Furthermore, especially in many instances where there is a large surgical area, a 26 ml applicator would be appropriate and convenient for use. I believe that the Division's recommendations to the sponsor in terms of labeling changes, in this regard (do not use 26 ml applicator for head and neck surgery) will at least in part address this problem, and the phase 4 commitment to better define drying times will also address this issue.

I believe it would be also be beneficial to actually identify the requirements for drying times in situations where DuraPrep gets onto hairy areas. At present the label says that drying times may be longer than 3 minutes but does not provide any additional recommendations to the user, other than to be sure the area is dry. It is unclear how drying times in hairy areas or in a setting where visualization is difficult, can be adequately quantified. It is reasonable to ask for a study to examine actual drying times in hairy areas, and a vapor assessment, as a phase 4 commitment. Trial design will need to be further discussed .

Recommendations:

Therefore, based on the above discussion, it is recommended that this NDA be approved. As the flammability issue is a preventable adverse event, the sponsor has committed to further study drying times and vapor assessment as a phase 4 commitment, especially in regards to Duraprep getting into hairy area. This information will allow the label to better inform users of appropriate drying times and should provide for the safe use of this product.

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M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: July 14, 2006

FROM: Jean Temeck, M.D.
Acting Team Leader
Pediatric and Maternal Health Team

THROUGH: Lisa Mathis, M.D.
OND Associate Director
Pediatric and Maternal Health Team

TO: Andrea Leonard Segal
Acting Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Drug Products

SUBJECT: Input requested from the Pediatric and Maternal Health Team (PMHT) regarding the appropriate age cut-off for use of DuraPrep Surgical Solution, an iodine-containing product, and the need for additional labeling

Background

DuraPrep Surgical Solution is a topical antimicrobial product indicated for pre-operative skin preparation. It contains two active ingredients, an iodophor (0.7% available iodine) and isopropyl alcohol (74% w/w). The product is applied topically to the pre-operative area, which may potentially cover an area from the neck to the groin. It is recommended that the product remain on the skin after the surgical procedure because it continues to kill bacteria for up to 12 hours and maintains low bacreia counts under dressings for up to 3 days. The film will gradually wear away.

DuraPrep Surgical Solution has been marketed in the United States as an OTC product since 1988 under the 1978 tentative final monograph (TFM) for OTC Health Care Antiseptics. An amended TFM was published in the Federal Register on June 17, 1994, which did not include the active iodine ingredient in DuraPrep. As such, DuraPrep was considered a new drug and required submission of an NDA. NDA 21-586 was submitted on October 27, 2003. In their NDA submission, the Sponsor, 3M, requested a full pediatric waiver. In a meeting held prior to the NDA submission End-of-Phase II meeting on November 6, 2000), the Review Division stated: "if 3M agreed to inclusion of contraindication for use in children less than 2 months of age, then a study in pediatrics

would not be required." The Sponsor has agreed to this and the current draft labeling reads: [redacted]

The Review Division believes that efficacy data in adults can be extrapolated to the pediatric population. However, they have concerns regarding safety. The consult specifically states: "Although below 2 months of age is the standard cut-off for other healthcare antiseptic 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 being appropriate to [redacted]

Of note, the Agency issued an approvable letter to the Sponsor on August 27, 2004 pending conduct of a clinical study in which a mean three $\log_{10}$ reduction in skin flora on the groin at 10 minutes post-application is demonstrated for DuraPrep Surgical Solution. The Sponsor has conducted this study and submitted it to the Agency on March 28, 2006. In a letter dated May 16, 2006, the Agency acknowledged the Sponsor's complete response to their August 27, 2004 action letter. The user fee goal date is September 29, 2006.

Review

Search of the literature and AERS was conducted to determine the risk of iodine-induced hypothyroidism.

Several articles in the literature were identified that reported primary hypothyroidism (i.e. elevated serum TSH and decreased T_4) in infants exposed to topical iodine-containing products. They are summarized below.

A prospective controlled study was conducted in the United States by Brown et al[1]. The objective of this study was to determine the effect of routine skin cleansing with 10% povidone-iodine (betadine, equal to 1% available iodine) on the thyroid function of pre-term neonates, ≤36 weeks of age. The iodine was applied to the skin prior to procedures such as lumbar puncture, blood culture, bladder tap or insertion of an umbilical or bladder catheter. The control group was treated with chlorhexidine, which does not affect thyroid function. After a single application of povidone-iodine, 1 of 5 infants in whom thyroid function was measured between day 1 (baseline, i.e. prior to exposure) and day 4 post-exposure, developed transient hypothyroidism. None of the 6 patients in the control group developed hypothyroidism during this period. After two or three applications of povidone-iodine, 1 of 7 neonates developed transient hypothyroidism compared to 0/2 in the control group. Urinary iodide excretion was markedly elevated, up to 88 times the control value. The authors recommend that iodine-containing solutions be used with caution in newborns, particularly in those of very-low-birthweight, and, if repeated skin cleansing is thought necessary, thyroid function should be monitored carefully.

[1] Brown Rosalind S et al. Routine Skin Cleansing with Povidone-Iodine Is Not a Common Cause of Transient Neonatal Hypothyroidism in North America: A Prospective Controlled Study. Thyroid 1997;7(3):395-400.

Smerdely et al[2] (Australia) compared thyroid function of very-low-birthweight (VLBW: <1500grams) infants admitted to neonatal intensive care units (NICU) at two hospitals. One hospital routinely used topical iodinated antiseptic agents (10% povidone-iodine solution) and the other used chlorhexidine-containing antiseptics for insertion of intravenous cannulae and blood gas determinations. Within 14 days, 25% (9/36) neonates exposed to iodine, had elevated serum TSH levels (>20 mIU/L). 4 of these 9 infants developed transient hypothyroidism; therefore, thyroxine therapy could be discontinued by hospital discharge.These disturbances in thyroid function correlated with elevations in urinary iodine excretion. None of the control infants (0/27) developed abnormalities of thyroid function. The authors conclude that since topical iodine-containing antiseptics may cause hypothyroidism during a critical period of neurological development in the newborn infant, the routine use of iodine antisepsis in VLBW infants should be avoided.

Weber et al[3] (Italy) conducted a retrospective study of 40 neonates (7 pre-term and 33 full-term) who had transient neonatal hypothyroidism to determine its etiology. The most common etiology (23/40= 58% neonates) of the transient hypothyroism was iodine overload due to maternal (n= 11) or neonatal exposure (n= 12). Regarding maternal exposure, antiseptics containing iodine were used for vaginal applications before and after giving birth in 2 mothers; at delivery, in 7 and for skin application during the second trimester in 2 mothers. Among the neonates, topical iodine antiseptics were applied in 7 [for skin disinfection (before and after surgical intervention) in 3 cases and for umbilical cord disinfection in 4] and iodine containing contrast media was administered to 5 neonates. Preventive measures recommended by the authors include: withdraw iodine disinfection from obstetric and neonatal clinics and substitute chlorhexidine; inform pregnant women of the adverse effects of iodine products (e.g. disinfectants) and monitor thyroid function when iodine us used.

In a study conducted by Jeng et al[4] (Taiwan), one VLBW newborn developed transient primary hypothyroidism after a single application of 10% povidone-iodine which was applied from the fingertips to the shoulder joint of one upper extremity for percutaneous central venous catheter insertion at 48 hours of age. The authors state that thyroid function should be monitored in VLBW infants who are treated with iodine-containing products and to avoid use of povidone-iodine as an antiseptic agent on a wide skin surface for VLBW infants, even in an area of high iodine intake.

Chabrolle JP and Rossier[5,6] (France) reported the development of transient primary hypothyroidism in 4/30 (17%) neonates (birthweight: 2200-3350grams, gestational age:

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[2] Smerdely P et al. Topical Iodine-Containing Antiseptics And Neonatal Hypothyroidism In Very-Low-Birthweight Infants. Lancet 1989;2:661-4.

[3] Weber G et al. Neonatal transient hypothyroidism: aetiological study. Arch Dis Child Fetal Neonatal Ed 1998;79:F70-F72.

[4] Jeng M-J et al. The Effect of Povidone-iodine on Thyroid Function of Neonates with Different Birth Sizes. Acta Paed Sin 1998;39:371-5.

[5] Chabrolle JP and Rossier A. Goitre and hypothyroidism in the newborn after cutaneous absorption of iodine. Archives of Disease in Childhood 1978;53:495-498.

[6] Chabrolle JP and Rossier A. Transient neonatal hypothyroidism. Pediatrics 1978;62(5):857.

not reported) who were exposed to repeated topical applications of 1% iodine alcohol for such procedures as heelsticks, venopunctures, scalp vein infusions and blood cultures for a mean duration of 4.8 days. The hypothyroidism was accompanied by goiter and marked ioduria. In all cases, resolution was attained with thyroxine replacement therapy for 15 days to 3 months. The authors conclude that iodine should not be used as a skin disinfectant in young infants.

Coakley JC et al[7](Australia) reported that 14 of 24 cases of transient primary hypothyroidism detected in the Victorian Neonatal Thyroid Screening Programme between May 1997 and December 1986 were due to excessive iodine intake. In two of these cases, this was due to maternal oral ingestion of iodine-containing medications during pregnancy and, in 12, the babies received 10% povidone iodine (Betadine) topically for post-operative antisepsis. The duration of Betadine application was listed as "nil" in 4 of the 12 cases, and, in the remaining 8, it ranged from 2 weeks-2 months. Treatment with thyroxine was instituted in 8 of these 12 patients (the other 4 patients became euthyroid upon cessation of Betadine). The authors conclude: "The large number of cases due to the topical application of iodine antiseptic emphasizes the need for caution when using this substance in neonates."

L'Allemand et al[8] (Germany) prospectively studied the effect of prenatal and perinatal exposure to povidone-iodine on thyroid function in 66 mothers and their infants compared to a control group of 18 mothers and their infants who were not exposed to iodine. For disinfection during labor and delivery, a catheter was attached to the scalp electrode for fetal heart rate monitoring and a 2% solution of povidone-iodine was pumped through with a velocity of 6 ml/min. In cases of premature ruptured membranes, the birth canal was continuously rinsed with 1% povidone-iodine solution until delivery. These solutions release 7-10% free iodine. The duration of treatment ranged from 5 to 30 hours, with a median of 17 hours.20% of the neonates in the iodine-exposed group developed transient primary hypothyroidism on days 3-5 of life compared to none in the control group. Thyroid function normalized on day 14 of life. The authors recommend that iodine not be used in pregnancy or in the neonate when follow-up of the newborn infant cannot be guaranteed.

Iodine-induced hypothyroidism has been reported in nursing infants (ages 14 days with unreported GA, age 29 days with GA 29 weeks, and age 6 weeks in a full-term infant) whose mother used topical or vaginal iodine-containing preparations during pregnancy or after delivery[9,10,11].

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[7] Coakley JC et al. Transient primary hypothyroidism in the newborn: Experience of the Victorian Neonatal Thyroid Screening Programme. Aust Paediatr J 1989;25:25-30.

[8] L'Allemand D et al. Iodine-induced alterations of thyroid function in newborn infants after prenatal and perinatal exposure to povidone iodine. J Pediatr 1983;102(6):935-938.

[9] Casteels K et al. Transient neonatal hypothyroidism during breastfeeding and post-natal maternal topical iodine treatment. European J Pediatr 2000;159(9):716-717.

[10] Danziger Y et al. Transient congenital hypothyroidism after topical iodine in pregnancy and lactation. Arch Dis Child 1987;62:295-296.

[11] Delange F et al. Topical iodine, breastfeeding and neonatal hypothyroidism. Letter to editor. Arch Dis Child 1988;63:106-107.

Hyperthyrotropinemia (elevated TSH) has been reported in full-term newborns after repeated topical applications of povidone-iodine[12,13].

A search of AERS conducted on 7/10/06 revealed 6 cases of neonatal hypothyroidism induced by exposure to iodine, 1 case of iodine-induced thyrotoxicosis in a 22 month old burn patient and 1 case of fatal iodine toxicity in a 9 week old infant.

The fatality (AERS report 3598776) occurred in a 9 week old infant who received an enema of 50ml of povidone-iodine diluted in 250ml of a bowel irrigant for the treatment of colic. When the enema was expelled, the infant was given 50ml of the described solution hourly for three doses by nasogastric tube. The infant was found lifeless three hours after the last dose and resuscitation was unsuccessful. Autopsy revealed a corroded and necrotic intestinal tract, serous fluid in body cavities and a massively elevated blood iodine level. This case was reported in Clinical Toxicology 1996;34(2):231-234.

The case of iodine-induced thyrotoxicosis in a 22 month old burn patient was reported in the Journal of Intensive Care Medicine 2002;28:1369. The mechanism of iodine-induced thyrotoxicosis is believed to be autonomy of thyroid function (AERS #3859363).

A brief summary of the 6 cases of hypothyroidism in neonates exposed to iodine follows:
-1 week old female infant of unreported gestational age (GA) was born to a mother who used betadine containing vaginal suppositories during the last week of pregnancy. The infant developed hypothyroidism (confirmed by thyroid function tests: TFTs) on day 3 of life. The hypothyroidism resolved within 5 weeks of initiation of l-thyroxine therapy (European report, AERS #3024170);

-A "newborn child" whose mother used povidone iodine surgical scrub 2-5x/day during first 6 months of pregnancy developed hypothyroidism (note: TFTs were not provided) (country of orgin was not reported, AERS #3790822);

-A pre-term infant (25 weeks GA) developed hypothyroidism (TFTs provided) after 20 days of treatment with povidone iodine applied tid to the scalp for thrombophlebitis and abscess from a peripheral venous catheter. The patient received l-thyroxine replacement therapy for 26 days. Delayed psychomotor development was noted at age 8 months and was thought to be secondary to prematurity. This case was reported in the literature (Khashu M et al. Iodine overload and severe hypothyroidism in a premature neonate. J Pediatr Surg 2005;40:E1-E4). The authors recommend that neonatal exposure to iodine should be minimized and if neonate is exposed to iodinated skin disinfectants, TSH should be routinely measured starting just after exposure (Canada, AERS #5768084).

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[12] Jackson H and Sutherland RM. Effect of Povidone-Iodine On Neonatal Thyroid Function. Lancet 1981:2:992.

[13] Lyen KR et al. Transient Thyroid Suppression Associated With Topically Appplied Povidone-Iodine. Am J Dis Child 1982;136:369-370.

-A 9 day old infant of 35 week GA became hypothyroid (TFTs provided) following pre-operative application of betadine for abdominal surgery (U.S. report, AERS #5980525);

-Premature twins (30 weeks GA) whose mother used polyvidone-iodine vaginal suppositories for 7 weeks during pregnancy developed transient hypothyroidism on day 5 of life. Both newborns had an enlarged thyroid gland on ultrasound and ioduria. L-thyroxine replacement therapy was begun on day 7 and discontinued during the 12th week of life. This case was reported in the literature (Muther S et al. Hypothyroidism in Dizygotic Premature Twins Due to Excessive Prepartum Vaginal Iodine Application to the Mother. Zentralbl Gynakol 2003;125:226-228). The authors conclude: "Due to the possible transfer of iodide to the fetus associated with the risk of iodine-induced hypothyroidism, it is recommended to abstain from vaginal application of iodine during pregnancy." (Germany, AERS #4034932 and 4034951)

Discussion and Conclusions

Iodine readily crosses the placenta and is also concentrated in the mammary gland and secreted in breast milk. Since iodine crosses the placenta it can suppress the thyroid gland of the developing fetus. After birth, the neonate, particularly the pre-term infant is vulnerable to hypothyroidism from exposure to iodine-containing products, including disinfectants. There are several reasons for this. Newborns are particularly susceptible to percutaneous drug toxicity due to their higher body surface area-to-weight ratio. Premature newborns are particularly vulnerable due to the immaturity of their epidermal barrier, immaturity of their drug metabolizing systems, immaturity of their kidneys (resulting in less efficient excretion of iodine) and immaturity of their thyroid gland function. High plasma iodide concentrations inhibit thyroid hormone production and release. This phenomenon, known as the Wolff-Chaikoff effect, is thought to be mediated by high intrathyroidal concentrations of inorganic iodide. Full-term newborns can inhibit iodide transport into the thyroid gland in response to an increased iodide load (i.e. they can down-regulate the thyroid/plasma iodide pump or counteract the Wolff-Chaikoff effect). However, since this compensatory mechanism does not mature until the last 4 weeks of pregancy, pre-term newborns are particularly vulnerable to hypothyroidism from excess iodine exposure. Although iodine-induced hypothyroidism is transient, even transient hypothyroidism should be avoided during this critical phase of brain development to prevent loss of intellectual capacity[14,15,16]. With regard to immaturity of the epidermal barrier, in pre-term infants, this barrier matures rapidly, over 2 to 4 weeks, although in ultra low birth weight infants, it may take significantly longer[17].

Both the literature and AERS highlight the suscetibility of the fetus and neonate, particularly the pre-term and very-low-birthweight neonate to the potential for thyroid

[14] Calaciura F et al. Childhood IQ measurements in infants with transient congenital hypothyroidism. Clinical Endocrinol 1995;43:473-477.
[15] Bongers-Schokking JJ et al. Influence of timing and dose of thyeroid hormone replacement on development of infants with congenital hypothyroidism. J Pediatr 2000;136(3):292-297.
[16] Fisher DA. The importance of early management in optimizing IQ in infants with congenital hypothyroidism. J Pediatr 2000;136(3):273-274.
[17] Mancini A. Skin. Pediatrics 2004;113(4):1114-1119.

suppression from exposure to excesss iodine. The risk is greater in areas of iodine-insufficiency such as certain European countries (e.g. Italy) compared to iodine-sufficient areas, such as the United States and Australia. This may be due to the more avid uptake of iodine by the thyroid gland in humans who live in iodine-deficient areas or areas of marginal iodine intake. However, even in iodine-sufficient areas, there are reports of iodine-induced hypothyroidism during the newborn period.

Of note, the OTC label for betadine (10% povidone-iodine which is equal to 1% available iodine) does not contain a contraindication regarding use below a certain age range. It is recommended that all iodine-containing antispetics warn of the risk of iodine-induced hypothyroidism in neonates, particularly pre-term and VLBW infants.

Recommendation
The age cut-off of 2 months which is the standard cut-off for healthcare antiseptic products as stated by the Review Division is also appropriate for DuraPrep Surgical Solution.

Regarding additional labeling recommendations, PMHT recommends that the Contraindication section of the proposed draft labeling for DursPrep Surgical Solution be revised to read: "

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Lisa Mathis
7/21/2006 05:43:19 PM
MEDICAL OFFICER
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REVIEW MEMORANDUM

Date: August 26, 2004

From: John K. Jenkins, MD
Director
Office of New Drugs

To: NDA 21-586

Subject: OND IO decision on action

This memorandum is written to document my decision on the issue of the appropriate regulatory action for this review cycle for the Duraprep Surgical Solution NDA. This application is the subject of an internal disagreement between the two divisions and offices responsible for its review for approval as a topical antiseptic for pre-operative skin preparation. I have carefully considered the reviews prepared by Drs. Mulinde, Soreth, Goldberger, Ganley, and Bull that are part of the action package. I have also met with the two review teams on two separate occasions to discuss this application and to hear the differing perspectives regarding the adequacy of the data presented in support of establishing the efficacy of this product for its intended use. I have also consulted with Dr. Robert Temple, the Associate Director for Medical Policy. After considering all the available data, I have determined that the sponsor has not presented substantial evidence to establish the efficacy of Duraprep for its intended use. I will briefly summarize the key issues below:

1. There is no disagreement that the sponsor has failed to meet the standard of a 3 log reduction of bacterial counts in the groin area in two separate studies. While there are legitimate questions about the validation of this standard and its link to clinical efficacy, the standard has been used for many years to evaluate topical antiseptics for pre-operative use and is the standard that other products have been required to meet. In my opinion, failure to meet the 3-log standard is not an absolute bar to approval of a topical antiseptic under an NDA. However, if the standard is not met, I believe that there must be clear and convincing data to support the effectiveness of the product from other sources before a determination can be made that the product is effective for the intended use. In this case, the sponsor has suggested that the finding that Duraprep was similar to the active control Hibiclens in one pivotal study and statistically significantly better than Hibiclens in the other pivotal study support approval. I do not find these arguments compelling. The active control was included in these studies as a tool to assess the adequacy of the methodology used in the study, not to facilitate non-inferiority or superiority comparisons. Such comparisons are not interpretable in a setting where the positive control does not have its expected effect. A move by the Agency to accept such comparisons in situations where the test product fails to meet the 3-log reduction standard could lead to a progressive erosion of the efficacy standard and the approval of potentially ineffective drugs. For

example, under the proposed active control comparison paradigm how would the Agency interpret a study where both active control and test agent achieved less than a 1 log reduction in bacteria, but the results **for the two products appeared "similar?"** By its very design the 3-log standard is admittedly arbitrary, but if it is consistently applied across all applications it is a fair standard. Doubts about the standard are not an adequate justification for accepting uninterpretable comparisons between the test drug and the positive control. Any such doubts about the standard should lead to scientific efforts to develop and validate a new standard. Therefore, I do not believe that the comparisons between Duraprep and the positive control in the pivotal studies are of any regulatory value in defining the efficacy of the drug.

2. The sponsor has also suggested that the bacterial challenge studies provide data that support the efficacy of this product. The challenge studies were specifically designed to address issues related to the combination policy (see below). I believe they are of no value at this time in defining the efficacy of Duraprep for the intended use. The challenge studies by design do not mimic the clinical setting for which the product is intended; i.e., pre-operative preparation of skin. While the challenge studies demonstrate that the iodine component of the Duraprep product is an active anti-microbial agent, I find the data uninterpretable with regard to demonstrating the efficacy of the product for the intended use. First, while large reductions in residual bacterial counts were seen with Duraprep, even larger reductions were observed with the betadine active control. The clinical significance of the large difference in residual bacteria between the two actives is not known, but is of sufficient magnitude to raise concern regarding the effectiveness of Duraprep. Second, there are no established standards for what degree of bacterial killing is considered clinically significant. Finally, the challenge model addresses killing of exogenous bacteria, not the endogenous normal flora of the skin and it is unclear how to extrapolate the data to the intended use. The bacterial challenge approach may be a ripe area for further study in attempt to validate this study model, but, the data provided in the application do not rise to a level that I believe can serve as substantial evidence to overcome the failure of Duraprep to achieve the 3-log reduction in bacterial counts in the two pivotal studies.

3. A second issue in question regarding this application is whether the sponsor has met the combination policy by demonstrating that both active ingredients contribute to the claimed effect of the product for its intended use. The sponsor attempted to address this in one pivotal study by including a Duraprep solution that did not contain the iodine component (i.e., it contained isopropyl alcohol and the film). In that study, however, no differences were noted between the two Duraprep solutions. This lack of observed differences was particularly surprising at the 6 and 24-hour time points since the effect of the isopropyl alcohol would have been expected to have lasted only a short time after application. It is possible that the film component of the Duraprep solution without iodine played some role in this finding, but that is purely speculative at this point. To demonstrate the contribution of the iodine component to the claimed effects of Duraprep, the sponsor performed two bacterial challenge studies. These studies clearly showed that the iodine component of Duraprep was an active anti-

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John Jenkins
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Medical Officer's Review

NDA: 21-586/N-010
Product Name: DuraPrep Surgical Solution
Use: Patient Preoperative Skin preparation
Type of Document: NDA Amendment
Date Submitted: March 28, 2006
Date Reviewed: July 19, 2006
Reviewer: Steven Osborne, M.D.

Table of Contents:

Purpose

The purpose of this review is to evaluate the Sponsor's resubmission of data following the August 2004 Approvable Letter for DuraPrep Surgical Solution.

Background

DuraPrep Surgical Solution is currently marketed as a patient preoperative skin preparation with professional labeling by 3M (the Sponsor). DuraPrep solution was introduced into the US market in 1988 as an over-the-counter (OTC) drug product under the 1978 Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products. In 1994, a second TFM was published that was more specific in its allowable active ingredient description (povidone-iodine rather than iodophor). DuraPrep is an antiseptic with 74% isopropyl alcohol and 0.7% available iodine as part of the active iodine acrylate copolymer solution. The copolymer remains dissolved in the isopropyl alcohol (IPA) until it is applied dermally. As the IPA evaporates from the skin, the copolymer forms a water insoluble film. In 1994 the Agency determined that DuraPrep was not covered

under the scope of the new TFM. The Agency further determined that DuraPrep solution would be allowed to stay on the market while 3M worked toward New Drug Application (NDA) submission. In October 2003 the Sponsor submitted an NDA for which an approvable letter was issued in August 2004. The primary deficiency in the submission was the data provided failed to show that DuraPrep achieved the 3-log standard for bacterial reduction in the groin. In addition the Sponsor's data provided failed to show that DuraPrep is effective for its intended use. To address these deficiencies the Sponsor was advised to repeat a clinical trial(s) and demonstrate that DuraPrep meets the 3-log reduction standard. The Sponsor was advised to submit trial(s) that included a DuraPrep arm, a DuraPrep arm without iodine, and an appropriate approved active control.

In accordance with the Approvable Letter, the Sponsor submitted a pivotal trial and also included a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). This safety update includes data from all non-clinical and clinical studies pertaining to DuraPrep solution, as well as updated marketed product complaint data. The Sponsor notes that there is no additional approved foreign labeling for DuraPrep solution that was not previously submitted in the original NDA.

Review

This review will focus on the safety aspects of the Sponsor's current submission. The microbiologist from the Office of Nonprescription Products will review the efficacy portion of the current submission.

Safety data included in this submission consisted of:

1. Safety data gathered during 5 new clinical studies:
    - 3M Study No. 05-010214
    - 3M Study No. I2MS 9981
    - 3M Study No. I2MS 10346
    - 3M Study No. I2MS 10125
    - 3M Study No. I2MS 10417

2. Analysis of overall safety data gathered from all clinical studies (15 original and 5 new)

3. Sponsor's post-marketing safety data since the beginning of DuraPrep marketing in 1988 until November 30, 2005.

4. FDA AERS Database Search

5. Literature Review

Safety results from 795 subjects enrolled in 20 studies are presented in the Sponsor's Clinical Summary. These studies included 6 pivotal efficacy studies (378 subjects), 12 pilot/post-marketing efficacy studies (129 subjects) and 2 safety studies (288 subjects).

Of these, 15 studies involving 672 subjects were previously reviewed in Dave Bostwick's NDA review, including 5 pivotal efficacy studies (312 subjects), 8 postmarketing pilot/postmarketing efficacy studies (66 subjects), and the same 2 safety studies (288 subjects). The Sponsor submitted the remaining five clinical studies in response to the primary deficiency noted in the Approvable Letter of August 2004. These studies include 123 subjects.

1. 3M Study No. 05-010214, "Study to Assess the Antimicrobial Effectiveness of 3M DuraPrep Surgical Solution Against Resident Human Skin Flora on the Groin Region"

2. 3M Study No. I2MS 9981, "Pilot Study to Evaluate the Durability and Antimicrobial Persistence of 3M DuraPrep Surgical Solution and ChloraPrep One-Step Skin Preparation Following Exposure to Saline Using a Bacterial Challenge Method"

3. 3M Study No. I2MS 10346, "Pilot Study to Assess the Antimicrobial Effectiveness of Hibiclens Cleanser and ChloraPrep Skin Prep Against Resident Human Skin Flora on the Groin Region.

4. 3M Study No. I2MS 10125, "Evaluation of Durability and Antimicrobial Persistence of DuraPrep Surgical Solution and ChloraPrep One-Step Skin Preparation Following Exposure to Saline Using a Bacterial Challenge Method"

5. 3M Study No. I2MS 10417, "Comparative Study on the Efficacy and Cost Between DuraPrep Skin Preparation and Conventional Povidone-Iodine Skin Preparation in Coronary Artery Bypass Surgery: A Prospective Randomized Trial"

Number 1 above, 3M Study No. 05-010214, is the Sponsor's pivotal study, whereas the remaining four clinical studies completed since the August 2004 Approvable Letter are supplementary for incorporation and integration into the NDA.

1. Adverse Event Reports from 5 New Clinical Studies:

1) Pivotal Clinical Study #05-010214

A brief outline of this study is as follows. Additional details may be found in the microbiologist's efficacy review.

Study Title: Pivotal Study to Assess the Antimicrobial Effectiveness of 3M DuraPrep Surgical Solution Against Resident Human Skin Flora on the Groin Region"

Investigator: [redacted]

Study Dates: August 12, 2005-October 30 2005

Study Objective: The following statement is taken directly from p. 2 of the study report:

> The primary objectives of this study were to demonstrate that DuraPrep solution met the 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) criteria for the inguinal region of 3-$\log_{10}$ reduction at 10 minutes post-preparation and that counts remained significantly below baseline at 6 hours post-preparation. The secondary objectives were to demonstrate the 24-hour efficacy of DuraPrep solution (counts remained significantly below baseline) and to compare the log reduction achieved by DuraPrep solution to that of Hibiclens. Antiseptic Skin Cleanser (Hibiclens cleanser).

Study design: This was a randomized, partially blinded, paired comparison study in 66 subjects, each of whom received DuraPrep solution and Hibiclens cleanser. Healthy subjects were entered into a 14-day Pretreatment Phase during which standardized, non-antimicrobial soaps, shampoos, and deodorants were used. Following the Pretreatment Phase, screening baseline samples were collected from the groin region. Subjects whose baseline samples met the minimum values (5.0 $\log_{10}$ Colony Forming Units /cm2) for inclusion in the study were invited to participate in the Treatment Phase of the study. Those subjects who qualified for the study continued to follow instructions until completion of the scheduled Treatment Day. Subjects were not allowed to shower or bathe the test areas for 48 hours prior to the Screening and Treatment Days. The Treatment Phase was scheduled no sooner than 72 hours and no later than 7 days from the screening baseline collection time.

Primary Endpoint: log reduction of skin flora at the groin site 10 minutes following application of the investigational materials with counts significantly below baseline at 6 hours post-preparation.

Secondary endpoint: log reduction of skin flora at the groin site at 24 hours following application of the investigational materials.

Inclusion criteria:

1) Healthy volunteers of either gender, any race, and are at least 18 years of age
2) Satisfied all Inclusion/Exclusion criteria and voluntarily signed the consent form
3) Had baseline bacterial counts on Screening and Treatment Days of at least 5.0 log10 CFU/cm2 per groin site
4) Had skin within 6 inches of the test areas that was free from cuts, acne, abrasions, and skin irritation
5) Willingness to follow instructions for the study; and

6) Willingness to return within 6 hours of treatment and again the next day for the 24-hour sampling.

Exclusion criteria:

1) Had any form of dermatitis, acne, open wounds, or other skin disorders on the groin test areas
2) Had a history of skin allergies
3) Had a known sensitivity to any products containing acrylate, iodine, chlorhexidine gluconate, or alcohol, or to medical tape or natural rubber latex
4) Had used antimicrobial soaps, lotions, dandruff shampoos, deodorants, or topical or systemic antibiotic medications within 14 days of the scheduled Screening or Treatment Day
5) Had exposure to any other topical medications, creams, or ointments on the test areas within 14 days of the scheduled Screening or Treatment Day
6) Had a history of skin cancer within 6 inches of the test areas
7) Had contact with biocide-treated swimming pools or hot tubs, tanning beds, hot waxes, or depilatories in the groin area within 14 days of the scheduled Screening or Treatment Day
8) Had bathed or showered the test areas within 48 hours prior to the scheduled Screening or Treatment Day
9) Had contact with solvents, acids, bases, or other household chemicals in the test areas within 14 days of the Screening or Treatment Day; or
10) Were pregnant, possibly pregnant, attempting pregnancy, or nursing.

Dosage and duration of treatment: After collection of the baseline sample, contralateral groin test areas were prepped with DuraPrep solution or Hibiclens cleanser in quantities based on the recommendations contained within the package inserts for these products. Treatments were randomized between left and right test areas, and baseline and post-preparation sampling times were randomized among the sampling sites within each test area. Quantitative cultures were obtained from skin sites at 10 minutes, 6 hours, and 24 hours using a modified cup scrub method.

Blinding: The investigational materials were not blinded from the Investigator due to differences in application technique, color, and other physical characteristics. The clinical microbiology technicians who evaluated the bacterial cultures were kept blinded to the study treatment.

Results: 81 subjects were randomized and 80 received treatment in the study. Sixty-six were evaluable for efficacy. Nineteen subjects did not complete the study, due to not meeting the treatment day baseline criteria. At 10 minutes, DuraPrep solution reduced the bacteria by 3.32 logs compared with 3.41 logs for Hibiclens. *Both of these preparations*

met the 3-log reduction criteria of the TFM. The difference in the log reduction between DuraPrep solution and Hibiclens cleanser at 10 minutes was significant (p=0.4716). Hibiclens cleanser was significantly more effective than DuraPrep at 6 and 24 hours (p=0.0499 and p=0.0004, respectively).

Adverse Events: Eighty of the 81 randomized subjects were evaluable for safety. Three subjects (Subjects 002G, 003G, and 025G) experienced an AE, application site erythema (skin redness upon removal of the tape), during this study. These events were not unexpected and were mild in intensity, The Investigator considered the AE to be probably related to study treatment (DuraPrep solution) for Subject 003G and not related for Subjects 002G and 025G.

Comments:

In prior studies Hibiclens had not shown a 3-log reduction in bacteria at ten minutes, while both DuraPrep and Hibiclens exceed a 3-log reduction in this study. As noted above, the microbiology reviewer will assess the efficacy results of this study.

The AE reported in this study is skin irritation and is not serious, though it is noted this is a single application study and surgical suite conditions such as exposure to cautery did not occur.

2) 3M Study No. I2MS 9981

Study Title: Pilot study to evaluate the durability and antimicrobial persistence of 3M DuraPrep Surgical Solution and ChloraPrep One-Step skin preparation following exposure to saline using a bacterial challenge method.

Investigator: Julie B. Stahl (sponsored in house study)

Study Dates: March 9, 2004-April 7, 2004

Objective: To examine the resistance to washoff and/ or inactivation of the active in ChloraPrep compared to DuraPrep solution by demonstrating the persistence of antimicrobial activity of CHG and iodine following contact with saline.

Methods:
Six subjects (completers) had one forearm prepped with DuraPrep and the other forearm prepped with ChloraPrep. Three sites were within the prepped area, and the fourth site was the recovery control site. One of the three prepped sites and the recovery control site received the saline rinse treatment (250 mL sterile saline slowly poured over the site). Another of the prepped sites received the saline soak treatment (sterile saline-saturated 2x2 gauze laid on top of the site for 1 min). The third prepped site served as the prepped control site with no saline treatment. The prepped sites were treated according to a randomization schedule. Challenge bacteria were then applied to all 4 sites on each

Study Title: Pilot Study to Assess the Antimicrobial Effectiveness of Hibiclens Cleanser and ChloraPrep Skin Prep Against Resident Human Skin Flora on the Groin Region.

Investigator: [redacted]

Study Dates: July 20, 2005-August 9, 2005

Study Objective: To demonstrate that Hibiclens cleanser and ChloraPrep skin prep meet the 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) criteria for the inguinal region of 3 $\log_{10}$ reduction at 10 minutes post-prep with each of two sampling solutions.

Methods:
Fourteen subjects (completers) had 2 test areas on the groin with 4 sampling sites each prepared for testing. Once the test areas were marked, 2 baseline samples were collected from randomized sites. Following the baseline sample collection, randomly assigned contralateral test areas were prepped with either Hibiclens cleanser or ChloraPrep skin prep. The test materials were applied per the Randomization Schedule and the Investigational Material Application Instructions. Two microbial samples were collected per test area at 10 minutes (±30 seconds) post-prep with two different sampling solutions, called HSS and SSS. Two technicians collected microbial samples concurrently using the cup scrub technique. Following the final sample collection, the remaining test material was removed from the subjects' skin with water.

Results: Both ChloraPrep and Hibiclens met the 3-log reduction criteria at 10 minutes on the groin with both sampling solutions. There were no significant differences in log reduction between the two preps or the two sampling solutions. The log reduction for ChloraPrep was 3.37 with SSS and 3.32 with HSS compared to 3.40 and 3.11 respectively, for Hibiclens.

Adverse Events: There were no adverse events reported with either treatment.

Comment:

Studies I2MS 9981, I2MS 10125, and I2MS 10346 involved a total of 56 subjects with limited exposure to DuraPrep Surgical Solution. The absence of any adverse events is not surprising. Also, these studies were not designed to assess safety per se.

5) *3M Study No. I2MS 10417*

This study was submitted as an English translation of the investigator's report.

Study Title: Comparative Study on the Efficacy and Cost Between DuraPrep Skin Preparation and Conventional Povidone-Iodine Skin Preparation in Coronary Artery Bypass Surgery (CABG): A Prospective Randomized Trial.

Investigator: [redacted]

Study Dates: December 2004-August 2005

Study Objective: The purpose of this study is to compare the disinfection effects and cost efficiency of DuraPrep with the existing Povidone-Iodine (PI) solution in patients who had open heart surgery.

Methods: Open heart surgery patients hospitalized at the [redacted] between [redacted] were selected in a prospective randomized manner. Some of them were disinfected with the existing Povidone-iodine solution prior to operations, whereas the others were disinfected with the DuraPrep solution.

Results:
A total of 247 patients participated in this clinical study: 127 patients were in the DuraPrep group and 120 in the Povidone-Iodine group. There was no significant difference between the two groups in terms of age and/or gender proportions. One hundred eighty nine (189) patients received CABG, 95 of which were in the DuraPrep group and 94 in the Povidone-Iodine group. There was no significant difference found between the two groups in the rate of surgical infections (3 DuraPrep, 5 Povidone-Iodine). The author found DuraPrep to be less expensive from the social, patient, and hospital perspective, but more expensive from the insurer's perspective if 2 x 26ml of DuraPrep was used.

Adverse Events: The investigator did not state whether there were or were not any adverse events in this study.

Comment:

This study compared the economics of use of DuraPrep with PI in a real clinical setting; however, the investigator unfortunately did not comment on AEs.

2. Sponsor's Clinical Summary of Safety (Update)

In addition to the data from the pivotal Study # 05-010214 and the four smaller studies (I2MS 9981, I2MS 10346, I2MS 10125, and I2MS 10417) discussed above, the Sponsor submitted a summary of safety data from initial marketing in1988-November 2005. The Sponsor termed this data an "Overall Safety Evaluation Plan Safety" and included results for 795 subjects enrolled in 20 studies including the 6 pivotal efficacy studies (378 subjects), 12 pilot/post-marketing efficacy studies (129 subjects) and 2 safety studies (288 subjects).

The efficacy studies consisted of 6 pivotal studies (LIMS 8304, LIMS 8918, LIMS 8197, LIMS 9302, LIMS 8198, and I2MS 05-010214) and 12 pilot/post-marketing studies (LIMS 7448, LIMS 7449, LIMS 7727, LIMS 7820, LIMS 7824, LIMS 8058, LIMS 8061, LIMS 8089, LIMS 8786, LIMS 8986, I2MS 05-009981, and I2MS 05-010125), with a total of 507 randomized subjects and 506 treated subjects (1 subject from Study I2MS 05-010214, Subject 030G, was excluded from the study as she had acne on the treatment site). Subject accountability, disposition, demography, and AE data from these studies were pooled for analysis. In the efficacy studies, subjects were exposed to a single application of all treatments to which they were randomized. Efficacy assessments as well as AE reporting were conducted in these studies. For pivotal studies conducted on abdomen and groin regions (LIMS 8304 and LIMS 8918), subjects were counted once in all groups for which they received treatment on either the abdominal and/or the groin body area.

The safety studies consisted of 2 studies (LIMS 7294 and LIMS 7296) with a total of 288 randomized subjects. Subject accountability, disposition, demography, and AE data from these studies were pooled for analysis. In the safety studies, subjects were exposed to repeated applications over the course of 3 weeks of all treatments to which they were randomized. In LIMS 7294 subjects received approximately 0.12 mL/ $inch^2$ of DuraPrep solution, DuraPrep without iodine (w/o I2), Betadine solution, 0.1% sodium lauryl sulfate (SLS), 0.9% sodium chloride, and 70% IPA delivered to a 1-$inch^2$ area via pipette for 21 days throughout the study. In LIMS 7296 subjects received approximately 0.02 mL of DuraPrep solution, DuraPrep w/o I2, Betadine solution, and 70% IPA delivered via pipette to a 1 in^2 area on 1 arm for 9 consecutive applications over a 3-week period and 2, 48-hour challenge doses (1 to the original site and 1 to a naïve site on the other arm) after a 10-14 day rest period. Cumulative irritation or contact sensitization potential, along with AE reporting, was evaluated in these studies.

Data from the efficacy and safety studies were not pooled because of differences in study designs and objectives. Information about these studies is briefly outlined below. Further details about these studies can be found in Dave Bostwick's review.

Overall Extent of Exposure:
All the efficacy studies, including the pilot methods studies had an exposure period of 24 hours or less and study treatments were used per intended application.

In the 2 safety studies, LIMS 7294 and LIMS 7296, exposure was as follows:

• LIMS 7294: The study lasted 22 days. Treatment lasted 21 days. Each subject received approximately 0.12 mL/in^2 DuraPrep solution via pipette of each test material per treatment day on intact skin.

• LIMS 7296: The study lasted approximately 42 days. Treatment lasted 24 days, with 9 applications given over a 3-week period, a 2-week rest period, and 2 challenge

applications. Each subject received approximately 0.02 mL/in^2 DuraPrep solution via pipette of each test material per application on intact skin.

Subject Disposition:

In the efficacy studies, the percentage of subjects in the safety population completing the studies included in the Integrated Safety Database for the Clinical Summary were similar among the untreated control, Betadine combination, Hibiclens cleanser, DuraPrep without iodine, DuraPrep solution, and ChloraPrep skin prep treatments (93.2%, 91.8%, 80.7%, 90.9%, 86.3%, and 100%, respectively). The percentage of subjects who discontinued early and the reasons for discontinuation were similar among treatments, except for the ChloraPrep skin prep treatment group where all subjects completed the study. The number and type of discontinuations did not suggest any treatment effect.

In the safety studies, the percentages of subjects in the safety population completing the studies included in the Integrated Safety Database for the Clinical Summary were similar among IPA, sodium chloride, sodium lauryl sulfate (SLS), DuraPrep w/o I2, Betadine solution, and DuraPrep solution treatments (82.2%, 80.0%, 80.0%, respectively, and 82.2% for the DuraPrep w/o I2, Betadine solution, and DuraPrep solution treatments). The percentage of subjects who discontinued early and the reasons for discontinuation were similar among the treatments, except for subjects who discontinued for other reasons. In the sodium chloride and sodium lauryl sulfate treatment groups, 10% of the subjects discontinued for other reasons, while in the remainder of treatments groups, only 1.7% of subjects discontinued for other reasons. The number and type of discontinuations due to AEs did not suggest any treatment effect.

Demographic and Other Characteristics of Study Population:
Demographic characteristics are presented for the studies included in the Integrated Safety Database. The following variables were summarized by treatment: age (in years and by proportion of subjects within the <65 years and ≥65 years age range), gender, ethnic origin, height (in inches), and weight (in pounds).

For the efficacy studies safety population, demographic characteristics were comparable across treatments; there were no important differences. For all subjects, the mean age was 42.7 years. The majority of subjects (86.0%) were <65 years of age and 86.7% were Caucasian. For all subjects, the mean weight was 178.4 pounds. Males and females were generally equally represented in all treatments, except in the DuraPrep w/o I2 treatment (61.0% male, 39.0% female) and the ChloraPrep skin prep treatment (23.8% male, 76.2% female). These data are shown in Appendix 1.

For the population of the safety studies, demographic characteristics were generally comparable across all treatments; there were no important differences. For all subjects, the mean age was 46.7 years. The majority of subjects (89.2%) were <65 years of age and Caucasian (97.6%). For all subjects, the mean weight was 172.6 pounds. Females outnumbered males by approximately 3 to 1 except in the sodium chloride and sodium

lauryl sulfate treatments in which there were 85.0% females and 15.0% males. These data are shown in Appendix 2.

Analysis of Adverse Events from the Efficacy Studies
In the efficacy studies, 8 subjects each had 1 AE; all were mild and none were serious. Six of these AEs were considered probably not or not related to study treatment. One subject had an application site erythema (verbatim term: 2 pin-sized red dots at the scrub site) considered possibly related to DuraPrep solution and one had an application site erythema considered probably related to DuraPrep solution (verbatim term: skin redness upon tape removal).

Analysis of Adverse Events from the Safety Studies (LIMS 7294 and LIMS 7296):
The number and percentage of subjects reporting AEs were presented by treatment, Medical Dictionary of Drug Regulatory Affairs (MedDRA) system organ class (SOC), and MedDRA preferred term. Additional summaries of AEs included AEs considered related to treatment (probably or possibly related), serious adverse events (SAEs), AEs leading to study withdrawal, or AEs resulting in death.

For the safety studies (LIMS 7294 and LIMS 7296), a total of 121 subjects (42.2%) had at least one treatment-emergent AE, regardless of relationship to study treatment. The number and percentage of subjects with AEs were variable across treatment and ranged from 27 subjects (9.4%) in the IPA treatment group to 19 subjects (47.5%) in the sodium lauryl sulfate treatment group. The number and percentage of subjects with AEs associated with DuraPrep solution (48 subjects [16.7%]) was similar to Betadine solution (36 subjects [12.5%]).

For the safety studies, by MedDRA SOC, the most common AEs, regardless of association with treatment, were general disorders and administration site conditions, reported by 92 subjects (32.1%). Across all study treatments tested, application site pruritus, burning, and pain were the most frequent AEs, reported by 77 (26.8%), 33 (11.5%), and 12 (4.2%) total subjects, respectively. All of these AEs were anticipated and not severe. Although there was a slight trend for these AEs to be more frequently associated with DuraPrep solution compared with the DuraPrep w/o I2, or Betadine solution, the percentages of DuraPrep solution-treated subjects were low (=16.7 % for any of these AEs) and less than for treatment with sodium chloride (=45.0%) or sodium lauryl sulfate (=47.5%).

The number and percentage of subjects with treatment-related (probably or possibly) AEs associated with DuraPrep solution (43 subjects, 15.0%) was similar for Betadine solution (30 subjects, 10.5%).

There were no SAEs associated specifically with DuraPrep solution, DuraPrep w/o I2, or Betadine solution treatments. Three subjects (1.0%) had SAEs (angina pectoris, parathyroid tumor benign, and depression); all were considered to be not related to study treatment.

These data are presented in Tables 1 and 2.

Table 1. Number and percentage of subjects with treatment-emergent adverse events in each antiseptic group in safety studies.

	No Specific Treatment (N=287)	Isopropyl Alcohol (N=287)	Sodium Chloride (N=40)	Sodium Lauryl Sulfate (N=40)	DuraPrep w/o I_2 (N=287)	Betadine Solution (N=287)	DuraPrep Solution (N=287)	Total (N=287)
Number (%) of Subjects with Any Treatment-Emergent Adverse Events Regardless of Relationship to Study Treatment	94 (32.8)	27 (9.4)	18 (45.0)	19 (47.5)	29 (10.1)	36 (12.5)	48 (16.7)	121 (42.2)
Number (%) of Subjects with Any Treatment-Emergent Adverse Events Related[a] to Study Treatment	4 (1.4)	23 (8.0)	16 (40.0)	17 (42.5)	23 (8.0)	30 (10.5)	43 (15.0)	53 (18.5)
Number (%) of Subjects with Any Treatment-Emergent Serious Adverse Events	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	3 (1.0)
Number (%) of Subjects with Any Treatment-Emergent Adverse Events Causing Subject Withdrawal from Study	9 (3.1)	2 (0.7)	1 (2.5)	1 (2.5)	2 (0.7)	2 (0.7)	2 (0.7)	11 (3.8)[b]
Number (%) of Subjects with Any Treatment-Emergent Adverse Events Resulting to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: This table includes data from studies LIMS 7294 and 7296.
Note: A subject may be counted in more than 1 treatment column, but only once under the total column.
[a] Probably or possibly related to study treatment.
[b] Data was from study discontinuation/completion page of CRF. In LIMS 7296, there was a discrepancy. Subjects 125 and 129 were listed as withdrawn due to AE, but "other" was checked as action for AE.

Table 2. Summary of treatment-emergent adverse events by MedDRA term related to antiseptic group in safety studies (number and percentage).

MedDRA System Organ Class/ Adverse Event	No Specific Treatment (N=287)	Isopropyl Alcohol (N=287)	Sodium Chloride (N=40)	Sodium Lauryl Sulfate (N=40)	DuraPrep w/o I_2 (N=287)	Betadine Solution (N=287)	DuraPrep Solution (N=287)	Total (N=287)
	Number (%) of Subjects							
Subjects with Any Treatment-Emergent Adverse Events Related@ to Study Treatment	4 (1.4)	23 (8.0)	16 (40.0)	17 (42.5)	23 (8.0)	30 (10.5)	43 (15.0)	53 (18.5)
General disorders and administration site conditions	4 (1.4)	23 (8.0)	16 (40.0)	17 (42.5)	23 (8.0)	30 (10.5)	42 (14.6)	52 (18.1)
Application site burning	1 (0.3)	4 (1.4)	1 (2.5)	1 (2.5)	4 (1.4)	7 (2.4)	13 (4.5)	18 (6.3)
Application site irritation	0 (0.0)	1 (0.3)	1 (2.5)	1 (2.5)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Application site pain	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.4)	9 (3.1)	10 (3.5)
Application site pruritus	3 (1.0)	20 (7.0)	15 (37.5)	16 (40.0)	20 (7.0)	24 (8.4)	31 (10.8)	41 (14.3)
Application site swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Tenderness NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.7)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)

MedDRA = Medical Dictionary for Drug Regulatory Activities; NOS = Not otherwise specified.
Note: This table includes data from studies LIMS 7294 and 7296.
Note: If a subject experienced more than 1 adverse event within a system organ class, the subject was counted once under that system organ class.
Note: A subject may be counted in more than 1 treatment column, but only once under the total column.
@ Probably or possibly related to study treatment.
Source: Section 2.7.4.7, Appendix Table 4.3, Subject Data Listing 3.2 (rtae.sas; T04.3_rtae.rtf.)

In the DuraPrep-solution, DuraPrep w/o I2, and Betadine treatments, 2 subjects (0.7%) in each treatment had AEs causing withdrawal from study. A total of 11 safety subjects (3.8%) were withdrawn from study due to an AE. There were no deaths reported.

The results of safety studies showed that DuraPrep solution was well tolerated. There were no significant safety risks identified in these clinical trials. There were no serious AEs (SAEs) related to DuraPrep solution. In safety studies, the number and percentage of

subjects with AEs considered by the investigator to be associated with Betadine solution (36 subjects [12.5%]) was similar to DuraPrep solution (48 subjects [16.7%]). The number and percentage of subjects with treatment-related AEs associated with Betadine solution (30 subjects [10.5%]) was similar to DuraPrep solution (43 subjects [15.0%]). Application site pruritus, burning, and pain were the most frequent treatment-related AEs, reported by 41 (14.3%), 18 (6.3%), and 10 (3.5%) total subjects, respectively. Although there was a slight trend for these AEs to be more frequently associated with DuraPrep solution compared with DuraPrep w/o I2 or Betadine solution, the percentages of DuraPrep solution-treated subjects were low (=10.8% with each of these AEs).

3. Postmarketing Safety Data from Sponsor:

DuraPrep has been marketed in the U.S. since 1988. Through November 30, 2005 about [redacted] units of the product were sold. There were a total of 660 AEs reported to the Sponsor during this same time period. Table 3 shows the overall complaints and Table 4 shows the complaints stratified by year from 1988-2005.

Table 3. All DuraPrep Solution Clinical Complaints 1988-November 30, 2005

Complaint	Total	Incident Rate
Skin irritation*	382	
Infection or infection rate increase	109	
Flammability	97	
Flaking/rolling/falling into wound	24	
Skin laceration/cut from glass	16	
Staff headache/watery eyes	7	
DuraPrep squirted on face	6	
Bronchial spasm	5	
Skin staining	4	
Eye irritation/damage	3	
Elevated temperature	1	
Film/color gone	1	
Cellulitis	1	
Anaphylaxis	1	
Unidentified Event	2	

* Includes redness, itching, rash, chemical burn, blistering, skin removal. To avoid skin injury, care should be taken when removing incise drapes, tapes, etc... applied over DuraPrep film. No skin injuries have been reported with the use of DuraPrep solution alone.

The data in Tables 3 and 4 shows that the most frequent overall complaint was skin irritation, with an incidence rate of [redacted], based on total number of units sold, [redacted] through 30 November 2005. There were 109 reports of infection or infection rate increase, an incidence of [redacted] Flammability incidents were the third most prevalent complaint with 97 reports, an incidence of [redacted].

Table 4. All DuraPrep solution clinical complaints, by year of complaint, as of November 30, 2005

Complaint	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total	Incident Rate
Skin irritation*	5	6	25	18	31	18	30	46	6	22	31	24	22	3	41	11	31	12	382	
Infection or rate increase	0	13	8	16	5	4	21	9	18	2	4	0	5	0	3	0	1	0	109	
Flammability	1	0	0	2	10	3	6	2	4	9	6	10	7	6	11	7	2	11	97	
Flaking/rolling/falling into wound	0	15	2	0	1	2	1	0	0	0	0	0	0	0	0	1	0	2	24	
Skin laceration/cut from glass	0	0	0	0	0	9	0	0	0	1	0	1	1	0	2	1	1	0	16	
Staff headache/watery eyes	0	0	0	1	0	0	1	0	0	0	4	0	0	0	1	0	0	0	7	
DuraPrep squirted on face	0	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	6	
Bronchial spasm	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	4	0	0	5	
Skin staining	0	1	0	1	0	0	0	0	0	0	0	0	2	0	0	0	0	0	4	
Eye irritation/damage	0	0	0	0	0	0	0	0	1	0	0	0	0	2	0	0	0	0	3	
Bowel placed on DuraPrep	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	
Elevated temperature	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	
Film/color gone	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
Cellulitis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	
Anaphylaxis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	
Unidentified Event Possibly	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	2	
																		Total	660	

*Includes redness, itching, rash, chemical burn, blistering, skin removal.
Note: Incident rate based on total solution sales of [redacted] through 30 November 2005.
Source: Data on file with 3M.

Comment:

Table 3 shows that three types of adverse events are distinctly more common than other adverse events. The category of infection or (infection) rate increase refers to efficacy rather than safety per se and needs no further discussion in this review. The categories flammability and skin irritation warrant further discussion.

A. Flammability

There have been 97 occurrences of fires with use of DuraPrep in 17 years. Only one incident was reported for the 6 mL size, while 96 fires have been reported with the 26 mL size. There were only three incidents reported through 1991. Since then, reports have varied between 2 and 11 per year. There were 11 reports in 2002 and 2005. Sales for the product have increased over the years ([redacted] total from 1988-2005) making the incidence fairly steady at around [redacted] units sold. The Sponsor assessed the incidents as associated with failure to let the preparation dry (33 cases), pooling of the preparation (24 cases) and use with oxygen (14 cases). These data are shown in Table 5 and 6 below and the severity of the burns (1988- 2002) is shown in Table 7.

DuraPrep solution consists of iodine povacrylex (0.7% available iodine) and IPA (74% w/w) and gives off flammable vapors while drying. The alcohol in the DuraPrep solution is necessary for rapid and effective skin antisepsis. The flammability limits, upper and lower, for IPA are [redacted] and [redacted] ppm, respectively.

DuraPrep solution 26-mL applicator is used in environments where flame hazards are present (e.g. cautery and oxygen in the operating room). In contrast, the Sponsor notes that the DuraPrep solution 6-mL applicator (as well as other recently approved competitor alcohol-based patient preparations), is primarily used in special procedures

areas such as cardiac catheterization laboratories and labor and delivery. The Sponsor states it is unusual for electrocautery or other ignition sources to be used in these special procedures areas, so it is not unexpected that the flammability incidence for the smaller applicator would be lower.

The 3 most prevalent characteristics associated with flammability incidents were as follows: preparation was not dried (37.1%), had pooled (45.4%), or incompletely dried solution was combined with the use of oxygen (16.5%). The head, neck, and face was the most frequent known body region (43.3%) involved in flammability incidents, followed by areas of the torso (32.0%) including the abdomen/pelvic/pubic area (9.3%), the shoulder/upper back/armpit (8.2%), and the axillary (7.2%). The total incident rate on limbs and extremities was (11.3%).

Comment:

The Sponsor tallied the total units of DuraPrep solution sold [redacted] from 1988-2005 but did not estimate the number of surgical operations in which electrocautery was used. Since not all operations use electrocautery or laser, and some procedures might have used more than one DuraPrep solution applicator, the incident rate of flammability events per operation is likely a to be higher than per DuraPrep applicator units sold.

Table 5. Sales of DuraPrep applicators and flammability incidents by year.

Year	Number Incidents with 26-mL Applicator or Unknown	Number of Incidents with 6-mL Applicator	26-mL Sales	6-mL Sales	[redacted] s	Incident Rate per Million per Year
1988	1	0				
1989	0	0				
1990	0	0				
1991	2	0				
1992	10	0				
1993	3	0				
1994	6	0				
1995	2	0				
1996	4	0				
1997	9	0				
1998	6	0				
1999	10	0				
2000	6	1				
2001	6	0				
2002*	11	0				
2003	7	0				
2004	2	0				
2005 through November**	11	0				
Subtotals	96	1				
Total Number of Incidents:					97	
Total Solution Sales:					[redacted]	
Total Incident Rate based on total units of solution sold:						
Incident Rate (for 26-mL units and unknown complaints) based on units of 26 mL sold:					[redacted]	
Incident Rate for 6-mL units based on units of 6 mL sold:						

* Sales given through 30 November 2005.
** Complaints reported through 30 November 2005.
Note: The incident rate calculation was based on the sales of the 26-mL and 6-mL size.
Source: Data on file with 3M.

The Sponsor summarized the types of flammability incidents along with their assessment of the cause as shown in Table 6.

Table 6. Summary of Complaint Analysis for DuraPrep Flammability Incidents as of 30 November 2005 by Incident Characteristics

Incident characteristic	Total Incident Number(s)	Explanation
Pooling of preparation (including 5 where reports conflicted)	44	Not wicking pool away or not removing solution-soaked materials.
Pooling with other complications noted by customer	22	Includes various other possible misuses of product.
Pooling with no other complications	18	
Did not let preparation dry	36	Not waiting until preparation is dry.
Presence of oxygen noted by customer	16	All materials are more flammable in a highly oxygenated environment.
Extended preparation area	10	Violates aseptic technique if occurs after draping
Add-on procedures	10	Not waiting until preparation is dry.
Emergency procedures	7	Not waiting until preparation is dry.
Prepping after draping	7	Gets drapes wet, will not dry quickly, violated aseptic technique.
Drape placed over wet preparation	5	Not waiting until preparation is dry.
Re-prepping	4	Not waiting until preparation is dry. Cannot predict dry time.
Preparation in skin folds	2	Product can pool in skin folds.
Electrocautery arcing	2	May be an electrocautery malfunction.
Prepped over Betadine	1	Not waiting until preparation is dry. Cannot predict dry time.
Prepped over a wet area (blood)	1	Not waiting until preparation is dry. Cannot predict dry time.
Flames shot out of electrocautery	1	May be an electrocautery malfunction.
Spark from the anesthesia circuit	1	May be an anesthesia circuit malfunction.
Prepped with alcohol and DuraPrep Solution	1	Not waiting until preparation is dry. Cannot predict dry time.

Note: Complaints might be listed in more than one category

The Sponsor presented burn severity data (Table 7 below) for the first 80 reports, which were from 1988 until late in 2002.

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Table 7. Burn severity: number of cases

Burn Severity (Degree of burn)*	Total (n=80)
first	15
second	33
third	14
unknown	18

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

Comments

Note: Dave Bostwick's NDA review contained some pertinent and excellent comments on flammability. This reviewer incorporated pertinent comments from that review in the discussion of flammability below.

The adverse events seen with most products typically result from an allergy, an overdose, or drug toxicity. The flammability incidents with DuraPrep are unique in that they have nothing to do with the intended action of the drug. The burns patients experienced are preventable in that introduction of a spark was necessary for their occurrence. The TFM for Health-Care Antiseptic Drug Products classifies isopropyl alcohol 70-91.3% as safe and effective as a patient preoperative preparation. The TFM also states that labeling for such products should contain the following warning: "Do not use with electrocautery procedures". The flammability warning for DuraPrep has been discussed internally, and it has been noted that such a warning would prevent most usage of the product, since surgery procedures commonly utilize 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, and to caution to allow extra drying time for the product in hirsute areas of the body. These label changes do not appear to have affected the rate of flammability incidents.

The volume of product available or used appears to be the primary determinant of flammability incidents. 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.

The Sponsor noted that 43.3% of the burn incidents were on the head, neck, or face. The 26 mL applicator label states that the smaller (6 mL) applicator should be used for procedures in this area. It is also notable that of the 14 third-degree burns, 10 were associated with head/neck surgery.

A consideration should be given to contraindicating use of DuraPrep with electrocautery procedures. If that is considered not feasible, then labeling revision is necessary to further minimize the risk of flammability. These revisions could be as follows:

- [redacted]
- *Contraindicating the 26 mL container in head and neck surgery*

- *Providing a suggested specific coverage area for the 26 mL size*
- [redacted]

Two additional studies have provided further data regarding flammability risk.

Dry Time

In I2MS 05-009855, nurses performed simulated patient preparations and evaluated the dry time of DuraPrep solution when applied to the back, neck, shoulder, or leg. The average dry time estimated by all nurses for all body parts was 1 minute, 32 seconds with a 95% confidence interval of 1 minute, 19 seconds; 1 minute, 46 seconds. All dry times were less than the dry time of [redacted] recommended on the DuraPrep solution product label.

Vapor Study

The results of an IPA vapor study (I2MS 05-009834) demonstrated that the alcohol vapors from DuraPrep solution quickly dissipate and reach a level below the lower flammability limit ([redacted] ppm) in about 1 minute. The Sponsor concluded that the [redacted] dry time stated in the DuraPrep solution Directions for Use would be expected to provide a sufficient interval of time between the presence of flammable IPA concentrations and the use of ignition sources. Also, the Sponsor believes that observing for dryness provides a significant margin of safety.

These results indicate that under normal and recommended application procedures, the [redacted] dry time recommended in the DuraPrep solution Directions for Use would be expected to provide a sufficient interval of time (i.e. margin of safety) between the presence of flammable IPA concentrations and the use of ignition sources. The results also indicate that focusing on apparent dryness also provides a significant margin of safety.

Comment:

The Sponsor's conclusion that the Directions for Use provides a substantial margin of safety between the presence of flammable concentrations of alcohol and the use of ignition sources should be tested in the clinical arena. Controlled laboratory experiments might not realistically reproduce the surgical setting in both scheduled and emergency procedures

Reducing Potential for Flammability

The Sponsor states "The risk of flammability-related events associated with the use of DuraPrep solution is exceedingly low and approaches zero when DuraPrep solution is applied and used under conditions specified in the product label". The Sponsor notes the following key points of the DuraPrep label regarding flammability:

- A warning that "DuraPrep solution contains alcohol and gives off flammable vapors [redacted]. Do not drape or use ignition source (e.g. cautery, laser) until [redacted] is dry."
- A warning that "[redacted] "Do not allow [redacted] to pool."
- A warning to "[redacted]

Comment:

The DuraPrep Surgical Solution label places the warning regarding hair in the Directions [redacted] section as a sub-bullet under "When Applying Solution". The label states: "avoid getting solution into hair. If this occurs, wipe hair with towel. [redacted]. This information is critical to avoid an operating room fire that could burn a patient as noted in reference 6 in the literature review below. This caution regarding " [redacted] deserves a separate category on the label, in bold, and placed in a prominent area under Warnings.

The Sponsor states that complete elimination of flammability incidents is dependent on proper product use. The key factors for proper use of DuraPrep solution have been elaborated by the Emergency Care Research Institute (ECRI) in its published investigation of a flammability incident (references 7 and 8) and by Erickson, Barker, Bentzen, and Bruley (references 9-12 respectively). The Sponsor notes that the ECRI makes 5 recommendations:

1. Read the directions for use and attend in-service
2. Apply product as a paint (i.e., do not apply it too thickly)
3. Wait until product has dried fully
4. Wick away any product drips or pools with gauze sponges
5. Either replace solution-soaked materials or allow them to dry before proceeding with the surgery.

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

the Sponsor's table 2.7.4.26 in the safety update submission, lists the types of disorders that were grouped under skin irritation.

Table 9. DuraPrep Solution Skin Irritation Complaints as of 30 November 2005

Complaint	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005 thru Nov-ember	Total	Incident Rate
Skin irritation	5	6	25	18	31	18	30	46	6	22	31	24	22	3	41	11	31	12	382	
Subcategories																				
Abrasion	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	2	5	
Allergy	0	0	0	0	0	2	3	1	1	0	0	3	0	0	1	1	0	0	12	
Blistering	3	4	13	8	10	6	7	13	2	11	26	15	17	0	20	4	14	2	175	
Bruise	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	
Chemical Burn	0	0	0	2	14	1	2	5	0	3	5	1	0	0	2	0	8	0	43	
Contact dermatitis	0	0	0	0	0	1	0	0	0	1	0	1	0	0	1	0	0	1	5	
Dehiscence of wound	0	0	0	0	0	0	1	0	0	4	0	0	0	0	0	0	0	0	5	
Rash, hives, itching, burning, irritation	0	1	5	2	3	5	10	18	2	3	0	1	4	0	14	4	5	2	79	
Redness	0	0	1	1	4	0	0	1	0	0	0	2	1	1	0	0	1	0	12	
Skin breakdown	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2	
Skin stripping	2	1	6	1	0	3	5	8	0	0	0	1	0	2	3	1	2	5	40	

Note: Incident rate based on total solution sales of [redacted] ugh 30 November 2005.
Source: DuraPrep Solution Skin Irritation Complaint Listing, Section 1.2.5, Appendix Table 1.2.5.2 and data on file with 3M.

The Sponsor notes that some of the subcategories are duplicative in that a report of blistering might also include skin stripping. Some reports contain multiple examples of the same type of reaction. For example, one hospital reported 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", defined as blisters caused by too-tight application of tape and/or dressing. The blisters occur when the tape is removed. Most of the reports concern blisters which were not tension blisters. Some of the more severe cases resulted in skin loss and an occasional infection. The blistering cases occurred in a wide range of ages, from infants to the elderly. Some of the reports had common patterns as listed below:

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

The skin stripping reports were often 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. 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.

Comments:

The Sponsor did not clearly state or show the ages of infants who sustained the chemical burns.
The incidence of skin irritation adverse events is low, given the wide use of the product. However, as some of these are severe, the labeling should refer to the possibility of blistering and skin loss.

Summary of Benefits and Risks:

The Sponsor makes the following statements about DuraPrep based on the studies it has done:

- DuraPrep solution has been shown to be efficacious as a pre-operative skin preparation. DuraPrep solution dries to a durable antimicrobial film that resists removal by irrigation or body fluids and keeps bacterial counts low for up to 24 hours.
- DuraPrep solution is unique among pre-operative skin preparations because it forms a water insoluble film, a property that makes it resistant to inadvertent removal during surgery.
- DuraPrep solution has been shown to improve incise drape adhesion compared with other surgical skin preparations. In a published clinical study, pre-operative skin preparation with DuraPrep solution resulted in fewer post-operative surgical site infections compared with aqueous povidone-iodine preparations.
- DuraPrep solution performed better for reduction of skin bacteria immediately after disinfection as well as for prevention of bacterial regrowth and epidural catheter colonization compared with other antibacterial products.
- DuraPrep solution is more persistent than Betadine solution and/or combination, as measured by visual examination.
- DuraPrep solution also requires less application time, making it desirable for emergency and add-on procedures.
- DuraPrep solution was well tolerated in safety and efficacy studies.

In addition, the Sponsor notes that there is no dose-toxicity, drug-drug interactions, or sub-population consideration with DuraPrep solution.

Summarizing, the Sponsor states that, under the conditions of labeling, the benefits of using DuraPrep solution, which include fast and persistent antimicrobial efficacy, as well as enhanced drape adhesion, infection rate-reduction benefits, improved user compliance, and reduced application time far exceed any risks associated with DuraPrep solution.

Comment:

While the risk of a fire in the operating room related to use of DuraPrep Solution might be low, the fact remains that this adverse event is potentially life-threatening and readily avoidable—by not using DuraPrep or at least by not using DuraPrep 26 mL. Alternative patient preoperative preparations are on the market and might not present the same risk

of flammability. While an efficacy evaluation is outside the scope of this review, internal discussions do not suggest that DuraPrep Solution has a commanding advantage in lowering post-operative infection rates. Granted, if other alcohol-containing patient preoperative preparations were in a 26 mL amount, and were used with electrocautery, then they might also have flammability risk. It is not clear that the sole risk of DuraPrep flammability is due to the IPA rather than to the IPA and the acrylate polymer.

4. Postmarketing Safety Data from AERS DataMart

A search by this reviewer of the AERS DataMart database from May 1, 2003-May 31, 2006 for all topical antiseptic 3M Company products used for any medical or surgical condition yielded zero adverse events. Changing the search criteria to any product with iodine and isopropyl alcohol made by any 3M Company also yielded zero adverse events. Changing the search criteria to *any* 3M Company product yielded 432 adverse events, all of which were for non-topical antiseptics, and none were adverse events for DuraPrep.

Comment:

It is unclear why the AERS DataMart query yielded zero AEs for a product that has been marketed since 1988. Possibly, this is due to the professional use-only aspect of the product. Of note is the fact that the Division of Medication Errors and Technical Support (DMETS) searched the AERS DataMart database in 2004 and also found zero adverse events. However, the DMETS searched the Drug Quality Reporting System database and found 10 flammability incidents from 1988-2004.

5. Literature Review

The Sponsor provided 5 references that did not add to the safety review (references 1-5). A PubMed literature search by this reviewer using the search term DuraPrep yielded 8 articles. The search term DuraPrep Surgical Solution yielded 7 articles, all of which were included in the above 8 articles. The search term DuraPrep and flammability yielded but one article that discussed aseptic techniques in a space station.

Of the 8 PubMed articles, one reference discussed flammability of DuraPrep since the last review by Dave Bostwick. This report [reference 6--Weber SM, Hargunani CA, Wax MK. DuraPrep and the risk of fire during tracheostomy. Head Neck. 2006 May 11; (Epub ahead of print)] described a case of fire that occurred on a hirsute patient during a tracheostomy procedure. Activation of electrocautery ignited a fire, and the patient was burned on his neck and shoulders. The fire was extinguished, and the patient recovered from both the tracheostomy and the burns. This reference, which has pictures of the operating site and the patient's burns, is attached as Appendix 5. The authors discussed other literature (references 7 and 8) and concluded that DuraPrep should be avoided in the hirsute patient, because body hair interferes with drying of this solution and increases the risk of fire.

Comment:

In a communication with FDA, a co-author of the report above noted that the 26 mL applicator was used and that 10-15 minutes elapsed between application of DuraPrep and turning on the cautery. The cautery setting was 20-20 (coagulation and cutting settings). The patient was not shaved on the chest or the lateral and posterior aspect of the neck.

Labeling

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, as part of the IND process, in support of their proposed labeling. Dave Bostwick reviewed the label in his NDA review of DuraPrep in March 2004 and suggested some changes to the Warnings, such as larger type size on the 6 mL bottle and changing one of the Directions to "———, DO NOT SCRUB". 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. In the current submission the Sponsor included final draft labeling that is identical to that submitted to the Agency on August 19, 2004 except that the USAN approved active ingredient name, Iodine Povacrylex, has been incorporated. The proposed label is shown in Appendix 3 while the current label is shown in Appendix 4.

Comments:

See the flammability section for other comments regarding labeling.

The proposed label shown in Appendix 3 contains the icons and warnings that have been advised by FDA. This label also states that the 26 mL applicator should not be used for head and neck surgery. The Sponsor's current label, as advertised on its website June 28, 2006, does not advise against use of the 26 mL applicator in head and neck procedures, although its August 19, 2004 proposed label incorporated this warning.

Sponsor's Monitoring Complaints and Improvement in Labeling

The Sponsor states it has been proactive in monitoring complaints and improving labeling. The DuraPrep solution label has been modified for safety over the last 5 years. Key changes to the label include specific instructions for application to avoid pooling (with methods stated to correct pooling), allow a wait time of ——— until the preparation is dry, and avoid the use of cautery or laser until the preparation is dry. These instructions are enhanced by international symbols. The Sponsor states it has 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.

Pediatric Waiver

The Office of Nonprescription Products, Division of Nonprescription Clinical Evaluation requested a consult from the Division of Pediatric Drug Development regarding a pediatric waiver. In particular, ONP asked if DuraPrep Surgical Solution use in the pediatric population should only be in children over two months of age, as with other health care antiseptics. Also, ONP asked if there should be any additional labeling on the product to address the potential for iodine toxicity and the possibility of subsequent hypothyroidism in children.

Summary

The Sponsor submitted one pivotal efficacy study (3M Study No. 05-010214), four supplemental nonpivotal studies, and a safety update in response to the primary deficiency notice in the Approvable Letter of August 2004. The Sponsor's pivotal efficacy study showed a 3-log bacterial count reduction at 10 minutes post application for both DuraPrep Surgical Solution and the active control, Hibiclens. The Sponsor did not use a vehicle control in this study. Three of the 81 subjects in Study No. 05-010214 experienced mild application site erythema. Of the nonpivotal studies, three of them had zero adverse events and the remaining study made no mention of adverse events.

The Sponsor's postmarketing update showed a total of 97 incidents of fires involving use of DuraPrep Surgical Solution since initial marketing in 1988. A PubMed literature review showed one additional case report in the literature in May 2006, in which a hirsute patient sustained burns on the neck and shoulders. The reporters stated they waited at least three minutes before starting electrocautery. The overall rate of flammability incidents is steady despite label changes in the past several years. The Sponsor states that the Directions for Use provide a substantial margin of safety between the presence of flammable concentrations of alcohol and the use of ignition sources (e.g., electrocautery). All but one flammability adverse event occurred with the 26 ml DuraPrep Solution applicator.

The Sponsor's postmarketing update showed a total of 382 incidents of skin irritation, including 175 instances of skin blistering, since initial marketing in 1988. There was no apparent increase in this incidence.

Conclusions

Safety data gathered during 5 additional clinical trials does not raise any safety concerns. However, postmarketing data continue to reveal new flammability events, one of which was highlighted in the published literature in May 2006. If the flammability warning regarding DuraPrep use in a hirsute individual had been better placed and highlighted on the label this latest published incident might have been avoided. Also, if the label had warned to avoid use of the 26 mL applicator in head and neck surgery this incident might have been avoided.

While the Directions for Use might provide some margin of safety towards avoiding flammability incidents, the fact remains that operating room fires continue to occur and patients continue to be burned. Most of the flammability events occur in head and neck surgical procedures, possibly where excess DuraPrep Surgical Solution was used (i.e. greater than 6 mL of product was used) or an inadequate drying time took place. However, based on continued reports of operating room fires with use of DuraPrep, the current precaution is inadequate, as it states in small type in the Directions section on the label: *avoid getting solution into hair. If this occurs, wipe hair with towel. Dry time in hair will be much longer than 3 minutes and will vary.*

Recommendations

1. The Agency should approve only the 6 mL applicator and not the 26 mL applicator.

2. The 6 mL applicator label should exclude use of this product for surgical procedures involving electrocautery. If this contraindication is considered inappropriate, then the following product label changes should be made:

- The label should state that use of the 26 mL applicator is contraindicated in head and neck surgery. (This warning is necessary only if the Agency approves use of the 26 mL applicator).

- The label should state a warning in a bolded, adequate font size, about the risk of flammability when the product is used with electrocautery, especially in hirsute areas of the body. To reduce this risk the surgical area should be shaved.

- The surgeon should verify that the DuraPrep solution has dried both on the patient and on any draping before using electrocautery. This might take considerably longer than three minutes. In instances when the solution was not dried and electrocautery was used fire has resulted in first, second, or third degree burns on the patient.

- [redacted]

- A warning about the possibility of skin blistering and skin loss should be considered.

Steven F. Osborne, M.D.
Medical Officer, HFD-560

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Concurrence

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Appendix 1. Demographics for Efficacy Studies (Safety Population)

Subject Demographics
Efficacy Studies
Safety Population

	Untreated Control (N=146)	Betadine Combination (N=170)	Hibiclens Cleanser (N=243)	DuraPrep w/o Iodine (N=154)	DuraPrep Solution (N=502)	ChloraPrep Skin Prep (N=42)	Total (N=506)
Age (yrs)							
N	146	170	243	154	502	42	506
Mean	46.9	40.5	43.0	35.7	42.9	65.0	42.7
S.D.	19.52	16.25	16.01	15.65	17.24	13.66	17.28
Median	48.0	38.0	42.0	30.5	41.0	68.5	41.0
Min	18	18	18	18	18	28	18
Max	81	73	73	74	81	81	81
<65 years	111 (76.0%)	152 (89.4%)	215 (88.5%)	145 (94.2%)	431 (85.9%)	16 (38.1%)	435 (86.0%)
>=65 years	35 (24.0%)	18 (10.6%)	28 (11.5%)	9 (5.8%)	71 (14.1%)	26 (61.9%)	71 (14.0%)
Gender [n (%)]							
Male	64 (43.8%)	90 (52.9%)	122 (50.2%)	94 (61.0%)	246 (49.0%)	10 (23.8%)	249 (49.2%)
Female	82 (56.2%)	80 (47.1%)	121 (49.8%)	60 (39.0%)	256 (51.0%)	32 (76.2%)	257 (50.8%)
Ethnic Origin [n (%)]							
Caucasian	128 (94.1%)	152 (95.0%)	194 (79.8%)	148 (96.1%)	427 (86.8%)	36 (85.7%)	430 (86.7%)
Black	6 (4.4%)	6 (3.8%)	18 (7.4%)	4 (2.6%)	31 (6.3%)	5 (11.9%)	31 (6.3%)
Asian	2 (1.5%)	1 (0.6%)	12 (4.9%)	0	14 (2.8%)	1 (2.4%)	14 (2.8%)
Hispanic	0	0	8 (3.3%)	0	8 (1.6%)	0	8 (1.6%)
Native American	0	0	1 (0.4%)	2 (1.3%)	3 (0.6%)	0	3 (0.6%)
Other	0	1 (0.6%)	3 (1.2%)	0	2 (0.4%)	0	3 (0.6%)
Middle Eastern / Arab	0	0	7 (2.9%)	0	7 (1.4%)	0	7 (1.4%)
Missing	10	10	0	0	10	0	10

Note: This table includes data from studies LIMS 8197, 8198, 8304, 8918, 9302, 7448, 7449, 7727, 7820, 7824, 8058, 8061, 8089, 8786, 8986, and I2MS 9981, 10125 and 10214.
Note: Since these are paired-design studies, a subject will be counted in all appropriate treatment columns, but only once under the total column.

Subject Demographics
Efficacy Studies
Safety Population

	Untreated Control (N=146)	Betadine Combination (N=170)	Hibiclens Cleanser (N=243)	DuraPrep w/o Iodine (N=154)	DuraPrep Solution (N=502)	ChloraPrep Skin Prep (N=42)	Total (N=506)
Height (in)							
N	136	160	243	154	492	42	496
Mean	67.6	68.2	67.4	68.9	67.7	66.0	67.7
S.D.	4.02	4.17	4.23	4.24	4.20	3.57	4.21
Median	68.0	68.0	67.0	69.0	68.0	66.0	68.0
Min	58	58	57	58	57	58	57
Max	76	76	76	77	77	76	77
Weight (lb)							
N	136	160	243	154	492	42	496
Mean	176.2	180.6	177.8	182.6	178.3	172.5	178.4
S.D.	37.94	36.92	37.92	36.01	37.97	44.08	37.92
Median	175.0	180.0	175.0	180.0	175.0	171.5	175.0
Min	110	106	105	105	105	110	105
Max	320	310	325	310	325	320	325

Note: This table includes data from studies LIMS 8197, 8198, 8304, 8918, 9302, 7448, 7449, 7727, 7820, 7824, 8058, 8061, 8089, 8786, 8986, and I2MS 9981, 10125 and 10214.
Note: Since these are paired-design studies, a subject will be counted in all appropriate treatment columns, but only once under the total column.

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Appendix 2. Demographics for Safety Studies (Safety Population)

Subject Demographics
Safety Studies
Safety Population

	Isopropyl Alcohol (N=287)	Sodium Chloride (N=40)	Sodium Lauryl Sulfate (N=40)	DuraPrep w/o Iodine (N=287)	Betadine Solution (N=287)	DuraPrep Solution (N=287)	Total (N=287)
Height (in)							
N	271	40	40	271	271	271	271
Mean	65.1	64.8	64.8	65.1	65.1	65.1	65.1
S.D.	3.45	2.69	2.69	3.45	3.45	3.45	3.45
Median	65.0	65.0	65.0	65.0	65.0	65.0	65.0
Min	55	59	59	55	55	55	55
Max	79	72	72	79	79	79	79
Weight (lb)							
N	286	40	40	286	286	286	286
Mean	172.6	165.2	165.2	172.6	172.6	172.6	172.6
S.D.	44.70	34.68	34.68	44.70	44.70	44.70	44.70
Median	165.5	159.0	159.0	165.5	165.5	165.5	165.5
Min	87	107	107	87	87	87	87
Max	402	249	249	402	402	402	402

Note: This table includes data from studies LIMS 7294 and 7296.
Note: A subject may be counted in more than one treatment column, but only once under the total column.

Subject Demographics
Safety Studies
Safety Population

	Isopropyl Alcohol (N=287)	Sodium Chloride (N=40)	Sodium Lauryl Sulfate (N=40)	DuraPrep w/o Iodine (N=287)	Betadine Solution (N=287)	DuraPrep Solution (N=287)	Total (N=287)
Height (in)							
N	271	40	40	271	271	271	271
Mean	65.1	64.8	64.8	65.1	65.1	65.1	65.1
S.D.	3.45	2.69	2.69	3.45	3.45	3.45	3.45
Median	65.0	65.0	65.0	65.0	65.0	65.0	65.0
Min	55	59	59	55	55	55	55
Max	79	72	72	79	79	79	79
Weight (lb)							
N	286	40	40	286	286	286	286
Mean	172.6	165.2	165.2	172.6	172.6	172.6	172.6
S.D.	44.70	34.68	34.68	44.70	44.70	44.70	44.70
Median	165.5	159.0	159.0	165.5	165.5	165.5	165.5
Min	87	107	107	87	87	87	87
Max	402	249	249	402	402	402	402

Note: This table includes data from studies LIMS 7294 and 7296.
Note: A subject may be counted in more than one treatment column, but only once under the total column.

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MEMORANDUM

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

Date: August 25, 2004

Re: NDA 21-586
Trade Name: DuraPrep ™ Surgical Solution

Generic Name: povidone-iodine acrylate copolymer (0.7% available Iodine) and isopropyl alcohol (74% w/w)

Applicant: 3M Healthcare

Pharmacologic Category: pre-operative surgical solution

Related Reviews:
Division Director Memorandum: Dr. Ganley
Division Director Memorandum: Dr. Soreth
Medical Officer Review: Dr. Mulinde
Medical Officer Consultation Report: ———
Labeling Comprehension Review: Dr. Osbourne
Microbiology Review: Dr. Coderre

Other relevant documents:
Citizen's Petition submitted by 3M filed June 16, 1995
Center Director Decisional Briefing Sept 9, 2002

Dosage Form and Route of Administration: Topical

This memorandum provides for my concurrence with the Division Director memorandum of Dr. Ganley.

There is a long and extensive regulatory history for this application which is well summarized in Dr. Mulinde's review. Of note, DuraPrep® solution was introduced into the US marketplace in 1988 by the applicant under the 1978 tentative final monograph for OTC Health Care Antiseptics. An amended tentative final monograph was published in the FEDERAL REGISTER on June 17, 1994, which did not include the active ingredient for DuraPrep. A warning letter was sent to 3M on February 8, 1995, advising that DuraPrep is a new drug and misbranded under the Food Drug and Cosmetic Act. Subsequently, the applicant filed on June 16, 1995, a citizen's petition requesting inclusion in the monograph and an IND on December 8, 1995. Due to the applicant's

good faith in its pursuit of an NDA filing, no further action has been undertaken by the CDER Office of Compliance.

The two studies submitted by the sponsor (LIMS 8304 and LIMS 8918) clearly fail to meet the 3 log/cm^2 by 10 minutes reduction for the groin, the "wet site". It can be inferred that the intent of the authors of the TFM was to set a minimum effectiveness criteria for public health protection for the proposed use of these products. Although the consultative report by_____ did not identify evidence in the literature to clinically validate the surrogate microbiologic endpoints of the TFM (defined as establishing a correlation with incidence and/or reduction of surgical site infections), this lack of evidence does not provide a basis on which to justify a lesser standard.

Other recent applications reviewed or under review have met the groin standard (NDA 21-669 Sage 2% CHG pre-operative washcloth approvable 7/1/04, and NDA 21-524 for 3.15% CHG, 70% IPA). On this basis alone, given regulatory precedent and an articulated standard, this application lacks sufficient evidence to support its approval for its intended use as a pre-operative preparation. I am in agreement that this standard needs review but not in the context of an action which would, in effect, lower our standard with significant public health implications for our regulatory oversight of these products.

The studies also raise concern as to the effectiveness of the Hibiclens comparator. Whether this represents diminishing effectiveness or methodology, these findings need further evaluation given the potential public health consequences attendant to the clinical use of this product. Furthermore, the demonstration of mean log reductions that were similar to or statistically significantly greater than Hibiclens by DuraPrep is not sufficient as an alternative effectiveness criteria, particularly given concern as to the validity of the historical evidence for Hibiclens as well as the potential development of resistance over time as a factor in its diminished log reductions.

The additional bacterial challenge studies submitted (LIMS 8197 and LIMS 9302) fail to provide sufficiently compelling supportive evidence for effectiveness. The findings were highly variable (for example, a 3 fold difference for the DuraPrep solution in mean log reduction of CFU/cm^{2}at 5 minutes between the two studies). As surrogate studies, these bacterial challenge findings provide some reassurance in substantiating antimicrobial effectiveness for bacterial species of particular interest for the groin. Although there is clearly "guilt by association", there is a lack of direct clinical correlation of the findings, and therefore the utility for regulatory decision making is limited.

In conclusion, my concerns and recommendations as to the approvability of this application are the following:

1. The applicant has failed to meet the agency standard for effectiveness of the log reduction in the groin for this product. It is unknown whether this deficiency reflects a true lack of effectiveness or is related to study methodology. The bacterial challenge studies, however supportive, are not adequate to fully address

this deficiency. It is recommended that the applicant conduct additional investigation (s) in consultation with the review divisions.

Although there is inadequate data to quantify the clinical significance of not meeting the 3 log/cm^2 reduction, the absence of better science as well as the seriousness of the clinical setting of use, argues for any revision to be scientifically and clinically grounded. Therefore, an approvable action is recommended.

2. The agency should immediately begin the process of planning an Advisory Committee to re-engage experts in this area and provide review of the important issues raised by this application for this class of products. An Advisory Committee may be of great help to resolve these unknowns (e.g., study methodology and data quality) and determine what changes are warranted.

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Division Director Memo

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

Date: August 23, 2004

From: Charles J. Ganley, M.D.
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: Division Director Memo NDA 21-586,
DuraPrep for pre-operative skin preparation

To: NDA 21-586 file

This memo provides a dissenting opinion to the recommendation of approval of NDA 21-586, DuraPrep, as endorsed in the reviews by HFD-520 (Division of Anti-Infective Drug Products).

Introduction

Patient preoperative skin preparation drug products claim to help reduce bacteria that potentially can cause skin infection. In vivo testing of products seeking these claims demonstrate a reduction of endogenous bacteria on the skin. At the time of the expert panel review for this category of product in 1974, the panel acknowledged the lack of data correlating specific amounts of reduction of endogenous bacteria with the prevention of infection even though there was a sense that antisepsis improved postoperative outcomes.[1] Instead of making specific recommendations on the tests to establish efficacy, the panel laid out guidelines and principles for consideration. The tentative final monograph (TFM) in 1994 proposed specific thresholds for reduction in endogenous bacteria counts (log reductions) on specific areas of the body (abdomen and groin). While it is not clear how these threshold numbers were derived, they have served as the gold standard for the approval of new drug applications for the past 15 – 20 years and defined the performance necessary to be considered an acceptable antiseptic in the monograph. In a regulatory and public health sense, it is rational that products used for the same indications, whether marketed under the monograph or NDA, should be held to the same standards. This is particularly true for this category of product where poor efficacy performance of a product can have serious consequences.

[1] In the late 1860's, principles of antisepsis dramatically reduced postoperative infection morbidity. There is no quantitative data correlating a reduction to a specific amount of bacteria on the skin to a specific infection rate or risk. The virulence of an organism will also influence the risk. (Guideline for Prevention of Surgical Site Infection, 1999, Center for Disease Control)

Results

Only the groin data from study 8304 and study 8918 will be presented because this is where the product has failed to meet the log reduction criteria. The differences in interpretation of these results lead to the divergent recommendations between HFD-520 and HFD-560.

The protocols are clearly detailed in Dr. Mulinde's review. Study 8304 and 8918 were conducted to evaluate the effectiveness of DuraPrep against endogenous human skin flora. These types of studies are required to assess the efficacy of any antiseptic product for pre-operative preparation indications whether marketed under a new drug application or a monograph. Each study was a randomized, blinded (only for the assessment of bacteria counts)[2], single center trials. The primary inclusion criteria required subjects to have at least a 3.0 log CFU/cm^2 on the abdomen sites and a 5.0 log CFU/cm^2 on the groin sites. All of the subjects in both studies were treated with DuraPrep on one groin. On the other groin, subjects in study 8304 were treated with either Hibiclens or DuraPrep without iodine. In study 8918, the other groin was treated with either Hibiclens or Betadine. All subjects who were treated are not in included in the analyses. There are additional criteria defining the evaluable population (see Dr. Mulinde's review). Table 1 outlines the objectives of the two studies.

Table 1. Objectives of Studies 8304 and 8918

Objectives	Study 8304	Study 8918
Primary	• Satisfy the 2 log reduction on the abdomen and 3 log reduction on the groin at 10 minutes • Compare the difference in the log reductions between DuraPrep and DuraPrep without iodine at 24 hours	• Satisfy the 2 log reduction on the abdomen and 3 log reduction on the groin at 10 minutes and
Secondary	• Compare the log reductions of DuraPrep with Hibiclens • Bacteria counts do not return to baseline at 6 hours	• Bacteria counts do not return to baseline at 6 hours • Compare the log reductions of DuraPrep to Hibiclens and Betadine

Table 2 provides the log reductions for the groin in study 8304 and 8918. The assessments include all subjects receiving DuraPrep treatment. At 10 minutes, the mean log reduction is 2.76 in study 8304 and 2.23 in study 8918. For the primary objective of assessing log reductions at the abdomen and groin, the primary analysis includes all DuraPrep treated subjects. DuraPrep does not meet the 3 log reduction for the groin at 10 minutes in either study. At 6 hours, the bacteria counts do not return to baseline (this fulfills the efficacy criteria).

[2] Study personnel were unblinded to the treatment of individual subjects because there are obvious differences between the appearance of the products and the method of application. It is critical that the products are applied appropriately as per the labeled instructions. If the products are not applied appropriately, the bacteria counts will be influenced. Investigators also have to be consistent regarding the collection of samples at each time point. Different investigators blinded to therapy conduct the testing of bacteria counts.

Table 2. Log Reductions for DuraPrep Subjects at the Groin Site

Time points	Study 8304		Study 8918	
	N	Mean (SD)	N	Mean (SD)
Baseline Value	70	6.4 (.476)	60	5.83 (.487)
Log reduction @ 10 minutes	70	2.76 (1.116)	60	2.23 (1.059)
Log reduction @ 6 hours	66	2.86 (1.359)	54	2.27 (.972)
Log reduction @ 24 hours	62	2.36 (1.385)	42	2.19 (.879)

One of the secondary objectives of each study was to compare the log reductions of DuraPrep to Hibiclens. These analyses include only subjects who received both DuraPrep and Hibiclens.[3] Table 3 lists the comparative data of Hibiclens and DuraPrep. The Hibiclens data includes all subjects treated with Hibiclens. In study 8918, DuraPrep had a log reduction of 2.37 compared to Hibiclens 1.94. The difference between treatments is statistically significant in favor of DuraPrep at 10 minutes. The log reduction for Hibiclens increases at later time points. For Hibiclens, the log reduction at 24 hours is greater than the 10 minute value. The difference between treatments is statistically significant in favor of Hibiclens. Although there is statistical significance, it is not clear whether this is an adequate basis to ascertain clinical significance. For study 8304, the log reduction was 2.95 for DuraPrep and 2.93 for Hibiclens. Neither treatment reached the 3 log reduction threshold at 10 minutes.

Table 3. Log Reductions for DuraPrep Subjects at the Groin Site

Time points	Study 8304		Study 8918	
	DuraPrep	Hibiclens	DuraPrep	Hibiclens
Baseline Value	6.40 (.486)	6.39 (.478)	5.82 (.511)	5.89 (.480)
Log reduction @ 10 minutes	2.95 (1.265)	2.93 (1.168)	2.37 (1.085) *	1.94 (.964)
Log reduction @ 6 hours	2.70 (1.318)	3.36 (1.087)	2.29 (.971)	2.31 (.971)
Log reduction @ 24 hours	2.51 (1.411)	2.92 (1.222)	2.13 (.796)	2.69 (.796) **

* DuraPrep significantly better than Hibiclens ($p = 0.003$). ** Hibiclens significantly better than DuraPrep ($p = 0.0061$)

Discussion

The sponsor has not met the 3 log reduction of endogenous flora on the groin in their pivotal in vivo studies. The bacterial challenge studies discussed in Dr. Corderro's and Mulinde's reviews do not provide sufficient supporting data to overcome this deficiency. In addition to methodological issues accounting for the failure to achieve the log reduction, there may also be problems with the application technique (e.g. the amount of drug product applied to the skin, the area of application). DuraPrep is simply applied to the skin with an emphasis on not pooling the product. This may have the unintended effect of limiting the amount of drug product applied to the skin. Unless the sponsor can provide clinically relevant alternative data to support the efficacy, they should be required to meet the 3 log reduction for the groin site. Other sponsors have been required to do this for antiseptic preoperative skin preparations.

I have no objection to changing the criteria for approving antiseptic preoperative products under NDAs or giving general recognition of efficacy to an ingredient under the monograph. When changing the criteria, however, we should understand the clinical implication of the change.

[3] Not all subjects receiving DuraPrep received Hibiclens. 39 of 70 subjects in Study 8304 and 47 of 60 subject in 8918 were treated with DuraPrep and Hibiclens. In this subgroup, each subject was treated with DuraPrep on one groin and Hibiclens on the other. These analyses represent a sub-population of all subjects enrolled.

The groin site is generally considered a "dirty" site compared to the abdomen because of a greater number of bacteria that are predominately gram negative. Consequently, it is critically important that products adequately reduce bacteria at the groin or comparable sites.

Over the past two weeks, many issues regarding the approval of this application have been discussed. These will be addressed in following questions and answer.

Hibiclens is not meeting the log reductions for the groin in many studies and it is an approved product. If DuraPrep appears to be as good as Hibiclens, why shouldn't DuraPrep be approved?

- The purpose of the active control is to validate the testing procedure, equipment, and facilities. If the active control fails to meet the log reduction criteria, the validity of the study can be questioned. As noted in other sections of the memo, methodological issues and conditions of use of the products can influence log reductions. Efforts should be made to determine why the products failed to meet the log reductions.
- Hibiclens has failed to meet the groin log reduction criteria in other studies by other manufacturers. Repeat studies have been conducted and in some case Hibiclens achieved the log reduction and in others it did not. This requires further investigation. Until this is resolved, equivalence to Hibiclens in failed studies is not an acceptable standard for approval.[4]

Does a statistically significant difference in log reduction between DuraPrep and Hibiclens (study 8918) support the approval of DuraPrep?

Statistical significance has little meaning unless a difference in log reduction that is clinically significant is defined. The log reduction difference would have to then meet the predefined clinically relevant difference and be statistically significant. Otherwise, large studies may establish a significant difference from the active control with a very small difference in log values. There is currently no clinically significant difference in log reduction defined.

Because of the unblinded design of portions of the study, there are problems with accepting any log reduction of an approved drug as an acceptable benchmark. The studies are unblinded for drug administration and sample collection. Sloppy, inconsistent methodology could result in bacteria counts below the expected for the active control. If the only criterion for approval is being statistically better than the active control without some clinical standard, we are likely to approve some products that may not be very effective.

In lieu of the failure to meet the 3-log reduction on the groin sites in two studies, do the bacterial challenge studies provide sufficient evidence of efficacy to overcome the failure to meet the log reduction?

The purpose of the product is to reduce endogenous flora on the skin prior to surgery. For most surgical site infections, the source of pathogens is the endogenous flora of the patient's skin[5]. The dose of bacteria is a factor at the surgical site. If the amount of endogenous flora at the surgical site is not adequately decreased, the patient's risk for surgical site infection will be increased.

The bacterial challenge studies do not assess the effect of drug on endogenous flora in vivo. The challenge study may be a surrogate for exogenous sources of surgical site pathogens but the predictability of this surrogate for endogenous flora in vivo is unknown. The challenge

[4] 3M in a 5/19/03 submission state that equivalence to Hibiclens should be an acceptable standard to approve DuraPrep. In their comments to the Docket for healthcare antiseptics, they make similar comments (75N-183H, Comment 78, August 25, 2003).

[5] Guideline for Prevention of Surgical Site Infection, 1999, Center for Disease Control

studies were conducted to assess the contribution of the iodine to the combination product to fulfill the combination policy. They have not been required of other sponsors with single ingredient antiseptics.[6] The data from the challenge studies cannot be extrapolated to predict an effect on the endogenous flora in vivo.

Do the threshold log reductions always have to be met when considering a new antiseptic under the NDA regulations?

If the product does not meet the log reductions, the sponsor can provide additional data to supplement this deficiency. For this NDA, the data provided (challenge studies) do not provide clinical data relevant to reduction in endogenous bacterial flora in vivo.

Much of the internal discussion has focused on the fact that our present standards were not derived on the basis of clinical correlation. The lack of a clinical correlation with the threshold reductions is not a justification to accept a lower standard. In fact, it makes it more difficult to accept a lower standard without understanding the clinical implications of the change. The abdomen and groin sites were chosen because they represent different areas of the skin relative to the number and types of organisms. The groin site has more bacteria that are more likely to be anaerobic and gram negative. The inability of a product to achieve the log reductions at the groin may reflect a problem with the conditions of use of the product rather then just methodological issues with the test procedure (see later discussions of NDA #21-669 and #21-524). If alternative clinical data is provided, it should be clinically supported and relevant to assessing the reduction of endogenous flora in vivo.

What are the implications for approving the product on future applications and for products to be marketed under the monograph?

- If the application is approved, this will set the new efficacy standard for this category of product. However, the lower limit will not be defined. For example, if an active control has a log reduction of 1.2 and the product under investigation is statistically different with a log reduction of 1.7, does this meet the standard?
- There are 16 ingredients listed in the TFM as category IIIE and 7 ingredients listed as category II for patient preoperative skin preparation. Efficacy data for these ingredients will need to be revisited to determine whether they achieve similar log reductions relative to the active control.
- Comments to the tentative final monograph have requested that the standard for the groin be lowered. They have not provided any data to support this change other than the failure of many ingredients to meet it.

Should the results of the study be deemed acceptable because the log reduction is near three?

Over the past 2 – 3 years, FDA statisticians involved in the review of antiseptic applications have expressed concerns about the variability associated with point estimates of the log reductions in the in vivo tests provided in NDAs for antiseptic products. In some cases, small percentages of study participants with large reductions were driving the mean values and less than half the subjects actually achieved the threshold log reductions. In addition to the mean log reduction threshold, some have suggested that there should also be a lower permissible limit of the 95% confidence interval. This would help insure that a greater percentage of subjects in these

[6] The sponsor was not able to establish the contribution of the iodine in study 8304. One of the primary objectives of the study was to compare the log reductions of DuraPrep against DuraPrep without iodine at 24 hours. There was no difference in log reductions at 24 hours between these treatments.

trials actually meet the threshold log reductions. This issue will be discussed at a future advisory committee meeting.

While this doesn't help with this application, it is sobering to note that in the studies conducted by the sponsor only 36% of the DuraPrep subjects in study 8304 and 21% in study 8919 met the 3-log reduction threshold. The amount of bacteria remaining on the skin in the DuraPrep subjects is displayed in table 4. There is still a significant amount of bacteria remaining on the skin in many individuals.

Table 4. Amount of Bacteria Remaining on the Skin (Groin Site) in DuraPrep Treated Subjects

Study	N	Mean	Median	Range
8304	70	3.63	3.74	0 – 5.54
8918	60	3.59	3.72	0 – 5.22

The log reduction for DuraPrep at the groin site was 2.76 in study 8304 and 2.23 in study 8919. Whether 2.76 is near 3 depends on the one's perspective. In terms of absolute value, 2.76 log is 58% of 3.0 log. A log 2.23 is 17% of 3. Also, they represent reductions in log count and the significance of the difference cannot be fully appreciated without knowing the baseline bacterial count. For example, a subject starting with a 6.5 log at baseline and having a 3 log reduction would have 3.5 log or 3,162 CFU/cm^2. If the reduction were 2.76, the remaining number of organisms would be 3.74 or 5,495 CFU/cm^2. This is a 74% increase in the absolute amount of bacteria. And finally, once a number is defined as near to another number, the lower limit becomes arbitrary. If 2.90 is near 3.0, is 2.89....2.88...2.87?

The sponsor was told that they did not need to conduct another clinical study in June of 2003 ~~1998~~ and could file the application. Is FDA reneging on that agreement?

FDA told the company that the NDA could be filed and that the agency would review the data. The minutes of the telecon indicate that "this does not mean that the application will be approved". Based on internal discussions and some comments in Dr. Soreth's memo, the failure to meet the 3 log reduction criteria was thought to be a methodological problem with the studies rather the failure of the products. This belief was based on the failure of an approved product, Hibiclens, to meet the 3-log criteria at the groin site in the study. The agency was aware of the failure of Hibiclens in other studies by other sponsors.

Subsequent to this communication, two NDAs have been filed for the same pre-operative anti-septic claims. NDA# 21-669 (CHG Antiseptic Cloths, chlorhexidine gluconate 2%) submitted by Sage Products[7] and the recently submitted NDA # 21-524 (Chlorascrub, 3.15% chlorhexidine with 70% isopropyl alcohol) submitted by Les Enterprise SoluMed Inc. In both of these applications, one of the pivotal studies did not demonstrate a 3-log reduction in bacteria count on the groin site. Both companies conducted another study on the groin and were able to achieve the 3-log reduction. In the case of NDA# 21-669, both the Sage Product and the active control were applied differently and log reductions of > 4 were achieved. In the case of NDA # 21-524, the sponsor determined that the size of the application area of the product influenced the log reduction. They decreased the application area of the product for the applicator being tested and were able to achieve a 3-log reduction. The data from these two applications suggest that the conditions of use of the products (i.e. directions for use) will influence the log reductions. Both of these companies conducted additional studies to assess why their products failed at the groin site. At the time FDA told DuraPrep that they did not have to conduct an additional it was based on the belief the failure was related to methodological issues of the test itself. The data from NDA # 21-669 and NDA # 21-524 applications suggest that methodological issues are not the only reason why a 3-log reduction is not met. Given the data in the Sage and Les Enterprise SoluMed

[7] Received an approvable letter on 6/29/04 because of pending chemistry issues

Inc., it is important to understand why the DuraPrep product does not meet the 3-log reduction. We should not assume that the failure was a result of methodological issues alone.

Summary

In vivo testing for pre-operative skin preparation indications has required products to demonstrate a 2 log reduction in resident bacterial flora on an abdomen site and by 3 log reduction on a groin site. Additionally, bacterial counts at six hours after product administration should not exceed baseline values.

- The sponsor provided sufficient data to support the 2 log reduction on the abdomen site and fulfilled the 6 hour criteria.
- The sponsor failed to provide data demonstrating a 3 log reduction in endogenous bacteria flora on the groin in their pivotal studies.

Conclusion

DuraPrep has failed to achieve a 3-log reduction on the groin site. The additional information provided by the challenge study does not adequately address this deficiency. The sponsor should conduct studies to assess the reason for the failure.

Recommendation

1. The application is approvable pending submission of data demonstrating that DuraPrep can achieve a 3-log reduction at the groin site or provide other clinical data related to the reduction of resident bacteria.
2. [illegible]

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NDA 21-586

Division of Anti-Infective Drug Products Director Memorandum for DuraPrep™ Surgical Solution [Iodophor (0.7% available iodine) and isopropyl alcohol (74% w/w)]

Indication: Patient Pre-Operative Skin Preparation

August 5, 2004

3M™ introduced DuraPrep™ Surgical Solution [Iodophor (0.7% available iodine) and isopropyl alcohol (74% w/w)] to the U.S. market in 1988 as an over-the-counter (OTC) drug product under the Food and Drug Administration (FDA) 1978 Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products. In 1994, FDA published a revised TFM that was more specific in its allowable active ingredient description (povidone-iodine rather than iodophor). 3M representatives met with FDA in December, 1994, to discuss the chemistry of DuraPrep™ Surgical Solution and the regulatory implications for the product given the revised TFM. The Agency indicated that DuraPrep could not be regulated under the revised TFM. 3M filed a Citizens' Petition with FDA asking that the TFM be modified to include the active ingredients in DuraPrep. In September, 1995, the Center Director, Dr. Janet Woodcock, communicated with the OTC Division Director that 3M should be allowed to stay on the market while pursuing submission of an NDA for DuraPrep™ Surgical Solution. A month later, the company met with FDA in a face-to-face meeting to discuss the contents of an Investigational New Drug (IND) submission. 3M filed the DuraPrep IND in December, 1995, targeting the indication of patient pre-operative skin preparation. FDA currently approves products for this indication based on a surrogate microbiologic endpoint of log reductions in bacteria cultured from "dry" and "wet" anatomic sites on healthy volunteer subjects. Proof of clinical benefit (reduction in post-operative infections), however, has not been required. Because DuraPrep™ Surgical Solution contains 2 active ingredients, iodine and isopropyl alcohol (IPA), FDA considered DuraPrep a combination product and asked 3M to show proof of the contribution of the iodophor component to bacterial killing.

Since the IND filing in December, 1995, and the NDA submission in October, 2003, 3M met with FDA in 6 face-to-face meetings and another dozen teleconferences to address clinical trial designs and their conduct, as well as safety issues (applicator design, flammability related incidents, "end-user" education, and labeling changes). In addition to asking for two studies in subjects to establish efficacy of the product in reducing bacterial counts on the skin, FDA requested further studies to document the contribution of the iodophor component, and further analyses of already-existing use-data (spontaneous "post-marketing" reports) to understand patient burn incidents. 3M conducted a total of 23 clinical and microbiologic studies from 1996 to 2002 which provide substantial evidence of efficacy and safety. DuraPrep™ Surgical Solution should thus be approved as a patient pre-operative skin preparation.

3M has demonstrated that skin preparation with DuraPrep™ Surgical Solution results in an immediate (10 minutes post-preparation) and sustained (at 6 hours) decrease in bacterial counts on the skin. In two independent studies (LIMS 8304 and LIMS 8918), DuraPrep solution satisfied the criteria defined in the FDA Proposed TFM for Health Care Antiseptic Drug Products, Effectiveness Testing of a Patient Preoperative Skin Preparation, published in the Federal Register on June 17, 1994 for demonstrating antimicrobial activity on the abdomen (a "dry" site); a greater than 2 $\log_{10}/cm^2$ mean reduction of bacterial counts by 10 minutes post-preparation that did not return to the baseline level by 6 hours was demonstrated. Data at the groin site for DuraPrep solution and Hibiclens Cleanser (4% chlorhexidine gluconate, the positive control) fell shy of the TFM defined criterion (greater than 3 $\log_{10}/cm^2$ mean reduction of bacterial counts at 10 minutes post-preparation) for demonstration of antimicrobial activity at the groin site in both of the two pivotal studies in which this endpoint was assessed (see Table 1.) At the 10 minute sampling time, however, DuraPrep solution did demonstrate mean log reductions that were similar to or statistically significantly greater than Hibiclens cleanser, an FDA approved product for the patient pre-operative preparation indication. In both studies, bacterial counts on the groin site remained below baseline at the 6 hour time point.

Furthermore, bacterial challenge studies (LIMS 8197 and LIMS 9302) were conducted to provide evidence of the contribution of iodine to the DuraPrep solution by demonstrating the persistence of the DuraPrep film activity against bacterial challenge up to 6 hours after site preparation. In LIMS 8197 at the 6 hours post-preparation/30-minute bacterial residence time point, the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film (2.96) than for DuraPrep w/o I_2 film (-0.18; $p<0.0001$, based on a paired t-test). In addition, at all of the time points assessed, the log reduction for DuraPrep film was greater than for DuraPrep w/o I_2 film (all of these differences were statistically significant ($p \leq 0.0003$, based on paired t-tests). Similarly in LIMS 9302, the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film (3.77) than for DuraPrep w/o I_2 film (0.05; $p<0.0001$, based on a paired t-test).

In an August, 2003 meeting with 3M and FDA, the company presented their data collected from studies conducted from 1996 to 2002 to representatives from the Division of Anti-Infective Drug Products and the Division of Over-the-Counter-Drugs. 3M asked the Agency if they should file their NDA. The full body of evidence considered, that is,

- results for DuraPrep studies in the abdominal test sites;
- near 3-log reduction in one groin study for both Duraprep and Hibiclens;
- a statistically superior result for Duraprep in a second groin study;
- bacterial challenge data for DuraPrep in two studies;
- data analyses of "post-marketing" patient pre-operative safety reports; and
- revisions of labels, directions for safe use, and end-user education developed since 1996

lead to the FDA recommendation to 3M to file their new drug application and forgo repeating the test at the groin site.

The finding of groin site data for DuraPrep (test product) or Hibiclens (positive control) not meeting a 3-log reduction does not appear to be unique to this NDA. Companies with other topical antiseptic products in development have reported similar experiences to FDA in information submitted to their INDs. The finding has prompted FDA inspections of some of the facilities that conduct these studies. FDA has identified multiple steps in testing procedures that could have a considerable impact on the ability to demonstrate a 3-log reduction. Furthermore, review of the NDA submission for Hibiclens Cleanser (1978) reveals inconsistencies in reaching 3-log reductions in all studies conducted at abdominal and groin sites (see Table 2). Of note, a greater variation in log reduction was found in studies at abdominal sites, some reaching a 3-log reduction, some a 2-log reduction. The FDA review of Hibiclens for the indication of patient pre-operative skin preparation sites the OTC Antimicrobial Panel Recommendations for testing topical antiseptics. These included:

- Product should be "fast acting" (*FDA Comment: "Fast" not further defined).*
- Product should result in at least a 3 log reduction in flora after use.
- Body sites that are tested should be those that reflect clinical use of product.

It is not clear from examination of the 1978 FDA review of Hibiclens Cleanser, and a similar product Hibitane, if these inconsistencies in study results lead to adopting a standard of 2-log reduction in the abdomen, and 3-log reduction in the groin. Moreover, a definitive link of decreasing bacterial counts on the skin of any order of magnitude (3 log or 2 log reduction) to clinical efficacy (reduction in the incidence of post-operative infections) has not been made. NDAs for topical antiseptic products have not examined this clinical endpoint, and a recent division literature review failed to identify published studies that validate the surrogate endpoint.

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Table 1

Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Hibiclens Cleanser-Treated Sites (Efficacy-Evaluable Population)

	Treatment Group			
Mean Log Reduction	**Hibiclens Cleanser**	**DuraPrep Solution**	**Paired Difference**	**p-value (95% CI)**
LIMS 8304				
Abdomen				
Mean (SD) Log Reduction at 10 Minutes	1.83 (1.647)	2.48 (1.444)	0.65 (1.872)	0.0616 (-0.03, 1.34)
Mean (SD) Log Reduction at 6 Hours	2.02 (1.522)	2.34 (1.520)	0 32 (1.657)	0.2960 (-0.29, 0.92)
Groin				
Mean (SD) Log Reduction at 10 Minutes	2.93 (1.168)	2.95 (1.265)	0.03 (1.137)	0.8843 (-0.34, 0.40)
Mean (SD) Log Reduction at 6 Hours	3.36 (1.087)	2.70 (1.318)	-0.66 (1.477)	0.0115 (-1.16, -0.16)
LIMS 8918				
Abdomen				
Mean (SD) Log Reduction at 10 Minutes	2.15 (1.302)	2.47 (1.146)	0.32 (1.581)	0.2433 (-0.23, 0.87)
Mean (SD) Log Reduction at 6 Hours	1.75 (1.149)	2.31 (1.266)	0.56 (1.329)	0.0221 (0.09, 1.03)
Groin				
Mean (SD) Log Reduction at 10 Minutes	1.94 (0.964)	2.37 (1.085)	0.43 (0.940)	0.0030 (0.15, 0.71)
Mean (SD) Log Reduction at 6 Hours	2.31 (0.947)	2.29 (0.971)	-0.02 (0.743)	0.8566 (-0.25, 0.21)

P value based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.

Mean Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.

SD = standard deviation; CI = confidence interval

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Table 2

Summary of Results of Mean Log_{10} Reductions in Bacterial Counts on the Skin at Groin and Abdomem Sites Reported in NDA 17,768 (Hibiclens, 4% chlorhexidine gluconate) and NDA 18,049 (Hibitane, 0.5% chlorhexidine gluconate/70% v/v isopropyl alcohol)

GROIN

HIBICLENS

Prep Site	Number Patients Studied	Mean Baseline Log_{10} Count	Log_{10} Reduction at 10 Minutes	Log_{10} Reduction at 30 Minutes
Overall Groin	149	4.54	3.62	3.69
McBride Groin	50	5.43	3.76	4.16
Birbaum Groin	50	3.60	3.60	3.56
Vorken Groin	51	4.59	3.48	3.32

HIBITANE

Prep Site	Number Patients Studied	Mean Baseline Log_{10} Count	Log_{10} Reduction at 10 Minutes	Log_{10} Reduction at 30 Minutes
Overall Groin	152	4.51	3.73	3.81
McBride Groin	50	5.08	3.93	4.07
Birbaum Groin	50	3.47	3.39	3.41
Vorken Groin	52	4.96	3.87	3.94

ABDOMEN

HIBICLENS

Prep Site	Number Patients Studied	Mean Baseline Log_{10} Count	Log_{10} Reduction at 10 Minutes	Log_{10} Reduction at 120 Minutes	Log_{10} Reduction at 240 Minutes
Overall Abdomen	144	3.83	3.41	3.34	3.18
McBride Abdomen	45	3.18	2.64	2.48	1.87
Deneen Abdomen*	50	5.05	4.95	4.95	4.93
Taplin Abdomen	49	3.18	2.53	2.49	2.61

HIBITANE

Prep Site	Number Patients Studied	Mean Baseline Log_{10} Count	Log_{10} Reduction at 10 Minutes	Log_{10} Reduction at 120 Minutes	Log_{10} Reduction at 240 Minutes
Overall Abdomen	154	3.63	3.21	3.19	2.91
McBride Abdomen	55	2.83	2.31	2.22	1.63
Deneen Abdomen*	50	5.11	4.86	4.88	4.80
Taplin Abdomen	49	3.03	2.53	2.54	2.41

^ In studies supporting these NDAs neutralizers were added to skin samples at later time points than those used in contemporary studies. The impact of delayed incorporation of neutralizer into samples in these studies can not be precisely defined, but is likely to have resulted in greater log reductions of bacterial counts.

* The design of this study differed from the other two in that the patients were shaved and a sterile towel was applied over site approximately 12 hours prior to preparation of the skin.

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NDA 21-586 Division Director Memo

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Application Type	NDA
Submission Number	21,586
Submission Code	000
Letter Date	October 24, 2003
Stamp Date	October 24, 2003
Reviewer Name	Jean M. Mulinde, M.D.
Review Completion Date	July 9, 2004
Revised	August 4, 2004
Established Name	Iodophor (0.7% available iodine) and isopropyl alcohol (74% w/w)
(Proposed) Trade Name	3M™ DuraPrep™ Surgical Solution
Therapeutic Class	Topical Antiseptic
Applicant	3M Medical Division
Priority Designation	S
Formulation	Solution
Dosing Regimen	Single use
Indication	Patient preoperative skin preparation.
Intended Population	Pediatric and adult patients ≥2 months of age

Twenty-one subjects entered the study and 16 were randomized and received study treatment. All subjects were evaluable for safety and 14 subjects were evaluable for efficacy. Two subjects (Subjects

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1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

DuraPrep™ Surgical Solution (DuraPrep solution) is a topical antimicrobial product consisting of 2 active ingredients, an iodophor (0.7% available iodine) and isopropyl alcohol (IPA) (74% w/w). The iodophor is an iodine acrylate copolymer solution, which remains dissolved in IPA until the solution is applied to the skin. Once applied the isopropyl alcohol/water component of the solution evaporates leaving a water insoluble film from which iodine, as I_2, is released.

DuraPrep solution is intended to be used for the indication of patient preoperative skin preparation. To support this indication the Applicant has submitted data from four pivotal efficacy studies. Studies LIMS 8304 and LIMS 8918 were conducted to provide evidence that preparation of skin with DuraPrep solution results in decreased bacterial counts on the skin. Studies LIMS 8197 and LIMS 9302 were conducted to provide evidence of the contribution of iodine to the DuraPrep solution by demonstrating the persistence of the DuraPrep film activity against bacterial challenge up to 6 hours after site preparation. The Applicant also conducted two additional clinical efficacy studies, which were non-pivotal to product approval, and thirteen method validation and pilot efficacy studies. In addition to efficacy studies, the Applicant conducted four studies to specifically address safety concerns (irritation and sensitization potentials, necessary drying time, and appropriate coverage area for a single unit).

A total of 505 subjects were exposed to DuraPrep solution in studies that support this Application. Three hundred eighty-four subjects received single use applications, which most closely simulate the intended clinical use of the product. One hundred twenty-one subjects received continuous extended duration exposures under occlusive dressings, which simulate "worst case scenario" conditions. Additionally, since DuraPrep solution has been marketed in the United States since 1988, patient exposure has been considerable (Applicant estimates sales approaching [redacted] units since 1988) and over 400 post-marketing safety reports were available for review in this NDA.

1.3.2 Efficacy

The Applicant has demonstrated that skin preparation with DuraPrep solution results in an immediate (10 minutes post-preparation) and sustained (at 6 hours) decrease in bacterial counts on the skin (LIMS 8304 and LIMS 8918). In two independent studies, DuraPrep solution satisfied the criteria defined in the FDA Proposed Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products, Effectiveness Testing of a Patient Preoperative Skin Preparation, published in the Federal Register on June 17, 1994 (TFM) for demonstrating antimicrobial activity on the abdomen (a "dry" site); a greater than 2 $\log_{10}/cm^2$ mean reduction of bacterial counts by 10 minutes post-preparation that did not return to the baseline level by 6 hours was demonstrated. DuraPrep solution did not satisfy the TFM defined criterion (greater than 3 $\log_{10}/cm^2$ mean reduction of bacterial counts at 10 minutes post-preparation) for demonstration of antimicrobial activity at the groin site in either of the two pivotal studies in which this endpoint was assessed; however, at the 10 minute sampling time point DuraPrep solution did

demonstrate mean log reductions that were similar to or statistically significantly greater than Hibiclens cleanser, an FDA approved product for the Patient Preoperative Preparation indication. In both studies bacterial counts on the groin site remained below baseline at the 6 hour time point. Results of these studies are summarized in the following table.

Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Hibiclens Cleanser-Treated Sites (Efficacy-Evaluable Population)

	Treatment Group			
Mean Log Reduction	**Hibiclens Cleanser**	**DuraPrep Solution**	**Paired Difference**	**p-value (95% CI)**
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Abdomen				
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P value based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.
Mean Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.
SD = standard deviation; CI = confidence interval

The Applicant has also demonstrated the contribution of iodine to DuraPrep solution in two independent bacterial challenge studies (LIMS 8304 and LIMS 8918), in which

DuraPrep solution consistently demonstrated significantly greater mean log reductions in bacterial counts on the skin for multiple challenge organisms over time.

Based on the findings in Studies LIMS 8304, LIMS 8918, LIMS 8197, LIMS 9302, and additional *in vitro* Studies completed by the Applicant, the Applicant has demonstrated that 3M™ DuraPrep™ Surgical Solution reduces bacterial counts on the skin, in a manner which is similar to or greater than currently approved products for this indication.

1.3.3 Safety

In safety studies, in which DuraPrep solution is used in a manner in which extreme conditions are simulated (applied continuously for extended durations under occlusive dressings), adverse events associated with use of DuraPrep solution occurred in 48 of 121 subjects (16.7%); these events were limited to transient episodes of mild to moderate skin irritation (described as skin pruritus, burning, irritation, pain, swelling, or tenderness). A total of 384 subjects were enrolled in fifteen pivotal or pilot efficacy/method validation studies in which product application more closely simulates actual clinical use (single application under non-occlusive conditions); in these studies a total of five (1.3%) treatment related adverse events related to skin irritation were reported.

Since DuraPrep solution has been marketed since 1988, the Applicant also summarized post-marketing safety reports for a greater than 15 year period in which approximately [redacted] units (6 mL and 26 mL containers combined) have been distributed in the United States. In this time period there have been 292 reports of skin reactions (including redness, itching, rash, chemical burn, blistering, and skin removal), 108 reports of "infection or rate increase", and 80 reports of ignition of the product resulting in burns to patients during surgical procedures.

Reports of burn secondary to ignition of DuraPrep solution appears to be primarily associated with inappropriate use of the product (failure to let preparation dry and pooling of preparation); all incidents were in association with the introduction of a spark (usually electrocautery) into the surgical field. Types of burns have ranged from first to third degree and have occurred most commonly on the head and neck. To minimize risk to patients, the Applicant has revised labeling on several occasions to more prominently display warnings about flammability risk and to provide detailed directions on appropriate application methods. In addition, the Applicant has undertaken an aggressive educational campaign, which includes video instruction followed by voluntary certification testing, of health care workers that may use this product. While the exact incidence of burn secondary to ignition of DuraPrep solution is impossible to calculate from post-marketing reports, based on sales volume, the yearly incidence appears to be approximately [redacted] units sold.

1.3.4 Dosing Regimen and Administration

DuraPrep solution is a single use product intended for patient preoperative skin preparation. The product is applied as a paint; it should not be applied as a scrub. The Applicant's directions for use should be revised to direct that only the 6 ml container be used for preparation of the head and neck to minimize the risk of excessive saturation of

the hair and drape materials, which may be associated with an increased risk of flammability when used in conjunction with electrocautery.

1.3.5 Drug-Drug Interactions

There are no known drug-drug interactions that affect this product's clinical use. Concomitant use with other topical products has not been investigated.

1.3.6 Special Populations

DuraPrep solution should not be used in pediatric patients less than 2 months of age due to concerns with iodine absorption through immature skin.

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proteins. Iodophors are organic complexes comprised of iodine and a carrier molecule. Iodine is slowly liberated from the carrier on reduction. The microbiocidal effect of the iodophors result from the disruption of protein and nucleic acid structure by free iodine[1, 2].

2.1.8 Regimen

The Applicant proposes the product for single use skin preparation prior to surgery. Directions for use are reviewed in detail in Section 10 of this review. The Applicant proposes that their 6 ml container may be used to prepare an area approximately 8" x 10" and that their 26 ml container may be used to prepare an area from " [redacted]

Medical Officer's Comment: The Applicant has completed a study (untitled study, results provided in October 4, 2001 submission to IND 49,411, which is discussed in detail in Mr. David Bostwick's Integrated Safety review of this NDA) that demonstrates area covered by the 26 ml container to be approximately [redacted] therefore, a more specific measure of surface area covered should be provided in the package labeling and package insert for the 26 ml container.

2.2 State of Armamentarium For Indication(s)

There are a large number of products that are currently marketed for the indication of Patient Preoperative Preparation that were approved via the NDA process or that are marketed under the current guidelines provided in the FDA Proposed Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products, Effectiveness Testing of a Patient Preoperative Skin Preparation, published in the Federal Register on June 17, 1994.

In the TFM the following ingredients are considered safe and effective for patient preoperative skin preparation and may be marketed for this indication: alcohol (60% to 95%), iodine tincture U.S.P., iodine topical solution U.S.P., povidone-iodine (5% to 10%), and isopropyl alcohol (70% to 91.3%).

Additional antiseptics that have been approved through the NDA process and are currently marketed for this indication include: 2% to 4% chlorhexidine gluconate and 2% chlorhexidine gluconate plus 70% isopropyl alcohol combination.

2.3 Availability of Proposed Product in the U.S.

DuraPrep solution has been marketed in the United States since 1988 as an over-the-counter drug product (see Section 2.5 Pre-submission Regulatory Activity for further discussion). The primary safety issue related to the use of DuraPrep solution for patient preoperative skin preparation has been reports of burns secondary to ignition of isopropyl

alcohol/associated vapors with use of electrocautery devices. Since initial marketing, the Applicant has revised the product label on four occasions to provide additional warnings and directions for use of the product in an attempt to eliminate burn incidents.

2.4 Important Issues with Pharmacologically Related Products

Use of other topical products containing iodine in infants has been associated with absorption of iodine and development of transient hypothyroxiniemia and hypothyroidism. In addition, use of topicals containing alcohol in infants (particularly under occlusive dressings) has been associated with development of measurable blood levels, local toxicity (irritancy, skin necrosis) and systemic toxicity[3].

2.5 Pre-submission Regulatory Activity

The regulatory history of DuraPrep solution is summarized in the following Table.

Table 1. Pre-Submission Regulatory Activity

DATE	PRE-SUBMISSION HISTORY
1988	3M™ DuraPrep™ Surgical Solution (DuraPrep solution) introduced into US market as an over-the-counter (OTC) drug product under the 1978 Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products
June 1994	Revised TFM for Health Care Antiseptic Drug Products published.
December 1994	3M met with FDA to discuss the chemistry of DuraPrep solution and the implications of the 1994 TFM. The Agency indicated that DuraPrep would not be considered a Category I product under the June 1994 TFM.
September 1995	The Center Director, Dr. Janet Woodcock, communicated with the OTC Division Director that 3M should be allowed to stay on the market while pursuing submission of an NDA for DuraPrep solution.
October 1995	Pre-IND face-to-face meeting held between 3M and FDA. Chemistry, toxicology, microbiology and clinical issues surrounding IND studies discussed.
December 1995	IND for DuraPrep solution filed.
March 13, 1996	Teleconference held to discuss test methods and sampling plans
August 13, 1996	Teleconference held to discuss the use of a modified sampling solution.
May 21, 1997	Teleconference held to discuss several studies; recovery of organisms from skin prepped with DuraPrep, Minimum Bactericidal Concentration Study, ASTM Pilot Protocol and the Time-Kill Assay, Dried Film Method.
July 28, 1998	Face-to-face meeting held to review the pilot data in support of the use of the Modified Sampling Solution (MSS) and to discuss statistical and safety issues.
October 13, 1998	Face-to-face meeting held to discuss the applicator design, flammability related incidents, in-service plans and labeling changes.

July 26, 1999	Face-to-face meeting held to discuss the proposed test method for demonstrating product persistence (i.e., the contribution of iodine) in the DuraPrep solution formulation.
April 10, 2000	Teleconference held to discuss the results of study LIMS #7820, the revised bacterial challenge protocol, draft labeling and whether or not the product can be marketed with an iodophor as an inactive.
November 6, 2000	Face-to-face End-of-Phase II Meeting held
October 4, 2001	Teleconference held to discuss the DuraPrep solution applicator design and product labeling (with strengthened warnings and directions for use).
November 5, 2001	Teleconference held to discuss the revised product labeling with regards to electrocautery
December 20, 2001	Teleconference held to discuss the Betadine/MSS Pilot Study, Neutralization Validation study, irritation/sensitization protocols, and to discuss the safety studies.
April 11, 2002	Teleconference held to review and discuss the final draft pivotal study protocols, and review the draft Target Product Information, as requested by the Agency.
October 17, 2002	Teleconference held to update 3M on the Center's interest on the status of the NDA submission for DuraPrep.
January 17, 2003	Teleconference held to discuss the format of the Common Technical Document (CTD).
June 12, 2003	Teleconference held to discuss the results of studies LIMS 8304 and LIMS 8918, "Pivotal Studies to Assess the Antimicrobial Effectiveness of 3M DuraPrep Solution Against Resident and Human Skin Flora on Abdomen and Groin Regions". FDA agreed that results of LIMS 8304 and LIMS 8918 were adequate to support filing of NDA.
August 21, 2003	Face-to-face meeting held with the Agency at which 3M presented their conclusions regarding the risk/benefit profile of DuraPrep solution.
August 29, 2003,	Teleconference held to discuss the dataset format and structure used in the NDA.

2.6 Other Relevant Background Information

DuraPrep™ Surgical Solution has been marketed in United States since 1988, as an over-the-counter (OTC) drug product. DuraPrep solution is also marketed in the following countries:

Country	Year of Product Introduction and Registration No.
Brazil	2002, Registration No. 10002070141
Canada	1989, Registered as Medical Device – No license number
Colombia	1997, Registration No. INVIMA V-001343

Costa Rica	1998, Registration No. 1005-XE-13050
Denmark	1988, Product registration not required
Dominican Republic	1998, Product registration not required
Italy	1993, Registration No. 17.552
Korea	2003 Registration Approval, Not yet introduced
Mexico	1996, Registration No. 287C9655A
South Africa	1997, Reg. No. 29/13.1/0296
United Arab Emirates	2000, Product registration not required
United Kingdom (UK)	1995, Registration No. 00068/0159
Venezuela	1998, Registration No. PMP-3510

There are no pending registrations for DuraPrep solution in any other foreign countries. DuraPrep solution has not been withdrawn from the market of any foreign country for any reason. According to the Applicant, of the total DuraPrep sales, less than [redacted] of 2002 sales were international.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Chemistry

At the time of this review, the Chemistry Review by Dr. Milton Sloan, is pending. Based on preliminary discussions with Dr. Sloan, there do not appear to be CMC issues that would prevent approval of this product.

3.2 Animal Pharmacology/Toxicology

From the Pharmacology/Toxicology perspective, Terry S. Peters, D.V.M., recommended that this Application be approved. Dr. Peters stated that there were no outstanding preclinical issues. Additionally, she noted that as the individual components of this product have been in clinical use for many years and since the DuraPrep product itself has been marketed since 1988, the safety profiles of the ingredients are well-characterized.

3.3 Division of Over-The-Counter Drug Products (OTC) Labeling Consultation

Michelle Jackson, Ph.D., has completed a labeling review for DuraPrep™ Surgical Solution and has requested a number of changes to the Applicant's proposed label to make it consistent with labeling for recently approved healthcare topical antiseptic OTC drug products. For details of this review, please see Dr. Jackson's review dated April 26, 2004.