4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Applicant conducted a total of 23 clinical studies and Study Reports for each of these studies were included in the NDA submission and utilized in the review of this product. The following additional materials were consulted in the review of this NDA.

1. Applicant's October 19, 2000 submission to IND 49,411
2. Applicant's October 4, 2001 submission to IND 49,411
3. Applicant's May 15, 2003 submission to IND 49,411
4. Post-marketing safety reports dating from 1988 to 2003.
5. 21 CFR Parts 333 and 369; Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products; Proposed Rule, Friday, June 17, 1994.
6. Literature as summarized in Section 8.6 of this review.
7. Literature as summarized in Section 1.6 of Mr. Bostwick's Safety Review.

4.2 Tables of Clinical Studies

Efficacy, Safety, and Pilot Efficacy and Validation studies are described in the following three Tables.

Table 2. Description of Clinical Efficacy Studies

Study ID	Number of Study Centers (Location)	Study Start and Completion Dates	Study Design	Study and Control Drugs (Dose, Route and Regimen)	Study Objective	No. of Subjects by Arm (Entered/Completed)	Duration
PIVOTAL EFFICACY STUDIES							
LIMS 8304							
	1 [redacted]	Start: 01 May 2002 Completed:23 Oct 2002	Randomized, partially blinded, paired-comparison study	Test=DuraPrep solution Control=DuraPrep w/o I2 Control=Hibiclens cleanser	To demonstrate that DuraPrep solution meets the TFM criteria for log reduction; and demonstrate the contribution of iodine to the formulation.	Abdomen (83/81) Groin (74/61)	24 hours
LIMS 8918							
	1 [redacted]	Start: 23 April 2002 Completed: 20 January 2003	Randomized, partially blinded, paired-comparison study	Test=DuraPrep solution Control=Hibiclens cleanser Control=Betadine Combination	To demonstrate that DuraPrep solution meets the TFM criteria for log reduction.	Abdomen (58/54) Groin: (69/47)	24 hours
LIMS 8197							
	1 [redacted]	Start: 30 January 2003 Completed: 19 March 2003	Randomized, partially blinded, paired-comparison study	Test=DuraPrep solution Control= DuraPrep w/o I2 Control=Betadine Combination	To assess the contribution of iodine to the antimicrobial activity of DuraPrep solution.	31/24	1 day (approximately 8 hours)
LIMS 9302							
	1 [redacted]	Start: 29 January 2003 Completed: 27 February 2003	Randomized, partially blinded, paired-comparison study	Test=DuraPrep solution Control= DuraPrep w/o I2 Control=Betadine Combination	To assess the contribution of iodine to the antimicrobial activity of DuraPrep solution.	28/24	1 day (approximately 8 hours)
NON-PIVOTAL EFFICACY STUDIES							
LIMS 8198							
	1 [redacted]	Start: 09 May 2002 Completed: 12 June 2002	Randomized, partially blinded, paired-comparison study	Test=DuraPrep solution Control=Betadine Combination*	To compare the durability and persistence of antimicrobial activity of the DuraPrep film and Betadine combination*	16/12	1 day, approximately 8 hours
LIMS 9567							
	1 3M Company St Paul, MN	Start: 30 April 2002 Completed: 7 May 2002	Randomized block design with replicates	Test=DuraPrep solution Control=DuraPrep w/o I2 Control=Hibiclens cleanser (applied to a 4"x4" skin patch test site)	To evaluate the drape adhesion characteristics of DuraPrep solution, Betadine combination, and Hibiclens cleanser	12/12	Less than 1 hour

[Source: Module 2 Clinical Summary Report (pages 10-30)]

Table 3. Description of Clinical Safety Studies

Study ID	Number of Study Centers (Location)	Study Start and Completion Dates	Study Design	Study and Control Drugs (Dose, Route and Regimen)	Study Objective	No. of Subjects (Entered/Completed)	Duration
LIMS 7294							
	1 [redacted]	Start: 02 May 2002 Completed: 23 May 2002	Comparative, single blind study using a within subjects randomized design, active- and vehicle- controlled	Test=DuraPrep solution Controls=DuraPrep w/o I2, Betadine solution, 0.1% sodium lauryl sulfate, 0.9% sodium chloride, and 70% isopropyl alcohol	To assess the cumulative irritation potential of topically applied DuraPrep solution compared to that of DuraPrep w/o I2, Betadine solution, 0.1% sodium lauryl sulfate, 0.9% sodium chloride, and 70% isopropyl alcohol	41/32	21 days
LIMS 7296							
	1 [redacted]	Group I Start: 23 April 2002 Completed: 20 January 2003 Group II Start: 8 July 2002 Completed: 16 August 2002	Comparative, single blind study, randomized design, active- and vehicle- controlled	Test=DuraPrep solution Controls=DuraPrep w/o I2, Betadine solution, and 70% isopropyl alcohol	To assess the contact sensitization potential of DuraPrep solution compared to DuraPrep w/o I2, Betadine solution, and 70% isopropyl alcohol	247/204	42 days
Study-05-00-09834							
	1 3M Company St. Paul, MN	Start: 1 May 2003 Completed: 1 May 2003	Uncontrolled	Test=DuraPrep solution	To measure the concentration of isopropyl alcohol vapors when DuraPrep is drying and when it appears to be dry	13/13	< 1 hour
Study-05-00-09855							
	1 3M Company St. Paul, MN	Start: 30 June 2003 Completed: 30 June 2003	Noncomparative, nonrandomized, unblinded study	Test=DuraPrep solution to subject's back, or leg, or neck and shoulder	To have nurses perform simulated patient preps and evaluate the dry time of DuraPrep solution	12/12	<15 minutes

[Source: Module 2 Clinical Summary Report (pages 10-30)]

Table 4. Description of Pilot Efficacy and Validation Studies

Study ID	Study Location	Study Objective	Number of Subjects Entered/Completed
LIMS 7179	3M Company St Paul, MN	To compare the recovery of resident aerobic skin flora using SSS versus Modified Sampling Solution.	10/10
LIMS 7721	3M Company St Paul, MN	To compare the recovery of resident aerobic skin flora using SSS versus Modified Sampling Solution.	10/10
LIMS 7448		To test the ability of Modified Sampling Solution to dissolve the DuraPrep solution copolymer and allow the recovery of *B. subtilis* spores from beneath the DuraPrep film	5/5
LIMS 7824	3M Company St Paul, MN	To test the ability of Modified Sampling Solution to dissolve the DuraPrep solution copolymer and allow the recovery of *B. subtilis* spores from beneath the DuraPrep film	10/10
LIMS 7727		To measure the reduction of normal aerobic bacterial flora on abdominal and groin test areas following treatment	Abdomen: 5/5 Groin: 5/5 Abdomen: 4/1 Groin: 4/3
LIMS 7449		To assess a modified microbial sampling solution and the test methods to be used in future pivotal studies to evaluate the antimicrobial effectiveness of DuraPrep solution	Abdomen: 14/10 Groin: 15/10
LIMS 8058		To confirm the use of a modified sampling solution for collection of microbial samples from skin sites prepped with DuraPrep solution and Betadine combination	Abdomen: 5/5 Groin: 6/5 Abdomen: 5/5 Groin: 5/5
LIMS 8786		To verify that Hibiclens cleanser produces a 3-log reduction in 10 minutes when sampled with MSS.	9/7
LIMS 8986		To compare the log reductions (on the groin) produced by Betadine combination using MSS versus SSS.	12/12
LIMS 7820		To evaluate the bacterial challenge test methodology used to assess the antimicrobial persistence of DuraPrep solution using a tetracycline-resistant strain of *S. aureus* on top of the DuraPrep film	6/6
LIMS 8089		To evaluate the bacterial challenge test methodology used to assess the antimicrobial persistence of DuraPrep solution using a tetracycline-resistant strain of *S. aureus* on top of the dry DuraPrep film	3/3
LIMS 8061		To evaluate the test methodology used to assess persistent antimicrobial activity following a wash with autologous blood and saline using a tetracycline-resistant strain of *S.aureus*.	5/5
SRFE 1513	3M Company St. Paul, MN	To evaluate the antimicrobial persistence of DuraPrep solution using a tetracycline-resistant strain of *S.aureus* as a challenge organism.	8/8

[Source: Module 2 Clinical Summary Report (pages 10-30)]

4.3 Review Strategy

Mr. David Bostwick conducted the Safety Review for this Application. He utilized data from 17 studies conducted by the Applicant to assess the overall safety profile of the product. He also reviewed in detail, four studies that were conducted solely to assess safety: LIMS 7294, LIMS 7296, Study-05-0009834, and Study-05-00-09855. In addition, since DuraPrep has been a marketed product in the United States since 1988, Mr. Bostwick reviewed over 400 reports of adverse events that had been submitted as spontaneous post-marketing reports.

The review of efficacy, included in this review, is based on four pivotal efficacy studies: LIMS 8304, LIMS 8918, LIMS 8197, and LIMS 9302. Studies LIMS 8198 and LIMS 9567 were non-pivotal efficacy studies, which are also briefly reviewed in Section 6 of this review. The remaining 13 studies, which included method validation studies and pilot efficacy studies are not specifically reviewed in this document, but are commented on as appropriate.

The literature noted in Section 8.6 provided additional pre-clinical and clinical safety information.

4.4 Data Quality and Integrity

DAIDP requested a Division of Scientific Investigations (DSI) inspection for LIMS #8918, conducted at [redacted]. This site was chosen for inspection based on the finding that in studies submitted in support of in this NDA, and other NDAs, that the reference test product (HIBICLENS® Antiseptic/Antimicrobial Skin Cleanser) did not achieve expected bacterial reductions. The DSI inspection was completed in April, 2004 and the conclusion resulting from the inspection was "the data submitted in support of this NDA appear acceptable." Of note, Frederick Marsik, Ph.D., a Microbiology Reviewer in the Division of Anti-Infective Drug Products, also accompanied the DSI inspector, Thomas Nojeck, on this inspection. Dr. Marsik specifically reviewed issues related to protocol design and implementation to determine whether factors could be identified that might explain why, in certain cases, the reference test product (HIBICLENS® Antiseptic/Antimicrobial Skin Cleanser) did not achieve the bacterial reductions specified in 21 CFR Part 333.470 (3). Dr Marsik was unable to identify a specific reason for unexpected findings in study LIMS #8918.

An audit of a 20% random sample of case report forms (CRF) was completed by the Medical Officer for each of the pivotal efficacy studies, LIMS #8304 and LIMS #8918. These reviews were completed with the reviewer blinded to study therapy to minimize introduction of bias. For the random samples reviewed, minimal inconsistencies with Applicant derived assessments were identified. These differences would not significantly impact overall conclusions of the studies; therefore, the datasets and analyses provided by the Applicant were considered acceptable.

4.5 Compliance with Good Clinical Practices

Informed Consents appear to have been appropriately administered to study subjects participating in clinical trials which support approval of this NDA. The Applicant appropriately listed and described protocol violations that occurred during the conduct of clinical trials which support approval of this NDA.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators. In the case of two employees of 3M, who were Principle Investigators for three clinical studies (LIMS #9567, LIMS #9855, and Study-05-0009834), the applicant has provided adequate evidence that appropriate steps were taken to minimize the potential bias of clinical study results that are provided in this submission. The disclosed financial arrangements do not raise questions about the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Charles R. Bonapace, Pharm.D, the Clinical Pharmacology and Biopharmaceutical Reviewer found the Application to be acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

Since DuraPrep solution is not intended for systemic use no clinical pharmacokinetic studies were conducted. The Applicant did assess the potential for iodine absorption in Study LIMS 1621, but they were unable to provide any analytical validation data for the study; therefore, Dr. Bonapace reported the observations of Study LIMS1621 for informational purposes only. The following is a summary of the observations made by Dr. Bonapace in his review:

> In this study, the sponsor assessed the absorption of a single application of DuraPrep surgical solution (equivalent to 0.08 g of iodine) compared to Betadine solution (equivalent to 0.08 g of iodine) and following three days of iodine-rich meals. Blood samples for iodine concentration determination were obtained for 28 hrs after application and urine samples were obtained for 72 hrs. The mean plasma concentration-time profiles of iodine (not corrected for baseline) were initially greater in subjects who received DuraPrep solution compared to Betadine solution, whereas the mean plasma concentration-time profiles were similar in subjects who received DuraPrep solution and three days of iodine-rich meals. The mean AUC_{0-28} for DuraPrep was slightly greater (6.0%) than the mean AUC_{0-28} for Betadine and similar to the mean AUC_{0-28} following three days of iodine-rich meals. Upon correction of iodine plasma concentrations for baseline values, mean plasma iodine concentrations were similar to or below baseline values after a single dose application of DuraPrep or Betadine and three days of iodine-rich meals. The mean amount of iodine excreted in urine during the 0-24 hr and 24-48 hr periods was greater for DuraPrep (224 *u*g and 228 *u*g, respectively) compared to Betadine (122 *u*g and 128 *u*g, respectively) and after three days of iodine-rich meals (177 *u*g and 114 *u*g, respectively). The sponsor also assessed the clinical

- impact of a single application of DuraPrep solution, Betadine solution, and three days of iodine-rich meals on thyroid function on days 1, 3, and 8. The mean T3, T4, and TSH concentrations were not significantly different between the three study arms. Although the mean plasma iodine AUC_{0-28} and urinary excretion of iodine were greater following a single application of DuraPrep compared to Betadine, the increased plasma concentrations do not appear to be clinically relevant compared to iodine-rich meals based on thyroid function.

Dr. Bonapace concluded, however, that since the Applicant was unable to provide validations data for the analytical method used to determine plasma and urine iodine concentrations in Study LIMS 1621 that data obtained from this study be used for informational purposes only and not for labeling. No additional studies were recommended to assess the absorption of iodine from topical administration of DuraPrep solution.

5.2 Pharmacodynamics

Since DuraPrep solution is not intended for systemic use no clinical pharmacodynamic studies were conducted. Results of Study LIMS 1621, which assessed systemic absorption, are described in the preceding section.

5.3 Exposure-Response Relationships

Specific exposure-response relationships were not explored by the Applicant.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Methods

The review of efficacy, included in this review, is primarily based on 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.

Two additional clinical efficacy studies, LIMS 8198 and LIMS 9567, which are non-pivotal to product approval, will be briefly commented on in this Section. Thirteen studies, which included method validation studies and pilot efficacy studies are not specifically reviewed in this document, but are commented on as appropriate.

For a complete listing of all clinical studies, conducted by the Applicant, the reader is referred to Section 4.1.

6.2 General Discussion of Endpoints

The LIMS 8304 and LIMS 8918 primary study endpoints were taken from 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. The TFM requires a mean 2 $\log_{10}$ reduction in bacterial counts from baseline on abdominal sites and a mean 3 $\log_{10}$ reduction in bacterial counts from baseline on inguinal sites 10 minutes after site preparation. In addition, the TFM also requires that the mean microbial counts on the abdominal and inguinal sites remain below baseline counts for six hours.

Medical Officer's Comment: ***It should be noted that these endpoints reflect only mean $\log_{10}$ reductions of bacterial counts on the skin; an association with these endpoints and reduction in postoperative surgical site infection has not been demonstrated.***

An additional issue with the study design recommended in the TFM for the patient preoperative preparation indication is that endpoints are based on mean log reductions, rather than individual subjects achieving specified reductions. Thus individual results may vary from increased to decreased counts on the skin for a given drug product, yet based on overall mean reductions the product could be considered efficacious. If one were to look at individual results in recent Applications, in which TFM prescribed mean log reductions were achieved, as many as 40-50% of individual subjects may not have achieved prescribed reductions on an individual basis.

Further complicating the interpretation of studies relying on TFM endpoints are recent reports by multiple FDA Stakeholders that the most frequently utilized positive control, Hibiclens® Antiseptic Skin Cleanser, frequently is unable to achieve prescribed TFM bacterial log reductions, particularly on groin sites. These unexpected findings have lead to careful reconsideration of the methodology recommended in the TFM and while it would seem the most likely explanation for failure of the positive control to perform as expected is application method, there are multiple other points in these studies in which variations in methods may lead to unexpected findings (e.g., sampling solution utilized, plating methods

utilized, counting methods, etc.). For example, the design of studies used to support the original Hibiclens® and Hibitane® NDA approvals for the patient preoperative skin preparation indication is significantly different than current study designs; therefore, results that vary from those in the original NDAs for these products is not unexpected. In addition, these studies have traditionally not contained negative controls, a fact that further complicated the Agency's ability to interpret such unexpected results.

The Agency is striving to refine methodologies recommended in the TFM and many of these issues will be addressed in a public forum at future Advisory Committee meetings.

Studies LIMS 8197 and LIMS 9302 were conducted to provide evidence of the contribution of iodine to the DuraPrep solution. The primary endpoint utilized in these studies was based on a demonstration of the persistence of the DuraPrep film activity against bacterial challenge (30 minute residence times) at 6 hours after site preparation.

Medical Officer's Comment: 3M representatives discussed this study design with staff in the Division of Anti-Infective Drug Products at a number of meetings (face-to-face and via teleconference). In 1999, representatives of the Agency and 3M agreed that if DuraPrep solution compared to DuraPrep w/o I_2 was shown to have a statistically significantly greater reduction in bacterial counts on the surface of the film (on the skin) at this time point in two independent studies that it would be considered adequate evidence of the contribution of iodine to the DuraPrep solution.

6.3 Efficacy Findings

6.3.1 LIMS #8304 "Pivotal Study to Assess the Antimicrobial Effectiveness of 3M Duraprep™ Surgical Solution Against Resident Human Skin Flora on Abdomen and Groin Regions Study-1"

6.3.1.1 Objective/Rationale

The objectives of the study, as stated by the Applicant, were:

Primary Objectives

- To demonstrate that 3M™ DuraPrep™ Surgical Solution (DuraPrep solution) meets the 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) criteria for log reduction of resident skin flora.
- To demonstrate the contribution of iodine to the formulation by showing significantly greater log reduction at 24 hours on sites treated with DuraPrep solution compared to those treated with DuraPrep solution formulated without I_2 (DuraPrep w/o I_2).

Secondary Objectives

- To demonstrate the 24-hour efficacy of DuraPrep solution (counts remain significantly below baseline).
- To compare the log reduction achieved by DuraPrep solution to that of Hibiclens® Antiseptic Skin Cleanser (Hibiclens cleanser).

Medical Officer's Comment: For the patient pre-operative preparation indication, the TFM states that for a product to be considered efficacious the test product must reduce the number of bacteria 2 log_{10}/cm^2 on the abdominal test site (a "dry" site) and 3 log_{10}/cm^2 on at the groin site (a "wet" site)

within 10 minutes after product use and that the bacterial cell count for each test site does not subsequently exceed baseline measurements 6 hours after product use.

The Applicant included the DuraPrep w/o I_2 arm in this study in an attempt to demonstrate the contribution of I_2 in DuraPrep solution.

6.3.1.2 Study Design

The study was a randomized, paired-comparisons design where each subject received DuraPrep solution and either Hibiclens cleanser or DuraPrep w/o I_2. This study was conducted at one center in the United States [redacted]

6.3.1.3 Protocol Overview

6.3.1.3.1 Population/Procedures

Population

A sufficient number of healthy volunteers were enrolled so that a total of at least 30 abdominal regions and 30 groin regions were evaluable for efficacy in the DuraPrep solution vs. Hibiclens cleanser series and 30 abdominal regions and 30 groin regions in the DuraPrep solution vs. DuraPrep w/o I_2 series at completion of the study.

A subject could have qualified for the abdominal portion of the study, the groin portion of the study, or both. The right and left sides of the abdomen and groin must have met the minimum baseline values stated in the Inclusion Criteria to qualify for the corresponding portion of the study. The following are noteworthy inclusion and exclusion criteria:

Inclusion Criteria

1. Healthy volunteers of both genders and any race that were between 18 and 75 years of age.
2. Subjects who satisfied all inclusion/exclusion criteria and voluntarily signed the consent form.
3. Subjects who had Screening Day baseline counts of at least 3.0 $\log_{10}$ /cm^2 per abdominal site and/or 5.0 $\log_{10}$ /cm^2 per groin site.
4. Subjects whose skin within 6 inches of the test areas was free from cuts, acne, abrasions, and skin irritation.
5. Subjects who were willing to follow instructions for the study.
6. Subjects who were willing to stay at the clinical site for the duration of the scheduled treatment day (approximately 8 hours) and return the next day for the 24-hour sampling.

In addition, enrolled groin subjects must also have met Treatment Day baseline counts of at least 3.2×10^4 (4.5 $\log_{10}$) CFU/cm^2 per groin site to be considered evaluable for efficacy. Seventy-five percent of abdomen subjects must have had minimum 3.0 $\log_{10}$ /cm^2 counts on both screening and treatment day; up to 25% of abdomen subjects had to have between 2.5 $\log_{10}$ /cm^2 and 3.0 $\log_{10}$ /cm^2 counts on one or both abdomen sites on treatment day.

Exclusion Criteria

1. Any form of dermatitis, acne, open wounds, or other skin disorders (on the applicable test areas).
2. A history of skin allergies.
3. Known sensitivity to acrylate-, iodine-, chlorhexidine gluconate-, or alcohol-containing products, or to medical tape or natural rubber latex.
4. Use of antibacterial soaps, lotions, dandruff shampoos, deodorants, or topical or systemic antibiotics within 14 days of the scheduled screening or treatment day.
5. Exposure to any other topical medications on the test areas within 14 days of the scheduled screening or treatment day.
6. A history of skin cancer within 6 inches of the test areas.
7. Contact with chlorinated swimming pools or hot tubs within 14 days of the scheduled screening or treatment day.
8. Bathing or showering the test areas within 48 hours prior to the scheduled screening or treatment day.
9. Contact with solvents, acids, bases, or other household chemicals in the test areas within 14 days of the screening or treatment day.
10. Pregnancy, possible pregnancy, attempting pregnancy, or nursing.

Medical Officer's Comment: ***The Applicant's inclusion and exclusion criteria are acceptable and in general accordance with recommendations in the TFM.***

Procedures

Participation in this study involved a 14-day pretreatment phase, a one-day screening phase, and a two-day treatment phase. Prior to the scheduled screening day, subjects underwent a minimum 14-day pretreatment phase, in which they refrained from the use of products containing antibacterial agents (per written instructions provided by the Study Investigator). Subjects were given product kits containing non-antimicrobial soaps, deodorants, and shampoos and were instructed to use these products through completion of the treatment phase. Following the pretreatment phase, subjects were required to visit the test facility for collection of screening baseline samples from the abdominal and groin regions. Subjects whose baseline samples met the minimum values described in the Inclusion Criteria were eligible for participation in the treatment phase of the study (treatment phase occurred no sooner than 72 hours and no later than 7 days from the screening baseline collection). During the treatment phase participants remained at the test facility for the duration of the first scheduled treatment day (for approximately 8 hours) and returned to the test facility on the second scheduled treatment day for the 24-hour sampling (for approximately 1 hour). In the event that a subject did not meet the entrance criteria on screening and/or treatment day, that subject was replaced. Subjects who qualified on screening day and began the treatment phase were not allowed to re-enter the study, regardless of whether or not they completed the study.

On the first treatment day, abdominal and groin test areas were prepared as follows:

Abdominal Region - The test site within the abdominal region was defined as the area below the umbilicus and above the groin. Using a 5" x 5" sterile template, the corners of each abdominal test area were marked directly onto the skin using a non-toxic skin marker. Five abdominal sampling sites were numbered within each abdominal test area, on each side of the abdomen region. The positioning and numbering of the abdominal sampling sites were standard for all subjects. Sampling sites on the contra lateral side of the abdomen were numbered in a mirror-image orientation. The five sampling sites within each abdominal test area represent the baseline (pre-prep) site and four post-prep sample sites.

Groin Region - The test site within the groin region was defined as the inner aspect of the upper thigh within and parallel to the inguinal crease below the groin. Using a 2" x 5" sterile template, the corners of each groin test area were marked directly on the skin using a non-toxic skin marker. Four sampling sites were numbered within each groin test area. The positioning and numbering of the groin sampling sites were standard for all subjects. Sampling sites on the contra lateral side of the groin were numbered in a mirror-image orientation. The four sampling sites within each groin test area represent a baseline (pre-prep) site and three post-prep sample sites.

After test areas were marked and sample sites were numbered, baseline samples were collected from site 5 on the abdomen and site 3 on the groin in each test area. Following baseline sample collection, randomly assigned contra lateral test areas were prepped with DuraPrep solution (total 60 subjects) and either Hibiclens cleanser (30 subjects) or DuraPrep w/o I_2 (30 subjects). Test areas on each subject's body regions were assigned according to a computer-generated randomization schedule to receive DuraPrep solution on one side of the region, and either Hibiclens cleanser or DuraPrep w/o I_2 on the contra lateral side. Randomization was balanced between left and right sides. Hibiclens cleanser was applied according to labeled instructions. DuraPrep solution and DuraPrep w/o I_2 were applied using the following application instructions:

1. Shake applicator vigorously for approximately 5 seconds (for DuraPrep w/o I_2 solution only).
2. Peel open packages to reveal and remove sterile applicator.
3. With sponge in downward position, press the cap end of the applicator allowing the fluid to flow on to the sponge.
4. Use sponge applicator to paint the test area. Begin when the fluid level reaches the indicator line on the applicator barrel. Do not scrub. Simply paint a single uniform application.
5. Paint site from center and work outward applying a uniform coating.
6. If pooling occurs, immediately blot with the sponge applicator.
7. Use a new applicator for each test area.

The timing of post-prep sampling was randomized to sites within each test area. Microbial samples were collected at +2 minutes (± 30 seconds), +10 minutes (± 1 min.), +6 hours (± 15 min.), and +24 hours (± 30 min.) post-prep (abdomen) and at +10 minutes (± 1 min.), +6 hours (± 15 min.) and +24 hours (± 30 min.) post-prep (groin). All

microbial samples were collected using the cup scrub technique. DuraPrep solution-treated and DuraPrep w/o I_2 treated sites were sampled with Modified Sampling Solution (MSS). Hibiclens cleanser-treated sites were sampled with Standard Sampling Solution (SSS). After the +10 minute post-prep samples were collected, a sterile non-occlusive dressing was secured over the remaining sample sites to allow subjects restricted mobility and to protect the sites from contamination between sampling times. After the 6 hour sampling, a new sterile non-occlusive dressing was secured to the remaining site and subjects were allowed to go home and return the next day for the 24-hour sampling.

All adverse events (AEs), whether or not considered to be investigational material-related, were to be reported immediately to the Clinical Monitor and recorded on an Adverse Drug Experience Record.

Medical Officer Comment: ***Of note, this study was not blinded because of the obvious difference in application technique, color, and other physical characteristics of the products; however, study staff that performed the bacterial enumeration were to have been blinded to the investigational materials when counting plates.***

While the design of this study is not entirely consistent with recommendations in the TFM, the study protocol was reviewed by FDA clinical and microbiology reviewers and was found to be acceptable; therefore, deviations from TFM guidelines (e.g., fewer than recommended subject number, etc.) should be considered acceptable provided outcomes are acceptable.

One protocol modification that should be specifically noted is the use of a Modified Sampling Solution (MSS) for sample collection in the DuraPrep arm and the DuraPrep w/o I_2 arm, which was required to dissolve the DuraPrep solution film. Standard Sampling Solution (SSS) was used to neutralize Hibiclens cleanser. The effectiveness and non-toxicity of these neutralizers was assessed to demonstrate that there was no effect on the growth of microorganisms and that the active ingredients are appropriately inactivated. For a more detailed discussion of the neutralizers used in this study and a detailed review of microbiologic methods utilized please see the review by Dr. Peter Coderre, the FDA Microbiology Reviewer.

6.3.1.3.2 Evaluability Criteria

Only subjects who met the minimum baseline inclusion criteria on the screening and treatment day of the study on both sides of the body (abdomen and/or groin sites) were considered evaluable for the efficacy for that region in the primary analysis, with the following exceptions:

- No more than 25% of the abdomen subjects included in analysis were permitted to have treatment day counts of 2.5 logs or higher but less than 3.0 logs. If more that 25% met this criterion they were not to be included in analyses, according to the original protocol.
- Lab accidents resulting in contaminated or unusable samples. (In the event of missing data at some but not all time points, paired data from the available times points was included in the analysis; however, since this was a paired design, if data from a treatment pair was not available, the data from the single side was not included in the comparative analysis.)

6.3.1.3.2.1 Endpoints

According to the protocol the primary measure of antimicrobial efficacy is the log_{10} reduction of skin flora at each body site, according to the TFM, following application of the investigational materials. The TFM states that for a product to be considered efficacious the test product must reduce the number of bacteria 2 log_{10}/cm^2 on the abdominal test site (a "dry" site) and 3 log_{10}/cm^2 on at the groin site (a "wet" site) within 10 minutes after product use and that the bacterial cell count for each test site does not subsequently exceed baseline measurements 6 hours after product use.

6.3.1.3.2.2 Statistical Considerations

Sample Size Calculation

According to the original protocol, the sample size needed to meet TFM criteria for log reduction was calculated based on the assumption that a standard deviation of 1.35 logs on the abdomen and 1.28 logs on the groin was expected (based on previous pilot studies). Therefore, to estimate the log reduction achieved by DuraPrep solution to +/- 0.5 logs with 95% confidence, a sample of 30 subjects for the groin region and 30 subjects for the abdominal region would be needed.

Statistical Analysis Methods

According to the original protocol, raw data (CFU/mL) was converted to log_{10} CFU/cm^2. Counts of less than 1 CFU /cm^2 were to be treated as 1 CFU/cm^2, such that the log transformation was zero. Data was analyzed separately for the abdomen and the groin regions. Log reductions were calculated by subtracting the post-treatment log recovery from the average of the screening and treatment day baseline log recovery.

The primary objective was assessed by calculating the mean log reduction on the abdomen and the groin for DuraPrep solution-treated sites. If a 2 log reduction on the abdomen and a 3 log reduction on the groin were achieved within 10 minutes, and if counts did not return to baseline within 6 hours, the criteria of the TFM were to have been considered to have been met. In assessing the primary objective, only sites which met both baseline and treatment day microbial inclusion criteria were to be used in the analysis. Descriptive statistics were to be provided for each body site and each post-prep sampling time point.

The "second" primary objective of this study, comparison of the difference in log reductions between DuraPrep solution and DuraPrep w/o I_2, was to occur at the 24 hour time point. A paired t-test was conducted at $p<0.05$ (2-tailed). The contribution of iodine was to be considered to be demonstrated if the log reduction for DuraPrep was significantly greater than the log reduction for I_2, on either the abdomen or groin sites.

The secondary objectives were to be assessed as follows. A) A paired t-test on the difference between baseline and the 24-hour post-prep counts was to be conducted ($p<0.05$; 1-tail) for the DuraPrep solution-treated sites. If the 24-hour post-prep counts were significantly below the baseline counts, the objective of demonstrating 24-hour efficacy was to have been met. B) The comparison of log reduction of DuraPrep solution to that of Hibiclens solution was to be assessed using a paired t-test conducted at $p<0.05$ (2-tailed).

6.3.1.4 Study Results

6.3.1.4.1 Evaluability

A total of 273 subjects were screened for microbial counts. Of subjects screened for microbial counts, 176 of 273 assessed (64.5%) did not pass minimal microbial count criteria on the abdomen and 8 of 102 assessed (7.8%) did not pass minimal microbial count criteria on the groin. Ultimately, 157 subjects were enrolled into the treatment phase of the study. Eighty-three subjects were enrolled and received study treatment on the abdomen site and 74 subjects were enrolled and received study treatment on the groin site (35 of these subjects qualified for treatment at both the abdomen and groin sites).

Of the 83 subjects treated at the abdominal anatomic site, 20 subjects (020A, 012A, 009A, 021A, 018A, 922A, 035A, 039A, 050A, 052A, 043A, 059A, 109A, 058A, 055A, 054A, 152A, 139A, 339A, and 309A) failed to meet baseline count criteria on the day of the test and the wrong sampling solution was used for 2 subjects (001A and 002A); thus a total of 22 subjects were not evaluable at the 10 minute, 6 hour and 24 hour time points. Overall, 61 subjects provided evaluable comparative data for the abdominal anatomic site at 10 minutes, 6 hours, and 24 hours time points.

Of the 74 subjects treated at the groin anatomic site, 4 subjects (001A, 002A003G, and 004G) were not evaluable at the 10 minute time point because incorrect sampling solutions were used. At the 6 hour time point, additional subjects that were not evaluable included: 1 subject (006G) who was not evaluable because both investigational products were applied to the same side, 1 subject (029G) who was not evaluable because he left the study for personal reasons, 1 subject (052G) who was not evaluable because the sampling time fell outside of 6 hours +/- 15 minutes and the technician did not collect samples, and 1 subject (306G) who was not evaluable because the right groin site was contaminated prior to sampling. In addition to subjects listed as unevaluable at prior time points, at 24 hours, 6 subjects (013G, 026G, 106G, 111G, 113G, and 306G) were considered unevaluable due to contamination of either the left or right groin site prior to sampling. Overall, 70 subjects provided evaluable comparative data for the groin anatomic site at 10 minutes, 66 subjects provided evaluable comparative data for the groin anatomic site at 6 hours, and 62 subjects provided evaluable comparative data for the groin anatomic site at 24 hours.

The following table summarizes subject disposition, according to the Applicant, for study LIMS 8304.

Table 5. LIMS 8304 Subject Disposition (All Randomized Subjects)

Disposition[1]	Abdomen Subjects N=83	Groin Subjects N=74
Number (%) of Subjects Evaluable for Safety[2]	83 (100.0%)	74 (100.0%)
Number (%) of Subjects Evaluable for Efficacy[3]	61 (73.5%)	70 (94.6%)
Evaluable for Efficacy at 10 Minutes	61 (73.5%)	70[4] (94.6%)
Evaluable for Efficacy at 6 Hours	61 (73.5%)	66 (89.2%)
Evaluable for Efficacy at 24 Hours	61 (73.5%)	62 (83.8%)
Number (%) of Subjects Experienced Adverse Events	0	0

1 Includes 27 subjects that were qualified for treatment at both abdomen and groin sites
2 Includes all randomized subjects who were treated with any study drug.
3 Includes all randomized subjects who were treated with any study drug, sampled with the correct sampling solution, and who met the minimum baseline inclusion criteria for bacterial counts on Screening and Treatment Days.
4 Includes Subject 006G who had two investigational materials applied to the same groin site and who the Applicant erroneously considered evaluable at the 10 minute time point.
[Source: LIMS 8304 Clinical Study Report (pages 38-39)]

Medical Officer's comment: The Applicant described a number of protocol deviations in the study report that the Medical Officer believes the Applicant appropriately addressed in the data analyses; therefore, they will not be further addressed in this review.

6.3.1.4.2 Demographics

The majority of subjects in both the abdomen group and the groin group were Caucasian (94.0% and 95.9%, respectively) and male (78.3% and 60.8%, respectively). The mean age for abdomen subjects was 34.2 years and for groin subjects was 34.6 years.

Demographic data for all randomized subjects are summarized in the following table.

Table 6. LIMS 8304 Demographic and Other Baseline Characteristics (All Randomized Subjects)

Demographic Characteristic	Abdomen Subjects (N=83)	Groin Subjects (N=74)
Age (years)		
Mean (SD)	34.2 (13.69)	34.6 (14.06)
Median	30.0	30.0
Min - Max	18 - 68	19 - 74
Gender (n [%])		
Male	65 (78.3)	45 (60.8)
Female	18 (21.7)	29 (39.2)
Race (n [%])		
Caucasian	78 (94.0)	71 (95.9)
Black	1 (1.2)	0
Asian	0	1 (1.4)
Hispanic	2 (2.4)	0
Native American	1 (1.2)	1 (1.4)
Other	1 (1.2)	1 (1.4)
Height (inches)		
Mean (SD)	69.7 (3.92)	68.0 (4.83)
Median	70.0	68.0
Min - Max	54 - 77	57 - 76
Weight (pounds)		
Mean (SD)	184.7 (39.14)	170.7 (35.91)
Median	180.0	165.0
Min - Max	110 - 325	105 - 300

SD = standard deviation; Min = minimum; Max = maximum
[Source: LIMS 8304 Clinical Study Report (page 41)]

Medical Officer's Comment: With the exception of Caucasian subjects, treatment experience among other Races is limited in this study. Data are also not available for subjects less than 18 years of age. However, this product has been marketed in the United States for a number of years and there are no reports in AERS or the literature to suggest that efficacy is affected by specific demographic factors.

6.3.1.4.3 Efficacy

The primary objective of this study was to demonstrate that DuraPrep solution results in a mean 2 $\log_{10}/cm^2$ reduction in bacteria on the abdominal test site (a "dry" site) and a mean 3 $\log_{10}/cm^2$ reduction in bacteria on the groin site (a "wet" site) within 10 minutes after product use and that the bacterial cell count for each test site did not subsequently exceed baseline measurements 6 hours after product use. A "second" primary objective was to demonstrate the contribution of iodine to the formulation by showing significantly greater log reduction at 24 hours on sites treated with DuraPrep solution compared to those treated with DuraPrep solution formulated without I_2 (DuraPrep w/o I_2). Secondary objectives were to: (1) demonstrate that at 24 hours mean log reductions in DuraPrep solution subjects remained significantly below baseline, and (2) to compare the log

reduction achieved by DuraPrep solution to that of Hibiclens cleanser and Betadine combination.

Abdominal Test Site

For all subjects with DuraPrep solution applied to the abdominal site (n=61), a mean 2.65 log reduction was achieved at 10 minutes and at 6 hours the mean log reduction was 2.49. At 24 hours, the mean log reduction was 2.06, a statistically significant reduction from baseline ($p<0.0001$). Overall, DuraPrep solution results on the abdominal site are summarized in the following Table.

Table 7. LIMS 8304 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites (Efficacy-Evaluable Population) - Abdomen Subjects

Sampling Time	DuraPrep Solution (N = 61)	p-value[1]
Baseline Value[2]		
N	61	
Mean (SD)	3.83 (0.613)	N/A
Median	3.78	
Min - Max	2.85 - 5.37	
Log Reduction[3] at:		
10 Minutes		
N	61	
Mean (SD)	2.65 (1.371)	<0.0001
Median	3.03	
Min - Max	-0.18 - 4.73	
95% CI	(2.3, 3.00)	
6 Hours		
N	61	
Mean (SD)	2.49 (1.512)	<0.0001
Median	3.04	
Min - Max	-1.36 - 4.78	
95% CI	(2.10, 2.88)	
24 Hours		
N	61	
Mean (SD)	1.95 (1.740)	<0.0001
Median	2.06	
Min - Max	-1.50 - 5.37	
95% CI	(1.50, 2.39)	

1 Based on paired t-test (1-tailed) on the log reduction (difference between baseline and the post-preparation log counts at a given sampling time point).
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.
SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval; ND = not done; N/A = not applicable.
[Source: LIMS 8304 Clinical Study Report (pages 44-45)]

The Applicant also compared DuraPrep solution to DuraPrep w/o I_2 in 30 subjects treated at the abdominal site in an attempt to demonstrate the contribution of iodine to the product. Results of these comparative groups are summarized in the following Table.

Table 8. LIMS 8304 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus DuraPrep w/o I_2-Treated Sites (Efficacy-Evaluable Population) - Abdomen Subjects

	Treatment Group			
Sampling Time	**DuraPrep w/o I_2 (N = 30)**	**DuraPrep Solution (N = 30)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
n	30	30	30	
Mean (SD)	3.72 (0.558)	3.82 (0.549)	0.10 (0.403)	0.1929
Median	3.85	3.96	0.13	
Min - Max	2.80 - 4.59	2.90 - 4.93	-0.62 - 1.04	
95% CI			(-0.05, 0.25)	
Log Reduction[3] at:				
10 Minutes				
N	30	30	30	
Mean (SD)	2.53 (1.233)	2.83 (1.291)	0.30 (1.345)	0.2352
Median	2.75	3.10	0.28	
Min - Max	-0.12 - 4.16	-0.18 - 4.27	-3.24 - 3.05	
95% CI			(-0.20, 0.80)	
6 Hours				
N	30	30	30	
Mean (SD)	2.19 (1.604)	2.64 (1.513)	0.45 (1.314)	0.0688
Median	2.80	3.11	0.35	
Min - Max	-1.22 - 4.17	-1.05 - 4.43	-2.73 - 3.03	
95% CI			(-0.04, 0.94)	
24 Hours				
N	30	30	30	
Mean (SD)	2.16 (1.592)	2.20 (1.804)	0.04 (1.581)	0.8817
Median	2.72	2.72	0.19	
Min - Max	-0.99 - 4.24	-1.50 - 4.65	-3.13 - 2.99	
95% CI			(-0.55, 0.63)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and DuraPrep w/o I_2 post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] 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; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8304 Clinical Study Report (pages 46-47)]

A secondary objective of the study were to compare the log reduction of bacterial counts on the abdominal site achieved with the application of DuraPrep solution with those

achieved with the application of Hibiclens cleanser. The results of baseline, 10 minute, and 6 hour comparisons are presented in the following Table.

Table 9. LIMS 8304 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Hibiclens Cleanser-Treated Sites (Efficacy-Evaluable Population) - Abdomen Subjects

	Treatment Group			
Sampling Time	**Hibiclens Cleanser (N = 31)**	**DuraPrep Solution (N = 31)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
N	31	31	31	
Mean (SD)	3.83 (0.491)	3.84 (0.678)	0.00 (0.488)	0.9665
Median	3.81	3.64	0.05	
Min - Max	3.05 - 5.08	2.85 - 5.37	-0.95 - 1.02	
95% CI			(-0.18, 0.18)	
Log Reduction[3] at:				
10 Minutes				
N	31	31	31	
Mean (SD)	1.83 (1.647)	2.48 (1.444)	0.65 (1.872)	0.0616
Median	1.52	2.79	0.56	
Min - Max	-1.49 - 4.23	-0.05 - 4.73	-4.05 - 3.85	
95% CI			(-0.03, 1.34)	
6 Hours				
N	31	31	31	
Mean (SD)	2.02 (1.522)	2.34 (1.520)	0 32 (1.657)	0.2960
Median	2.37	2.88	0.26	
Min - Max	-0.72 - 4.74	-1.36 - 4.73	-4.27 - 3.59	
95% CI			(-0.29, 0.92)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] 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; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8304 Clinical Study Report (page 50)]

Medical Officer's Comment: At the abdominal site, DuraPrep solution achieved a greater than mean 2 log reduction at 10 minutes and mean log counts remained below baseline at 6 hours. Hibiclens cleanser achieved a less than mean 2 log reduction at 10 minutes; however, mean log counts remained below baseline at 6 hours. Results found for Hibiclens cleanser may have been secondary to any of a variety of reasons as were previously discussed in Section 6.2 of this review.

The contribution of iodine to the bacterial activity of DuraPrep solution was not demonstrated by the comparison of mean log reductions of DuraPrep solution to DuraPrep w/o I_2. At 10 minutes, 6 hours, and 24 hours, the mean log reduction of bacteria for DuraPrep solution was not statistically significantly different from the log reduction for DuraPrep w/o I_2.

In the DuraPrep solution versus Hibiclens cleanser comparative group, a statistically significant difference in log reductions was not demonstrated at either the 10 minute time point or the 6 hour time point.

Groin Test Site

For all subjects where DuraPrep solution was applied to the groin site (n=70), a mean 2.76 log reduction was achieved at 10 minutes, and at 6 hours the mean log reduction was 2.86. At 24 hours, the log reduction was 2.36, a statistically significant reduction from baseline ($p<0.0001$). Overall, DuraPrep solution results on the groin site are summarized in the following Table.

Table 10. LIMS 8304 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites (Efficacy-Evaluable Population) - Groin Subjects

Sampling Time	DuraPrep Solution (N = 70)	p-value[1]
Baseline Value[2]		
N	70	
Mean (SD)	6.4 (0.476)	N/A
Median	6.42	
Min - Max	5.10 - 7.34	
Log Reduction[3] at:		
10 Minutes[4]		
N	70	
Mean (SD)	2.76 (1.110)	<0.0001
Median	2.78	
Min - Max	0.60-5.62	
95% CI	(2.50, 3.03)	
6 Hours[5]		
N	67	
Mean (SD)	2.86 (1.359)	<0.0001
Median	2.72	
Min - Max	0.29-7.21	
95% CI	(2.52, 3.19)	
24 Hours[6]		
N	68	
Mean (SD)	2.36 (1.385)	<0.0001
Median	2.18	
Min - Max	-0.35 - 5.97	
95% CI	(2.02, 2.69)	

1 Based on paired t-test (1-tailed) on the log reduction (difference between baseline and the post-preparation log counts at a given sampling time point).
2 Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
3 Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.
4 Includes Subject 006G who had two investigational materials applied to the same groin site and who the Applicant erroneously considered evaluable at the 10 minute time point.
5 Includes one subject not included in comparative analyses due to contamination of contra lateral site at 6 hours.
6 Includes six subject not included in comparative analyses due to contamination of contra lateral site at 24 hours.
SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval; ND = not done; N/A = not applicable.
[Source: LIMS 8304 Clinical Study Report (pages 44-45)]

The Applicant also compared DuraPrep solution to DuraPrep w/o I_2 in 31 subjects treated at the groin site in an attempt to demonstrate the contribution of iodine to the product. Results of these comparative groups are summarized in the following Table.

Table 11. LIMS 8304 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus DuraPrep w/o I_2-Treated Sites (Efficacy-Evaluable Population) - Groin Subjects

	Treatment Group			
Sampling Time	**DuraPrep w/o I_2 (N = 31)**	**DuraPrep Solution (N = 31)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
N	31	31	31	
Mean (SD)	6.38 (0.550)	6.41 (0.472)	0.03 (0.292)	0.5508
Median	6.39	6.32	0.06	
Min - Max	5.36 - 7.19	5.43 - 7.21	-0.45 - 0.59	
95% CI			(-0.08, 0.14)	
Log Reduction[3] at:				
10 Minutes[4]				
N	31	31	31	
Mean (SD)	2.58 (0.935)	2.53 (0.839)	-0.06 (1.109)	0.7837
Median	2.58	2.62	-0.07	
Min - Max	0.76 - 5.60	0.75 - 4.48	-2.57 - 3.49	
95% CI			(-0.46, 0.35)	
6 Hours				
N	30	30	30	
Mean (SD)	2.72 (1.396)	2.97 (1.381)	0.25 (1.525)	0.3772
Median	2.36	2.96	0.20	
Min - Max	0.74 - 7.01	1.01 - 7.21	-3.81 - 5.21	
95% CI			(-0.32, 0.82)	
24 Hours				
N	30	30	30	
Mean (SD)	2.26 (1.068)	2.27 (1.478)	0.01 (1.176)	0.9742
Median	2.01	2.23	-0.11	
Min - Max	0.69 - 5.26	-0.35 - 5.97	-2.08 - 3.38	
95% CI			(-0.43, 0.45)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and DuraPrep w/o I_2 post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.
[4] Includes Subject 006G who had two investigational materials applied to the same groin site and who the Applicant erroneously considered evaluable at the 10 minute time point.
SD = standard deviation; CI = confidence interval; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8304 Clinical Study Report (page 48)]

A secondary objective of the study was to compare the log reduction of bacterial counts on the groin site achieved with the application of DuraPrep solution with those achieved with the application of Hibiclens cleanser. The results of baseline, 10 minute, and 6 hour comparisons are presented in the following Table.

Table 12. LIMS 8304 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Hibiclens Cleanser-Treated Sites (Efficacy-Evaluable Population) - Groin Subjects

	Treatment Group			
Sampling Time	**Hibiclens Cleanser (N = 39)**	**DuraPrep Solution (N = 39)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
N	39	39	39	
Mean (SD)	6.39 (0.478)	6.40 (0.486)	0.01 (0.332)	0.8893
Median	6.40	6.46	-0.04	
Min - Max	5.19 - 7.36	5.10 - 7.34	-0.62 - 0.93	
95% CI			(-0.10, 0.11)	
Log Reduction[3] at:				
10 Minutes				
N	39	39	39	
Mean (SD)	2.93 (1.168)	2.95 (1.265)	0.03 (1.137)	0.8843
Median	3.02	2.92	-0.05	
Min - Max	0.75 - 6.35	0.60 - 5.62	-1.77 - 2.96	
95% CI			(-0.34, 0.40)	
6 Hours				
N	36	36	36	
Mean (SD)	3.36 (1.087)	2.70 (1.318)	-0.66 (1.477)	0.0115
Median	3.07	2.64	-0.49	
Min - Max	1.91 - 6.53	0.29 - 6.57	-4.26 - 3.37	
95% CI			(-1.16, -0.16)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] 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; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8304 Clinical Study Report (page 52)]

Medical Officer's Comment: It should be noted that the Applicant's analyses at the 10 minute time point include data from Subject 006G who, according to the Study Report, had the two investigational materials applied to the same groin site and who the Applicant erroneously considered evaluable at the 10 minute time point. The removal of this subject from the evaluable population, however, does not significantly impact the result of the mean log reduction in the 10 minutes analysis (with data from 006G removed, mean log reduction at 10 minutes for DuraPrep solution is 2.77 as compared to 2.76, which was reported by the Applicant).

At the groin site, DuraPrep solution did not achieve a greater than mean 3 log reduction at 10 minutes; it achieved a 2.65 mean log reduction. Mean log counts remained below baseline at 6 hours.

The contribution of iodine to the bacterial activity of DuraPrep solution was not demonstrated by the comparison of mean log reductions of DuraPrep solution to DuraPrep w/o I_2. At 10 minutes, 6 hours, and 24 hours, the mean log reduction of bacteria for DuraPrep solution was not statistically significantly different from the log reduction for DuraPrep w/o I_2.

In the DuraPrep solution versus Hibiclens cleanser comparative group, a statistically significant difference in log reductions was not demonstrated at the 10 minute time point, but at the 6 hour time point Hibiclens cleanser achieved a statistically significantly greater mean log reduction than DuraPrep solution ($p<0.015$). It should be noted that in the group in whom a direct comparison of outcomes may be assessed that neither product met the TFM prescribed mean 3 log reduction for the groin site. DuraPrep solution achieved a 2.95 mean log reduction and Hibiclens cleanser achieved a 2.93 mean log reduction.

6.3.1.5 Medical Reviewer's Comments/Conclusion of Study

At the abdominal site, DuraPrep solution satisfied the criteria defined in the TFM for demonstrating antimicrobial activity. There was 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. Hibiclens cleanser did not achieve a 2 log_{10}/cm^2 mean reduction of bacterial counts by 10 minutes post-preparation; although it did achieve a 2 log_{10}/cm^2 mean reduction of bacterial counts by 6 hours.

At the groin site, neither DuraPrep solution nor Hibiclens cleanser satisfied the criteria defined in the TFM for demonstration of antimicrobial activity. In the comparative group (DuraPrep solution versus Hibiclens cleanser) for DuraPrep solution there was a 2.95 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 and for Hibiclens cleanser there was a 2.93 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. Of note, the 95% confidence interval (-0.34, 0.40) for the log_{10}/cm^2 mean reduction of bacterial counts at 10 minutes post-preparation for the comparison of DuraPrep solution and Hibiclens cleanser was relatively narrow. Based on the point estimates for log reductions and the 95% confidence interval, this Medical Officer considers the efficacy of the two products to be similar, despite the fact that the TFM prescribed 3 log_{10}/cm^2 mean reduction at 10 minutes was not achieved.

The fact that Hibiclens, the "positive control", did not perform as prescribed in the TFM at either the abdominal site or at the groin site is concerning; however, based on reports of similar findings from multiple recent FDA stakeholders it is not clear that use of Hibiclens as a positive control and/or that the TFM prescribed log reductions that the "positive control" must meet are appropriate in these studies. Therefore, when it comes to log_{10}/cm^2 mean reduction of bacterial counts on the skin at 10 minutes post preparation, this Medical Officer concludes that DuraPrep solution performs similarly to Hibiclens cleanser at both the abdominal and groin sites

The contribution of iodine to the bacterial activity of DuraPrep solution was not demonstrated by the comparison of mean log reductions of DuraPrep solution to DuraPrep w/o I_2 at either the abdominal site or the groin site. At 10 minutes, 6 hours, and 24 hours, the mean log reduction of bacteria for DuraPrep solution was not statistically significantly different from the log reduction for DuraPrep w/o I_2.

6.3.2 LIMS #8918 "Pivotal Study to Assess the Antimicrobial Effectiveness of 3M DuraPrep™ Surgical Solution Against Resident Human Skin Flora on Abdomen and Groin Regions-Study 2"

6.3.2.1 Objective/Rationale

The objectives of the study, as stated by the Applicant, were:

Primary Objective

To demonstrate that 3M™ DuraPrep™ Surgical Solution (DuraPrep solution) meets the 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) criteria for log reduction of resident skin flora.

Secondary Objectives

- To demonstrate the 24-hour efficacy of DuraPrep solution (counts remain significantly below baseline).
- To compare the log reduction achieved by DuraPrep solution to that of Hibiclens® Antiseptic Skin Cleanser (Hibiclens cleanser) and Betadine® Surgical Solution plus Betadine® Solution (Betadine combination).

Medical Officer's Comment: ***For the patient pre-operative preparation indication, the TFM states that for a product to be considered efficacious the test product must reduce the number of bacteria 2 log_{10}/cm^2 on the abdominal test site (a "dry" site) and 3 log_{10}/cm^2 on at the groin site (a "wet" site) within 10 minutes after product use and that the bacterial cell count for each test site does not subsequently exceed baseline measurements 6 hours after product use.***

6.3.2.2 Study Design

The study was a randomized, paired-comparisons design where each subject received DuraPrep solution and either Hibiclens cleanser or Betadine combination. This study was conducted at one center in the United States.

6.3.2.3 Protocol Overview

6.3.2.3.1 Population/Procedures

Population

A sufficient number of healthy volunteers were enrolled so that a total of at least 30 abdominal regions and 30 groin regions were evaluable for efficacy in the DuraPrep solution vs. Hibiclens cleanser series and 10 abdominal regions and 10 groin regions in the DuraPrep solution vs. Betadine combination series at completion of the study.

A subject could have qualified for the abdominal portion of the study, the groin portion of the study, or both. The right and left sides of the abdomen and groin must have met the minimum baseline values stated in the Inclusion Criteria to qualify for the corresponding portion of the study. The following are noteworthy inclusion and exclusion criteria:

Inclusion Criteria

7. Healthy volunteers of both gender and any race that were between 18 and 75 years of age.
8. Subjects who satisfied all inclusion/exclusion criteria and voluntarily signed the consent form.
9. Subjects who had Screening Day baseline counts of at least 3.0 $\log_{10}$ /cm^2 per abdominal site and/or 5.0 $\log_{10}$ /cm^2 per groin site.
10. Subjects whose skin within 6 inches of the test areas was free from cuts, acne, abrasions, and skin irritation.
11. Subjects who were willing to follow instructions for the study.
12. Subjects who were willing to stay at the clinical site for the duration of the scheduled treatment day (approximately 8 hours) and return the next day for the 24-hour sampling.

In addition, enrolled groin subjects must also have met Treatment Day baseline counts of at least $3.2x10^4$ (4.5 $\log_{10}$) CFU/cm^2 per groin site to be considered evaluable for efficacy. Seventy-five percent of abdomen subjects must have had minimum 3.0 $\log_{10}$ /cm^2 counts on both screening and treatment day; up to 25% of abdomen subjects had to have between 2.5 $\log_{10}$ /cm^2 and 3.0 $\log_{10}$ /cm^2 counts on one or both abdomen sites on treatment day.

Exclusion Criteria

11. Any form of dermatitis, acne, open wounds, or other skin disorders (on the applicable test areas).
12. A history of skin allergies.
13. Known sensitivity to acrylate-, iodine-, chlorhexidine gluconate-, or alcohol-containing products, or to medical tape or natural rubber latex.
14. Use of antibacterial soaps, lotions, dandruff shampoos, deodorants, or topical or systemic antibiotics within 14 days of the scheduled screening or treatment day.
15. Exposure to any other topical medications on the test areas within 14 days of the scheduled screening or treatment day.
16. A history of skin cancer within 6 inches of the test areas.
17. Contact with chlorinated swimming pools or hot tubs within 14 days of the scheduled screening or treatment day.
18. Bathing or showering the test areas within 48 hours prior to the scheduled screening or treatment day.
19. Contact with solvents, acids, bases, or other household chemicals in the test areas within 14 days of the screening or treatment day.
20. Pregnancy, possible pregnancy, attempting pregnancy, or nursing.

Medical Officer's Comment: ***The Applicant's inclusion and exclusion criteria are acceptable and in general accordance with recommendations in the TFM.***

Procedures

Participation in this study involved a 14-day pretreatment phase, a one-day screening phase, and a two-day treatment phase. Prior to the scheduled screening day, subjects

underwent a minimum 14-day pretreatment phase, in which they refrained from the use of products containing antibacterial agents (per written instructions provided by the Study Investigator). Subjects were given product kits containing non-antimicrobial soaps, deodorants, and shampoos and were instructed to use these products through completion of the treatment phase. Following the pretreatment phase, subjects were required to visit the test facility for collection of screening baseline samples from the abdominal and groin regions. Subjects whose baseline samples met the minimum values described in the Inclusion Criteria were eligible for participation in the treatment phase of the study (treatment phase occurred no sooner than 72 hours and no later than 7 days from the screening baseline collection). During the treatment phase participants remained at the test facility for the duration of the first scheduled treatment day (for approximately 8 hours) and returned to the test facility on the second scheduled treatment day for the 24-hour sampling (for approximately 1 hour). In the event that a subject did not meet the entrance criteria on screening and/or treatment day, that subject was replaced. Subjects who qualified on screening day and began the treatment phase were not allowed to re-enter the study, regardless of whether or not they completed the study.

On the first treatment day, abdominal and groin test areas were prepared as follows:

Abdominal Region - The test site within the abdominal region was defined as the area below the umbilicus and above the groin. Using a 5" x 5" sterile template, the corners of each abdominal test area were marked directly onto the skin using a non-toxic skin marker. Five abdominal sampling sites were numbered within each abdominal test area, on each side of the abdomen region. The positioning and numbering of the abdominal sampling sites were standard for all subjects. Sampling sites on the contra lateral side of the abdomen were numbered in a mirror-image orientation. The five sampling sites within each abdominal test area represent the baseline (pre-prep) site and four post-prep sample sites.

Groin Region - The test site within the groin region was defined as the inner aspect of the upper thigh within and parallel to the inguinal crease below the groin. Using a 2" x 5" sterile template, the corners of each groin test area were marked directly on the skin using a non-toxic skin marker. Four sampling sites were numbered within each groin test area. The positioning and numbering of the groin sampling sites were standard for all subjects. Sampling sites on the contra lateral side of the groin were numbered in a mirror-image orientation. The four sampling sites within each groin test area represent a baseline (pre-prep) site and three post-prep sample sites.

After test areas were marked and sample sites were numbered, baseline samples were collected from site 5 on the abdomen and site 3 on the groin in each test area. Following baseline sample collection, randomly assigned contra lateral test areas were prepped with DuraPrep solution (total 40 subjects) and either Hibiclens cleanser (30 subjects) or Betadine combination (10 subjects). Test areas on each subject's body regions were assigned according to a computer-generated randomization schedule to receive DuraPrep solution on one side of the region, and either Hibiclens cleanser or Betadine combination on the contra lateral side. Randomization was balanced between left and right sides.

Hibiclens cleanser and Betadine combination were applied according to labeled instructions. DuraPrep solution was applied using the following application instructions:

1. Peel open packages to reveal and remove sterile applicator.
2. With sponge in downward position, press the cap end of the applicator allowing the fluid to flow on to the sponge.
3. Use sponge applicator to paint the test area. Begin when the fluid level reaches the indicator line on the applicator barrel. Do not scrub. Simply paint a single uniform application.
4. Paint site from center and work outward applying a uniform coating.
5. If pooling occurs, immediately blot with the sponge applicator.
6. Use a new applicator for each test area.

The timing of post-prep sampling was randomized to sites within each test area. Microbial samples were collected at +2 minutes (± 30 seconds), +10 minutes (± 1 min.), +6 hours (± 15 min.), and +24 hours (± 30 min.) post-prep (abdomen) and at +10 minutes (± 1 min.), +6 hours (± 15 min.) and +24 hours (± 30 min.) post-prep (groin). All microbial samples were collected using the cup scrub technique. DuraPrep solution-treated and Betadine combination-treated sites were sampled with Modified Sampling Solution (MSS). Hibiclens cleanser-treated sites were sampled with Standard Sampling Solution (SSS). After the +10 minute post-prep samples were collected, a sterile non-occlusive dressing was secured over the remaining sample sites to allow subjects restricted mobility and to protect the sites from contamination between sampling times. After the 6 hour sampling, a new sterile non-occlusive dressing was secured to the remaining site and subjects were allowed to go home and return the next day for the 24-hour sampling.

All adverse events (AEs), whether or not considered to be investigational material-related, were to be reported immediately to the Clinical Monitor and recorded on an Adverse Drug Experience Record.

***Medical Officer Comment:** Of note, this study was not blinded because of the obvious difference in application technique, color, and other physical characteristics between products; however, study staff that performed the bacterial enumeration were to have been blinded to the investigational materials when counting plates.*

While the design of this study is not entirely consistent with recommendations in the TFM, the study protocol was reviewed by FDA clinical and microbiology reviewers and was found to be acceptable; therefore, deviations from TFM guidelines (e.g., fewer than recommended subject number, etc.) should be considered acceptable provided outcomes are acceptable.

One protocol modification that should be specifically noted is the use of a Modified Sampling Solution (MSS) for sample collection in the DuraPrep arm and the Betadine combination arm, which was required to dissolve the DuraPrep solution film. Standard Sampling Solution (SSS) was used to neutralize Hibiclens cleanser. The effectiveness and non-toxicity of these neutralizers were assessed to demonstrate that there was no effect on the growth of microorganisms and that the active ingredients are appropriately inactivated. For a more detailed discussion of the neutralizers used in this study and a detailed review of microbiologic methods utilized, please see the review by Dr. Peter Coderre, the FDA Microbiology Reviewer.

6.3.2.3.2 Evaluability Criteria

Only subjects who met the minimum baseline inclusion criteria on the screening and treatment day of the study on both sides of the body (abdomen and/or groin sites) were considered evaluable for efficacy for that region in the primary analysis, with the following exceptions:

- No more than 25% of the abdomen subjects included in analysis were permitted to have treatment day counts of 2.5 logs or higher but less than 3.0 logs. If more that 25% met this criterion they were not to be included in analyses, according to the original protocol.
- Lab accidents resulting in contaminated or unusable samples. (In the event of missing data at some but not all time points, paired data from the available times points was included in the analysis; however, since this was a paired design, if data from a treatment pair was not available, the data from the single side was not included in the comparative analysis.)

6.3.2.3.3 Endpoints

According to the protocol the primary measure of antimicrobial efficacy is the $\log_{10}$ reduction of skin flora at each body site, according to the TFM, following application of the investigational materials. The TFM states that for a product to be considered efficacious the test product must reduce the number of bacteria 2 $\log_{10}/cm^2$ on the abdominal test site (a "dry" site) and 3 $\log_{10}/cm^2$ on at the groin site (a "wet" site) within 10 minutes after product use and that the bacterial cell count for each test site does not subsequently exceed baseline measurements 6 hours after product use.

6.3.2.3.4 Statistical Considerations

Sample Size Calculation

According to the original protocol, the sample size needed to meet TFM criteria for log reduction was calculated based on the assumption that a standard deviation of 1.35 logs on the abdomen and 1.28 logs on the groin was expected (based on previous pilot studies). Therefore, to estimate the log reduction achieved by DuraPrep solution to +/- 0.5 logs with 95% confidence, a sample of 30 subjects for the groin region and 30 subjects for the abdominal region would be needed.

Statistical Analysis Methods

According to the original protocol, raw data (CFU/mL) was converted to $\log_{10}$ CFU/cm^2. Counts of less than 1 CFU /cm^2 were to be treated as 1 CFU/cm^2, such that the log transformation was zero. Data was analyzed separately for the abdomen and the groin regions. Log reductions were calculated by subtracting the post-treatment log recovery from the average of the screening and treatment day baseline log recovery.

The primary objective was assessed by calculating the mean log reduction on the abdomen and the groin for DuraPrep solution-treated sites. If a 2 log reduction on the abdomen and a 3 log reduction on the groin were achieved within 10 minutes, and if counts did not return to baseline within 6 hours, the criteria of the TFM were to have been considered to have been met. In assessing the primary objective, only sites which met both baseline and treatment day microbial inclusion criteria were to be used in the

analysis. Descriptive statistics were to be provided for each body site and each post-prep sampling time point.

The secondary objectives were to be assessed as follows. A) A paired t-test on the difference between baseline and the 24-hour post-prep counts was to be conducted ($p<0.05$; 1-tail) for the DuraPrep solution-treated sites. If the 24-hour post-prep counts were significantly below the baseline counts, the objective of demonstrating 24-hour efficacy was to have been met. B) The comparison of log reduction of DuraPrep solution to that of Hibiclens solution was to be assessed using a paired t-test conducted at $p<0.05$ (2-tailed). Descriptive statistics were to be provided for the 10 abdomens and groins treated with DuraPrep solution and Betadine combination.

6.3.2.4 Study Results

6.3.2.4.1 Evaluability

A total of 284 subjects were screened for microbial counts. Of subjects screened for microbial counts, 218 of 284 assessed (76.8%) did not pass minimal microbial count criteria on the abdomen and 76 of 169 assessed (45%) did not pass minimal microbial count criteria on the groin. Ultimately, 100 subjects were enrolled into the treatment phase of the study. Fifty-eight subjects were enrolled and received study treatment on the abdomen site and 69 subjects were enrolled and received study treatment on the groin site (27 of these subjects qualified for treatment at both the abdomen and groin sites).

Of the 58 subjects treated at the abdominal anatomic site, 13 subjects (004A, 010A, 020A, 026A, 027A, 034A, 035A, 037A, 038A, 134A, 222A, 0234A, and 334A) failed to meet baseline count criteria on the day of the test and were not evaluable for the 10 minute, 6 hour, and 24 hour time points. In addition, 3 subjects were not evaluable for the 24 hour time point (022A, 024, and 110A) due to site contamination and 1 subject (122A) was not evaluable at the 6 hour time point due to the use of the wrong sampling solution for sample collection at this time point. Overall, 45 subjects provided evaluable comparative data for the abdominal anatomic site at 10 minutes, 44 subjects provided evaluable comparative data for the abdominal anatomic site at 6 hours, and 42 subjects provided evaluable comparative data for the abdominal anatomic site at 24 hours.

Of the 69 subjects treated at the inguinal anatomic site, 9 subjects (009G, 023G, 031G, 026G, 038G, 123G, 134G, 211G, and 223G) failed to meet baseline count criteria on the day of the test and were not evaluable for the 10 minute, 6 hour, and 24 hour time points. In addition, 18 subjects were not evaluable for the 24 hour time point (006G, 007G, 011G, 016G, 020G, 033G, 034G, 039G, 040G, 111G, 116G, 126G, 133G, 139G, 239G, 311G, 323G, and 411G) due to site contamination and 6 additional subjects (006G, 011G, 020G, 036G, and 323G) were not evaluable at the 6 hour time point due to site contamination. Overall, 60 subjects provided evaluable comparative data for the groin anatomic site at 10 minutes, 54 subjects provided evaluable comparative data for the groin anatomic site at 6 hours, and 42 subjects provided evaluable comparative data for the groin anatomic site at 24 hours.

The following table summarizes subject disposition for study LIMS 8918.

Table 13. LIMS 8918 Subject Disposition (All Randomized Subjects)

Disposition[1]	Abdomen Subjects N=58	Groin Subjects N=69
Number (%) of Subjects Evaluable for Safety[2]	58 (100.0%)	69 (100.0%)
Number (%) of Subjects Evaluable for Efficacy[3]	45 (77.6%)	60 (87.0%)
Evaluable for Efficacy at 10 Minutes	45 (77.6%)	60 (87.0%)
Evaluable for Efficacy at 6 Hours	44 (75.9%)	54 (78.3%)
Evaluable for Efficacy at 24 Hours	42 (72.4%)	42 (60.1%)
Number (%) of Subjects Experienced Adverse Events	-	1 (1.4%)[4]

1 Includes 27 subjects that were qualified for treatment at both abdomen and groin sites
2 Includes all randomized subjects who were treated with any study drug.
3 Includes all randomized subjects who were treated with any study drug, sampled with the correct sampling solution, and who met the minimum baseline inclusion criteria for bacterial counts on Screening and Treatment Days.
4 Subject #006G was withdrawn due to AE prior to 24 hour sample collection
[Source: LIMS 8918 Clinical Study Report (pages 39-41)]

6.3.2.4.2 Demographics

The majority of subjects in both the abdomen group and the groin group were Caucasian (77.6% and 88.4%, respectively) and female (56.9% and 66.7%, respectively). The mean age for abdomen subjects was 52.9 years and for groin subjects was 57.4 years.

Demographic data for all randomized subjects are summarized in the following table.

Table 14. LIMS 8918 Demographic and Other Baseline Characteristics (All Randomized Subjects)

Demographic Characteristic	Abdomen Subjects (N=58)	Groin Subjects (N=69)
Age (years)		
Mean (SD)	52.9 (12.70)	57.4 (10.96)
Median	53.5	59.0
Min - Max	23 - 73	23 - 73
Gender (n [%])		
Male	25 (43.1)	23 (33.3)
Female	33 (56.9)	46 (66.7)
Race (n [%])		
Caucasian	45 (77.6)	61 (88.4)
Black	13 (22.4)	7 (10.1)
American Indian	0	1 (1.4)
Height (inches)		
Mean (SD)	67.1 (3.96)	66.1 (3.88)
Median	66.5	66.0
Min - Max	59 - 74	59 - 74
Weight (pounds)		
Mean (SD)	187.0 (34.02)	178.8 (33.41)
Median	182.5	180.0
Min - Max	120 - 270	106 - 270

SD = standard deviation; Min = minimum; Max = maximum
[Source: LIMS 8918 Clinical Study Report (pages 41-42)]

Medical Officer's Comment: With the exception of Caucasian and Black subjects, treatment experience among other Races is limited in this study. Data are also not available for subjects less than 23 years of age. However, this product has been marketed in the United States for a number of years and there are no reports in AERS or the literature to suggest that efficacy is affected by specific demographic factors.

6.3.2.4.3 Efficacy

The primary objective of this study was to demonstrate that DuraPrep solution results in a mean 2 $\log_{10}/cm^2$ reduction in bacteria on the abdominal test site (a "dry" site) and a mean 3 $\log_{10}/cm^2$ reduction in bacteria on the groin site (a "wet" site) within 10 minutes after product use and that the bacterial cell count for each test site did not subsequently exceed baseline measurements 6 hours after product use. Secondary Objectives were to: (1) demonstrate that at 24 hours mean log reductions in DuraPrep solution subjects remained significantly below baseline, and (2) to compare the log reduction achieved by DuraPrep solution to that of Hibiclens cleanser and Betadine combination.

Abdominal Test Site

For all subjects where DuraPrep solution was applied to the abdominal site (n=45), a mean 2.35 log reduction was achieved at 10 minutes and at 6 hours the mean log reduction was 2.31. At 24 hours, the mean log reduction was 1.27, a statistically

significant reduction from baseline ($p<0.0001$). Overall, DuraPrep results on the abdominal site are summarized in the following Table.

Table 15. LIMS 8918 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites (Efficacy-Evaluable Population) - Abdomen Subjects

Sampling Time	DuraPrep Solution (N = 45)	p-value[1]
Baseline Value[2]		
N	45	
Mean (SD)	3.53 (0.415)	N/A
Median	3.47	
Min - Max	2.85 - 4.40	
Log Reduction[3] at:		
10 Minutes		
N	45	
Mean (SD)	2.35 (1.251)	<0.0001
Median	2.81	
Min - Max	-0.29 - 4.17	
95% CI	(1.98, 2.73)	
6 Hours		
N	45	
Mean (SD)	2.31 (1.196)	<0.0001
Median	2.54	
Min - Max	-0.45 - 4.38	
95% CI	(1.95, 2.66)	
24 Hours		
N	45	
Mean (SD)	1.27 (1.233)	<0.0001
Median	1.37	
Min - Max	-1.39 - 3.80	
95% CI	(0.90, 1.64)	

1 Based on paired t-test (1-tailed) on the log reduction (difference between baseline and the post-preparation log counts at a given sampling time point).
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.
SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval; ND = not done; N/A = not applicable.
[Source: LIMS 8918 Clinical Study Report (pages 45-46)]

Additional secondary objectives of the study were to compare the log reduction of bacterial counts on the abdominal site achieved with the application of DuraPrep solution with those achieved with the application of Hibiclens cleanser and to compare the log reduction of bacterial counts achieved with the application of DuraPrep solution with those achieved with the application of Betadine combination. The results of baseline, 10 minute, and 6 hour comparisons are presented in the following Tables.

Table 16. LIMS 8918 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Hibiclens Cleanser-Treated Sites (Efficacy-Evaluable Population) - Abdomen Subjects

	Treatment Group			
Sampling Time	**Hibiclens Cleanser (N = 34)**	**DuraPrep Solution (N = 34)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
N	34	34	34	
Mean (SD)	3.51 (0.329)	3.52 (0.433)	0.01 (0.358)	0.8193
Median	3.51	3.43	-0.05	
Min - Max	3.02 - 4.46	2.85 - 4.39	-0.67 - 0.96	
95% CI			(-0.11, 0.14)	
Log Reduction[3] at:				
10 Minutes				
N	34	34	34	
Mean (SD)	2.15 (1.302)	2.47 (1.146)	0.32 (1.581)	0.2433
Median	2.43	2.83	0.30	
Min - Max	-0.21 - 4.46	-0.29 - 4.17	-3.32 - 3.91	
95% CI			(-0.23, 0.87)	
6 Hours				
N	33	33	33	
Mean (SD)	1.75 (1.149)	2.31 (1.266)	0.56 (1.329)	0.0221
Median	2.13	2.59	0.25	
Min - Max	-0.94 - 3.39	-0.45 - 4.38	-2.37 - 2.86	
95% CI			(0.09, 1.03)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] 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; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8918 Clinical Study Report (pages 48-49)]

Table 17. LIMS 8918 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Betadine Combination-Treated Sites (Efficacy-Evaluable Population) - Abdomen Subjects

	Treatment Group			
Sampling Time	**Betadine Combination (N = 11)**	**DuraPrep Solution (N = 11)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
N	11	11	11	
Mean (SD)	3.44 (0.364)	3.53 (0.373)	0.09 (0.234)	0.2338
Median	3.44	3.48	0.14	
Min - Max	2.79 - 3.91	2.97 - 4.40	-0.37 - 0.49	
95% CI			(-0.07, 0.25)	
Log Reduction[3] at:				
10 Minutes				
N	11	11	11	
Mean (SD)	2.68 (0.885)	1.98 (1.533)	-0.69 (1.426)	0.1379
Median	2.66	2.79	-0.59	
Min - Max	1.07 - 3.72	-0.14 - 3.80	-2.99 - 1.14	
95% CI			(-1.65, 0.26)	
6 Hours				
N	11	11	11	
Mean (SD)	2.60 (0.843)	2.49 (0.823)	-0.11 (0.814)	0.6674
Median	2.79	2.31	-0.18	
Min - Max	0.77 - 3.72	1.09 - 3.93	-1.66 - 0.91	
95% CI			(-0.66, 0.44)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Betadine combination post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] 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; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8918 Clinical Study Report (pages 52-53)]

Medical Officer's Comment: At the abdominal site, DuraPrep solution achieved a greater than mean 2 log reduction at 10 minutes and mean log counts remained below baseline at 6 hours. Hibiclens cleanser and Betadine combination arms also achieved a greater than mean 2 log reduction at 10 minutes and mean log counts remained below baseline at 6 hours. At the 10 minute time point, neither the DuraPrep solution and Hibiclens cleanser comparison nor the DuraPrep solution and Betadine combination comparison demonstrated statistically significant different log reductions. At the 6 hour time point, the DuraPrep solution demonstrated a statistically significant greater mean log reduction than Hibiclens cleanser (p<0.025).

Groin Test Site

For all subjects where DuraPrep solution was applied to the groin site (n=60), a mean 2.23 log reduction was achieved at 10 minutes, and at 6 hours the mean log reduction was

2.27. At 24 hours, the log reduction was 2.19, a statistically significant reduction from baseline ($p<0.0001$).

Table 18. LIMS 8918 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites (Efficacy-Evaluable Population) - Groin Subjects

Sampling Time	DuraPrep Solution (N = 60)	p-value[1]
Baseline Value[2]		
N	60	
Mean (SD)	5.83 (0.487)	N/A
Median	5.82	
Min - Max	4.99-6.96	
Log Reduction[3] at:		
10 Minutes		
N	60	
Mean (SD)	2.23 (1.059)	<0.0001
Median	2.09	
Min - Max	0.46-5.40	
95% CI	(1.96, 2.50)	
6 Hours		
N	59	
Mean (SD)	2.27 (0.972)	<0.0001
Median	2.11	
Min - Max	0.36-4.83	
95% CI	(2.02, 2.53)	
24 Hours		
N	55	
Mean (SD)	2.19 (0.879)	<0.0001
Median	1.98	
Min - Max	0.63-4.46	
95% CI	(1.95, 2.43)	

1 Based on paired t-test (1-tailed) on the log reduction (difference between baseline and the post-preparation log counts at a given sampling time point).
2 Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
3 Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.
SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval; ND = not done; N/A = not applicable.
[Source: LIMS 8918 Clinical Study Report (pages 45-46)]

Additional secondary objectives of the study were to compare the log reduction of bacterial counts on the groin site achieved with the application of DuraPrep solution with those achieved with the application of Hibiclens cleanser and to compare the log reduction of bacterial counts achieved with the application of DuraPrep solution with those achieved with the application of Betadine combination. The results of baseline, 10 minute, and 6 hour comparisons are presented in the following Tables.

Table 19. LIMS 8918 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Hibiclens Cleanser-Treated Sites (Efficacy-Evaluable Population) - Groin Subjects

	Treatment Group			
Sampling Time	**Hibiclens Cleanser (N = 47)**	**DuraPrep Solution (N = 47)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
n	47	47	47	
Mean (SD)	5.89 (0.480)	5.82 (0.511)	-0.07 (0.387)	0.2481
Median	5.85	5.82	-0.07	
Min - Max	5.02 - 6.91	4.99 - 6.96	-1.08 - 1.29	
95% CI			(-0.18, 0.05)	
Log Reduction[3] at:				
10 Minutes				
n	47	47	47	
Mean (SD)	1.94 (0.964)	2.37 (1.085)	0.43 (0.940)	0.0030
Median	1.84	2.17	0.39	
Min - Max	0.36 - 4.45	0.46 - 5.40	-1.84 - 3.27	
95% CI			(0.15, 0.71)	
6 Hours				
n	42	42	42	
Mean (SD)	2.31 (0.947)	2.29 (0.971)	-0.02 (0.743)	0.8566
Median	2.17	2.36	0.01	
Min - Max	0.72 - 4.39	0.36 - 4.18	-1.92 - 1.54	
95% CI			(-0.25, 0.21)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] 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; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8918 Clinical Study Report (page 50)]

Table 20. LIMS 8918 Summary of Log Reduction of Bacterial Counts (CFU/cm^2) For DuraPrep Solution-Treated Sites versus Betadine Combination-Treated Sites (Efficacy-Evaluable Population) - Groin Subjects

	Treatment Group			
Sampling Time	**Betadine Combination (N = 11)**	**DuraPrep Solution (N = 11)**	**Paired Difference**	**p-value[1]**
Baseline Value[2]				
n	13	13	13	
Mean (SD)	5.79 (0.479)	5.86 (0.408)	0.07 (0.329)	0.4461
Median	5.77	5.82	0.09	
Min - Max	5.03 - 6.84	5.13 - 6.58	-0.49 - 0.76	
95% CI			(-0.13, 0.27)	
Log Reduction[3] at:				
10 Minutes				
n	13	13	13	
Mean (SD)	1.99 (1.030)	1.72 (0.801)	-0.27 (1.008)	0.3501
Median	1.78	1.53	-0.42	
Min - Max	0.89 - 4.29	0.46 - 2.96	-2.37 - 1.73	
95% CI			(-0.88, 0.34)	
6 Hours				
n	12	12	12	
Mean (SD)	2.48 (1.000)	2.19 (1.179)	-0.29 (0.700)	0.1857
Median	2.29	1.80	-0.41	
Min - Max	1.21 - 4.92	0.68 - 4.83	-1.09 - 1.46	
95% CI			(-0.73, 0.16)	

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Betadine combination post-preparation log counts.
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] 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; Min = minimum; Max = maximum.
Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.
[Source: LIMS 8918 Clinical Study Report (page 54)]

Medical Officer's Comment: At the groin site, DuraPrep solution did not achieved a mean 3 log reduction at 10 minutes; it achieved a mean 2.23 log reduction. Mean log counts remained below baseline at 6 hours. Neither Hibiclens cleanser (mean log reduction=1.94) nor Betadine combination (mean log reduction=1.99) achieved a 3 log reduction at 10 minutes either; although, both maintained mean log counts below baseline at 6 hours.

In the direct comparison between DuraPrep solution and Hibiclens cleanser, at the 10 minute time point, the DuraPrep solution with a mean log reduction of 2.37, demonstrated a statistically significantly greater mean log reduction than Hibiclens cleanser with a mean log reduction of 1.94 (p=0.003).

6.3.2.5 Medical Reviewer's Comments/Conclusion of Study

At the abdominal site, DuraPrep solution satisfied the criteria defined in the TFM for demonstrating antimicrobial activity. There was 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. At the abdominal site, Hibiclens cleanser also satisfied criteria defined in the TFM for demonstrating antimicrobial activity.

At the groin site, neither DuraPrep solution nor Hibiclens cleanser satisfied the criteria defined in the TFM for demonstrating antimicrobial activity. In the comparative group (DuraPrep solution versus Hibiclens cleanser) for DuraPrep solution there was a 2.27 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 and for Hibiclens cleanser there was a 1.94 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. DuraPrep solution did not demonstrate efficacy based on the primary endpoint; however, it was significantly more effective than Hibiclens cleanser on the groin at 10 minutes (p=0.0030). As Hibiclens, the "positive control", performed as prescribed in the TFM in the same study on the abdomen, this Medical Officer believes that one can conclude that the conduct of this study should be considered valid. This Medical Officer also concludes that an adequate demonstration of efficacy at the groin site has been demonstrated for DuraPrep solution based on the demonstration that preparation with DuraPrep solution resulted in a statistically significantly greater log_{10}/cm^2 mean reduction of bacterial counts than Hibiclens cleanser, an FDA product approved for the patient preoperative preparation indication.

In the small number of subjects studied in the DuraPrep solution versus Betadine combination series, both preparations met the TFM requirement of a 2-log reduction on the abdomen. Neither preparation met the TFM requirement of a 3-log reduction on the groin.

6.3.3 LIMS 8197 "Evaluation of the Persistent Antimicrobial Activity of 3M™ DuraPrep™ Surgical Solution and DuraPrep w/o I_2 Control Using a Bacterial Challenge Method (Study 1)"

6.3.3.1 Objective/Rationale

The primary objective of this study, as stated by the Applicant, was to "assess the contribution of iodine to the antimicrobial activity of DuraPrep solution."

6.3.3.2 Study Design

The study was a randomized, partially blinded, paired-comparisons design where each subject received DuraPrep solution, DuraPrep w/o I2, and Betadine combination. This study was conducted at one center in the United States.

6.3.3.3 Protocol Overview

6.3.3.3.1 Population/Procedures

Population

An adequate number of volunteers were enrolled to ensure that 26 healthy adult volunteers (24 for main study and 2 for neutralization validation) were fully evaluable. The following are noteworthy inclusion and exclusion criteria:

Inclusion Criteria

1. Were healthy volunteers of either gender, any race, and between 18 and 70 years of age;
2. Satisfied all Inclusion/Exclusion criteria and voluntarily signed the ICF;
3. Their backs were free from cuts, acne, abrasions, and skin irritation;
4. Were cooperative, willing to present themselves promptly at the designated test times required by the study, and were willing to follow all study instructions;
5. Were willing to remain at the test facility for the duration of the Treatment Day (about 8 hours);
6. Were able to lie in a prone position (on their stomach) for 1 to 2 hours at a time; and
7. Had no visible hair on their backs.

Exclusion Criteria

1. Had any form of dermatitis, acne, open wounds, or other skin disorders on the back;
2. Had a history of skin allergies;
3. Had damaged or altered skin within the test areas (included sunburn, tattoos, scars, previous skin cancer, or other disfiguration);

4. Had diabetes or were immunocompromised;
5. Had sensitivity to any alcohol-, acrylate- or iodine-containing product;
6. Had sensitivity to more than 1 antibiotic;
7. Had allergies to natural rubber, latex, tape, or gauze;
8. Were pregnant or lactating;
9. Had contact with chlorinated swimming pools or hot tubs within 7 days of the Treatment Day;
10. Had used antibacterial soaps, dandruff shampoos, or topical or systemic antibiotic medications within 7 days of the Treatment Day; or
11. Had a small back that would not allow for the placement of four 5"x 7" test areas.

Procedures

Participation in this study involved a 7-day pretreatment phase, a one-day treatment phase, and a follow-up visit for dermatologic evaluation to ensure no infection was present at 4 to 8 days post treatment. Prior to the scheduled screening day, subjects underwent a 7-day pretreatment phase, in which they refrained from the use of products containing antibacterial agents (per written instructions provided by the Study Investigator). Subjects were given product kits containing non-antimicrobial soaps, deodorants, and shampoos and were instructed to use these products through completion of the treatment phase.

Following the pretreatment phase, subjects were assigned a treatment number and randomized to treatment and bacterial strain on the Treatment Day. Four test areas (5" x 7" each) on each subject's back were marked and randomized for each of the four treatments, DuraPrep solution, DuraPrep w/o I_2, Betadine combination, and the untreated recovery control according to the randomization schedule. Each test area contained six individual test sites (for three inoculation times and two bacterial residence times). Each test area was prepped with the assigned treatment. Immediately after the preparation was dry (minimum 10 minutes) and at 2 hours and 6 hours post-prep, individual sites within each test area were inoculated with 50 uL of the bacterial suspension (approximately 10^8 CFU/mL). The test organism remained in situ for 5 or 30 minutes before sample collection. All microbial samples were collected using the cup scrub technique with Standard Sampling Solution (SSS). After all sample collections were completed the inoculated sites will be disinfected with 70% isopropyl alcohol. The following Table provides an outline with timing parameters used in this study.

TABLE 21. LIMS 8197 Schedule of Procedures and Assessments

Number of Subjects	31
Treatments[1]	3M™ DuraPrep™ Surgical Solution DuraPrep w/o I_2 Control (DuraPrep solution without iodine) Betadine Surgical Scrub and Betadine Solution Untreated Recovery Control
Test Organisms	*Staphylococcus aureus* (ATCC 27217) *Serratia marcescens* (ATCC 14756) *Enterococcus faecalis* (ATCC 10741) *Escherichia coli* (ATCC 25922)
Test Organism Inoculation Time[2]	Immediately after the prep is dry At 2 hours (+/- 5 min) post-prep[3] At 6 hours (+/- 15 min) post-prep[3]
Bacterial Residence Time[4]	5 minutes (+/- 30 sec.) 30 minutes (+/- 1 min)
Collection Time[5] of Test Organisms	1. When prep is dry + 5 minutes bacterial residence time 2. When prep is dry + 30 minutes bacterial residence time 3. At 2 hours post-prep + 5 minutes bacterial residence time 4. At 2 hours post-prep + 30 minutes bacterial residence time 5. At 6 hours post-prep + 5 minutes bacterial residence time 6. At 6 hours post-prep + 30 minutes bacterial residence time

[1] Order of treatments defined by randomization scheme.
[2] Inoculation time is the time at which the test site is inoculated with the challenge organism.
[3] Post-prep timing begins at completion of prep application.
[4] Bacterial Residence time is the time between inoculation of the test site and the sample collection.
[5] Collection time is the time at which the challenge organisms are collected from the test site
[Source: LIMS 8197 Study Report, page 24]

All adverse events (AEs), whether or not considered to be investigational material-related, were to be reported immediately to the Clinical Monitor and recorded on an Adverse Drug Experience Record.

Medical Officer Comment: ***Of note, Modified Sampling Solution (MSS) for sample collection was not used in this study for sample collection because bacterial counts were to be assessed on the surface of the applied preparation; therefore, it was not necessary to dissolve the DuraPrep solution film. The effectiveness and non-toxicity of this neutralizer was assessed to demonstrate that there was no effect on the growth of microorganisms and that the active ingredients were appropriately inactivated. For a more detailed discussion of the neutralizers used in this study and a detailed review of microbiologic methods utilized please see the review by Dr. Peter Coderre, the FDA Microbiology Reviewer.***

6.3.3.3.2 Evaluability Criteria

All randomized subjects that were treated with study drug were considered evaluable for safety analyses. All randomized subjects that were treated with study drug and that had an available pair of efficacy measurements from DuraPrep solution and DuraPrep without I_2 were considered evaluable for efficacy. If efficacy data were missing at some, but not all time points, paired data from the available time points were included in the analyses.

6.3.3.3.3 Endpoints

Log reductions were determined for each of the four bacterial strains at the three post-preparation time points and two organism residence times. The contribution of iodine in DuraPrep solution was determined by comparing the log reduction on DuraPrep sites to the log reduction on sites treated with DuraPrep without I_2. The primary endpoint was the difference in log reduction, across all organisms, at the 6 hour post-preparation time point, with a 30 minute organism residence time.

6.3.3.3.4 Statistical Considerations

The differences in the log reduction of a bacterial challenge between DuraPrep solution treated sites and sites treated with DuraPrep w/o I_2 were assessed. Based on previous pilot studies (LIMS 1513, 7822, and 8089), a substantial difference in log reductions was expected between DuraPrep solution and DuraPrep w/o I2. An estimate of 0.7 logs was assumed (from pilot study LIMS 8089) for the standard deviation of the paired differences in log reduction. This study was designed to detect a difference between treatments of 0.5 logs across organisms with a 2-sided alpha of 0.05 and power of 80%. Based on these assumptions, a sample size of 18 subjects was considered sufficient to detect this difference; however, because 4 organisms were being tested the Applicant increased the sample size per organism to 6 subjects (total of 24 subjects) because they believed this represented a more desirable sample size on which nonparametric tests could be conducted.

The test lab reported raw data from all treatments as average CFU/mL per test site and the Applicant completed data processing and statistical analysis. Raw data (CFU/mL) were converted to Log_{10} CFU/cm^2. Counts of less than 1 CFU/cm^2 were treated as 1 CFU/cm2 such that the log transformation will be zero. Log reductions for each condition studied were calculated by subtracting the recovery log count from the treated sample from that of the appropriate recovery control.

Significance of the difference in log reduction between treatments was assessed at each time period using a paired t-test. The primary analysis was across organisms on the 6 hour post-preparation time point, with a 30 minute organism residence time. Success was to be a significantly greater log reduction for DuraPrep solution compared to DuraPrep w/o I_2. Significance was assessed at alpha = 0.05 (2-sided). In addition, the 95% confidence limit on the paired difference between treatments was calculated for each organism at each time period and a nonparametric analysis (Wilcoxon signed rank test) was conducted to verify the results.

6.3.3.4 Study Results

6.3.3.4.1 Evaluability

Thirty-one subjects were randomized and received study treatment. All subjects were evaluable for safety and 31 subjects were evaluable for efficacy. Twenty-four subjects completed all study assessments; seven (22.6%) subjects (Subjects 002, 005, 010, 011, 012, 016, and 020) did not complete the study because of protocol deviations (multiple sampling time errors, multiple test site/test area randomization errors, and/or plating >30 minutes after sampling) and were replaced.

6.3.3.4. 2 Demographics

The majority of subjects were Caucasian (100%) and male (90.3%). The mean age was 23.9 years. Demographic data for all randomized subjects are summarized in the following table.

Table 22. LIMS 8197 Demographic and Other Baseline Characteristics (All Randomized Subjects)

Demographic Characteristic	All Subjects (N=31)
Age (years) Mean (SD) Median Min - Max	 23.9 (6.32) 22.0 18 - 43
Gender (n [%]) Male Female	 28 (90.3) 3 (9.7)
Race (n [%]) Caucasian	 31 (100)
Height (inches) Mean (SD) Median Min - Max	 71.7 (3.07) 72.0 64 - 76
Weight (pounds) Mean (SD) Median Min - Max	 198.0 (34.65) 185.0 155 - 310

SD = standard deviation; Min = minimum; Max = maximum
[Source: LIMS 8197 Clinical Study Report (page 39)]

Medical Officer's Comment: With the exception of Caucasian male subjects, treatment experience is limited in this study. Data are also not available for subjects less than 18 years of age. However, this product has been marketed in the United States for a number of years and there are no reports in AERS or the literature to suggest that efficacy is affected by specific demographic factors.

6.3.3.4.3 Efficacy

For the primary endpoint, the mean log reduction of the bacterial challenge between DuraPrep film versus DuraPrep w/o I_2 film at the 6 hours post-preparation/30-minute residence 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). Results of these analyses are summarized in the following Table.

Table 23. LIMS 8197 Summary of Log Reduction of Bacterial Challenge(CFU/cm^2) – DuraPrep Solution Versus DuraPrep w/o I_2 (Efficacy-Evaluable Population)

Inoculation Time/ Contact Time	DuraPrep w/o I_2 (N = 31)	DuraPrep Solution (N = 31)	Paired Difference in Log Reduction[1]	P-value[2]	P-value[3]
When Preparation is Dry					
5 Minutes					
n	30[4]	30[4]	30[4]		
Mean (SD)	-0.05 (0.507)	1.45 (1.550)	1.49 (1.486)	<0.0001	<0.0001
Median	0.01	0.97	1.16		
Min – Max	-2.41 – 1.15	-0.22 – 4.77	-0.04 – 4.66		
95% CI			(0.94, 2.05)		
30 Minutes					
n	30[5]	30[5]	30[5]		
Mean (SD)	-0.67 (0.895)	2.82 (1.924)	3.49 (2.165)	<0.0001	<0.0001
Median	-0.20	3.20	4.23		
Min – Max	-2.84 – 0.18	-2.27 – 5.41	-1.26 – 6.13		
95% CI			(2.68, 4.30)		
2 Hours Post-Preparation					
5 Minutes					
n	31	31	31		
Mean (SD)	0.22 (1.083)	1.26 (1.621)	1.05 (1.416)	0.0003	<0.0001
Median	0.01	0.72	0.61		
Min – Max	-0.19 – 5.99	-0.12 – 5.99	-0.66 – 4.98		
95% CI			(0.53, 1.56)		
30 Minutes					
n	31	31	31		
Mean (SD)	-0.52 (0.804)	3.04 (1.782)	3.56 (2.000)	<0.0001	<0.0001
Median	-0.13	3.54	4.04		
Min – Max	-2.60 – 0.23	-0.19 – 6.21	0.32 – 6.22		
95% CI			(2.83, 4.30)		
6 Hours Post-Preparation					
5 Minutes					
n	31	31	31		
Mean (SD)	0.03 (0.194)	1.82 (1.781)	1.79 (1.782)	<0.0001	<0.0001
Median	0.01	1.28	1.28		
Min – Max	-0.25 – 0.95	-0.04 – 5.87	-0.03 – 5.98		
95% CI			(1.14, 2.45)		
30 Minutes					
n	31	31	31		
Mean (SD)	-0.18 (0.841)	2.96 (1.761)	3.14 (2.061)	<0.0001	<0.0001
Median	-0.14	3.57	3.82		
Min – Max	-2.20 – 2.91	-1.54 – 5.69	-3.12 – 5.77		
95% CI			(2.38, 3.89)		

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval.
[1] Calculated by subtracting the log reduction of DuraPrep w/o I2 from the log reduction of DuraPrep solution.
[2] Based on a paired t-test.
[3] Based on a Wilcoxon Signed Rank Test.
[4] Subject 011 was missing the assessment at 5-minute residence time when preparation was dry due to technician error.
[5] Subject 205 was missing the assessment at 30-minute residence time when preparation was dry, due to technician error.
[Source: LIMS 8197 Study Report, pages 43-44]

The Applicant also provided analyses for each of the 4 test organisms at the 6 hours post-preparation/30 minute residence time point. The mean log reduction of the bacterial challenge was significantly greater for DuraPrep film than for DuraPrep w/o I_2 film ($p \leq 0.0009$) for each of the bacterial organisms tested except *E. faecalis*. The log reductions of the bacterial counts following treatment with DuraPrep solution for DuraPrep w/o I_2 for each of the 4 test organisms, at the 6 hours post-preparation/30 minute residence time point, are summarized in the following Table.

Table 24. LIMS 8197 Summary of Log Reduction of Bacterial Challenge(CFU/cm^2) – DuraPrep Solution Versus DuraPrep w/o I_2 (Efficacy-Evaluable Population) - Individual Test Organism

Inoculation Time/ Contact Time	DuraPrep w/o I_2 (N = 31)	DuraPrep Solution (N = 31)	Paired Difference in Log Reduction[1]	P-value[2]	P-value[3]
6-Hours Post-Preparation					
30 Minutes					
S. aureus					
N	8	8	8		
Mean (SD)	-0.15 (0.185)	4.07 (0.509)	4.22 (0.455)	<0.0001	0.0078
Median	-0.19	3.97	4.18		
Min - Max	-0.37 – 0.16	3.44 – 4.79	3.69 – 4.96		
95% CI			(3.84, 4.60)		
S. marcescens					
N	7	7	7		
Mean (SD)	-0.81 (0.679)	3.35 (2.324)	4.16 (1.732)	0.0007	0.0156
Median	-0.71	4.23	4.58		
Min - Max	-1.91 – 0.03	-1.54 – 5.69	0.37 – 5.66		
95% CI			(2.56, 5.76)		
E. faecalis					
N	9	9	9		
Mean (SD)	0.29 (0.990)	1.24 (1.243)	0.95 (1.942)	0.1823	0.1641
Median	-0.03	0.58	0.51		
Min - Max	-0.16 – 2.91	-0.21 – 3.01	-3.12 –3.04		
95% CI			(-0.55, 2.44)		
E. coli					
N	7	7	7		
Mean (SD)	-0.19 (0.960)	3.51(1.065)	3.70 (1.617)	0.0009	0.0156
Median	-0.10	3.57	3.46		
Min - Max	-2.20 – 0.64	1.88 – 5.23	1.24 – 5.77		
95% CI			(2.21, 5.20)		

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval.
[1] Calculated by subtracting the log reduction of DuraPrep w/o I2 from the log reduction of DuraPrep solution.
[2] Based on a paired t-test.
[3] Based on a Wilcoxon Signed Rank Test.
[Source: LIMS 8197 Study Report, pages 45-46]

The Applicant also provided an accounting of log reductions across all treatment arms at each of the inoculation time/contact time points, which is summarized in the following Table.

Table 25. LIMS 8197 Summary of Log Bacterial Counts (CFU/cm^2) - Efficacy-Evaluable Population

Inoculation Time/ Contact Time	Untreated Control (N = 31)	Betadine Combination (N = 31)	DuraPrep w/o I_2 (N = 31)	DuraPrep Solution (N = 31)
When Preparation is Dry				
5 Minutes				
n	31	31	31	30[1]
Mean (SD)	6.33 (0.771)	0.59 (1.024)	6.38 (0.522)	4.86 (1.860)
Median	6.25	0	6.29	5.23
Min - Max	3.27 – 7.48	0 – 3.09	5.68 – 7.35	1.16 – 7.21
30 Minutes				
n	30[2]	31	31	31
Mean (SD)	5.54 (1.422)	0.42 (0.750)	6.21 (0.766)	2.70 (2.468)
Median	6.08	0	6.25	1.88
Min - Max	2.89 – 7.33	0 – 2.80	3.87 – 7.34	0 – 6.95
2 Hours Post-Preparation				
5 Minutes				
n	31	31	31	31
Mean (SD)	6.40 (0.475)	0.70 (1.003)	6.18 (1.259)	5.13 (1.917)
Median	6.36	0	6.28	5.56
Min - Max	5.77 – 7.31	0 – 3.12	0 – 7.34	0 – 7.25
30 Minutes				
n	31	31	31	31
Mean (SD)	5.64 (1.286)	0.43 (0.818)	6.16 (0.849)	2.59 (2.522)
Median	6.08	0	6.25	2.01
Min - Max	2.98 – 7.29	0 – 2.36	3.67 – 7.28	0 – 6.96
6 Hours Post-Preparation				
5 Minutes				
n	31	31	31	31
Mean (SD)	6.38 (0.507)	0.55 (0.890)	6.36 (0.548)	4.56 (2.155)
Median	6.30	0	6.34	5.07
Min - Max	5.70 – 7.36	0 – 3.25	4.85 – 7.35	0 – 7.27
30 Minutes				
n	31	31	31	31
Mean (SD)	5.52 (1.321)	0.56 (0.970)	5.70 (1.345)	2.56 (2.320)
Median	6.05	0	6.14	1.92
Min - Max	3.04 – 7.26	0 – 3.47	2.40 – 7.27	0 – 6.94

SD = standard deviation; Min = minimum; Max = maximum.
[1] Subject 011 was missing the assessment at 5-minute residence time when preparation was dry due to technician error.
[2] Subject 205 was missing the assessment at 30-minute residence time when preparation was dry, due to technician error.
[Source: LIMS 8197 Study Report, pages 41-42]

Medical Officer's Comment: At the 6 hours post-preparation/30-minute residence time point the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film than for DuraPrep w/o I_2 film ($p<0.0001$).

Regarding outcomes for individual organisms tested, it is unclear why DuraPrep solution did not produce as great a log reduction for E. faecalis as it did for the other organisms. Point estimates did, however, favor the DuraPrep solution arm.

While direct comparisons of the 4 treatment arms were not described as endpoints in the original study protocol and formal statistical analyses of comparisons between all arms were not planned or performed, the comparisons provided by the Applicant in the Final Study Report are of interest. Of note, at each time point the DuraPrep w/o I_2 arm seemed to perform similarly to the Untreated Control arm based on point estimates. It is also notable that based on point estimates, in a study of this design, the Betadine combination arm consistently demonstrated lower bacterial counts than the DuraPrep solution arm.

6.3.3.5 Medical Reviewer's Comments/Conclusion of Study

Based on the Division's prior agreement that a study of this design was adequate, the Applicant has provided evidence that iodine contributes to the efficacy of DuraPrep solution in this study.

6.3.4 LIMS 9302 "Evaluation of the Persistent Antimicrobial Activity of 3M™ DuraPrep™ Surgical Solution and DuraPrep w/o I_2 Control Using a Bacterial Challenge Method (Study 2)"

6.3.4.1 Objective/Rationale

The primary objective of this study, as stated by the Applicant, was to "assess the contribution of iodine to the antimicrobial activity of DuraPrep solution."

6.3.4.2 Study Design

The study was a randomized, partially blinded, paired-comparisons design where each subject received DuraPrep solution, DuraPrep w/o I_2, and Betadine combination. This study was conducted at one center in the United States [redacted]

6.3.4.3 Protocol Overview

The protocol for this study was identical to that of Study LIMS 8197. Please see Section 6.3.3.3 of this review for a summary of the Population/Procedures, Evaluability Criteria, Endpoints, and Statistical Considerations that were used in this study.

6.3.4.4 Study Results

6.3.4.4.1 Evaluability

Twenty-eight subjects were randomized and received study treatment. All subjects were evaluable for safety and 24 subjects were evaluable for efficacy and completed the study. Four (14.3%) subjects (Subjects 007, 008, 009, and 010) did not complete the study because of a protocol deviation (the media for plating the m-Enterococcus was prepared incorrectly).

6.3.4.4.2 Demographics

The majority of subjects were Caucasian (96.4%) and female (78.6%). The mean age was 57.2 years. Demographic data for all randomized subjects are summarized in the following table.

Table 26. LIMS 9302 Demographic and Other Baseline Characteristics (All Randomized Subjects)

Demographic Characteristic	All Subjects (N=28)
Age (years)	
Mean (SD)	57.2 (9.91)
Median	58.0
Min - Max	24 - 70
Gender (n [%])	
Male	6 (21.4)
Female	22 (78.6)
Race (n [%])	
Caucasian	27 (96.4)
Black	1 (3.6)
Height (inches)	
Mean (SD)	65.4 (2.92)
Median	65.5
Min - Max	58 - 72
Weight (pounds)	
Mean (SD)	167.9 (27.10)
Median	164.0
Min - Max	132 - 250

SD = standard deviation; Min = minimum; Max = maximum
[Source: LIMS 9302 Clinical Study Report (page 39)]

Medical Officer's Comment: With the exception of Caucasian female subjects, treatment experience is limited in this study. Data are also not available for subjects less than 24 years of age. However, this product has been marketed in the United States for a number of years and there are no reports in AERS or the literature to suggest that efficacy is affected by specific demographic factors.

6.3.4.4.3 Efficacy

For the DuraPrep film versus DuraPrep w/o I_2 film at the 6 hours post-preparation/30-minute residence time analysis 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 addition, with the exception of the initial time point, at all of the other 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 ($p \leq 0.0185$, based on paired t-tests). Results of these analyses are summarized in the following Table.

Table 27. LIMS 9302 Summary of Log Reduction of Bacterial Challenge(CFU/cm^2) – DuraPrep Solution Versus DuraPrep w/o I_2 (Efficacy-Evaluable Population)

Inoculation Time/ Contact Time	DuraPrep w/o I_2 (N = 24)	DuraPrep Solution (N = 24)	Paired Difference in Log Reduction[1]	P-value[2]	P-value[3]
When Preparation is Dry					
5 Minutes					
n	24	24	24		
Mean (SD)	-0.02 (0.136)	0.51 (1.346)	0.53 (1.326)	0.0626	<0.0001
Median	-0.02	0.19	0.24		
Min – Max	-0.29 – 0.20	-0.05 – 6.68	-0.10 - 6.60		
95% CI			(-0.03, 1.09)		
30 Minutes					
n	24	24	24		
Mean (SD)	-0.39 (0.701)	3.47 (1.905)	3.86 (2.243)	<0.0001	<0.0001
Median	-0.09	3.87	4.19		
Min – Max	-2.40 – 0.24	0.55 – 6.63	0.54 - 7.18		
95% CI			(2.91, 4.80)		
2 Hours Post-Preparation					
5 Minutes					
n	24	24	24		
Mean (SD)	-0.02 (0.139)	0.75 (1.485)	0.77 (1.482)	0.0185	<0.0001
Median	-0.01	0.32	0.33		
Min – Max	-0.34 – 0.20	-0.03 – 6.64	-0.17 - 6.57		
95% CI			(0.14, 1.39)		
30 Minutes					
n	24	24	24		
Mean (SD)	-0.03 (1.261)	3.39 (1.702)	3.42 (2.354)	<0.0001	<0.0001
Median	-0.03	3.17	3.56		
Min – Max	-2.35 – 4.85	1.05 – 6.79	-3.80 - 7.20		
95% CI			(2.43, 4.42)		
6 Hours Post-Preparation					
5 Minutes					
n	24	24	24		
Mean (SD)	0.02 (0.111)	0.71 (1.146)	0.69 (1.159)	0.0079	<0.0001
Median	0.02	0.38	0.35		
Min – Max	-0.22 – 0.19	-0.05 – 4.47	0.07 - 4.69		
95% CI			(0.20, 1.18)		
30 Minutes					
n	24	24	24		
Mean (SD)	0.05 (0.612)	3.77 (1.699)	3.72 (1.601)	<0.0001	<0.0001
Median	-0.06	3.88	4.01		
Min – Max	-1.25 – 1.89	1.44 – 6.62	1.53 - 6.22		
95% CI			(3.04, 4.39)		

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval.
[1] Calculated by subtracting the log reduction of DuraPrep w/o I2 from the log reduction of DuraPrep solution.
[2] Based on a paired t-test.
[3] Based on a Wilcoxon Signed Rank Test.
[Source: LIMS 9302 Study Report, pages 43-44]

The Applicant also provided analyses for each of the 4 test organisms at the 6 hours post-preparation/30 minute residence time point. The mean log reduction of the bacterial

challenge was significantly greater for DuraPrep film than for DuraPrep w/o I_2 film ($p \leq 0.0034$) for each of the bacterial organisms tested. The log reductions of the bacterial counts following treatment with DuraPrep solution for DuraPrep w/o I_2 for each of the 4 test organisms, at the 6 hours post-preparation/30 minute residence time point, are summarized in the following Table.

Table 28. LIMS 9302 Summary of Log Reduction of Bacterial Challenge(CFU/cm^2) – DuraPrep Solution Versus DuraPrep w/o I_2 (Efficacy-Evaluable Population) - Individual Test Organism

Inoculation Time/ Contact Time	DuraPrep w/o I_2 (N = 24)	DuraPrep Solution (N = 24)	Paired Difference in Log Reduction[1]	P-value[2]	P-value[3]
6-Hours Post-Preparation					
30 Minutes					
S. aureus					
N	6	6	6		
Mean (SD)	-0.13 (0.284)	3.45 (1.457)	3.58 (1.675)	0.0034	0.0313
Median	-0.10	3.27	3.40		
Min - Max	-0.63 – 0.19	1.59 – 5.59	1.55 - 6.22		
95% CI			(1.82, 5.34)		
S. marcescens					
N	6	6	6		
Mean (SD)	0.05 (0.378)	4.16 (2.016)	4.12 (1.913)	0.0033	0.0313
Median	-0.05	4.85	4.52		
Min - Max	-0.31 – 0.75	1.72 – 6.11	1.72 - 6.04		
95% CI			(2.11, 6.13)		
E. faecalis					
N	6	6	6		
Mean (SD)	-0.07 (0.121)	2.25 (0.799)	2.32 (0.762)	0.0007	0.0313
Median	-0.08	2.19	2.18		
Min - Max	-0.24 – 0.13	1.44 – 3.57	1.53 - 3.59		
95% CI			(1.52, 3.12)		
E. coli					
N	6	6	6		
Mean (SD)	0.35 (1.151)	5.20 (0.956)	4.86 (0.793)	<0.0001	0.0313
Median	0.11	5.27	4.71		
Min - Max	-1.25 – 1.89	3.88 – 6.62	3.93 - 5.81		
95% CI			(4.02, 5.69)		

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval.
[1] Calculated by subtracting the log reduction of DuraPrep w/o I2 from the log reduction of DuraPrep solution.
[2] Based on a paired t-test.
[3] Based on a Wilcoxon Signed Rank Test.
[Source: LIMS 9302 Study Report, pages 45-46]

The Applicant also provided an accounting of log reductions across all treatment arms at each of the inoculation time/contact time points, which is summarized in the following Table.

Table 29. LIMS 9302 Summary of Log Bacterial Counts (CFU/cm^2) - Efficacy-Evaluable Population

Inoculation Time/ Contact Time	Untreated Control (N = 24)	Betadine Combination (N = 24)	DuraPrep w/o I_2 (N = 24)	DuraPrep Solution (N = 24)
When Preparation is Dry				
5 Minutes				
n	24	24	24	24
Mean (SD)	6.72 (0.235)	0.16 (0.204)	6.74 (0.202)	6.22 (1.314)
Median	6.69	0.12	6.72	6.48
Min - Max	6.32 – 7.37	0.12 – 1.12	6.48 – 7.37	0.12 – 7.03
30 Minutes				
n	24	24	24	24
Mean (SD)	6.20 (0.575)	0.51 (0.938)	6.59 (0.292)	2.73 (2.220)
Median	6.49	0.12	6.63	2.36
Min - Max	4.90 – 6.78	0.12 – 3.23	5.72 – 7.30	0.12 – 5.99
2 Hours Post-Preparation				
5 Minutes				
n	24	24	24	24
Mean (SD)	6.71 (0.190)	0.36 (0.621)	6.73 (0.211)	5.96 (1.480)
Median	6.70	0.12	6.69	6.40
Min - Max	6.37 – 7.35	0.12 – 2.46	6.52 – 7.32	0.12 – 6.99
30 Minutes				
n	24	24	24	24
Mean (SD)	6.23 (0.542)	0.35 (0.610)	6.26 (1.039)	2.84 (1.862)
Median	6.36	0.12	6.51	2.68
Min - Max	4.70 – 6.91	0.12 – 2.20	1.80 – 7.32	0.12 – 5.60
6 Hours Post-Preparation				
5 Minutes				
n	24	24	24	24
Mean (SD)	6.71 (0.216)	0.38 (0.702)	6.69 (0.186)	6.01 (1.121)
Median	6.72	0.12	6.65	6.32
Min - Max	6.40 – 7.32	0.12 – 3.20	6.46 – 7.30	1.93 – 6.87
30 Minutes				
n	24	24	24	24
Mean (SD)	6.34 (0.409)	0.23 (0.297)	6.29 (0.602)	2.57 (1.840)
Median	6.43	0.12	6.47	2.75
Min - Max	5.08 – 6.87	0.12 – 1.20	4.81 – 7.27	0.12 – 4.93

SD = standard deviation; Min = minimum; Max = maximum.
[Source: LIMS 9302 Study Report, pages 41-42]

Medical Officer's Comment: At the 6 hours post-preparation/30-minute residence time point the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film than for DuraPrep w/o I_2 film ($p<0.0001$).

Regarding outcomes for individual organisms tested, as apposed to Study LIMS 8197, DuraPrep solution provided statistically significantly greater log reductions for all 4 organisms.

While direct comparisons of the 4 treatment arms were not described as endpoints in the original study protocol and formal statistical analyses of comparisons between all arms were not planned or performed, the comparisons provided by the Applicant in the Final Study Report are of interest. Of note, at each time point the DuraPrep w/o I_2 arm seemed to perform similarly to the Untreated Control arm based on point estimates. It is also notable that based on point estimates that in a study of this design, the

Betadine combination arm consistently demonstrated lower bacterial counts than the DuraPrep solution arm.

6.3.4.5 Medical Reviewer's Comments/Conclusion of Study

Based on the Division's prior agreement that a study of this design was adequate, the Applicant has provided evidence that iodine contributes to the efficacy of DuraPrep solution in this study.

6.3.5 LIMS 8198

6.3.5.1 Objective/Rationale

The purpose of this study was to compare the durability and persistence of the antimicrobial activity of the DuraPrep film (DuraPrep Solution once it is dry) and Betadine Surgical Scrub and Betadine Solution (hereafter referred to as Betadine combination) following a wash with autologous blood and saline.

The Applicant stated that they expected that the results of this study would demonstrate that "DuraPrep film is insoluble in water, will resist wash away, and has antimicrobial activity on top of the film up to 6-hours post-prep."

6.3.5.2 Study Design

The study was a randomized, paired-comparisons design where each subject received DuraPrep solution and Betadine combination. This study was conducted at one center in the United States.

6.3.5.3 Protocol Overview

6.3.5.3.1 Population/Procedures

Population

Sixteen healthy subjects with no dermatological conditions or known history of sensitivity to acrylates, natural rubber latex, alcohol or iodine were enrolled into the study. The following are noteworthy inclusion and exclusion criteria:

Inclusion Criteria

1. Healthy subjects of either gender and any race between the ages of 18 and 70;
2. Subjects who are willing to answer questions on the Screening Inclusion/Exclusion case report form and voluntarily sign the Consent Form;
3. Subjects whose backs are free from cuts, acne, abrasions, and skin irritation;
4. Subjects who are cooperative, are willing to present themselves promptly at the designated test times required by the study, and are willing to follow all study instructions;
5. Subjects who are willing to remain at the test facility for the duration of the Treatment Day (~8 hours);
6. Subjects who are able to lie in a prone position (on their stomach) for 1-2 hours at a time.

Exclusion Criteria

1. Any form of dermatitis, acne, open wounds, or other skin disorders on the back;
2. History of skin allergies;

3. Damaged or altered skin within the test areas (includes sunburn, tattoos, scars, previous skin cancer, or other disfiguration);
4. Diabetics and persons who are immunocompromised;
5. Sensitivities to any alcohol, acrylate- or iodine-containing product;
6. Sensitivities to more than one antibiotic;
7. Allergies to natural rubber latex, tape, or gauze;
8. A history of anemia or low blood counts;
9. Any person pregnant or lactating;
10. Contact with chlorinated swimming pools or hot tubs within 7 days of Treatment Day;
11. Use of antibacterial soaps, dandruff shampoos, topical or systemic antibiotic medications within 7 days of Treatment Day;
12. A small back that will not allow for the placement of 3, 5"x 7" test areas;
13. Blood donation within 6 weeks of the scheduled Treatment Day;
14. A history of hepatitis or other known blood borne pathogens.

Procedures

Participation in this study involved a 7-day pretreatment phase, a one-day treatment phase, and a follow-up visit for dermatologic evaluation to ensure no infection was present at 4 to 8 days post treatment. Prior to the scheduled screening day, subjects underwent a 7-day pretreatment phase, in which they refrained from the use of products containing antibacterial agents (per written instructions provided by the Study Investigator). Subjects were given product kits containing non-antimicrobial soaps, deodorants, and shampoos and were instructed to use these products through completion of the treatment phase.

On the Treatment Day, subjects were assigned a study number and 30 mL of blood were obtained via venipuncture. Three test areas (5" x 7" each) on each subject's back were marked and randomized for each of the three treatments, DuraPrep solution, Betadine combination, and the untreated recovery control according to the randomization schedule. Each test area contained four individual test sites (for two inoculation times and two bacterial residence times). Each test area was prepped with the assigned treatment. Ten minutes after preparation (when sites were expected to be dry), sites were washed (gauze soaked with blood and gauze soaked with saline were laid on top of site) with autologous blood and saline to simulate exposure to fluids during surgery. At 15 minutes and 6 hours post-preparation, individual sites within each test area were inoculated with 50 uL of the bacterial suspension (approximately 10^8 CFU/mL). The test organism remained in situ for 5 or 30 minutes before sample collection. All microbial samples were collected using the cup scrub technique with Standard Sampling Solution (SSS). After all sample collections were completed the inoculated sites were disinfected with 70% isopropyl alcohol. The following Table provides an outline with timing parameters used in this study.

TABLE 30. LIMS 8198 Schedule of Procedures and Assessments

Number of Subjects	16
Treatments[1]	3M™ DuraPrep™ Surgical Solution Betadine Surgical Scrub and Betadine Solution Untreated Recovery Control
Wash with Autologous Blood Followed by Saline	10 minutes after preparations were applied
Test Organisms	*Staphylococcus aureus* (ATCC 27217)
Test Organism Inoculation Time[2]	At 15 minutes (+/-1 min) post-prep[3] (including blood and saline wash) At 6 hours (+/- 15 min) post-prep[3]
Bacterial Residence Time[4]	5 minutes (+/- 30 sec.) 30 minutes (+/- 1 min)
Collection Time[5] of Test Organisms	1. At 15 minutes post-prep[3] + 5 minutes bacterial residence time 2. At 15 minutes post-prep[3] + 30 minutes bacterial residence time 3. At 6 hours post-prep[3] + 5 minutes bacterial residence time 4. At 6 hours post-prep[3] + 30 minutes bacterial residence time

[1] Order of treatments defined by randomization scheme.
[2] Inoculation time is the time at which the test site is inoculated with the challenge organism.
[3] Post-prep timing begins at completion of prep application.
[4] Bacterial Residence time is the time between inoculation of the test site and the sample collection.
[5] Collection time is the time at which the challenge organisms are collected from the test site
[Source: LIMS 8198 Study Report, page 22]

All adverse events (AEs), whether or not considered to be investigational material-related, were to be reported immediately to the Clinical Monitor and recorded on an Adverse Drug Experience Record.

Medical Officer Comment: ***Of note, Modified Sampling Solution (MSS) for sample collection was not used in this study for sample collection because bacterial counts were to be assessed on the surface of the applied preparation; therefore, it was not necessary to dissolve the DuraPrep solution film. The effectiveness and non-toxicity of this neutralizer was assessed to demonstrate that there was no effect on the growth of microorganisms and that the active ingredients were appropriately inactivated. For a more detailed discussion of the neutralizers used in this study and a detailed review of microbiologic methods utilized please see the review by Dr. Peter Coderre, the FDA Microbiology Reviewer.***

6.3.5.3.2 Evaluability Criteria

6.3.5.3.3 Endpoints

According to the Applicant, the primary objective of the study was to assess the difference between DuraPrep solution and Betadine combination in the log reduction of a bacterial challenge after a wash-off procedure simulating surgery. The protocol defined primary analysis was at the 6-hour post-prep time point, with a 30 minute organism residence time.

6.3.5.3.4 Statistical Considerations

An estimate of the standard deviation of the paired differences in log reduction, between DuraPrep solution and Betadine combination, of 2.2 was based on a previous pilot study (LIMS 8061). This study was designed to detect a difference in log reduction of 2 logs with a 2-sided alpha = 0.05 and power = 80%. Based on these assumptions, it was calculated that a sample size of 12 subjects would be needed.

The test lab reported raw data from all treatments as average CFU/mL per test site and the Applicant completed data processing and statistical analysis. Raw data (CFU/mL) were converted to Log_{10} CFU/cm^2. Counts of less than 1 CFU/cm^2 were treated as 1 CFU/cm2 such that the log transformation was zero. Log reductions for each condition studied were calculated by subtracting the recovery log count from the treated sample from that of the appropriate recovery control.

Significance of the difference in log reduction between treatments was assessed at each time period using a paired t-test. The primary analysis was across organisms on the 6 hour post-preparation time point, with a 30 minute organism residence time. Success was to be a significantly greater log reduction for DuraPrep solution compared to Betadine combination. Significance was assessed at alpha = 0.05 (2-sided). In addition, the 95% confidence limit on the paired difference between treatments was calculated for each organism at each time period and a nonparametric analysis (Wilcoxon signed rank test) was conducted to verify the results.

6.3.5.4 Study Results

6.3.5.4.1 Evaluability

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 201 and 202) were not evaluable for efficacy at any time point because non-sterile gauze was used on study sites.

6.3.5.4. 2 Demographics

The majority of subjects were Caucasian (93.8%) and female (56.3%). The mean age was 43.6 years.

6.3.5.4.3 Efficacy

At the primary analysis time point (6 hours post-preparation, 30-minute residence time), the log reduction of the bacterial challenge was statistically significantly greater on DuraPrep film (mean log reduction = 4.191) than on Betadine combination (mean log reduction = 2.667) (p = 0.0098, based on a paired t-test). Results of these analyses are summarized in the following Table.

Table 31. LIMS 8198 Summary of Log Reduction[1] of Bacterial Counts (Efficacy Evaluable Population)

	Betadine Combination (N = 14)	DuraPrep Solution (N = 14)	Paired Difference In Log Reduction[2]	Paired t-test p-value	Wilcoxon Signed Rank Test p-value
15 Minutes Post-Preparation					
5-minute residence time					
N	14	14	14		
Mean (SD)	2.839 (1.8576)	1.731 (1.3756)	-1.107 (2.5813)	0.1325	0.1228
Median	2.550	1.295	-1.385		
Min - Max	0.10 - 6.49	0.25 - 4.75	-5.54 - 3.45		
95% CI			(-2.60, 0.38)		
30-minute residence time					
N	13	13	13		
Mean (SD)	3.326 (1.7265)	3.749 (1.3803)	0.423 (1.9831)	0.4566	0.5693
Median	2.720	4.200	0.000		
Min - Max	0.78 - 5.98	0.60 - 5.41	-1.82 - 3.92		
95% CI			(-0.78, 1.62)		
6 Hours Post-Preparation					
5-minute residence time					
N	14	14	14		
Mean (SD)	2.366 (1.6098)	2.586 (1.8654)	0.219 (2.6174)	0.7589	0.6698
Median	1.970	2.295	0.350		
Min - Max	0.29 - 5.50	0.34 - 6.07	-3.55 - 4.59		
95% CI			(-1.29, 1.73)		
30-minute residence time					
N	14	14	14		
Mean (SD)	2.667 (1.7721)	4.191 (0.9408)	1.524 (1.8879)	0.0098	0.0139
Median	2.990	4.400	1.695		
Min - Max	-0.34 - 6.18	2.56 - 6.04	-1.75 - 4.42		
95% CI			(0.43, 2.61)		

1 Calculated by subtracting the recovery log count from the treated sample from that of the appropriate untreated recovery control.
2 Calculated by subtracting the log reduction of Betadine from the log reduction of DuraPrep.
SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval
[Source: LIMS 8198 Study Report, page 40]

Medical Officer's Comment: For the protocol designated primary analysis, at the 6 hours post-preparation/30-minute residence time point, the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film than for Betadine combination ($p<0.015$). At no other time point sampled was the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film than for Betadine combination.

While the primary endpoint was achieved in this study, this Medical Officer does not consider this study to have provided conclusive evidence that DuraPrep solution provides a superior level of persistent antimicrobial effect in the clinical setting due to the following:

- ***There is no evidence that the amount or method of application of blood and saline to prepared skin (soaked gauze laid on top of prepped areas) appropriately simulates real life conditions experienced in the operating room.***
- ***No supportive evidence is provided by a trend favoring DuraPrep solution across all time points. In fact, trends in point estimates, favored Betadine combination at the 15 minutes post-preparation/5 minute residence time point.***
- ***This study utilized a single organism, S. aureus, for bacterial challenges.***
- ***Findings in this study have not been independently corroborated by a second source.***

6.3.5.5 Medical Reviewer's Comments/Conclusion of Study

The mean log reduction of the bacterial challenge (at the 6 hours post-preparation/30-minute residence time point) was significantly greater for DuraPrep film than for Betadine combination ($p<0.015$) in the protocol designated primary analysis in this study. However, results of this study alone are inadequate to support the conclusion that the durability and persistence of DuraPrep solution are superior to those of Betadine Surgical Scrub and Betadine Solution in the surgical setting.

6.3.6 LIMS 9567 "Adhesion to Skin"

6.3.6.1 Objective/Rationale

According to the Applicant, the objective of this study was to "evaluate the drape adhesion characteristics of three marketed products (Betadine® Surgical Scrub plus Betadine® Solution, Hibiclens® Antimicrobial Skin Cleanser, and 3M™ DuraPrep™ Surgical Solution)."

6.3.6.2 Study Design

Medical Officer's Comment: The NDA contained only a brief Study Report describing this study. The original protocol for the study was not submitted in the NDA; therefore, a detailed description of the Protocol Overview is not available. Case Report Forms for subjects enrolled in this study were also not provided for review.

6.3.6.3 Protocol Overview

6.3.6.3.1 Population/Procedures

Population

Twelve volunteers (6 male and 6 female) were enrolled in this study. The following are noteworthy inclusion and exclusion criteria:

Inclusion Criteria (Summarized from Appendix III of Study Report)

1. Between the ages of 18 and 65 years old.
2. Healthy
3. No history of skin conditions (i.e. diabetes, dermatitis, psoriasis) or skin reactions (unexplained dermatitis)
4. Have not participated in any drug studies utilizing the back in the last 2 weeks
5. Have used lotions on your back in the last 24-hours
6. Current evidence of sunburn or skin infection on back
7. Adequate surface area on back
8. Subject has an adequate skin surface area on the back to administer study preparations
9. Back is without signs of blemishes or rashes
10. Subject has signed Informed Consent

Exclusion Criteria (Summarized from Appendix II of Study Report)

Subjects were to be excluded if they had any of the following:

1. Sensitivity to medical adhesives, particularly the components commonly found in 3M adhesive products
2. Know sensitivity to iodine or chlorhexidine gluconate
3. Psoriasis
4. Active dermatitis and/or active skin infection on your back
5. Are pregnant or potentially pregnant
6. Currently nursing

Procedures

This study utilized three test products:

- Betadine® Surgical Scrub plus Betadine® Solution (Betadine combination)
- Hibiclens® Antimicrobial Skin Cleanser (Hibiclens cleanser)
- 3M™ DuraPrep™ Surgical Solution (Betadine solution)

After randomization for placement of products (applied according to currently labeled directions), the adhesion of drapes to product was assessed under both dry and wet conditions on the back as follows:

> Dry Sites (taken directly from page 5, LIMS 9567 Study Report)
> "Any hair present on the left or right will be clipped with an electric clipper from the test sites. DuraPrep solution, Hibiclens cleanser, and Betadine combination will be applied to the designated test sites at appropriate times. At 1/2 of the test sites the preps will be applied and allowed to dry for 2 minutes, after which the Betadine sites will be blotted with sterile gauze. Two drape samples per test condition will then be placed on these sites. At the remaining 1/2 of the test sites, the preps will be applied and allowed to dry for 5 minutes after which two drape samples per test condition will be applied. The roller will be used to secure the drape samples approximately 5-minutes after drape application. Twenty minutes after drape sample application, the drape samples will be removed using pull-peel tester."
>
> Wet Sites (taken directly from page 6, LIMS 9567 Study Report)
> "Wet Condition - At 1/2 of the test sites the preps will be applied and allowed to dry for 2 minutes, after which the Betadine sites will be blotted with sterile gauze. Two drape samples will then be placed on each site. At the remaining 1/2 of the test sites, the preps will be applied and allowed to dry for 5 minutes after which two drape samples will be applied. The roller will be used to secure the drape samples approximately 5-minutes after drape application. Ten minutes after applying the drape samples, gauze pads saturated with saline will be applied on top of the test sites. Five minutes after application of the gauze pad, an additional 3-mL of saline will be applied to each test site covered with a gauze pad. Five minutes later, the gauze pads will be removed, followed by drape samples removal using the pull-peel tester."

[Applicant Note on Protocol Deviation: For the wet condition for both the 2-minute and 5-minute time points, at 15 minutes after the drape samples were applied (which is 5 minutes after the saline-saturated gauze was applied), an additional 3 mL of saline was not added to the gauze lying upon the test site.]

All adverse events (AEs), whether or not considered to be investigational material-related, were to be reported immediately to the Clinical Monitor and recorded on an Adverse Drug Experience Record.

6.3.6.3.2 Evaluability Criteria

Not described

6.3.6.3.3 Endpoints

According to the Applicant "the primary analysis will be the wet-gauze condition after 5-min."

6.3.6.3.4 Statistical Considerations

The Applicant stated that based in part on information from a small pilot study (LIMS 9090), the paired standard deviation of adhesion values was estimated to be 200 gm; therefore, the Applicant designed the current study to detect a difference in adhesion (wet condition after 5-minutes) between DuraPrep and Hibiclens of 200 gm. with 80% power and 2-sided alpha=0.05. This would require 10 subjects, but due to uncertainty of estimates, 12 subjects were enrolled.

This study was a mixed model, randomized block design with replicates. An analysis of variance was planned to be conducted separately on adhesion values for dry and wet-gauze conditions at each dry time. The ANOVA model was to include terms for Subject, Prep, and the Subject*Prep interaction. Since Subject was considered a random rather than fixed effect, the error from the Subject*Prep interaction was used in the F-test of Prep. If the effect of Prep was significant, then a multiple comparisons t-test was to be conducted to determine which preps differ from each other. Significance was assessed at $p<0.05$ (2-tailed).

6.3.6.4 Study Results

6.3.6.4.1 Evaluability

Not described

6.3.6.4. 2 Demographics

Not described

6.3.6.4.3 Efficacy

According to the Applicant, under the wet gauze condition after 5 minutes there was a significant effect of prep on adhesion. Results of this study are summarized in the following Table.

Table 32. LIMS 9567 Results of Adhesion Study

CONDITION/ DRY TIME /PREP	ADHESION			
	N	MEAN	STD	t-grouping*
DRY				
2 MIN				
BETADINE	24	92.3	43.2	a
HIBICLENS	24	32.8	14.9	b
DURAPREP	24	100.7	54.4	a
5 MIN				
BETADINE	24	85.2	29.8	a
HIBICLENS	24	34.6	13.9	b
DURAPREP	24	91.0	53.6	a
WET				
2 MIN				
BETADINE	24	37.3	25.0	b
HIBICLENS	24	17.3	15.5	b
DURAPREP	24	103.8	61.3	a
5 MIN				
BETADINE	24	44.4	23.4	b
HIBICLENS	24	13.7	14.8	b
DURAPREP	24	125.2	72.3	a

*means with the same letter at the same time and condition are not significantly different.

[Source: LIMS 9567 Study Report, page 2]

Medical Officer's Comment: The Applicant did not provide datasets for this study; therefore, the Applicant's analyses could not be independently assessed.

While the primary endpoint, according to the Applicant, was achieved in this study, this Medical Officer does not consider this study to have provided conclusive evidence that DuraPrep solution provides superior adhesion in the clinical setting. There is no evidence that the amount or method of application of saline to prepared skin (soaked gauze laid on top of prepped areas) appropriately simulates real life conditions experienced in the operating room.

6.3.6.5 Medical Reviewer's Comments/Conclusion of Study

Results of this study are inadequate to support the conclusion that drape adhesion to subjects' skin prepared with DuraPrep solution is superior to Betadine combination or Hibiclens cleanser in the surgical setting.

6.4 Clinical Microbiology

The Microbiology reviewer, Peter Coderre, Ph.D., noted that despite the inability of both DuraPrep and Hibiclens to meet the mean 3 log reduction criterion in the TFM for the inguinal site, DuraPrep had larger bacterial log reductions than the positive control (Hibiclens) at either the abdominal or inguinal sites in the clinical simulations. Based on this finding, the success of DuraPrep bacterial challenge studies, and the findings in *in vitro* studies, Dr. Coderre has recommended that the Application be approved.

Medical Officer's comment: A unique aspect of DuraPrep solution is that it dries to a water-insoluble film that resists being washed away during surgery. Since test methods specified in the TFM are generally applicable to water-soluble formulations, the Applicant performed a series of test-method development studies to identify and validate appropriate modifications to the TFM test methods for use with their product. Based on these studies, modifications to the TFM methods (i.e., use of a modified sampling solution for use on sites prepared with DuraPrep solution) were identified. These methods were reviewed by and found acceptable by the FDA for use in the pivotal efficacy studies. In addition, a bacterial challenge method, where bacteria were placed on top of the dried DuraPrep film, was developed to show the contribution of iodine. The bacterial challenge method was also reviewed by FDA staff and found to be acceptable for use in pivotal efficacy studies intended to show the contribution of iodine in DuraPrep solution.

6.5 Medical Reviewer's Overall Efficacy Conclusions

From a clinical perspective, 3M™ DuraPrep™ Surgical Solution may be approved for the indication of Patient Preoperative Skin Preparation.

At the abdominal site, in Study LIMS 8304 and Study LIMS 8918, DuraPrep solution satisfied the criteria defined in the TFM for demonstrating antimicrobial activity. There was 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.

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 Study LIMS 8304 or Study LIMS 8918; 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 (Study LIMS 8304 and Study LIMS 8918, respectively), an FDA approved product for the Patient Preoperative Skin Preparation indication. In both studies bacterial counts remained below baseline at the 6 hour time point. While provision of additional data from subjects treated at the groin site might further clarify the comparative efficacy of DuraPrep solution to Hibiclens, this Medical Officer believes that adequate evidence has been provided to establish that DuraPrep solution is at least as effective as a product

(Hibiclens® Antimicrobial Skin Cleanser) currently approved by the FDA for this indication.

Based on the Agency's prior agreement with the design of Study LIMS 8197 and Study LIMS 9302, the Applicant has provided adequate evidence that iodine contributes to the efficacy of DuraPrep solution.

Based on the findings (summarized above) in Studies LIMS 8304, LIMS 8918, LIMS 8197, LIMS 9302, and additional *in vitro* Studies (discussed in the FDA Microbiology review completed by Peter Coderre, Ph.D.), 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.

7 INTEGRATED REVIEW OF SAFETY

The Integrated Review of Safety was performed by Mr. David Bostwick. Please refer to his review for this section.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

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. [redacted]

Since 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] a more specific measure of surface area covered should be provided in the package labeling and package insert for the 26 ml container.

8.2 Drug-Drug Interactions

As I_2 is minimally absorbed through the skin in populations with fully keratinized skin (that is, ≥2 months of age), no studies were performed to investigate its pharmacologic effects when used concomitantly with other medications. No studies were conducted to assess potential interactions with other topically applied drug products.

Medical Officer's Comment: Since studies were not conducted to assess potential interactions with other topically applied products, concomitant use of such products should be avoided as such use may impact the safety and/or efficacy of these products.

8.3 Special Populations

As I_2 is minimally absorbed through the skin in populations with fully keratinized skin (that is, ≥2 months of age), there do not appear to be special dosing considerations for this product in patients with hepatic or renal failure, pregnant or lactating women, or the elderly for the single use indication of Patient Preoperative Skin Preparation. Increased absorption may occur in infants less than 2 months of age; therefore, this product should not be used on infants less than 2 months of age.

8.4 Pediatrics

The Applicant has requested a Waiver for Studies in Pediatric Patients less than 2 months of age based on the concern that the skin of these pediatric patients is not as competent as that of older children and adults, and that use of the product in the less than 2 month of age population may lead to increased iodine absorption and associated toxicity[3]. For pediatric patients ≥2 months of age, the Applicant proposed that skin type, microbial flora on the skin, and need for preoperative preparation were sufficiently similar to adults

such that safety and efficacy data from adults could be extrapolated to this population. At the End-of-Phase II meeting between the Applicant and the Agency (held November 6, 2000) Division of Anti-Infective Drug Products (DAIDP) representatives agreed with this approach; in summary, pediatric labeling down to 2 months of age may be extrapolated based on a demonstration of safety and efficacy in adults and a partial waiver for pediatric studies will be granted for pediatric patients <2 months of age.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

The following items were reviewed in relation to this NDA submission and are summarized below:

Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule. 21 CFR Parts 333 and 339. Federal Register. Friday June 17, 1994, pp. 31402-31452.

Mancini, A.J. Skin. *Pediatrics* 113 (4 Suppl):1114-1119, 2004.
Review that summarizes reasons for differing vulnerability to topical agents in the embryo, infant, child, and adolescent. The paper also includes a discussion of percutaneous absorption of topically applied substances and the potential for resultant drug toxicities in the child including:

- A commentary regarding findings of increased plasma and urinary iodine levels and concerns for development of transient hypothyroxiniemia and hypothyroidism in infants (particularly premature infants) exposed to iodine containing products
- A commentary regarding findings of elevated blood alcohol levels, local skin reactions, systemic toxicity, and hemorrhagic skin necrosis in infants exposed to alcohol containing products.

Kurt, T.L., Morgan, M.L., Hnilica, V., Bost, R., and C. S. Petty. Fatal iatrogenic iodine toxicity in a nine-week old infant. *J Toxicol.Clin Toxicol.* 34 (2):231-234, 1996.

Report of fatality of 9 week old infant after internal gastrointestinal use of povidone-iodine (enema composed of 50 mL of povidone-iodine diluted in 250 mL of a bowel irrigant and 50 mL of the described solution hourly for three doses by nasogastric tube). The infant was found dead three hours after the last dose. Autopsy showed a corroded and necrotic intestinal tract, serous fluid in body cavities, a blood total iodine of 14,600 micrograms/dL, protein-bound iodine of 3,400 micrograms/dL and inorganic iodine of 11,700.

Roberts, A.J., Wilcox, K., Devineni, R., Harris, R.B., and M.A. Osevala. Skin preparations in CABG surgery: a prospective randomized trial. Comp Surg 1995; 14(6): 724, 741-744, 747.
This was a prospective, randomized, unblinded study that enrolled 200 consecutive consenting adults that were having CABG surgery. Patients received either DuraPrep

solution or a 5- to 10- minute scrub with aqueous idophor followed by application of iodophor solution (to both chest and legs). An iodophor containing antimicrobial incise drape was also applied to the chest of all patients. The overall infection rate, leg infection rate, and chest infection rate were not significantly different between the two treatment groups. When outcomes in diabetic versus nondiabetic patients were compared, overall infection and leg infection rates appeared to be significantly greater in the diabetic population enrolled in this study.

Birnbach, D.J., Stein, D.J., Murray, O., Thys, D.M., and E.M. Sordillo. Povidone iodine and skin disinfection before initiation of epidural anesthesia. Anesthesiology 1998; 88(3): 668-672.
This study enrolled 60 women in active labor who requested epidural analgesia. They were randomized 1:1 to receive skin preparation with either povidone-iodine solution or DuraPrep solution. Three swab cultures (pre-moistened with sterile saline) were obtained for each patient, immediately pre-preparation, immediately post-preparation, and just before catheter removal. The distal tips of catheters were also culture on removal. The authors reported that use of DuraPrep solution resulted in a statistically significantly lower log CFU at the catheter removal time point than povidone-iodine solution ($p=0.03$) only. Authors also reported that use of DuraPrep solution resulted in a statistically significantly lower rate of positive tip cultures than povidone-iodine solution.

> ***Medical Officer's Comment: Data presented in this reference are of interest; however, it should be noted that no evidence was provided that skin cultures were obtained using validated methods. Based on information provided by the Applicant, it would seem that the sampling and neutralization methods used for skin cultures in DuraPrep solution prepared subjects were inadequate and may have resulted in an overestimation of effectiveness. While colony counts of tip cultures were significantly less in DuraPrep treated subjects, this study was not powered to assess infection rates; it did not demonstrate a decreased incidence of epidural catheter related infection.***

Meadows, W.E., Birnbach, D.J., Stein, D.J., Murray, O., and E.M. Sordillo. Skin disinfection prior to initiation of epidural anesthesia. A comparison of two methods of antisepsis. Anesthesiology 1997; 87 (3 Supplement): A894.
Abstract presentation of partial data contained in the preceding article in which D. J. Birnbach is the lead author.

Squier, C., Miller, T., DiLucia, B., Bechtold, C., Hardesty, R. and Muder, R.R. Cardiac bypass surgery: intervention to decrease surgical site infections. 4th Decennial International Conference on Nosocomial and Healthcare-Associated Infections in conjunction with the 10th Annual Meeting of SHEA. Atlanta, GA March 5-9, 2000, p66.
Abstract presentation describing reductions in SSI rate after a combination of three changes were made to standard procedures in patients undergoing cardiac bypass surgery: (1) a physician's assistant was hired to harvest saphenous veins, (2) DuraPrep solution was implemented as the intra-operative prep, (3) pre- and post- operative wound care standards were developed and implemented.

Additional literature references that relate to product safety were reviewed and summarized by Mr. David Bostwick in his Integrated Review of Safety for this NDA; reviews and summaries of these references will not be repeated in this document.

8.7 Other Relevant Materials

The Medical Officer also reviewed an instructional VHS tape provided by the Applicant, which is used to instruct hospital personnel in the safe and appropriate use of Durarep solution.

9 OVERALL ASSESSMENT

9.1 Conclusions on Available Data

Based on the findings in Studies LIMS 8304, LIMS 8918, LIMS 8197, LIMS 9302, and additional *in vitro* studies (discussed in the FDA Microbiology review completed by Peter Coderre, Ph.D.), 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. In addition, given the post-marketing experience that is available for this product, the Applicant has demonstrated that its use is safe when used as directed and the Applicant has demonstrated a commitment to ongoing efforts to ensure that it is safely used as a patient preoperative skin preparation.

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 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 Skin Preparation indication. In both studies bacterial counts on the groin site remained below baseline at the 6 hour time point. While provision of additional data from subjects treated at the groin site might further clarify the comparative efficacy of DuraPrep solution to Hibiclens, this Medical Officer believes that adequate evidence has been provided to establish that DuraPrep solution is at least as effective as a product (Hibiclens® Antimicrobial Skin Cleanser) currently approved by the FDA for this indication.

The contribution of iodine to the antimicrobial activity of DuraPrep solution was demonstrated in two independent bacterial challenge studies (LIMS 8197 and LIMS 9302) in which the mean log reduction for DuraPrep solution was significantly greater

than for DuraPrep w/o I_2 solution at the 6 hours post-preparation/30-minute residence time point (the protocol specified primary endpoint).

The Applicant has not provided adequate evidence to support a conclusion that DuraPrep provides superior drape adhesion (LIMS 9567) or a conclusion that DuraPrep solution provides superior durability and persistence in the surgical setting (LIMS 8198) or a conclusion that use of DuraPrep solution prevents post-operative infection (see references provided by the Applicant and summarized in Section 8.6).

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.

The Applicant has conducted an active surveillance program to identify cases of ignition/burns related to DuraPrep solution use. Reports of burn secondary to ignition of DuraPrep solution appears to be primarily associated with inappropriate use of the product (e.g., use of electrocautery prior to complete drying, in setting of pooled solution, etc.). 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. Active surveillance for ignition/burn incidents and risk management strategies developed by the Applicant should be continued indefinitely post-approval in order to minimize risk of burns to patients.

9.2 Recommendation on Regulatory Action

From a clinical perspective, 3M™ DuraPrep™ Surgical Solution may be approved for the indication of Patient Preoperative Skin Preparation. The Applicant has provided evidence that DuraPrep solution results in reduction of bacterial counts on the skin that

1. The Agency requests that the Applicant commit to performing a Phase 4 study, in which the relative efficacy of DuraPrep solution and Hibiclens cleanser may be further clarified.
2. The Agency requests that the Applicant commit to continue ongoing active surveillance for flammability related incidents and to continue to encourage active participation in product in-service training prior to use.

10 APPENDICES

10.1 Review of Individual Study Reports

Individual study report reviews are included in the body of this review.

10.2 Line-by-line Labeling Review

This is a Topical Antiseptic drug product. The labeling review is a joint effort between the Division of Anti-Infective Drug Products and the Division of Over-the-Counter Drug Products. Please see Mr. Bostwick's and Dr. Jackson's reviews for recommendations regarding revisions to the immediate container labels, bulk case labels, and the "inserts" (the front and back sides of the label that are inserted in the plastic carton with the dispenser).

A line-by-line review of the Target Product Information leaflet is provided below. Edits and comments provided by this Medical Officer are in red.

PRODUCT TITLE

8 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Jean Mulinde
8/5/04 11:55:46 AM
MEDICAL OFFICER

Janice Soreth
8/5/04 06:08:13 PM
MEDICAL OFFICER

Appears This Way
On Original

SAFETY REVIEW COVER SHEET

NDA 21-586

DuraPrep (iodophor and isopropyl alcohol)
Surgical Solution

Sponsor: 3M Health Care
St. Paul, MN 55144

Date of Submission: October 24, 2003

Date CDER Received: October 27, 2003

Date Assigned to Reviewer: October 31, 2003

Date Review Initiated: December 8, 2003

Date Review to Supervisor: March 31, 2004

Ten-Month Deadline: August 27, 2004

Please note: This review concerns only the safety information submitted in support of this NDA. Please see the Clinical Review for information on efficacy. The "Integrated Review of Safety" which is number 1 in this review is the same as item 7 in CDER's Clinical Review Template.

1. Integrated Review of Safety

1.1 Brief Statement of Findings

Safety for the use of DuraPrep Surgical Solution is established by the following:

- A predictive irritancy study in humans
- A predictive sensitization study in humans
- A flammability/vapor dissipation study
- A study of the drying time for the product
- A study of skin area coverage by two container sizes
- Adverse event reports

Because this product has been marketed since 1988, there are two types of reports to be considered: those which occurred during the clinical testing program, and spontaneous reports of events observed by those using the product. Since the clinical testing and spontaneous reports were gathered in a dissimilar fashion, the two types will be analyzed separately.

a. Predictive irritancy study

This study is designed to produce conditions conducive to irritation in order to determine what the potential of the test products might be to cause irritancy during normal use. Study products were applied continuously and repeatedly under occlusive dressings for 21 days. The results indicate that DuraPrep has a high potential for irritation when tested under standard procedures. Since DuraPrep is intended for one-time use only, its potential to produce cumulative irritation does not disqualify it from approval.

b. Predictive sensitization study

This study examines the potential for the test products to produce allergic reactions under extreme testing conditions. Study products were applied continuously and repeatedly under occlusive dressings for 3 weeks. A two week rest period (no drug application) was observed, followed by challenge of the subject at the original test site and at a naïve (previously unpatched) test site for 48 hours. The results indicate that DuraPrep did not exhibit potential to cause sensitization reactions.

c. Flammability/vapor dissipation study

There is concern that the vapors given off by DuraPrep as it dries may be flammable even if the product appears to be dry on the skin. A study was performed to determine the concentration of vapors on or near the skin during the drying cycle. It was determined that while vapor concentrations are at a flammable level when the product is newly applied, the level drops to a safe value when the product is allowed to dry for an

appropriate time period (see d. below).

d. Drying time study

Because DuraPrep has ignited when electrocautery was used during surgical procedures when it is not permitted to dry (or is permitted to pool under the subject), it is critical that it be completely dry before an electrical spark is permitted in the operating field. A series of studies were performed to ascertain the drying time for the product under various conditions. It was determined that when used correctly, the product will be completely dry in 3 to 4 minutes.

e. Skin coverage study

One of the elements which contributes to the flammability problem seen in connection with DuraPrep is runoff of the product from the patient's skin (the product is formulated in alcohol and thus is very runny). The sponsor was asked to compare the skin area covered by the presently marketed 26 mL container and by a container containing 20 mL.

f. Adverse event reports

i. Reports during clinical testing

There were 5 pivotal efficacy studies and 10 pilot efficacy studies with a total of 384 subjects. There were also 2 safety studies (see above) with a total of 288 subjects. In the efficacy studies, there were 5 reported adverse events (1.3%). Four of these were skin reactions, and one was "discomfort", which could not be specifically associated with DuraPrep. This patient voluntarily withdrew from the study.

In the safety studies a total of 121 subjects (42.2%) had at least one adverse event, with events related to DuraPrep found in 48 subjects (16.7%). It is noted that these studies are purposely conducted under extreme conditions and are not representative of what would be expected in general use.

ii. Spontaneous postmarketing reports

In the 15 years that DuraPrep has been marketed, almost [redacted] units (6 mL and 26 mL) have been sold. (This information covers the years 1988-2002. Please see the safety update section for more current information). 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 during surgical procedures. Since these reports are voluntary in nature, there is no way of establishing what the true incidence of these (and other, less frequently reported) reactions might be.

1.2. Materials Utilized in the Review

The NDA safety database has been consulted, as well as safety materials submitted in IND 49,411. Specifically, the skin coverage study was submitted in an

amendment to the IND dated October 4, 2001.

1.3. Description of Patient Exposure

A total of 672 subjects were enrolled in the clinical and safety studies performed in support of the NDA. There were 384 subjects in the pivotal and pilot efficacy studies, with 380 of these exposed to DuraPrep.

In the safety studies, 0.12 mL of the products were applied to a designated site for 21 consecutive days during the irritation studies (the drug was reapplied daily), and 0.02 mL was applied for the same time period during the sensitization study (the drug was reapplied 9 times during the course of the study). The application sites were constantly occluded during the irritation and sensitization studies.

In the pivotal efficacy studies, test sites measuring 5 x 5 inches (abdomen) or 2 x 5 inches (groin) were prepped with the test products and left on the skin for up to 24 hours. There were also pivotal bacterial challenge studies which utilized four 5x7 inch test sites on the back. The test products were left in place on these sites for up to 6 hours.

As noted above, [redacted] units of this product have been marketed, though the actual number of patient exposures is lower. The product is commonly used on large body areas, so that multiple containers might be necessary for one patient.

1.4. Safety Findings from Clinical Studies and Spontaneous Adverse Event Reporting.

A. Cumulative Irritation Study

Study Title: A Twenty-One Day Cumulative Irritation Test to Assess Irritation of Topically Applied 3M DuraPrep Surgical Solution vs. Active Controls (Protocol No. 02-109761-111-LIMS 7294).

Investigator: [redacted]

Study Dates: May 2-23, 2002

Study Objectives: The following is taken directly from p. 17 of the study report:

> The objective of this study was to assess the cumulative irritation potential of topically applied DuraPrep solution compared to that of DuraPrep w/o I_2, Betadine solution, 0.1% sodium lauryl sulfate (SLS), 0.9% sodium chloride and 70% isopropyl alcohol (IPA). The primary endpoint for evaluation of irritation potential was the Base 10 Cumulative Irritation score. The primary comparative endpoint (for statistical comparison of formulations) was the individual subject's cumulative score of skin irritation scored 30 minutes after patch removal for visits 2-22. Secondary comparative endpoints were the individual daily scores of skin irritation.

Method:

1. Study design: This was a paired comparison of DuraPrep, the DuraPrep vehicle, Betadine Solution, 0.1% sodium lauryl sulfate (positive control), 0.9% sodium chloride