CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-669

MEDICAL REVIEW

Division Director Memorandum

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

Date: April 25, 2005

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

Subject: NDA 21-669, Sage Products, Inc.; 2% Chlorhexidine Gluconate Cloth

There are two issues raised in the microbiology and medical reviews that warrant comment.

1. The microbiology reviewer expressed concerns about the lack of a negative control in the simulation studies. Although I agree with the substance of his argument, the sponsor was not advised that a negative control was essential to the conduct of a satisfactory study. A negative control (presumably vehicle) would allow for an assessment of the reduction in bacteria attributable to the active ingredient. The current testing measures the effect of the active ingredient and the mechanical effect of rubbing with the cloth on bacteria reduction. The current testing by the sponsor met the criteria agreed to by FDA. This, however, should not preclude FDA from requesting a negative control in the simulation studies from future sponsors.
2. The positive control failed to meet the bacterial log reduction criteria in some of the simulation tests. The 2% Chlorhexidine Gluconate Cloth met the threshold criteria in 2 of 2 abdominal tests and in 2 of 3 groin tests. The active control (Hibiclens) met the threshold criteria in 1 of 2 abdominal tests and in 1 of 3 groin tests. The approval is based on one abdominal and one groin study where both the active control and the 2% Chlorhexidine Gluconate Cloth meet the bacterial log reduction criteria. This data is supported by one groin and one abdominal study where the 2% Chlorhexidine Gluconate Cloth meets the bacteria log reduction criteria and the active control does not. The failure of the active control to meet the threshold in at least two studies raises concerns about the variability of the methodology and the conditions of use of Hibiclens. This will require further investigation of Hibiclens by FDA.

Insert name of document and where filed in OTC

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/s/

Charles Ganley
4/25/05 10:16:48 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-669
Submission Code	N-000 (BZ)
Letter Date	October 21, 2004
Stamp Date	October 25, 2004
PDUFA Goal Date	April 25, 2005
Reviewer Name	Peter W. Kim, MD, MS
Review Completion Date	March 14, 2005
Revised	April 19, 2005
Proposed Established Name	2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth)
Trade Name	None proposed
Therapeutic Class	Topical Antiseptic
Applicant	Sage Products, Inc.
Priority Designation	S
Formulation	Cloth impregnated with 2% Chlorhexidine gluconate
Dosing Regimen	Topical
Indication	Patient Preoperative Skin Preparation
Intended Population	Pediatric $\geq$ 2 months of age and Adult Patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, the Applicant's proposed product, 2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth), may be approved for the single use indication of Patient Preoperative Skin Preparation. As is true for other products that have been granted this indication in the past, the Applicant has provided data that supports the conclusion that use of this product results in decreased bacterial counts on the skin; however, the Applicant has not provided direct evidence that supports the conclusion that use of this product [redacted] It is unclear if this product will have wide use as a Patient Preoperative Skin Preparation. In addition, this product should be distributed only to healthcare settings for use by healthcare professionals as inappropriate use may result in serious adverse events if applied to the eyes, ears, or mucous membranes.

1.2 Recommendation on Post marketing Actions

1.2.1 Risk Management Activity

No additional post marketing risk management activities are recommended beyond those generally employed to all drug products post-approval.

1.2.2 Required Phase 4 Commitments

From a clinical standpoint, no Phase 4 commitments are indicated.

1.2.3 Other Phase 4 Requests

From a clinical standpoint, no Phase 4 requests are indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Applicant has not proposed a product trade name. The proposed generic name is: 2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth). The proposed product will be referred to as 2% Chlorhexidine gluconate* Cloth throughout this review. The route of administration is: topical use only. The indication studied is: Patient Preoperative Skin Preparation. The proposed product was studied in adults aged 18-79 years.

Efficacy was established in adults aged 18-69 years old. Four hundred ninety-nine subjects enrolled in nine trials were evaluated for safety. This included 200 subjects enrolled in the three pivotal "efficacy" trials, 248 subjects enrolled in two pivotal "safety" trials, and 51 subjects enrolled in four pilot trials designed to evaluate the efficacy trial protocols. A total of 417 subjects were exposed to the study drug. There were no other pertinent clinical data sources.

1.3.2 Efficacy

The Applicant's proposed product, 2% Chlorhexidine gluconate* Cloth, fulfills the efficacy criteria delineated in the FDA Proposed Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products, *Effectiveness Testing of a Patient Preoperative Skin Preparation*, published in the Federal Register on June 17, 1994 for the indication of Patient Preoperative Skin Preparation.

For additional details on product efficacy, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

1.3.3 Safety

Based on data provided by the Applicant, this product is safe for single use as a Patient Preoperative Skin Preparation. There are no unresolved safety issues. The safety testing of 2% Chlorhexidine gluconate* Cloth for the proposed single use indication of Patient Preoperative Skin Preparation is adequate. There were no severe adverse events, deaths, or overdosage exposures.

For additional details on product safety, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

1.3.4 Dosing Regimen and Administration

The 2% chlorhexidine gluconate in 2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth), in the two-pack configuration appears to be safe and effective based on the results of the studies performed to support this NDA. As a topical product, two factors may affect the dosing and administration of 2% Chlorhexidine gluconate* Cloth. The number of cloths used on a patient affects the dose delivered to the surgical preparation area. In addition, the operator may affect the efficacy of the proposed topical product by varying the amount of pressure used when applying the cloth to the surgical preparation area.

The dosing regimen originally submitted by the Applicant was found in the sample label provided in Serial No. N-000(BZ) dated February 24, 2004 in "Attachment 2" on page 000019. The "Directions" stated, [redacted] The Applicant revised this on March 17, 2004 in submission N-000(BZ) to [redacted]

The Medical Officer disagreed with both recommended dosing regimens. This is based upon the fact that the Applicant stated on page 1 in NDA Amendment, N-000(BZ), dated March 17, 2004, "According to the application instructions provided in the protocols, one towelette (cloth) was to be used for each area to be prepped. The preparation area on the abdomen ("dry" anatomic site) was 5 x 5 inches (25 in^2 or 161 cm^2) and the preparation area on the inguinal ("wet" anatomic site) was 2 x 5 inches (10 in^2 or 65 cm^2)."

The Medical Officer reasoned that the labeling of the proposed product should be consistent with the preparation instructions provided by the Applicant for the pivotal "efficacy" studies in which the area covered by one cloth differed between "dry" and "wet" (also referred to as "moist") anatomic sites.

The Applicant submitted revised labeling in NDA Amendment N-000(BZ), dated October 21, 2004. The Applicant's revised labeling was found in "Attachment 29" on page 000263 and follows.

> "Dry surgical sites (such as abdomen or arm): use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to air dry for one (1) minute. Do not rinse"
>
> "Moist surgical sites (such as inguinal fold): use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to air dry for one (1) minute. Do not rinse."

The application regimen originally recommended by the Applicant was found in the sample label submitted in Serial No. N-000(BZ) dated February 24, 2004 in "Attachment 2" on page 000019. The "Directions" stated, [redacted]

The Medical Officer disagreed with this recommended application regimen. This is based on the fact that the efficacy of the Applicant's product may be directly related to the amount of pressure exerted when applying 2% Chlorhexidine gluconate* Cloth. Evidence for this is suggested by the fact that the two efficacy studies that successfully met the TFM-required mean log reductions in the inguinal or "wet" anatomic site stated that "vigorous" scrubbing of the skin surface should be used, whereas the trial site that used [redacted] failed to meet the TFM-required mean log reductions in the inguinal or "wet" anatomic site.

The Applicant's revised labeling for this issue follows:

"Vigorously scrub the skin back and forth..."

[redacted]

The Applicant has changed the packaging to a configuration similar to the two-pack configuration. The packaging is now designed to be torn open by hand or cut open with sterile scissors. This facilitates cloth removal without contamination by external packaging, and prevents re-use of a previously opened package.

For additional details on the dosing regimen and administration, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

1.3.5 Drug-Drug Interactions

There do not appear to be any drug-drug interactions that affect the product's clinical use.

1.3.6 Special Populations

Please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Established Drug Name

2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth)

2.1.2 Proposed Trade Name

None proposed

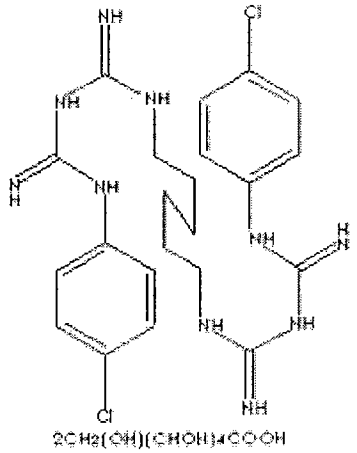
2.1.3 Chemical name

1,1'-hexamethylenebis [5-(4-chlorophenyl) biguanide] gluconate

2.1.4 Molecular formula

$C_{22}H_{30}Cl_2N_{10}\bullet 2C_6H_{12}O_7$

2.1.5 Chemical Structure



2.1.6 Drug Class

Topical Antiseptic

2.1.7 Applicant's Proposed Indication

Patient Preoperative Skin Preparation

2.1.8 Dose

2% Chlorhexidine Gluconate (equivalent to 500 mg chlorhexidine gluconate per cloth)

2.1.9 Mechanism of Action

The antibacterial activity of chlorhexidine gluconate (CHG) is due to its di-cation properties enabling CHG to bind to negatively-charged bacterial membranes. CHG may bind better to Gram-positive bacteria because they are more negatively charged. After binding, CHG disrupts cell wall integrity. CHG is bacteriostatic at low concentrations, interfering with cell membrane function. CHG is bactericidal at high concentrations, causing irreversible damage to the cell membrane and leakage of intracellular contents.

2.1.10 Regimen

The Applicant revised the regimen in the "Directions" section of the proposed label located on page 000263 of the present NDA resubmission.

> "**dry surgical sites** (such as abdomen or arm): use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to air dry for one (1) minute. Do not rinse"
>
> "**moist surgical sites** (such as inguinal fold): use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to air dry for one (1) minute. Do not rinse."

Medical Officer's comment: The Applicant is missing a period after "dry surgical sites ...Do not rinse"

The Applicant further revised the "Directions" section of the proposed label in a submission to the NDA dated February 25, 2005. This revision included clarification on proper opening and storage of the proposed product package.

Medical Officer's comment: The Applicant's revised directions on the proper opening and storage of the proposed product package are adequate.

2.1.11 Age Groups

The Applicant states that the proposed product may be used as a Patient Preoperative Skin Preparation on patients ≥ 2 months of age. The Applicant has provided literature to support this statement. The Applicant requests a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy, and children less than 2 months of age due to the potential for irritation and enhanced absorption.

Medical Officer's comment: As noted in the Medical Officer's original NDA review, the literature submitted by the Applicant on June 14, 2004 supports the Applicant's claim that the proposed product may be used in patients ≥ 2 months of age. The Medical Officer agrees with the Applicant's premise that data supporting use in adults may be extrapolated to pediatric patients ≥ 2 months of age. Based on the similarity of skin structure, similarity of skin flora, and similarity of disease process (surgical site infection), between adults and pediatric patients ≥ 2 months, differences in safety and efficacy would not be expected. The Applicant's request for a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy and children less than 2 months of age due to the potential for irritation and enhanced absorption is acceptable. Of note, the pivotal "efficacy" studies were performed in subjects between the ages of 18 and 69 years of age.

2.2 Currently Available Treatment for Indications

This product is to be used for the indication of Patient Preoperative Skin Preparation. There are a number of topical CHG products presently marketed, though most are liquids that are rinsed off after use. Currently marketed products that contain 2% CHG are: NDA 19-422, Exidine Solution (Xttrium Laboratories); NDA 19-258, Cida – Stat Solution (Ecolab); and NDA 20-832, ChloraPrep Sponge, which contains 2% CHG and 70% isopropanol (Mediflex). NDA 21-074, Avagard (3M), is a hand preparation that contains 1% CHG and 61% ethanol and is the only approved CHG-containing product intended to be left on after use. In addition, on page 31442, the TFM states that products containing: 60-95% alcohol, iodine tincture U.S.P., iodine topical solution U.S.P., 70-91.3% isopropyl alcohol, and/or 5-10% povidone-iodine may be labeled for the indication of Patient Preoperative Skin Preparation.

2.3 Availability of Proposed Active Ingredient in the United States

A number of topical CHG products are presently on the market. Please see Section 2.2.

2.4 Important Issues With Pharmacologically Related Products

Chlorhexidine gluconate (CHG)-based products used for the indication of Patient Preoperative Skin Preparation are generally labeled as not for use in children less than two months of age because of the potential for excessive skin irritation and increased drug absorption; not for use in preparation for lumbar puncture or in contact with meninges; and not for use on open skin wounds or as a general skin cleanser. In addition, CHG-based products should be kept out of the

eyes, ears, and mouth because they may cause blindness, deafness, or severe irritation if permitted to enter and remain in such sites.

2.5 Pre submission Regulatory Activity

Please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

2.6 Post submission Regulatory Activity

Please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

Since June 28, 2004, the following regulatory activity has occurred.

July 1, 2004. The Division sent an Approvable letter to the Applicant for NDA 21-669. The majority of the deficiencies pertained to chemistry, manufacturing, and controls (CMC) (see Section 3.1) and product labeling (see Section 9.4).

July 7, 2004. The Applicant submitted a letter to the Division to acknowledge receipt of the Approvable letter for NDA 21-669. The Applicant stated their intent to file an NDA amendment with responses to deficiencies listed in the July 1, 2004 Approvable letter.

August 6, 2004. The Applicant submitted an outline for their strategic plan to address the deficiencies noted in the July 1, 2004 Approvable letter for NDA 21-669. The Applicant stated that they intend to use this plan to address deficiencies found with both the two-pack and [redacted] packaging configurations.

October 25, 2004. The Division received the current Amendment to NDA 21-669, Serial No. N-000(BZ). It contains chemistry, packaging, and labeling information.

February 7, 2005. Face-to-face meeting between the Division and the Applicant. This mid-cycle review meeting focused on the main chemistry deficiencies outlined in the approvable action letter. The Division commented that the Applicant's original dosage form of [redacted] was unacceptable. "Cloth" may be appropriate; however "cloth" was not recognized as a CDER standard dosage form. If the dosage form could not be determined prior to April 25, 2005, the PDUFA goal date, then the product may be categorized as "unassigned." The issue of content uniformity and the distribution of chlorhexidine gluconate (CHG) solution in each cloth were discussed for both the 2-pack and the [redacted] The Division stated that the Applicant's proposal of [redacted] of CHG per cloth was not supported by the data in the original NDA as the actual variation in the 2-pack was approximately $\pm$ 1.5 grams. The Applicant stated that the $\pm$ 6 grams tolerance was based on statistical extrapolation. The Division reminded the Applicant that the Division had requested the actual numbers in the stability data for PCA and microbial limits rather than the Applicant stating that the data conformed to specification. In addition, the Applicant stated that the color of the proposed product package will be [redacted] The Applicant

demonstrated how the proposed product package should be opened to avoid contamination. The Applicant agreed to: (1) identify the location of the content data for the [redacted] in the submission, (2) revise the labeling to include information on properly opening and storing the product, (3) provide the actual numbers in the stability data for PCA and microbial limits, (4) submit performance testing, (5) establish a link of comparability between the 2-pack and [redacted] and between the two cloths (from separate manufacturers). The Division sent a facsimile to the Applicant on February 18, 2005 containing the questions discussed during the February 7, 2005 meeting. Additionally, the Division asked for clarification on the product lot numbers used in the clinical studies.

February 22, 2005. The CDER Dosage Form and Nomenclature Committee met to discuss NDA 21-669. There was unanimous agreement to propose the new established name, 2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth). Action items included establishing the dosage form, "cloth," in the CDER Data Standards Manual (DSM) and revising the current definitions of "sponge" and "swab" in the CDER DSM.

February 25, 2005. The Applicant submitted chemistry, manufacturing, and controls (CMC) responses to questions posed in the February 7, 2005 meeting and in the February 18, 2005 facsimile. In addition, draft labels were provided as discussed during the February 7, 2005 meeting.

2.7 Other Relevant Background Information

The Applicant's product is not approved in any other countries.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The Chemistry review of the resubmission for NDA 21-669 was not available at the time of completion of this review.

Milton Sloan, Ph.D., the Chemistry reviewer, noted a number of deficiencies with the chemistry, manufacturing, and controls (CMC) section of the original NDA 21-669 submission. The deficiencies pertained to the following issues: (1) Identification of impurities in the drug product. (2) Explanation of the analytical method used for determining the content of drug product in individual cloths, that is, that each cloth contains [redacted] of chlorhexidine gluconate solution at a 2% concentration (equivalent to 500 mg chlorhexidine gluconate). (3) Demonstration of stability data for the two-packs and [redacted] from both Sage Products, Inc. [redacted] (4) Explanation of how cloths may be removed from packaging without causing contamination when cloths inadvertently touch the outer package.

Medical Officer's comment: As discussed in the Medical Officer's original review of NDA 21-669, the Division discussed the chemistry deficiencies with the Applicant on June 8, 2004. As mentioned above, the Chemistry reviewer noted a lack of CMC studies verifying cloth-to-cloth uniformity in the content of CHG for both the two- and [redacted] Since efficacy was established using the two-packs in the pivotal "efficacy" studies, the Division reasoned that the two-pack configuration used in the efficacy studies could be approved prior to the completion of definitive demonstration of cloth-to-cloth content uniformity, provided that other CMC deficiencies were adequately addressed in the Applicant's June 15, 2004 submission.

According to the Chemistry reviewer, Milton Sloan, Ph.D., information submitted by the Applicant on June 15, 2004 adequately addressed some of the deficiencies. However, a number of deficiencies remained unresolved. For example, (1) identification of [redacted] impurities in the finished product and (2) establishment of cloth-to-cloth content uniformity. Dr. Sloan addressed additional chemistry deficiencies in his review of the original NDA submission.

The Applicant's original dosage form of [redacted] was found to be unacceptable. "Cloth" may be appropriate; however "cloth" is not recognized as a CDER standard dosage form. If the dosage form cannot be determined prior to April 25, 2005, the PDUFA goal date, then the product may be categorized as "unassigned." On February 22, 2005, the CDER Dosage Form and Nomenclature Committee met to discuss NDA 21-669. There was unanimous agreement to propose the new established name, 2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth). Action items included establishing the dosage form, "cloth," in the CDER Data Standards Manual (DSM) and revising the current definitions of "sponge" and "swab" in the CDER DSM.

Medical Officer's comment: Currently, the Applicant is not proposing a proprietary name.

As discussed in the "Background" section of this review, several additional chemistry issues were discussed during the February 7, 2005 mid-cycle review meeting with the Applicant and clarified in a facsimile from the Division to the Applicant on February 18, 2005.

Medical Officer's comment: As of the time of the completion of this clinical review, the following outstanding issues remain and may impact on the decision to approve this resubmitted NDA from a Chemistry standpoint. The Applicant must: (1) [redacted] (2) provide the actual numbers in the stability data for PCA (impurity) and microbial limits, (3) submit performance testing, (4) [redacted]

Based on statistical extrapolation, the Applicant has proposed a ± 6 gram tolerance around the [redacted] CHG content uniformity per cloth. The acceptability of a ± 6 gram variance remains under discussion. From a clinical perspective, there is concern that a cloth with as little as [redacted] grams of CHG will provide equivalent efficacy to cloths utilized in pivotal efficacy studies. Therefore, the Applicant should demonstrate that cloths with this degree of variance will remain efficacious (i.e., produce the expected mean log reductions). Based on the actual data supplied by the Applicant, the variation in the two-pack was much less, ± 1.5 grams CHG.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology/toxicology is submitted in the resubmission of NDA 21-669.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

There is no new clinical data in the resubmission for NDA 21-669. The resubmission package contains responses to chemistry reviewer comments and the Applicant's revised product label.

5 CLINICAL PHARMACOLOGY

No new clinical pharmacology is submitted in the resubmission of NDA 21-669.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication – Patient Preoperative Skin Preparation

The Applicant's proposed product, 2% Chlorhexidine gluconate* Cloth, fulfills the efficacy criteria delineated in the FDA Proposed Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products, *Effectiveness Testing of a Patient Preoperative Skin Preparation*, published in the Federal Register on June 17, 1994 for the indication of Patient Preoperative Skin Preparation.

For additional details, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

7 INTEGRATED REVIEW OF SAFETY

Based on data provided by the Applicant, this product is safe for single use as a Patient Preoperative Skin Preparation. There are no unresolved safety issues. The safety testing of 2% Chlorhexidine gluconate* Cloth for the proposed single use indication of Patient Preoperative Skin Preparation is adequate. There were no severe adverse events, deaths, or overdosage exposures.

For additional details, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The 2% chlorhexidine gluconate in 2% Chlorhexidine gluconate* Cloth, *(equivalent to 500 mg chlorhexidine gluconate per cloth) in the two-pack configuration appears to be safe and effective based on the results of the studies performed to support this NDA. As a topical product, two factors may affect the dosing and administration of 2% Chlorhexidine gluconate* Cloth. The number of cloths used on a patient affects the dose delivered to the surgical preparation area. In addition, the operator may affect the efficacy of the proposed topical product by varying the amount of pressure used when applying the cloth to the surgical preparation area.

The dosing regimen originally submitted by the Applicant was found in the sample label provided in Serial No. N-000(BZ) dated February 24, 2004 in "Attachment 2" on page 000019. The "Directions" stated, [redacted] .." The Applicant

revised this on March 17, 2004 in submission N-000(BZ) to [redacted]

The Medical Officer disagreed with both recommended dosing regimens. This is based upon the fact that the Applicant stated on page 1 in NDA Amendment, N-000(BZ), dated March 17, 2004, "According to the application instructions provided in the protocols, one towelette (cloth) was to be used for each area to be prepped. The preparation area on the abdomen ("dry" anatomic site) was 5 x 5 inches (25 in^2 or 161 cm^2) and the preparation area on the inguinal ("wet" anatomic site) was 2 x 5 inches (10 in^2 or 65 cm^2)."

The Medical Officer reasoned that the labeling of the proposed product should be consistent with the preparation instructions provided by the Applicant for the pivotal "efficacy" studies in which the area covered by one cloth differed between "dry" and "wet" anatomic sites.

The Applicant submitted revised labeling in NDA Amendment N-000(BZ), dated October 21, 2004. The Applicant's revised labeling was found in "Attachment 29" on page 000263 and follows.

> "**dry surgical sites** (such as abdomen or arm): use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to air dry for one (1) minute. Do not rinse"
>
> "**moist surgical sites** (such as inguinal fold): use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to air dry for one (1) minute. Do not rinse."

The application regimen originally recommended by the Applicant was found in the sample label submitted in Serial No. N-000(BZ) dated February 24, 2004 in "Attachment 2" on page 000019. The "Directions" stated, [redacted] .."

The Medical Officer disagreed with this recommended application regimen. This is based on the fact that the efficacy of the Applicant's product may be directly related to the amount of pressure exerted when applying 2% Chlorhexidine gluconate* Cloth. Evidence for this is suggested by the fact that the two efficacy studies that successfully met the TFM-required mean log reductions in the inguinal or "wet" anatomic site stated that "vigorous" scrubbing of the skin surface should be used, whereas the trial site that used [redacted] failed to meet the TFM-required mean log reductions in the inguinal or "wet" anatomic site.

The Applicant's revised labeling for this issue follows:

"Vigorously scrub the skin back and forth..."

Medical Officer's comment: The Applicant submitted revised labeling on February 25, 2005. The Applicant's revised directions on the proper opening and storage of the proposed product package are adequate.

For additional details on the dosing regimen and administration, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

8.2 Drug-Drug Interactions

The Applicant has not submitted any new information on drug-drug interactions. For additional details, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

8.3 Special Populations

The Applicant has not submitted any new information on special populations. For additional details, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

8.4 Pediatrics

The Applicant has not submitted any new information on the use of the proposed product in pediatric populations. For additional details, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

No new literature has been reviewed. For a list of literature reviewed for the original NDA submission, please refer to the Medical Officer's original review of NDA 21-669 signed into DFS June 28, 2004.

8.7 Post marketing Risk Management Plan

No extraordinary post marketing risk management activities are indicated.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Medical Officer concludes that the Applicant has demonstrated that the proposed product, 2% Chlorhexidine gluconate* Cloth, is effective for the proposed indication for Patient Preoperative Skin Preparation. As per conditions agreed upon by the Division prior to the Applicant's submission of NDA 21-669, data from the pivotal "efficacy" studies conducted at [redacted] sufficiently support the proposed indication at the abdominal ("dry") site and data from the pivotal "efficacy" studies conducted at [redacted] sufficiently support the proposed indication at the inguinal ("wet") site. No additional information is needed at this time to determine the efficacy of the Applicant's product for the proposed indication.

Under the testing procedures defined in the TFM, 2% Chlorhexidine gluconate* Cloth appears to be at least as effective as the positive control product, Hibiclens®, which is already FDA-approved for the indication of Patient Preoperative Skin Preparation.

Based on the available safety information, the Applicant's proposed product, 2% Chlorhexidine gluconate* Cloth, is safe for the single use indication of Patient Preoperative Skin Preparation. Given the lack of systemic absorption, no additional safety evaluation is needed for the single use indication of Patient Preoperative Skin Preparation.

The irritancy study conducted by the Applicant demonstrated that 2% Chlorhexidine gluconate* Cloth is a "Class 4 Irritant" (experimental cumulative irritant) when repeatedly applied under occlusive dressings. Only the positive control, sodium lauryl sulfate 1% solution, demonstrated a higher irritancy potential in this study. [redacted]

The Repeat Insult Patch Test study conducted by the Applicant did not demonstrate the occurrence of sensitization with repeated application and subsequent re-challenge with 2% Chlorhexidine gluconate* Cloth in the population studied. The higher rate of "level 2" irritation and higher rate of discontinuation due to predefined irritancy criteria in subjects greater than 65 years of age, however, suggests that the Applicant's product may cause greater skin irritation in the elderly population.

There do not appear to be racial differences in the safety profile for the Applicant's product; however, this conclusion is qualified by the fact that the overall number of non-Caucasian subjects exposed to the Applicant's product is relatively few in number.

9.2 Recommendation on Regulatory Action

From the clinical perspective, based on the studies performed in this NDA, the Applicant's proposed product, 2% Chlorhexidine gluconate* Cloth, is safe and effective for the single use indication of Patient Preoperative Skin Preparation. The Applicant has adequately addressed the labeling deficiencies noted in the original NDA 21-669 submission. Therefore, the Medical Officer recommends that this new drug application (NDA) be approved from a clinical perspective, provided that remaining CMC issues are adequately addressed by the Applicant.

9.3 Recommendation on Post marketing Actions

9.3.1 Risk Management Activity

The Medical Officer does not recommend any additional post marketing risk management activities beyond those generally employed to all drug products post-approval.

9.3.2 Required Phase 4 Commitments

The Medical Officer does not recommend a Phase 4 commitment.

9.3.3 Other Phase 4 Requests

The Medical Officer does not recommend a Phase 4 request.

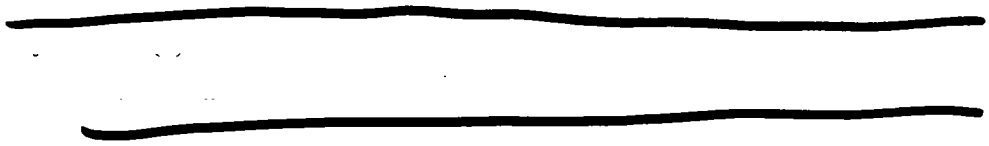
2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 1



9.5 Comment to Applicant

The following comment refers to labeling text located in "Attachment 29," pages 000263 and 000264 under the heading entitled, "Directions." This comment also refers to the draft label provided by the Applicant on February 25, 2005, page 000005 under the heading entitled, "Directions" for the two-pack. The text reads:

> "**dry surgical sites** (such as abdomen or arm): use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to air dry for one (1) minute. Do not rinse"

Add a period at the end of the phrase, "Do not rinse" so the phrase will read "Do not rinse."

Additional comments may be provided by the Division of Over-The-Counter Drug Products review staff based on their review of the labeling provided in this resubmission.

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable.

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 section 9.4 for the Medical Officer's concerns with the Applicant's proposed label, as well as, the labeling review of Michelle Jackson, Ph.D. of the Division of Over-The-Counter Drug Products.

REFERENCES

Not applicable.

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/s/

Peter Kim
4/19/05 12:01:44 PM
MEDICAL OFFICER

Peter Kim
4/19/05 12:02:40 PM
MEDICAL OFFICER

Jean Mulinde
4/19/05 12:46:10 PM
MEDICAL OFFICER

Janice Soreth
4/19/05 01:01:43 PM
MEDICAL OFFICER

Application Type	NDA
Submission Number	21,669
Submission Code	N-000
Letter Date	August 29, 2003
Stamp Date	September 4, 2003
Reviewer Name	Peter W. Kim, MD, MS
Review Completion Date	May 27, 2004
Revised	June 21, 2004
Established Name	chlorhexidine gluconate 2% solution
(Proposed) Trade Name	CHG Antiseptic Cloths
Therapeutic Class	Topical Antiseptic
Applicant	Sage Products, Inc.
Priority Designation	S
Formulation	Cloth impregnated with 2% chlorhexidine gluconate
Dosing Regimen	Topical
Indication	Patient Preoperative Skin Preparation
Intended Population	Pediatric $\geq$ 2 months of age and Adult Patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Approvability

From a clinical perspective, the Applicant's proposed product, CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution), may be approved for the single use indication of Patient Preoperative Skin Preparation. As is true for other products that have been granted this indication in the past, the Applicant has provided data that supports the conclusion that use of this product results in decreased bacterial counts on the skin; however, the Applicant has not provided direct evidence that supports the conclusion that use of this product [redacted] It is unclear if this product will have wide use as a Patient Preoperative Skin Preparation. In addition, this product should be distributed only to healthcare settings for use by healthcare professionals as inappropriate use may result in serious adverse events if applied to the eyes, ears, or mucous membranes.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

No post-marketing risk management activities are indicated.

1.2.2 Required Phase 4 Commitments

From a clinical standpoint, no Phase 4 commitments are indicated.

1.2.3 Other Phase 4 Requests

From a clinical standpoint, no Phase 4 requests are indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The proposed product trade name is: CHG Antiseptic Cloths. The proposed generic name is: chlorhexidine gluconate 2% solution. The route of administration is: topical use only. The indication studied is: Patient Preoperative Skin Preparation. The proposed product was studied in adults aged 18-79 years. Efficacy was established in adults aged 18-69 years old. Four hundred ninety-nine subjects enrolled in nine trials were evaluated for safety. This included 200 subjects enrolled in the three pivotal "efficacy" trials, 248 subjects enrolled in two pivotal "safety" trials, and 51 subjects enrolled in four pilot trials designed to evaluate the efficacy trial protocols. A total of 417 subjects were exposed to the study drug. There were no other pertinent clinical data sources.

1.3.2 Efficacy

Protocols [redacted] -01-109381-11 [redacted] -020125-103 [redacted], and [redacted] -500-102 [redacted] are all Phase 3, pivotal "efficacy", two-arm studies comparing the Applicant's

proposed product, CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution), with a positive control product approved by the FDA, Hibiclens® with 4% chlorhexidine gluconate, as Patient Preoperative Skin Preparations.

The Applicant's proposed product, CHG Antiseptic Cloths, fulfills the efficacy criteria delineated in the FDA Proposed Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products, *Effectiveness Testing of a Patient Preoperative Skin Preparation*, published in the Federal Register on June 17, 1994 for the indication of Patient Preoperative Skin Preparation. The Applicant's proposed product demonstrates reproducible mean 3 $\log_{10}$ and 2 $\log_{10}$ reductions in bacterial counts at inguinal and abdominal test sites, respectively, at ten minutes with a sustained response below baseline bacterial counts at six hours. (Two of the three efficacy studies performed on the inguinal anatomic site, [redacted] -020125-103 [redacted] and [redacted] -500-102 [redacted], met the TFM criteria for the indication of Patient Preoperative Skin Preparation. Both of the efficacy studies performed on the abdominal anatomic site, [redacted] -01-109381-11 [redacted] and [redacted] -020125-103 [redacted], met the TFM criteria for the indication of Patient Preoperative Skin Preparation.)

The three efficacy studies summarized in the following table have nearly identical study designs and protocols. The study subjects were randomized. Neither the on-site investigators/technicians nor the study subjects were blinded to treatment during the course of these studies due to differences in the physical appearance and application procedures of the two treatments. The microbiologists and laboratory technicians who plated the site cultures and assessed for bacterial growth were blinded to treatment assignment.

The following summary table was modified from a table provided by the Applicant, entitled, "Table 3: Controlled Safety and Efficacy Studies: Design," and found in volume 15 of the NDA on page 006428.

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Table 1. Pivotal "Efficacy" Studies: Design

Protocol Number	Indication Studied	Principal Investigator	Study Design	Formulation / Dosage	Positive Control CHG Product	Number of Subjects	Duration
[redacted] 01-109381-11	Patient Preoperative Skin Preparation	[redacted]	▪ Block Randomized ▪ Laboratory Blinded	Finished dosage form applied for 3 minutes	Hibiclens®	69 Enrolled **Evaluable:** 31 inguinal 31 abdomen	6 hours
[redacted] 020125-103	Patient Preoperative Skin Preparation		▪ Block Randomized ▪ Laboratory Blinded	Finished dosage form applied for 3 minutes	Hibiclens®	88 Enrolled **Evaluable:** 30 inguinal 30 abdomen	6 hours
[redacted] 500-102	Patient Preoperative Skin Preparation		▪ Block Randomized ▪ Laboratory Blinded	Finished dosage form applied for 3 minutes	Hibiclens®	43 Enrolled **Evaluable:** 32 inguinal	6 hours

In Study [redacted] 01-109381-11 [redacted], the Applicant's proposed product met the TFM-required 2 $\log_{10}$ mean reduction in bacteria at abdominal test sites. However, the proposed product did not meet the TFM-required 3 $\log_{10}$ mean reduction in bacteria at the inguinal sites. Of note, the positive control product, Hibiclens®, did not meet the required $\log_{10}$ mean reductions at either the abdominal or inguinal sites. Based on these results the Division prompted the Applicant to initiate protocol [redacted] 500-102 to perform a third study on inguinal sites at [redacted] Please see the tables below for details. Shaded cells with **bold** numbers indicate mean results that failed to meet the TFM-required criteria.

Table 2. [redacted] Pivotal "Efficacy" Results [redacted] -01-109381-11): Abdomen

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	2.37	2.41
Hibiclens®	**1.95**	2.29

* TFM threshold is a 2 $\log_{10}$ reduction from baseline.

Table 3. [redacted] Pivotal "Efficacy" Results [redacted] 1-109381-11): Inguinal

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	**2.63**	3.18
Hibiclens®	**1.96**	2.46

*TFM threshold is a 3 $\log_{10}$ reduction from baseline.

In Study [redacted] -020125-103 [redacted], the Applicant's proposed product met the TFM-required 2 $\log_{10}$ mean reduction in bacteria at abdominal sites and 3 $\log_{10}$ mean reduction at the inguinal sites. The positive control product, Hibiclens®, met the required 2 $\log_{10}$ mean reduction at the abdominal sites, however it did not meet the required 3 $\log_{10}$ mean reduction at the inguinal sites. Please see the tables below for details. Shaded cells with **bold** numbers indicate mean results that failed to meet the TFM-required criteria.

Table 4. [redacted] Pivotal "Efficacy" Results ([redacted] -020125-103): Abdomen

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	2.50	2.54
Hibiclens®	2.18	2.19

* TFM threshold is a 2 $\log_{10}$ reduction from baseline.

Table 5. [redacted] Pivotal "Efficacy" Results [redacted] -020125-103): Inguinal

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	3.45	3.64
Hibiclens®	2.78	3.15

* TFM threshold is a 3 log_{10} reduction from baseline.

In Study [redacted] -500-102 [redacted], the Applicant's proposed product met the TFM-required 3 log_{10} mean reduction at the inguinal anatomic sites. Please see the table below for details.

Table 6. [redacted] Pivotal "Efficacy" Results ([redacted] -500-102): Inguinal

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes	6 hours
CHG Antiseptic Cloths	4.19	3.12
Hibiclens®	3.83	3.03

* TFM threshold is a 3 log_{10} reduction from baseline.

In conclusion, based on past precedence set during the approval of Hibiclens®, these studies demonstrate that the Applicant's proposed product, CHG Antiseptic Cloths, is an effective Patient Preoperative Skin Preparation. Based on these three efficacy studies, CHG Antiseptic Cloths appear to be at least as efficacious as Hibiclens®.

1.3.3 Safety

Based on data provided by the Applicant, this product is safe for single use as a Patient Preoperative Skin Preparation. There are no unresolved safety issues. The safety testing of CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution) for the proposed single use indication of Patient Preoperative Skin Preparation is adequate. There were no severe adverse events, deaths, or overdosage exposures.

Out of 417 subjects exposed to the Applicant's proposed product, only 5 adverse events (1.2%) were noted. All were manifestations of skin irritation. Three adverse events were treatment-related (0.7%); two of these events (0.5%) occurred in subjects in the pivotal "safety" studies, in which the product is applied multiple times to assess the product's maximal cumulative irritation and sensitization potential. Both of these subjects were discontinued from the studies due to treatment-related adverse events. One treatment-related adverse event (0.24%) occurred during an efficacy study that simulated the proposed clinical use: "redness" at the application site that resolved without intervention in 6 hours and did not require participant discontinuation. The three treatment-related adverse events are described in further detail in the following table.

Table 7. Treatment-related Adverse Events (n=417 subjects treated)

Study	Type of Study	Subject ID and Demographics	Adverse Event	Investigator's Interpretation of Severity	Outcome
Study No. 500-102	Efficacy	Subject No. 12, a 47 y.o. Caucasian woman.	"Redness" on test site, time of onset unknown, resolved by 6-hr sampling time point.	Moderate	Subject completed study.
21-Day Cumulative Irritation Test No. NWU-515-001	Safety	Subject No. 24, a 27 y.o. Black woman.	On Day 3, Subject noted "burning" sensation over test site and on Day 4 noted "small petechial erosions and/or scabs."	Mild	Subject withdrew from study on Day 5.
Repeat Insult Patch Test No. SGNC-001	Safety	Subject No. 160, an 18 y.o. Caucasian-American Indian woman.	"Papules" noted within 1st 24hrs of patch placement. Progressed to "moderate erythema, possible presence of mild edema" by Day 18.	None provided	Subject withdrew from study on Day 21. Would have had 18 more days in the study.

The 21-Day Cumulative Irritation Test demonstrated that the product has a strong potential to cause mild to moderate cumulative irritation (Class 4 Irritant) when used under "worst case scenario" conditions (that is, multiple applications under full occlusion, site wet). Data from the Repeat Insult Patch Test demonstrated that the Applicant's product did not have a sensitization potential in the population studied. The skin irritation seen in the clinical studies correlates with the skin irritation seen in the animal studies reviewed by Amy Ellis, Ph.D. The following summary table was modified from tables provided by the Applicant, entitled, "Table 1: Controlled Safety Studies: Design" and "Table 2: Controlled Safety Studies: Objectives and Results," found in volume 15 of the NDA on page 006427.

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Table 8. Pivotal "Safety" Studies: Design and Results

Study	Principal Investigator	Study Design	Formulation / Dosage	Positive Control CHG Products	Number of Subjects	Age in Years (Evaluables)	Gender (Evaluables)	Duration	Result
21-Day Cumulative Irritation (Protocol No. NWU-515-001)[1]	Dennis West, Ph.D. Northwestern University's Department of Dermatology, Chicago, IL	-Double-blinded -Occluded -Randomized	65 mL bulk drug product applied to 8x8 mm of cloth	• Exidine (2%CHG) ▪ Hibiclens® (4%CHG)	30 (Enrolled) **23 (Evaluable)**	22 - 60	21:2 (F:M)	21 days	CHG Antiseptic Cloths had strong potential for mild to moderate cumulative irritation under the conditions of the study
Repeat Insult Patch Test (Protocol No. SGNC-001)[2]	[redacted]	-Double-blinded -Occluded -Randomized	0.3 mL bulk drug product applied to ¾ x ¾ inches of cloth	• Exidine (2%CHG) ▪ Hibiclens® (4%CHG)	218 (Enrolled) **204 (Evaluable)**	18 - 79	155:49 (F:M)	Induction: 3 weeks Challenge: 72 hours	CHG Antiseptic Cloths exhibited low to moderate irritancy in one-third of the test population. No evidence that it induced allergic reactions on repeated application.

1 Used to determine the skin irritation potential of the test articles when applied daily under occlusion over a 21-day period
2 Used to determine the primary or cumulative irritation potential and/or allergic potential of the proposed product when applied repeatedly

The Pharmacologist/Toxicologist, Amy Ellis, PhD., concluded that there were no concerns with reproductive toxicity related to use of this product based on the summary of literature provided by the Applicant and based on the Agency's prior findings of safety for products containing chlorhexidine gluconate.

Currently, there is no evidence to suggest drug-demographic interactions, drug-disease interactions, drug-drug interactions, withdrawal phenomena or abuse potential with single use of this product.

Recommended warnings include the following:

- Avoid contact with eyes, ears, and mucous membranes,
- Due not use in contact with meninges,
- Due not use in infants <2 months of age,

1.3.4 Dosing Regimen and Administration

The 2% CHG in CHG Antiseptic Cloths in the two-pack configuration appears to be safe and effective based on the results of the studies performed to support this NDA. As a topical product, two factors may affect the dosing and administration of CHG Antiseptic Cloths. The number of cloths used on a patient affects the dose delivered to the surgical preparation area. In addition, the operator may affect the efficacy of the proposed topical product by varying the amount of pressure used when applying the cloth to the surgical preparation area.

The dosing regimen recommended by the Applicant is found in the sample label submitted in Serial No. N-000(BZ) dated February 24, 2004 in "Attachment 2" on page 000019. The "Directions" state, The Applicant revised this on March 17, 2004 in submission N-000(BZ) to

The Medical Officer disagrees with both recommended dosing regimens. This is based upon the fact that the Applicant stated on page 1 in NDA Amendment, N-000(BZ), dated March 17, 2004, "According to the application instructions provided in the protocols, one towelette (cloth) was to be used for each area to be prepped. The preparation area on the abdomen ("dry" anatomic site) was 5 x 5 inches (25 in^2 or 161 cm^2) and the preparation area on the inguinal ("wet" anatomic site) was 2 x 5 inches (10 in^2 or 65 cm^2)."

The labeling of the proposed product should be consistent with the preparation instructions provided by the Applicant for the pivotal "efficacy" studies in which the area covered by one cloth differed between "dry" and "wet" anatomic sites.

The recommended revised labeling follows.

> "Dry anatomic site: One cloth may prepare a 5 x 5 inch (25 in^2 or 161 cm^2) area of skin surface for the indication of Patient Preoperative Skin Preparation."

"Wet anatomic site: "One cloth may prepare a 2 x 5 inch (10 in^2 or 65 cm^2) area of skin surface for the indication of Patient Preoperative Skin Preparation."

The application regimen recommended by the Applicant is found in the sample label submitted in Serial No. N-000(BZ) dated February 24, 2004 in "Attachment 2" on page 000019. The "Directions" state,

The Medical Officer disagrees with this recommended application regimen. This is based on the fact that the efficacy of the Applicant's product may be directly related to the amount of pressure exerted when applying CHG Antiseptic Cloths. Evidence for this is suggested by the fact that the two efficacy studies that successfully met the TFM-required mean log reductions in the inguinal or "wet" anatomic site stated that "vigorous" scrubbing of the skin surface should be used, whereas the trial site that used , failed to meet the TFM-required mean log reductions in the inguinal or "wet" anatomic site. Further discussion of this issue is found in the labeling section of this review.

The recommended revised labeling follows:

"Vigorously rub the skin back and forth..."

1.3.5 Drug-Drug Interactions

There do not appear to be any drug-drug interactions that affect the product's clinical use.

1.3.6 Special Populations

No special population studies were performed to support this NDA.

The three efficacy studies enrolled healthy, non-pregnant volunteers between the ages of 18 and 69 years. The "21-Day Cumulative Irritation Test" enrolled healthy, non-pregnant volunteers between the ages of 19 and 60 years. The "Repeat Insult Patch Test" enrolled healthy, non-pregnant volunteers between the ages of 18 and 79 years.

The Applicant states that the proposed product may be used as a Patient Preoperative Skin Preparation on patients $\geq$ 2 months of age. The Applicant has provided literature to support this

statement. The Applicant requests a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy, and children less than 2 months of age due to the potential for irritation and enhanced absorption.

The Medical Officer notes that there was a 2:1, female to male ratio among the subjects enrolled in the entire study program. All three treatment-related adverse events occurred in women. This apparent gender preference may simply be due to chance, as currently, a relatively small number of subjects have been treated with CHG Antiseptic Cloths. There do not appear to be ethnic or racial differences in the adverse event profile for this product; however, only three drug-related adverse events were noted in the 417 subjects exposed to the Applicant's product.

The following two tables summarize available demographic data for the 417 study subjects exposed to CHG Antiseptic Cloths.

Appears This Way
On Original

Table 9. Age Distribution by Study

	Pivotal "Efficacy" Studies			Pilot "Efficacy" Studies				Pivotal "Safety" Studies		Total
Age Group (years)	#01-109381-11	#020125-103.01	#500-102	#01-109628-11	#02-120904-106	#020418-103	#500-101	21-Day Cumulative Irritation	Repeat Insult Patch Test	
18-40	8	25	23	1	0	Unknown	10	17	68	152
41-64	26	9	13	5	6	Unknown	9	7	86	161
65-74	17	1	0	6	4	Unknown	0	0	48	76
>74	0	0	0	0	0	Unknown	0	0	16	16
Sub - Total										405
Total	51	35	36	12	10	12*	19	24	218	417*

*Twelve subjects are added to the subtotal from the Pilot Study #020418-103. Individual ages of subjects from the Pilot Study were not provided in submitted CRFs.

Table 10. Racial Distribution by Study

Race	Pivotal "Efficacy" Studies			Pilot "Efficacy" Studies				Pivotal "Safety" Studies		Total
	#01-109381-11	#020125-103.01	#500-102	#01-109628-11	120904-106	#020418-103	#500-101	21-Day Cumulative Irritation	Repeat Insult Patch Test	
Caucasian	49	33	25	11	9	12	15	8	180	342
Black	2	0	3	1	1	0	1	10	9	27
Hispanic	0	1	1	0	0	0	0	6	24	32
Native American	0	1	0	0	0	0	0	0	2	3
Asian	0	0	7	0	0	0	3	0	3	13
Total	51	35	36	12	10	12	19	24	218	417

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Established Drug Name

chlorhexidine gluconate 2% solution

2.1.2 Proposed Trade Name

CHG Antiseptic Cloths

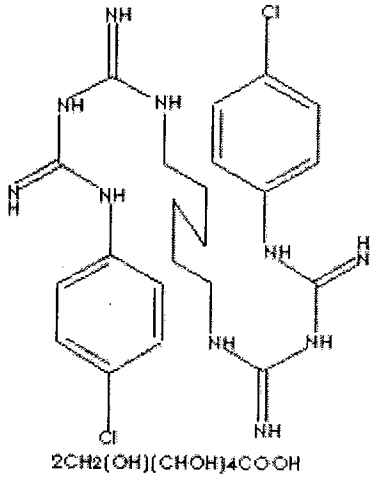
2.1.3 Chemical name (structure optional)

1,1'-hexamethylenebis [5-(4-chlorophenyl) biguanide] gluconate

2.1.4 Molecular formula

$C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$

2.1.5 Chemical Structure



2.1.6 Drug Class

Topical Antiseptic

2.1.7 Applicant's Proposed Indication

Patient Preoperative Skin Preparation

2.1.8 Dose

2% Chlorhexidine Gluconate

2.1.9 Mechanism of Action

The antibacterial activity of chlorhexidine gluconate (CHG) is due to its di-cation properties enabling CHG to bind to negatively-charged bacterial membranes. CHG may bind better to Gram-positive bacteria because they more negatively charged. After binding, CHG disrupts cell wall integrity. CHG is bacteriostatic at low concentrations, interfering with cell membrane function. CHG is bactericidal at high concentrations, causing irreversible damage to the cell membrane and leakage of intracellular contents.

2.1.10 Regimen

The Applicant states the "recommended surgical preparation area for one cloth is approximately 161 cm^2 (approximately 5 x 5 inches)." This information was submitted on March 17, 2004 in submission N-000 (BZ).

2.1.11 Age Groups

The Applicant states that the proposed product may be used as a Patient Preoperative Skin Preparation on patients $\geq$ 2 months of age. The Applicant has provided literature to support this statement. The Applicant requests a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy, and children less than 2 months of age due to the potential for irritation and enhanced absorption.

Medical Officer's comment: The literature submitted by the Applicant on June 14, 2004 supports the Applicant's claim that the proposed product may be used in patients $\geq$ 2 months of age. The Medical Officer agrees with the Applicant's premise that data supporting use in adults may be extrapolated to pediatric patients $\geq$2 months of age. Based on the similarity of skin structure, similarity of skin flora, and similarity of disease process (surgical site infection), between adults and pediatric patients $\geq$2 months, differences in safety and efficacy would not be expected. The Applicant's request for a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy and children less than 2 months of age due to the potential for irritation and enhanced absorption is acceptable. Of note, the pivotal "efficacy" studies were performed in subjects between the ages of 18 and 69 years of age.

2.1.12 State of Armamentarium for the Indication

This product is to be used for the indication of Patient Preoperative Skin Preparation. There are a number of topical CHG products presently marketed, though most are liquids that are rinsed off after use. Currently marketed products that contain 2% CHG are: NDA 19,422, Exidine Solution (Xttrium Laboratories); NDA 19,258, Cida – Stat Solution (Ecolab); and NDA20,832, ChloraPrep Sponge, which contains 2% CHG and 70% isopropanol (Mediflex). NDA 21,074, Avagard (3M), is a hand preparation that contains 1% CHG and 61% ethanol and is the only approved CHG-containing product intended to be left on after use. In addition, on page 31442, the TFM states that products containing: 60-95% alcohol, iodine tincture U.S.P., iodine topical solution U.S.P., 70-91.3% isopropyl alcohol, and/or 5-10% povidone-iodine may be labeled for the indication of Patient Preoperative Skin Preparation.

2.2 Availability of Proposed Product in the U.S.

This product is not currently available in the United States.

2.3 Important Issues with Pharmacologically Related Products

Chlorhexidine gluconate (CHG)-based products used for the indication of Patient Preoperative Skin Preparation are generally labeled as not for use in children less than two months of age because of the potential for excessive skin irritation and increased drug absorption; not for use in preparation for lumbar puncture or in contact with meninges; and not for use on open skin wounds or as a general skin cleanser. In addition, CHG-based products should be kept out of the eyes, ears, and mouth because they may cause blindness, deafness, or severe irritation if permitted to enter and remain in such sites.

2.4 Pre-submission Regulatory Activity

June 17, 1994. 21 CFR Parts 333 and 369; Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products; Proposed Rule, Friday, June 17, 1994. According to the TFM for Patient Preoperative Skin Preparation products, the requirements are: 2 $\log_{10}$ mean reduction of the microbial flora per square centimeter at a "dry" (abdomen) anatomic test site and a 3 $\log_{10}$ mean reduction at a "wet" (inguinal) anatomic test site within 10 minutes after the application of the proposed product. The bacterial cell count at both anatomic test sites may not subsequently exceed the baseline bacterial counts within 6 hours after the application of the product. At least 96 subjects per treatment arm (with the required baseline bacterial counts) should be enrolled to give adequate evidence of efficacy. Paired t-tests (within treatment) may be used to analyze the reductions from baseline at 10 minutes and 6 hours after application of the proposed product.

August 21, 2001. The Applicant, Sage Products, Inc., submits a pre-IND package.

February 8, 2002. The Applicant submits IND 64,143. It contains chemistry information, pharmacology/toxicology information, protocols for human skin irritation and sensitization testing, protocols for testing of the product as a Patient Preoperative Skin Preparation and [redacted]

May 16, 2002. Teleconference between the Division and the Applicant, Sage Products, Inc. Details of the protocol entitled, ' [redacted]

[redacted]

August 23, 2002. Fax from the Applicant to the Division. The Applicant states that in [redacted] efficacy study, No. 01-109381-11, neither the proposed product, CHG Antiseptic Cloths, nor the positive control product, Hibiclens®, meet all of the efficacy criteria for the indication of Patient Preoperative Skin Preparation proposed in the TFM.

September 9, 2002. Fax from Division to the Applicant. The Division states that the Applicant's 2% chlorhexidine gluconate product will need to be labeled as an eye irritant.

September 12, 2002. Teleconference between the Division and the Applicant. During the teleconference, the Division states that the two Preoperative Skin Preparation efficacy studies [redacted] and [redacted] may not be acceptable because the results do not meet the requirements as outlined in the 1994 Tentative Final Monograph (TFM). The Applicant states that according to the test laboratories, the results seen with Hibiclens® (the positive control) are not unusual. The Division states that this is the first time they have seen Hibiclens® results that do not meet the TFM in the inguinal area. The Division states that the [redacted] study may be acceptable based on further analysis, however, the [redacted] study clearly fails and is not acceptable. The Division reminds the Applicant that the positive control, Hibiclens®, is used to validate the conduct of the study. In conclusion, the Applicant agrees to submit to the IND a statistical analysis for the [redacted] study. The Division and the Applicant agree to further discuss how to move the development of the proposed product, CHG Antiseptic Cloths, forward.

October 22, 2002. Fax from the Division to the Applicant. The Division makes recommendations with regard to two pivotal "safety" studies: "Exclusive Repeated Patch Test" ("Repeat Insult Patch Test" or RIPT) and the "21-Day Cumulative Irritation Testing of Various Skin Care Products in Normal Subjects." Regarding the "Repeat Insult Patch Test," the Division recommends that the induction phase of the protocol be revised to provide for constant occlusion of the test site. In addition, the Division recommends that the first sensitization reading be made within one hour of patch removal and that evaluator blinding procedures be specified in the protocol. Regarding the "21-Day Cumulative Irritation Testing of Various Skin Care Products in Normal Subjects." The Division requests that the Applicant disclose the names of the proposed comparator products to be used in the study.

October 25, 2002. Teleconference between the Division and the Applicant. The purpose of the teleconference is to discuss modifications to the efficacy study to be repeated at [redacted]. The Division concurs that a repeat inguinal study is acceptable along with the results of the previous abdominal site study performed at [redacted] The Division states that if the second [redacted] study is conducted at 4 minutes (instead of 3 minutes as used previously), then the product will need to be labeled for a 4-minute application time. In conclusion, the Applicant agrees to submit a revised [redacted]

protocol. (The Applicant later decided not to perform another pivotal "efficacy" study at [redacted] Instead, the Applicant performed the third pivotal "efficacy" study at [redacted]

December 20, 2002. Amendment to IND 64,143. The Applicant submits the complete reports for the [redacted] studies, along with a separate analysis of both studies performed by [redacted] The analysis consists of three presentations: (1) pooling of data from the two studies into one dataset; (2) analysis of the ratio of antimicrobial effect between the Applicant's product and Hibiclens® at a specific time point; and (3) a meta-analysis which purports to demonstrate that the Applicant's product produces at least a 3 $\log_{10}$ reduction at the inguinal anatomic site at all sampling times for both test laboratories.

March 5, 2003. Fax from the Division to the Applicant. The conclusions of the Clinical reviewer regarding the December 20, 2002 submission are provided to the Applicant. Additional information communicated to the Applicant: (1) the third study will only need to involve the inguinal anatomic site, (2) Hibiclens® should remain the positive control product in the third study, and (3) the meta-analysis is not a solution to estimate the efficacy of the product because the study outcomes of the two previous studies produced conflicting results.

July 17, 2003. Fax from the Division to the Applicant, entitled, "Statistical Reviewer comments in preparation for Monday, July 21, 2003 teleconference." The Statistical reviewer, Thamban Valappil, Ph.D., recommends that the following analyses be performed for each time period: (1) paired t-tests that compare log reduction of the two treatments, the Applicant's product and control product, Hibiclens®, within subjects, (2) corresponding treatment difference point-estimates and confidence intervals (using paired data), and (3) point estimates and confidence intervals of log reductions within treatments. In addition, the Statistical reviewer wants to confirm that the data will be provided electronically, and that the Applicant provides the structure of the datasets to see if any modifications may streamline the review process.

July 21, 2003. Teleconference between the Division and the Applicant. The Applicant states that they will do the following: (1) a t-test will be performed comparing the positive control product (Hibiclens®) to the proposed product (CHG Antiseptic Cloths) for each time period from each laboratory. This will be within subjects because the same subjects were treated with the positive control and proposed product at each laboratory. (2) The difference between the control and test results for each subject at each time period will be calculated and the mean, variance/standard deviation, and confidence interval (95% CI) will be calculated for the total of all differences within each laboratory. (3) The mean, variance/standard deviation, and confidence interval (95% CI) will be calculated for the control and proposed products at each time period for each laboratory. Based on this teleconference, the Applicant will re-evaluate the timing of the submission and will update the Division as to the anticipated submission date. Additional chemistry discussions will be requested as necessary. An electronic copy of the labeling is requested by the Division.

July 23, 2003. Teleconference between the Division and the Applicant to discuss the impurities profile for the Finished Drug Product and Drug Substance. The Division comments that the Applicant's July 22, 2003 proposal to conduct impurities testing as a Phase 4 commitment is not acceptable. The Division comments that although chlorhexidine gluconate is not a new drug entity, this new drug product packaged as a cloth must be evaluated independently.

August 12, 2003. Teleconference between the Division and the Applicant to outline the Applicant's impurities plan for the Drug substance [redacted]) and the Finished Drug Product (2% CHG solution impregnated cloth) and its acceptability by the FDA for NDA submission. The sources of the Drug substance [redacted]) are: (1) [redacted] The Applicant states that [redacted] will be the main supplier. The sources of the Finished Drug Product (2% CHG solution) are: (1) [redacted] and (2) Sage Products, Inc. The Applicant agrees to perform a complete impurities profile, as per guidance documents for the 2% CHG finished product. Impurities found to be greater than 0.1% will be identified and become part of the finished drug product specification. These impurities will be monitored during stability testing. The Applicant comments that the product will be sold directly to acute care hospitals and that the product will be applied to patients by trained clinical personnel. Patients will not be using the washcloth themselves.

August 29, 2003. The Applicant submits the current new drug application, NDA 21,669.

2.5 Post-submission Regulatory Activity

November 7, 2003. The filing review letter from the Division to the Applicant. The filing review letter states that the Applicant's application is sufficiently complete to permit a substantive review. However, it is noted that the Drug Master File for [redacted] is inadequate and therefore a potential review issue. In addition, the Division requests the following: (1) SAS transport files and the computer programs used to create the SAS files, (2) a data dictionary for all of the data, (3) time-kill studies in the form of log reductions, not percentages, (4) graphic specifications for the ***Drug Facts*** labeling, and additional labeling detailing how to handle the antiseptic to minimize the risk of contamination once the package is opened.

[redacted]

December 5, 2003. The Chemistry report of an inspection at the Sage Products, Inc. (Sage) plant. Form 483 is issued.

January 5, 2004. Fax from the Division (Division of Anti-Infective Drug Products) to the Division of Scientific Investigation. Request for clinical inspection of [redacted]

February 2, 2004. Fax from the Division to the Applicant. The Division requests the following from the Applicant: (1) provide the trade name of the proposed product; (2) clearly delineate subject flow through all of the safety and efficacy studies and demonstrate which subjects were withdrawn from all safety and efficacy studies and provide explanations why they were withdrawn; and (3) provide adequate demographic information (gender, age, race) for all subjects admitted, all subjects treated with the Applicant's product, and all evaluable subjects in the three efficacy studies.

February 5, 2004. Fax from Division to Applicant. The Microbiology reviewer, Peter Coderre, Ph.D., requests the TFM-required minimal inhibitory concentration (MIC) data for *Candida albicans*. The Microbiology reviewer also asks for validation for the neutralization studies.

February 10, 2004. Fax from Division to Applicant. The Division requests that Sage provide the following: (1) information on the surface area(s) covered by a single cloth during the three efficacy studies for both the abdominal and inguinal areas, and (2) an estimate of the cm^2 area that is covered by a unit dose to provide guidance in labeling for a given type of surgery.

February 24, 2004. The Applicant submits Serial No. N-000(BZ). The Applicant responds to information requests made by the Division in the November 7, 2003 Filing Review Letter and a fax sent on February 2, 2004. Of note, the Applicant provides: (1) graphic specifications for the *Drug Facts* labeling, (2) . (3) the trade name, (4) assurance that no adverse events occurred during the pilot studies, (5) additional detail as to why subjects were withdrawn from the safety and efficacy studies, and (6) time-kill kinetic studies in the form of log reductions, not percentages.

March 15, 2004. Teleconference between the Division and the Applicant to clarify information provided in Serial No. N-000(BZ) submitted February 28, 2004, regarding subject disposition. The Clinical Reviewer provides specific examples of how subjects cannot be clearly followed through the efficacy studies.

March 17, 2004. The Applicant submits Serial No. N-000(BZ). The Applicant responds to information requests made by the Division in faxes sent on February 5, 2004 and February 10, 2004. In particular, the Applicant states that in the three efficacy studies, the preparation area on the abdomen was 5 x 5 inches (25 in^2 or 161 cm^2) and the preparation area on the inguinal area was 2 x 5 inches (10 in^2 or 65 cm^2). The Applicant proposes that based on the maximum area prepared during the efficacy studies, the label will be revised to contain the direction: "recommended surgical preparation area for one cloth is approximately 161 cm^2 (approximately 5 x 5 inches)."

March 19, 2004. Fax from the Applicant to the Division. In response to the teleconference held on March 15, 2004, the Applicant provides more detailed subject flow charts.

April 9-26, 2004. Division of Scientific Investigations (DSI) inspection of] Frederic Marsik, Ph.D., Microbiologist in Division of Anti-Infective Drug Products, accompanied the DSI Inspector for period April 12-16, 2004.

April 20, 2004. The Applicant submits information amendment N-000(BM) to the Division. This information amendment contains demographic information, including racial backgrounds of the subjects in the "Repeat Insult Patch Test."

May 18, 2004. Fax from Division to Applicant. The Clinical reviewer asks the Applicant to submit: (1) an assessment as required in The Pediatric Research Equity Act of 2003, and (2) the Curriculum Vitae of [redacted] Principal Investigator for the third pivotal "efficacy" study at [redacted] 500-102.

May 26, 2004. Fax from Division to Applicant. The Division submits comments to the Applicant on the Applicant's proposed product label.

June 3, 2004. Teleconference between the Division and the Applicant. The purpose is to alert the Applicant that the Division will be faxing the Applicant nineteen deficiencies noted by the Chemistry reviewer, Milton Sloan, Ph.D. The deficiencies are faxed to the Applicant later that day.

June 7, 2004. Fax from the Division to the Applicant. Additional chemistry deficiencies are sent to the Applicant.

June 8, 2004. Teleconference between the Division and the Applicant. The parties discuss potential solutions to the Chemistry deficiencies. The Applicant agrees to respond to all of the chemistry deficiencies by close of business on June 16, 2004.

June 10, 2004. Teleconference between the Division and the Applicant. The Division and the Applicant discuss the labeling comments submitted to the Applicant on May 26, 2004. The Applicant agrees to a timely submission of responses to the labeling comments faxed to the Applicant on May 26, 2004, and to clinical questions faxed to the Applicant on May 18, 2004.

June 14, 2004. The Applicant submits Serial No. N-000(BZ). The submission contains a literature review to support labeling of the proposed product down to infants $\geq$ 2 months of age, a request for partial wavier of pediatric studies in infants < 2 months of age, responses to FDA comments on draft labeling, and revised draft labeling.

June 15, 2004. The Applicant submits responses to deficiencies noted by the Chemistry reviewer, Milton Sloan, Ph.D.

2.6 Other Relevant Background Information

The Applicant's product is not approved in any other countries.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Chemistry

Chemistry: Milton Sloan, Ph.D., the Chemistry reviewer, has noted as number of deficiencies with the chemistry, manufacturing, and controls (CMC) section of this NDA. The deficiencies pertain to the following issues: (1) Identification of impurities in the drug product. (2) Explanation of the analytical method used for determining the content of drug product in individual cloths, that is, that each cloth contains [redacted] of chlorhexidine gluconate at a 2% concentration. (3) Demonstration of stability data for the two-packs [redacted] from both Sage Products, Inc. and [redacted] (4) Explanation of how cloths may be removed from packaging without causing contamination when cloths inadvertently touch the outer package.

Medical Officer's comment: The Division discussed the chemistry deficiencies with the Applicant on June 8, 2004. As mentioned above, the Chemistry reviewer noted a lack of CMC studies verifying cloth-to-cloth uniformity in the content of CHG for both the two- and [redacted] Since efficacy was established using the two-packs in the pivotal "efficacy" studies, the Division reasoned that the two-pack configuration used in the efficacy studies could be approved prior to the completion of definitive demonstration of cloth-to-cloth content uniformity, provided that other CMC deficiencies were adequately addressed in the Applicant's June 15, 2004 submission. [redacted]

According to the Chemistry reviewer, Milton Sloan, Ph.D., information submitted by the Applicant on June 15, 2004 adequately addressed some of the deficiencies. However, a number of deficiencies remain unresolved. For example, (1) identification of impurities in the finished product and (2) establishment of cloth-to-cloth content uniformity. Dr. Sloan addresses additional chemistry deficiencies in his review.

[redacted]

3.2 Animal Pharmacology/Toxicology

Amy Ellis, Ph.D., the Animal Pharmacology and Toxicology reviewer, has found the drug product to be acceptable from an animal pharmacology and toxicology point of view. Additional details may be found in Dr. Ellis' review.

3.3 Division of Over-The-Counter Drug Products Labeling Review

Dr. Michelle Jackson, Ph.D., the OTC reviewer has found a number of problems with currently proposed labeling for the product. Dr. Jackson's recommendations include: (1) that clear, deliberate language be used to emphasize the fact that the Applicant's product is to be labeled for the indication of Patient Preoperative Skin Preparation [redacted] (2)That the principal display panel includes the statement "Single Use" to indicate that once the package is opened it cannot be reused. (3) That directions for use are consistent with the manner in which the product was evaluated in clinical studies. (4) That appropriate warning statements be included. Additional details may be found in Dr. Jackson's review.

Medical Officer's comment: Of note, the Applicant responded to the FDA comments on draft labeling and provided revised draft labeling in their June 14, 2004, Serial No. N-000(BZ) submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Applicant conducted a total of nine clinical studies. Data from all nine studies were used to support safety. Two of these studies were solely used to assess safety: the "21-Day Cumulative Irritation Test" and the "Repeat Insult Patch Test." The overall demonstration of efficacy for the drug product was based on three of the remaining seven studies: [redacted] -01-109381-11 [redacted] 020125 [redacted] 500-102 [redacted] The remaining four studies were uncontrolled, pilot studies used to assess methodology: [redacted]-01-109628, [redacted] -02-120904-106, [redacted] -020418-103, and [redacted] -500-101.

The following additional materials were consulted in the review of this NDA.

1. 21 CFR Parts 333 and 369; Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products; Proposed Rule, Friday, June 17, 1994.
2. NDA 17, 768. ICI Americas, Inc. Hibiclens®, 4% CHG.
3. NDA 18, 049. ICI Americas, Inc. Hibitane® Tinted Tincture, 0.5% CHG formulated in isopropyl alcohol.
4. Literature as summarized in Section 8.6 of this review.

4.2 Tables of Clinical Studies

The following summary tables were modified from tables provided by the Applicant, entitled, "Table 1: Controlled Safety Studies: Design," "Table 3: Controlled Safety and Efficacy Studies: Design," and "Table 5: Uncontrolled Pilot Studies Objectives and Results" found in volume 15 of the NDA on pages 006427-006429.

Table 1. Pivotal "Safety" Studies: Design

Protocol Number	Issue Studied	Principal Investigator	Study Design	Formulation / Dosage	Positive Control CHG Products	Number of Subjects	Duration
NWU-515-001	21-Day Cumulative Irritation	Dennis West, Ph.D.	Double-blinded, occluded, randomized	65 micro liters bulk drug product applied to 8x8 mm of cloth	Exidine (2% CHG) and Hibiclens® (4% CHG)	Enrolled=30 **Evaluable=23**	21 Days
SGNC-001	Repeat Insult Patch Test to study Irritation and/or sensitization	[redacted]	Double-blinded, occluded, randomized	0.3 mL bulk drug product applied to ¾" x ¾" of cloth	Exidine (2% CHG) and Hibiclens® (4% CHG)	Enrolled=218 **Evaluable=204**	3-week induction, 72-hour challenge

Table 2. Pivotal "Efficacy" Studies: Design

Protocol Number	Indication Studied	Principal Investigator	Study Design	Formulation / Dosage	Positive Control CHG Products	Number of Subjects	Duration
-01-109381-11	Patient Preoperative Skin Preparation	[redacted]	Block-randomized, Laboratory-blinded	Finished dosage form applied for 3 minutes	Hibiclens®	Enrolled=69 **Evaluable: inguinal=31, abdominal=30**	6 hours
020125-103	Patient Preoperative Skin Preparation		Block-randomized, Laboratory-blinded	Finished dosage form applied for 3 minutes	Hibiclens®	Enrolled=88 **Evaluable: inguinal=30, abdominal=30**	6 hours
500-102	Patient Preoperative Skin Preparation		Block-randomized, Laboratory-blinded	Finished dosage form applied for 3 minutes	Hibiclens®	Enrolled=43 **Evaluable: inguinal=32**	6 hours

Table 3. Pilot "Efficacy" Studies: Design

Protocol No.	Study Title	Objective	Study Site Location	Number of Subjects	Result
[redacted] 01-109628-11	Pre-operative preparation pilot study	Determine correlation between application time & efficacy	[redacted]	12 qualified inguinal sites	Greater efficacy was seen as time increased
[redacted] 020418-103	Pre-operative preparation pilot study	Determine correlation between application time & efficacy		12 qualified inguinal sites	Greater efficacy was seen as time increased
[redacted] -02-120904-106	Pre-operative preparation pilot study	Determine the effect of treatment application time on efficacy		10 qualified inguinal sites	Equal efficacy was seen with both preparation times
[redacted] -500-101	Pre-operative preparation pilot study	Familiarize the testing laboratory with the proposed product in preparation for a larger study		10 qualified inguinal sites	Proposed product met required log reduction

4.3 Review Strategy

Data from all nine studies were reviewed to assess the safety of the Applicant's product. Two of these studies were solely used to assess safety: NWU-515-001 and SGNC-001. A review of the efficacy of the drug product was based on three of the remaining seven studies: [redacted] -01-109381-11, [redacted] -020125-103, and [redacted] -500-102. The remaining four studies were uncontrolled, pilot studies: [redacted] -01-109628-11, [redacted] -020418-103, [redacted] 02-120904-106, and [redacted] -500-101.

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

4.4 Data Quality and Integrity

A Division of Scientific Investigation (DSI) investigation audited the data at the [redacted] The audit occurred from April 9-26, 2004. The DSI inspector concluded that data obtained at the [redacted] site was acceptable to support the NDA. Neither the DSI Inspector nor Dr. Marsik were able to identify specific reasons to explain why the Applicant's product and the positive control, Hibiclens®, failed to meet the TFM-required mean $\log_{10}$ reductions in bacteria. However, Dr. Marsik noted a number of areas in the methods by which these types of studies are conducted that may have resulted in variability of results (e.g., application method, cup scrub technique, neutralization solution utilized, method of sample plating, automated versus manual colony count, etc.).

4.5 Compliance with Good Clinical Practices

Informed consent appeared adequate for all nine studies submitted to support this NDA. All of the studies appeared to be performed with good clinical practices.

4.5.1 Protocol deviations occurred during the following studies.

In the pivotal "efficacy" study at [redacted] five protocol deviations occurred during abdominal site studies. In all five subjects, culture sites were cultured out of sequence. For example, on Subject No. 41's left abdomen (prepared with the Applicant's proposed product), the 10-minute and 30-minute sites were cultured in reverse. All five subjects (No.'s 9, 15, 28, 41 and 42) remained in the evaluable population.

In the pivotal "efficacy" study at [redacted] seven protocol deviations occurred. The following reasons for deviations were provided by the Applicant. Three subjects' culturing times exceeded the predetermined sampling time intervals (Subject No.'s 16, 59, and 68). Subject No. 48 had the right inguinal 6-hour sample taken 16 minutes early. Subject No. 29 was admitted to the study with an initial left abdominal baseline value below the 2.5 $\log_{10}$ inclusion criterion. Subject No. 52 participated in the baseline screening portion of the study twice in 30 days. (Subject No. 52 qualified during the first screening, but was unable to participate due to a schedule conflict. The Subject was later allowed to re-screen; however, they did not qualify on the second re-screening.) Subject No. 7 was mistakenly admitted to the study after showering within 48 hours of the start of the study. (Subject No. 7 still met the baseline count criteria.)

In the pivotal "safety" study, entitled, "21-Day Cumulative Irritation Test," the Applicant reported one protocol deviation. The Applicant had originally planned to obtain 25 subjects with evaluable information. Thirty subjects were enrolled, but only 23 subjects were included in the evaluable population.

Medical Officer's comment: None of the protocol deviations appeared to alter the outcomes of these pivotal studies.

4.6 Financial Disclosures

The financial disclosure is acceptable. [redacted], Ph.D. participated as a clinical investigator in the "[redacted] performed from [redacted] Dr. [redacted] is on retainer as a consultant to Sage Products, Inc. Dr. [redacted] received $72,000 from [redacted] for his services. There is no evidence to suggest that the study integrity was compromised as the investigator was blinded to treatment assignment.

5 CLINICAL PHARMACOLOGY

The Clinical Pharmacology and Biopharmaceutics review was performed by Charles R. Bonapace, Ph.D. Pharmacokinetic studies were not performed with this submission. The

Applicant provided a review of the scientific literature. Chlorhexidine gluconate is poorly absorbed following oral and dermal administration.[1] The Applicant requested a waiver of evidence of *in vivo* bioavailability or bioequivalence based on currently marketed products containing chlorhexidine gluconate as the active ingredient. Dr. Bonapace concluded that the data submitted supports granting a waiver of evidence of *in vivo* bioavailability or bioequivalence. No further studies are necessary to support the *in vivo* bioavailability of CHG Antiseptic Cloths.

5.1 Pharmacokinetics

Not applicable. Please see above paragraph.

5.2 Pharmacodynamics

Not applicable. Please see above paragraph.

5.3 Exposure-Response Relationships

Not applicable. Please see above paragraph.

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6 INTEGRATED REVIEW OF EFFICACY

6.1 Methods

A review of the efficacy of the Applicant's drug product was based on the following three pivotal "efficacy" studies: -01-109381-11 -020125-103 , and -500-102

The following summary table was modified from a table provided by the Applicant, entitled, "Table 3: Controlled Safety and Efficacy Studies: Design," found in volume 15 of the NDA on pages 006428.

Table 4. Pivotal "Efficacy" Studies: Design

Protocol Number	Indication Studied	Principal Investigator	Study Design	Formulation / Dosage	Positive Control CHG Products	Number of Subjects	Duration
-01-109381-11	Patient Preoperative Skin Preparation		Block-randomized, Laboratory-blinded	Finished dosage form applied for 3 minutes	Hibiclens®	Enrolled=69 **Evaluable: inguinal=31, abdominal=30**	6 hours
020125-103	Patient Preoperative Skin Preparation		Block-randomized, Laboratory-blinded	Finished dosage form applied for 3 minutes	Hibiclens®	Enrolled=88 **Evaluable: inguinal=30, abdominal=30**	6 hours
-500-102	Patient Preoperative Skin Preparation		Block-randomized, Laboratory-blinded	Finished dosage form applied for 3 minutes	Hibiclens®	Enrolled=43 **Evaluable: inguinal=32**	6 hours

6.2 General Discussion of Endpoints

The 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 the abdominal sites and a mean 3 $\log_{10}$ reduction in bacterial counts from baseline on the inguinal sites 10 minutes after 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.

6.3 Efficacy Findings

6.3.1 Trial #1 was performed at [redacted]

It is entitled, [redacted] STUDY NO. 01-109381-11, Determination of the Antimicrobial Efficacy of a Chlorhexidine Gluconate Impregnated Cloth Wipe as a Patient Pre-Operative Skin Preparation." The details of this study were found in volume 20 of the Medical Officer's NDA packet.

Objective/Rationale
The objective of the study was to evaluate the antimicrobial effectiveness of the proposed product, CHG Antiseptic Cloths, against a positive control formulation approved by the FDA, Hibiclens®, as Patient Preoperative Skin Preparations.

Design
The study subjects were randomized. Neither the on-site investigators/technicians nor study subjects were blinded during the course of this study due to differences in the physical appearance and application procedures of the two treatments. The microbiologists and laboratory technicians who plated the site cultures and assessed for bacterial growth were blinded to treatment assignment.

Protocol
The study protocol was based on the FDA Proposed Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products, Effectiveness Testing of a Patient Pre-Operative Skin Preparation, published in the Federal Register on June 17, 1994. Using bilateral applications 46 inguinal and 42 abdominal sites were prepped with each test article. Not all of the same subjects were treated at both anatomic sites. The anatomic sites were sampled for baseline microbial levels prior to preparation. The anatomic sites were sampled for residual levels of microorganisms at ten minutes, thirty minutes, and six hours after preparation. (The TFM does not include a thirty-minute sample point. It will therefore not be discussed in this review.)

Population, procedures

Subjects
The investigator planned to collect initial baseline bacterial counts from sixty healthy subjects between and including the ages of eighteen to sixty-nine years with the expectation of having enough subjects at the end of the study to provide approximately thirty evaluable abdominal anatomic sites and thirty evaluable inguinal anatomic sites. Subjects were to be of mixed age, race, and gender, and free of dermatoses or injury to the skin areas sampled. Eligibility was to be determined from a medical history collected on a screening-day inclusion/exclusion form and treatment-day inclusion/exclusion form.

Inclusion Criteria (verbatim from protocol)

- Male and female subjects between the ages of 18 and 69 years.
- Subjects are cooperative and willing to answer questionnaires and sign a consent form.

- Are in general good health.
- Have skin within 6 inches of the test site that is free of tattoos, dermatoses, abrasions, cuts, lesions or other skin disorders.

Exclusion Criteria (verbatim from protocol)

- Have been exposed to topical or systemic antimicrobials during the two-week pretest conditioning period. This restriction includes, but is not limited to, shampoos, lotions, soaps, body powders, and materials such as solvents, acids, or alkalis.
- Have been medically diagnosed as having a medical condition, which would preclude participation such as: diabetes, hepatitis, an organ transplant, a medical surgical implant or an immune compromised system.
- Have any medical condition, which in the opinion of the Investigator would preclude participation.
- Have bathed in chemically treated pools or hot tubs two weeks prior to any microbial sampling.
- Have used UV tanning lamps two weeks prior to any microbial sampling.
- Have bathed or showered less than 48 hours prior to any microbial sampling.
- Have a known sensitivity to chlorhexidine gluconate (CHG).
- Have a known sensitivity to latex products.
- Have a known sensitivity to fragrances.
- Are pregnant or nursing.
- Are not willing to fulfill the requirements of the protocol.

Procedures

Pre-Test Period

A period of at least two weeks prior to the first baseline sampling was designated the "pre-test" period. During this time, subjects were instructed to use only soaps, shampoos, and deodorants supplied by the Investigator for personal hygiene and were told to avoid skin contact with solvents, acids, and bases. Subjects were prohibited from using UV tanning lamps and from bathing in chemically-treated pools and or hot tubs. Subjects were instructed not to shave the anatomic sites within five days prior to being treated with the test products. Additionally, the subjects were not allowed to bathe or shower forty-eight hours prior to being sampled. This regimen was to allow for the stabilization of the normal microbial flora of the skin.

Baseline Week

The week following the pre-test period was called the baseline week. Subjects were not to shower within forty-eight hours of being sampled. All subjects were sampled for a baseline microbial count at least seventy-two hours prior to the test period. Subjects were sampled at the two anatomic sites (that is, the inguinal region, and the abdominal region on both the left and right sides). Left- and right-sided abdominal baseline samples were collected from randomly selected sites within each treatment area. Left- and right-sided baseline samples were taken from the upper regions of both inguinal treatment areas. There were a minimum of seventy-two hours between the time the baseline period ended and the test period began. Subjects were eligible to continue the study based upon

adequate baseline microbial counts of at least 2.5 $\log_{10}$ CFU/cm^2 at abdominal sites and 5.0 $\log_{10}$ CFU/cm^2 at inguinal sites. A second and final baseline sample was collected at each anatomic site prior to being prepped on the first test day. Post-treatment count data were excluded from the data analysis if they failed to exhibit a level of bacteria at the second baseline sampling sufficient to permit detection of a 3.0 $\log_{10}$ mean reduction in the inguinal region and a 2.0 $\log_{10}$ mean reduction in the abdominal region. Anatomic sites were clipped at least forty-eight hours prior to the test day. All sampling was performed using the [redacted]

Test Period
Prior to being sampled, the subjects were questioned regarding their adherence to protocol restrictions. Subjects were visually examined at the anatomic sites to ensure the absence of injury and dermatoses. On the day of the test, the abdominal region and the inguinal region, in the area of the femoral vein, were sampled for the final baseline (second baseline) culture and then prepped using the assigned proposed product and positive control. The sites were sampled at ten minutes, thirty minutes, and six hours post-preparation. All samples were taken using the cylinder sampling technique. Preparation included a drying time that was recorded for each subject. A sterile gauze pad was placed over the prepared areas to help prevent microbial contamination. The gauze pad was held in place with a non-occlusive sterile catheter dressing [redacted]

Randomization
The two products were assigned randomly to the subjects, so that the proposed product and positive control would be applied to sites contralateral to one another. Sampling sites for each designated sampling time (screening baseline, test day baseline, ten minutes, thirty minutes, and six hours) were assigned randomly.

Prepping Technique
Proposed product (CHG Antiseptic Cloths)
An individual cloth was applied "gently" to the proposed topical sampling site for 3 minutes. The cloth was turned over halfway through the application. This was followed by a one minute drying time. Contact time was initiated when drying was completed.

Medical Officer's comment: [redacted] ***was the only study center where the protocol specified that the technician should apply the CHG Antiseptic Cloths "gently." At both*** [redacted] ***the protocols specified that the CHG Antiseptic Cloths should be applied "vigorously." This was also the only study center where CHG Antiseptic Cloths failed to meet the TFM-required 3 $\log_{10}$ mean reduction at the inguinal site.***

Positive control product (Hibiclens®)
The product was applied for 2 minutes, wiped dry with a sterile gauze pad, and then the procedure was repeated. Contact time was initiated after the site was wiped dry a second time.

Microbiological Methods
These methods will be described in detail in the Microbiology review written by Peter Coderre, PhD. Please also refer to section 6.4, "Clinical Microbiology," of this review for additional details.

Statistical considerations
Raw data (CFU/mL) was converted to $\log_{10}$ CFU/cm^2. Counts of less than 1 CFU/cm^2 were treated as 1 CFU/cm^2 such that the log transformation was zero. Log reductions were calculated by subtracting the post-treatment log counts from the average of the two baseline counts (the screening and treatment day baselines) obtained at each test site. Only subjects who met the inclusion criteria for baseline bacterial counts on the screening day and the treatment day of the study were included in the analysis. Statistical analyses were performed to determine the immediate and persistent antimicrobial effects of the proposed product, CHG Antiseptic Cloths, and positive control product, Hibiclens®. In addition to determining the mean log reductions (between baseline and 10 minutes post-application) of the test and control drug products as specified in the TFM, the Applicant performed additional statistical analyses. The results of these additional analyses will not be discussed or critiqued in this review as they are not applicable to the approval decision.

Results
Evaluability
Sixty-nine subjects were enrolled into the study. Initial baseline counts were obtained from 60 healthy subjects between the ages of 18 and 69 years. Out of 60 subjects who were cultured for initial baseline counts, 9 were withdrawn from the study because they did not meet the minimum baseline bacterial counts of 2.5 $\log_{10}$ on the abdomen or 5 $\log_{10}$ on the inguinal region at screening assessment. As a result, 51 subjects were treated with the Applicant's product, CHG Antiseptic Cloths, and the positive control, Hibiclens®.

Out of these 51 subjects, 42 subjects were treated on the abdominal anatomic site. Out of the 42 subjects treated at the abdominal anatomic site, 11 subjects failed to meet baseline count criteria on the day of the test. Therefore, 31 subjects provided evaluable data for the abdominal anatomic site.

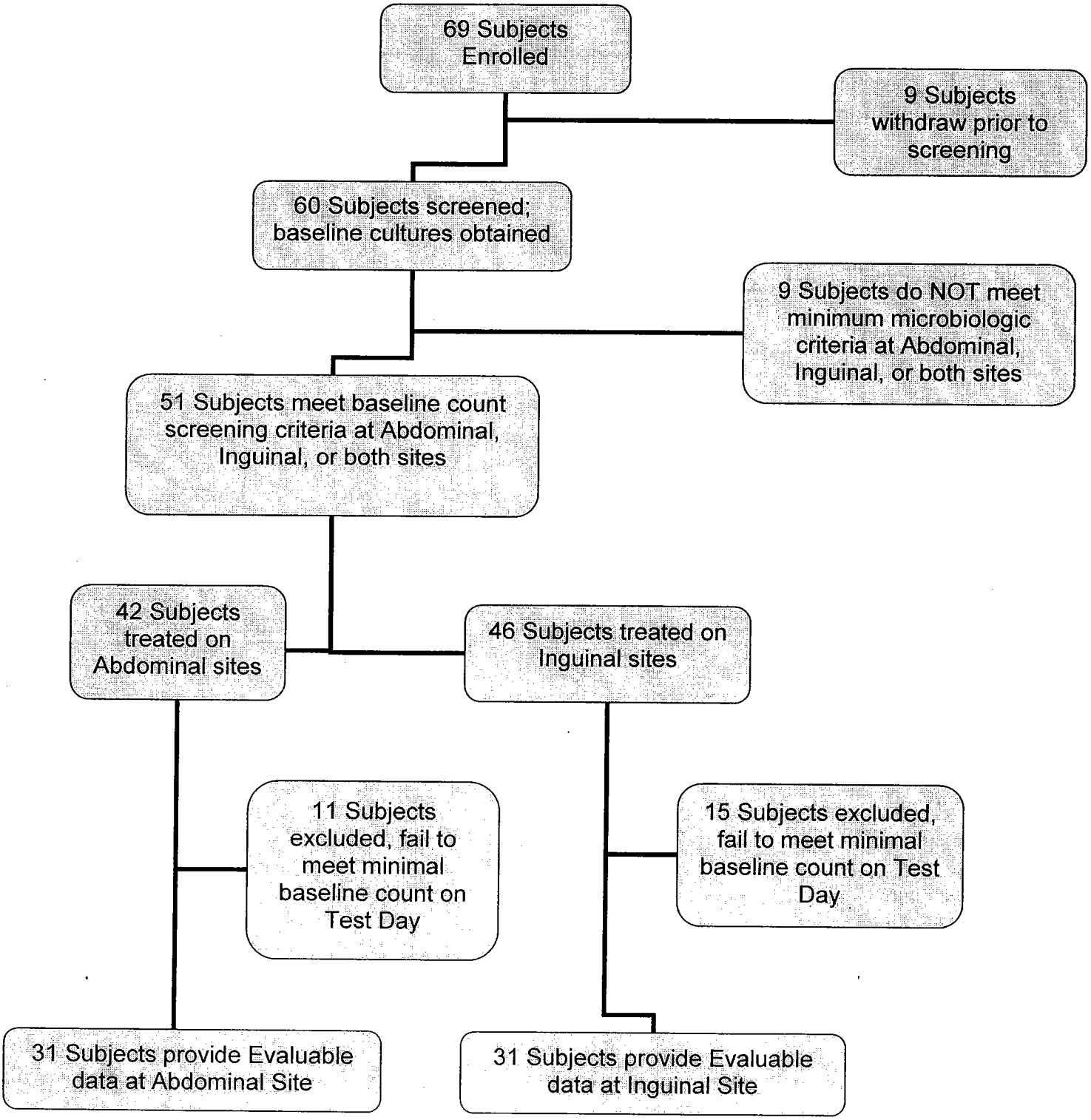
Out of the 51 subjects, 46 subjects were treated on the inguinal anatomic site. Out of the 46 subjects treated at the inguinal anatomic site, 15 subjects failed to meet baseline count criteria on the day of the test. Therefore, 31 subjects provided evaluable data for the inguinal anatomic site.

Medical Officer's comment: Due to the nature of the study design, the size of the study population was relatively small. The study enrolled 69 healthy subjects. Subject comparability is limited to the baseline demographic data presented in the "Demographics" section of this review. Once a subject was withdrawn from the study due to not meeting baseline bacterial count criteria, no additional data was collected that would be useful in assessing comparability. Based on the limited sample size, the

Medical Officer did not detect unusual rates of withdrawal among a particular segment of the study's gender, age, or racial demographic.

Please see the following subject flow chart created by the Medical Officer from data presented in the NDA for the [redacted] efficacy study, [redacted] STUDY NO. 01-109381-11.

Figure 1. [redacted] Subject Flow Chart for Pivotal "Efficacy" Study



The Applicant, Sage Products, Inc., noted that the study site had a disproportionate number of subjects with inguinal sites that failed the inclusion criterion at baseline (33%- 11%- 0%-). The number failing the inclusion criterion at baseline at for the abdominal site was also higher than at , 26% versus 14%, respectively, but this was not a statistically significant difference. The Applicant suggested that the microbiologic data from the inguinal sites should be discarded because the number of inguinal site exclusions from the study was unusually large.

Medical Officer's comment: The DSI investigation performed at from April 9-26, 2004 found no reason to suspect a lack of data integrity in the subject records.

Demographics
Sixty-nine subjects were initially enrolled into the study. Initial baseline counts were obtained from sixty healthy subjects between the ages of twenty-one and sixty-nine. Thirty-one subjects provided evaluable data for the abdominal anatomic site. Thirty-one subjects provided evaluable data for the inguinal anatomic site. The eligibility of each subject was determined from a medical history collected on a screening inclusion/exclusion form and a treatment inclusion/exclusion form. The following table created by the Medical Officer, from data provided in the NDA, summarizes the demographics of the study.

Table 5. Demographics for Pivotal "Efficacy" Study

	All Enrolled	Subjects with Abdominal Sites Treated with CHG	Subjects with Inguinal Sites Treated with CHG	Evaluable Subjects with Abdominal Sites Treated with CHG	Evaluable Subjects with Inguinal Sites Treated with CHG
Number (%) of Subjects	69 (100%)	42 (61%)	46 (67%)	31 (45%)	31 (45%)
Median Age (years)	57	62	63	63	62
Age Range (years)	21-69	21-69	27-69	21-69	27-69
Gender ratio (male:female)	19:50	17:25	19:27	13:18	14:17
Racial Distribution					
Caucasian	66	40	44	29	29
Black	3	2	2	2	2
Hispanic	0	0	0	0	0
Native American	0	0	0	0	0
Asian	0	0	0	0	0
Other	0	0	0	0	0

Efficacy Results
The following table created by the Medical Officer, from data provided in the NDA, provides the actual data from subjects who participated in the efficacy study performed at for the inguinal and abdominal anatomic sites.

Table 6. [redacted] : Results by Subject for Pivotal "Efficacy" Study [Measured in Log_{10} Reductions (10 minute bacterial count subtracted from baseline)]

ID#	INGUINAL		ABDOMINAL	
	Test[A]	Reference[B]	Test[A]	Reference[B]
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
33				
35				
36				
37				
38				
39				
40				
42				
43				
44				
45				
48				

50	[redacted]			
Total	81.55	60.83	73.39	60.45
Mean Log_{10} Reductions	2.63	1.96	2.36	1.95
% of Subjects who Failed to Meet TFM-required Log_{10} Reduction at 10-minutes*	**61.29%**	**90.32%**	**29.03%**	**45.16%**

*TFM-required reduction at 10 minutes: 3 log_{10} on inguinal and 2 log_{10} on abdomen. Shaded boxes indicate average values failing to meet TFM-required criteria. [A]Test = CHG Antiseptic Cloths, [B]Reference = Hibiclens®

Medical Officer's comment: The mean log reductions will be discussed in the following paragraphs. The Medical Officer calculates that 61% and 29% of the individual subjects treated with the proposed product, CHG Antiseptic Cloths, did not achieve a 3 log_{10} and 2 log_{10} reduction at the inguinal and abdominal anatomic sites, respectively. In comparison, the Medical Officer calculates that 90% and 45% of individual subjects treated with the positive control product, Hibiclens®, did not achieve a 3 log_{10} and 2 log_{10} reduction at the inguinal and abdominal anatomic sites, respectively. These percents indicate that a large number of the subjects treated with both the proposed product, CHG Antiseptic Cloths, and the control product, Hibiclens®, failed to meet the 10-minute TFM requirements at both anatomic sites on an individual basis.

It is especially unsettling that Hibiclens®, a FDA-approved Patient Preoperative Skin Preparation, had such high individual failure rates at both the inguinal and abdominal anatomic sites.

Abdominal region

The log_{10} mean reductions achieved at the ten-minute sampling interval by the CHG Antiseptic Cloths at the abdominal site exceeded the TFM's proposed 2 log_{10} mean reduction criteria. Abdominal sites treated with Hibiclens® failed to demonstrate the prescribed 2 log_{10} mean reduction (see table below, shaded square with bolded number). However, the Division felt that the result was close enough to the 2 log_{10} mean reduction that the Hibiclens®-treated abdominal site data were deemed acceptable. Both the proposed product and the positive control suppressed the bacterial populations below baseline at the six-hour post-treatment sampling interval. The following table was created by the Medical Officer from data included in the NDA.

Table 7. [redacted] Pivotal "Efficacy" Results ([redacted]-01-109381-11): Abdomen

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	2.37	2.41
Hibiclens®	**1.95**	2.29

* TFM threshold is a 2 log_{10} reduction from baseline.

Inguinal region

Neither the test drug product, CHG Antiseptic Cloths, nor the positive control drug product, Hibiclens®, met the TFM criteria of a 3 log_{10} mean reduction in the inguinal region at ten minutes post-treatment. Both the proposed product and positive control suppressed the bacterial count in the inguinal region below baseline at the six-hour post-treatment sampling interval. Values that failed to meet TFM criteria are bolded and shaded in the following table created by the Medical Officer from data provided in the NDA.

Table 8. [redacted] Pivotal "Efficacy" Results ([redacted]-01-109381-11): Inguinal

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	**2.63**	3.18
Hibiclens®	**1.96**	2.46

*TFM threshold is a 3 log_{10} reduction from baseline.

The following summary table for the [redacted] efficacy study was created in collaboration with the FDA Statistical reviewer, Dr. Valappil from data provided in the NDA. It demonstrates the 95% confidence interval limits around the mean log_{10} reductions at the abdominal and inguinal anatomic sites for both the test and control products, the standard deviations, and the actual numbers (and percents) of subjects who failed to meet the mean log_{10} reductions required in the TFM.

Table 9. [redacted] : Summary of Pivotal "Efficacy" Results

Study Center, Anatomic Site, and Test Product	Mean Log Reduction at 10 minutes	95% CI	Standard Deviation	No. (%) of Subjects who Failed to Meet TFM-required Log_{10} Reduction at 10-minutes
[redacted]				
Abdominal - CHG Antiseptic Cloths	2.37	(2.01, 2.73)	0.983	9 (29)
Abdominal - Hibiclens®	1.95	(1.62, 2.28)	0.9043	14 (45.2)
Inguinal - CHG Antiseptic Cloths	2.63	(2.26, 3.00)	1.0145	19 (61.3)
Inguinal - Hibiclens®	1.96	(1.63, 2.30)	0.9146	28 (90.3)

*Shaded cells indicate mean log_{10} reductions not meeting those required in the TFM.

Reviewer Conclusions
The proposed product, CHG Antiseptic Cloths, met the pre-specified 2 log_{10} mean reduction criteria at the abdominal site, however the proposed product did not meet the specified 3 log_{10} mean reduction at the inguinal site. The positive control product, Hibiclens®, failed to meet the pre-specified log_{10} mean reduction at both the inguinal and abdominal sites. The Applicant communicated the results of this study to the Division before the actual submission of the NDA. As per the "Pre-Submission Regulatory Activity" section of the review, the Division agreed to accept the abdominal site data as evidence toward the Patient Preoperative Skin Preparation indication.

6.3.2 Trial #2 was performed at [redacted]

It is entitled, "Protocol No. 020125-103.01 Evaluation of the Antimicrobial Efficacy of One 2% Chlorhexidine Gluconate Antimicrobial Test Towelette Test Product and One Reference Used as Patient Preoperative Preparations." The details of this study were found in volume 21 of the Medical Officer's NDA packet.

Objective/Rationale
The objective of the study was to evaluate the antimicrobial effectiveness of the proposed product, CHG Antiseptic Cloths, against a positive control formulation approved by the FDA, Hibiclens®, as Patient Preoperative Skin Preparations.

Design
The study subjects were randomized. Neither the on-site investigators/technicians nor study subjects were blinded during the course of this study due to differences in the physical appearance and application procedures of the two treatments. The microbiologists and laboratory technicians who plated the site cultures and assessed for bacterial growth were blinded to treatment assignment.

Protocol
The study protocol was based on the FDA Proposed Tentative Final Monograph for Health Care Antiseptic Drug Products, Effectiveness Testing of a Patient Preoperative Skin Preparation, published in the Federal Register on June 17, 1994. Using bilateral applications, thirty inguinal and thirty-five abdominal sites were prepped with the proposed product, CHG Antiseptic Cloths, and the positive control, Hibiclens®. The sites were sampled for baseline microbial levels prior to prepping. The sites were sampled for residual levels of microorganisms ten minutes, thirty minutes and six hours after prepping. (The TFM does not include a thirty-minute sample point. It will therefore not be discussed in this review.) Not all thirty-five subjects were prepped at both anatomic sites.

Population, procedures
Subjects
The investigator planned to collect initial baseline bacterial counts from at least sixty healthy subjects between and including the ages of eighteen to sixty-nine years with the expectation of having enough subjects at the end of the study to provide approximately thirty evaluable abdominal anatomic sites and thirty evaluable inguinal anatomic sites. Subjects were to be of mixed age, race, and gender, and free of dermatoses or injury to the skin areas sampled. Eligibility was to be determined from a medical history collected on a screening-day inclusion/exclusion form and treatment-day inclusion/exclusion form.

Inclusion Criteria
Same as Trial #1 performed at [redacted]

Exclusion Criteria
Same as Trial #1 performed at [redacted]

Procedures
Same as Trial #1 performed at [redacted]

Medical Officer's comment: One slight difference noted in the protocol is that the "Prepping Technique" for CHG Antiseptic Cloths specified that the technician should apply the CHG Antiseptic Cloths "vigorously" to the proposed anatomic study sites. The [redacted] protocol specified that the CHG Antiseptic Cloths should be applied "gently." This will affect the way the product is labeled in the "Directions" section.

Statistical considerations
Same as Trial #1 performed at [redacted]

Results
Evaluability
Eighty-eight subjects were enrolled into the study. Initial baseline counts were obtained from 64 healthy subjects between the ages of 18 and 69 years. Out of 64 subjects who were cultured for initial baseline counts, 27 were withdrawn from the study because they did not meet the minimum baseline bacterial counts of 2.5 $\log_{10}$ on the abdomen or 5 $\log_{10}$ on the inguinal region at screening assessment. Two additional subjects who met the initial baseline counts withdrew for "personal reasons" prior to the Test Day. As a result, 35 subjects were treated with the Applicant's product, CHG Antiseptic Cloths, and the positive control, Hibiclens®.

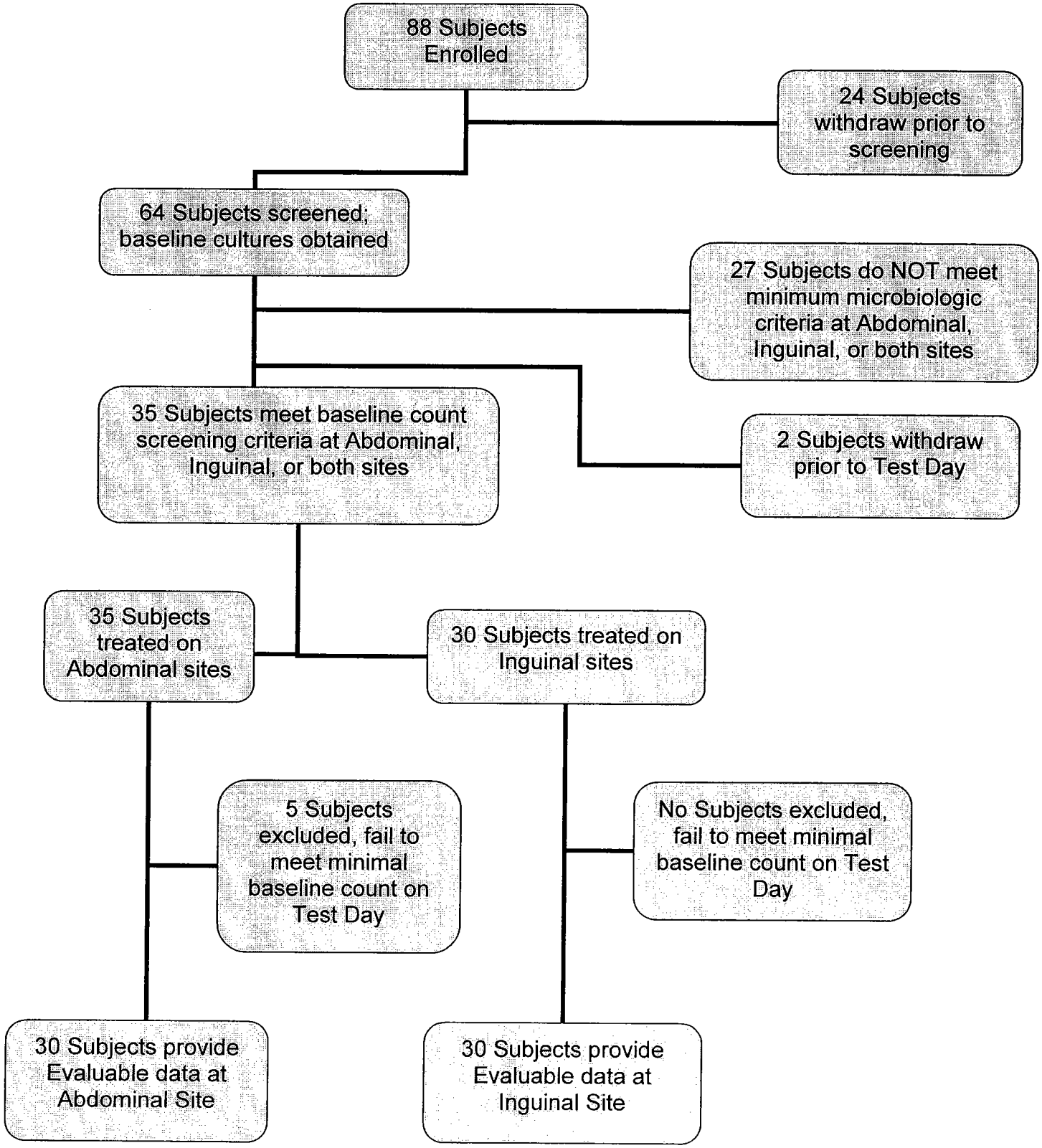
All 35 subjects were treated on the abdominal anatomic site. Out of the 35 subjects treated at the abdominal anatomic site, 5 subjects failed to meet baseline count criteria on the day of the test. Therefore, 30 subjects provided evaluable data for the abdominal anatomic site.

Out of the 35 subjects, 30 subjects were treated on the inguinal anatomic site. Out of the 30 subjects treated at the inguinal anatomic site, no subjects failed to meet baseline count criteria on the day of the test. Therefore, 30 subjects provided evaluable data for the inguinal anatomic site.

Medical Officer's comment: Due to the nature of the study design, the size of the study population was relatively small. The study enrolled 88 healthy subjects. Subject comparability is limited to the baseline demographic data presented in the "Demographics" section of this review. Once a subject was withdrawn from the study due to not meeting baseline bacterial count criteria, no additional data was collected that would be useful in assessing comparability. Based on the limited sample size, the Medical Officer did not detect unusual rates of withdrawal among a particular segment of the study's gender, age, or racial demographic.

Please see the following subject flow chart created by the Medical Officer, from data provided in the NDA, for the [redacted] efficacy study, [redacted] STUDY NO. 020125-103.

Figure 2. Subject Flow Chart for Pivotal "Efficacy" Study



Demographics
Eighty-eight healthy subjects between the ages of eighteen and sixty-nine years were admitted into the study. Thirty subjects provided evaluable data at the abdominal site. Thirty subjects provided evaluable data at the inguinal site. The eligibility of each subject was determined from a medical history collected on a screening inclusion/exclusion form and a treatment inclusion/exclusion form.

The following table created by the Medical Officer, from data provided in the NDA, summarizes the demographics of the study.

Table 10. Bioscience: Demographics for Pivotal "Efficacy" Study

	All Enrolled	Subjects with Abdominal Sites Treated with CHG	Subjects with Inguinal Sites Treated with CHG	Evaluable Subjects with Abdominal Sites Treated with CHG	Evaluable Subjects with Inguinal Sites Treated with CHG
Number (%) of Subjects	88 (100%)	35 (40%)	30 (34%)	30 (34%)	30 (34%)
Median Age (years)	29	25	25	29	25
Age Range (years)	18-69	19-69	19-69	19-62	19-69
Gender ratio (male:female)	40:48	25:10	22:8	21:9	22:8
Racial Distribution					
Caucasian	81	33	28	28	28
Black	0	0	0	0	0
Hispanic	3	1	1	1	1
Native American	4	1	1	1	1
Asian	0	0	0	0	0
Other	0	0	0	0	0

Efficacy Results
The following table created by the Medical Officer, from data provided in the NDA, provides the actual data from subjects who participated in the efficacy study performed at [redacted] for the inguinal and abdominal anatomic sites.

Table 11. [redacted] Results by Subject for Pivotal "Efficacy" Study [Measured in Log_{10} Reductions (10 minute bacterial count subtracted from baseline)]

ID#	INGUINAL		ABDOMINAL	
1				
7				
8				
11				
12				
13				
15				
16				
17				
18				
19				
29				
33				
34				
39				
46				
47				
48				
49				
50				
59				
62				
63				
64				
68				
71				
72				
74				
76				
79				
81				
83				
86				
87				
88				
Total				
Mean Log_{10} Reductions	3.46	2.78	2.51	2.18
% of Subjects who Failed to Meet TFM-required Log_{10} Reduction at 10-	**33.33%**	**63.33%**	**30%**	**36.67%**

minutes*				

*TFM-required reduction at 10 minutes: 3 $\log_{10}$ on inguinal and 2 $\log_{10}$ on abdomen. Shaded boxes indicate average values failing to meet TFM-required criteria. [A]Test = CHG Antiseptic Cloths, [B]Reference = Hibiclens®

Medical Officer's comment: The mean log reductions will be discussed in the following paragraphs. The Medical Officer calculates that 33% and 30% of individual subjects treated with the proposed product, CHG Antiseptic Cloths, did not achieve a 3 $\log_{10}$ and 2 $\log_{10}$ reduction at the inguinal and abdominal anatomic sites, respectively. In comparison, the Medical Officer calculates that 63% and 37% of individual subjects treated with the positive control product, Hibiclens®, did not achieve a 3 $\log_{10}$ and 2 $\log_{10}$ reduction at the inguinal and abdominal anatomic sites, respectively. These percents indicate that a large number of the subjects treated with both the proposed product, CHG Antiseptic Cloths, and the control product, Hibiclens®, failed to meet the 10-minute TFM requirements at both anatomic sites on an individual basis even when the mean log reduction met the criteria set in the TFM.

It is unsettling that between 30-37% of individual subjects treated with Hibiclens®, FDA-approved for Patient Preoperative Skin Preparation, failed to meet the TFM criteria for bacterial $\log_{10}$ reduction.

The Applicant's proposed product met the primary outcome measure for clinical benefit of a required 2 $\log_{10}$ mean reduction at abdominal sites and a 3 $\log_{10}$ mean reduction at the inguinal sites. The positive control product, Hibiclens®, met the required 2 $\log_{10}$ mean reduction at the abdominal sites, however it did not meet the required 3 $\log_{10}$ mean reduction at the inguinal sites (the value is bolded and highlighted in the following table on inguinal site results). In this study, the Applicant's product, CHG Antiseptic Cloths, met the TFM requirement at both anatomic sites. The following tables were created by the Medical Officer.

Table 12. [redacted] Pivotal "Efficacy" Results [redacted] -020125-103): Abdomen

Test Article	Mean $\log_{10}$ Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	2.50	2.54
Hibiclens®	2.18	2.19

* TFM threshold is a 2 $\log_{10}$ reduction from baseline.

Table 13. [redacted] Pivotal "Efficacy" Results [redacted] -020125-103): Inguinal

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	3.45	3.64
Hibiclens®	2.78	3.15

* TFM threshold is a 3 log_{10} reduction from baseline.

The following summary table for the [redacted] efficacy study was created in collaboration with the FDA Statistical reviewer, Dr. Valappil, from data provided in the NDA. It demonstrates the 95% confidence interval limits around the mean log_{10} reductions at the abdominal and inguinal anatomic sites for both the test and control products, the standard deviations, and the actual numbers (and percents) of subjects who did not meet the mean log_{10} reductions required in the TFM.

Table 14. [redacted] Summary of Pivotal "Efficacy" Results

Study Center, Anatomic Site, and Test Product	Mean Log Reduction at 10 minutes	95% CI	Standard Deviation	No. (%) of Subjects who Failed to Meet TFM-required Log_{10} Reduction at 10-minutes
[redacted]				
Abdominal - CHG Antiseptic Cloths	2.51	(2.20, 2.82)	0.8273	9 (30)
Abdominal - Hibiclens®	2.18	(1.77, 2.59)	1.094	11 (36.7)
Inguinal - CHG Antiseptic Cloths	3.46	(3.10, 3.82)	0.9581	10 (33.3)
Inguinal - Hibiclens®	2.78	(2.40, 3.17)	1.0381	19 (63.3)

*The shaded cell indicates a mean log_{10} reduction not meeting the TFM requirement.

Reviewer Conclusions

The proposed product, CHG Antiseptic Cloths, met the pre-specified 2 log_{10} mean reduction criteria at the abdominal site and the pre-specified 3 log_{10} mean reduction at the inguinal site. The positive control product, Hibiclens®, met the pre-specified 2 log_{10} mean reduction at the abdominal site. Hibiclens® did not meet the pre-specified 3 log_{10} mean reduction at the inguinal site.

6.3.3 Trial #3 was performed at [redacted]

It is entitled, "Protocol No. 500-102, Evaluation of the Antimicrobial Efficacy of 2% Chlorhexidine Gluconate Antimicrobial Towelette Preoperative Skin Preparation." The details of this study were found in volume 22 of the Medical Officer's NDA packet. This investigation only studied inguinal sites. This third efficacy study of inguinal sites was performed in lieu of the failed inguinal study performed by [redacted]

Objective/Rationale
The objective of the study was to evaluate the antimicrobial effectiveness of the proposed product, CHG Antiseptic Cloths, against a positive control formulation approved by the FDA, Hibiclens®, as Patient Preoperative Skin Preparations.

Design
The study subjects were randomized. Neither the on-site investigators/technicians nor study subjects were blinded during the course of this study due to differences in the physical appearance and application procedures of the two treatments. The microbiologists and laboratory technicians who plated the site cultures and assessed for bacterial growth were blinded to treatment assignment.

Protocol
The study protocol was based on the FDA Proposed Tentative Final Monograph for Health Care Antiseptic Drug Products, Effectiveness Testing of a Patient Preoperative Skin Preparation, published in the Federal Register on June 17, 1994. Using bilateral applications, the inguinal sites of 36 subjects were prepared with the test and positive control products. The sites were sampled for baseline microbial levels prior to preparation. The sites were sampled for residual levels of microorganisms ten minutes, thirty minutes and six hours after preparation. (The TFM does not require a thirty-minute sample point. It will therefore not be discussed in this review.)

Population, procedures

Subjects
The investigator planned to collect initial baseline bacterial counts from "a number" of healthy subjects between and including the ages of eighteen to sixty-nine years with the expectation of having enough subjects at the end of the study to provide approximately thirty subjects with evaluable inguinal anatomic sites. Subjects were to be of mixed age, race, and gender, and free of dermatoses or injury to the skin areas sampled. Eligibility was to be determined from a medical history collected on a screening-day inclusion/exclusion form and treatment-day inclusion/exclusion form.

Inclusion Criteria
Same as Trial #1 performed at [redacted]

Exclusion Criteria
Same as Trial #1 performed at [redacted]

Procedures
Same as Trial #1 performed at [redacted]

Medical Officer's comment: As with [redacted] a slight difference was noted in the protocol. The "Prepping Technique" for CHG Antiseptic Cloths specified that the technician should apply the CHG Antiseptic Cloths "vigorously" to the proposed anatomic study sites. The [redacted] protocol specified that the CHG Antiseptic Cloths should be applied "gently." This will affect the way the product is labeled in the "Directions" section.

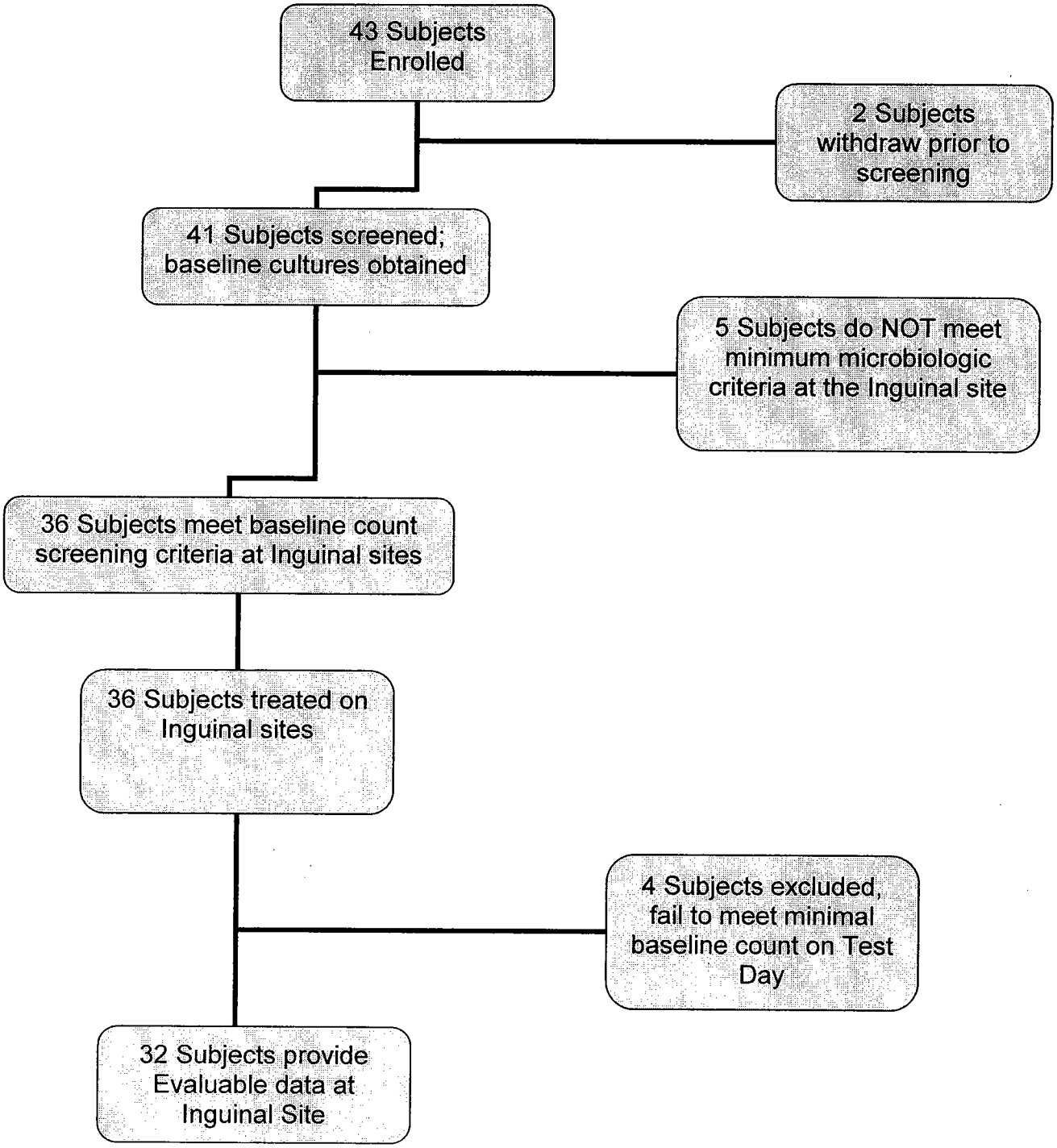
Statistical considerations
Same as Trial #1 performed at [redacted]

Results
Evaluability
Forty-three subjects were enrolled in the study. Two subjects withdrew from the study before screening began. Five subjects failed the screening baseline, were excluded from the study, and were not treated with the proposed product, CHG Antiseptic Cloths, or the positive control product, Hibiclens®. Thirty-six subjects passed the screening baseline and were treated with the test and positive control products. Four subjects failed the baseline on the day of treatment and were excluded from the study. Thirty-two subjects passed the baseline on the day of treatment and provided evaluable data for the final analysis.

Medical Officer's comment: Due to the nature of the study design, the size of the study population was relatively small. The study enrolled forty-three healthy subjects. Subject comparability is limited to the baseline demographic data presented in the "Demographics" section of this review. Once a subject was withdrawn from the study because she/he did not meet baseline bacterial count criteria, no additional data was collected that would be useful in assessing comparability. Based on the limited sample size, the Medical Officer did not detect unusual rates of withdrawal among a particular segment of the study's gender, age, or racial demographic.

Please see the following subject flow chart created by the Medical Officer, from data in the NDA, for the [redacted] efficacy study, [redacted] STUDY NO. 500-102.

Figure 3. [redacted] Subject Flow Chart for Pivotal "Efficacy" Study



Demographics
Forty-three healthy subjects between the ages of eighteen and sixty-nine years were admitted into the study. Thirty-two subjects provided evaluable data at the inguinal anatomic site. The eligibility of each subject was determined from a medical history collected on a screening inclusion/exclusion form and a treatment inclusion/exclusion form.

The following table created by the Medical Officer, from data in the NDA, summarizes the demographics of the study.

Table 15. [redacted] Demographics for Pivotal "Efficacy" Study

	All Enrolled	Subjects with Inguinal Sites Treated with CHG	Evaluable Subjects with Inguinal Sites Treated with CHG
Number (%) of Subjects	43 (100%)	36 (84%)	32 (74%)
Median Age (years)	39	39	39
Age Range (years)	18-61	18-61	18-61
Gender ratio (male:female)	21:22	16:20	14:18
Racial Distribution			
Caucasian	29	25	22
Black	3	3	3
Hispanic	1	1	1
Native American	0	0	0
Asian	10	7	6
Other	0	0	0

Efficacy Results
The following table created by the Medical Officer, from data provided in the NDA, provides the actual data from subjects who participated in the pivotal "efficacy" study performed at [redacted] for the inguinal anatomic site.

Table 16. [redacted] Results by Subject for Pivotal "Efficacy" Study
[Measured in Log_{10} Reductions (10 minute bacterial count subtracted from baseline)]

ID#	INGUINAL ONLY
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
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23	
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25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	

40		
41		
42		
43		
Total	134.02	122.73
Mean Log Reductions	4.19	3.84
% of Subjects who Failed to Meet TFM-required Log_{10} Reduction at 10-minutes*	**6.25%**	**12.50%**

*TFM-required reduction at 10 minutes: 3 log_{10} on inguinal and 2 log_{10} on abdomen. Shaded boxes indicate average values failing to meet TFM-required criteria. [A]Test = CHG Antiseptic Cloths, [B]Reference = Hibiclens®

Medical Officer's comments: The mean log reductions will be discussed in the following paragraphs. The Medical Officer calculates that 6% of the individual subjects treated with the proposed product, CHG Antiseptic Cloths, did not achieve a 3 log_{10} reduction at the inguinal anatomic site. In comparison, the Medical Officer calculates that 13% of individual subjects treated with the positive control product, Hibiclens®, did not achieve a 3 log_{10} reduction at the inguinal anatomic site. These percents were much lower that those observed in the other two efficacy studies.

At this time, it is unclear what led to such drastic differences in outcomes between the study centers. One hypothesis is that the technicians at scrubbed the inguinal anatomic sites more "vigorously" than at . Of the three efficacy studies, only noted an adverse event after the application of CHG Antiseptic Cloths. It was "redness" at the application site. It resolved by the six-hour sample time point.

The proposed product, CHG Antiseptic Cloths, produced a mean log_{10} reduction at ten minutes of 4.19 for the inguinal site. The microorganism populations for the 6-hour application samples remained below the baseline level. The reduction obtained for the proposed product, CHG Antiseptic Cloths, met the specified mean log_{10} bacterial reduction defined by the Tentative Final Monograph. The following table was created by the Medical Officer, from data provided in the NDA.

Table 17. [redacted] Pivotal "Efficacy" Results [redacted] -500-102): Inguinal

Test Article	Mean Log_{10} Reductions from Baseline	
	10 minutes*	6 hours
CHG Antiseptic Cloths	4.19	3.12
Hibiclens®	3.83	3.03

* TFM threshold is a 3 log_{10} reduction from baseline.

The following summary table for the [redacted] efficacy study was created in collaboration with the FDA Statistical reviewer, Dr. Valappil from data provided in the NDA. It demonstrates the 95% confidence interval limits around the mean log_{10} reductions at the inguinal anatomic sites for both the test and control products, the standard deviations, and the actual numbers (and percents) of subjects who failed to meet the mean log_{10} reductions required in the TFM.

Table 18. [redacted] Summary of Pivotal "Efficacy" Results

Study Center, Anatomic Site, and Test Product	Mean Log Reduction at 10 minutes	95% CI	Standard Deviation	No. (%) of Subjects who Failed to Meet TFM-required Log_{10} Reduction at 10-minutes
[redacted]				
Inguinal - CHG Antiseptic Cloths	4.19	(3.87, 4.50)	0.8697	2 (6.3)
Inguinal - Hibiclens®	3.84	(3.48, 4.19)	0.9833	4 (12.5)

Reviewer Conclusions

The proposed product, CHG Antiseptic Cloths, met the pre-specified 3 log_{10} mean reduction at the inguinal site. The positive control product, Hibiclens®, met the pre-specified 3 log_{10} mean reduction at the inguinal site.

6.4 Clinical Microbiology

The Microbiology reviewer, Peter Coderre, Ph.D., noted the following in his review. The proposed product demonstrated efficacy against a broad spectrum of microorganisms *in vitro* with adequate time kill kinetics as per TFM criteria. [redacted] In addition, Dr. Coderre noted that the following gram-positive bacteria had slower time-kill kinetics: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*,

Enterococcus faecalis, *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enteroccoci (VRE).

In the three pivotal "efficacy" studies, Dr. Coderre noted study-to-study variability in: (1) scrub cup diameter, (2) neutralization composition, (3) processing of bacterial samples, and (4) the formula used to calculate CFU/cm^2. Dr. Coderre also noted a lack of negative controls.

Dr. Coderre recommends surveillance for the emergence of decreased susceptibility and antimicrobial resistance among target organisms and additional clinical simulation studies with appropriate negative controls.

Medical Officer's comment: The Medical Officer agrees that it would be appropriate for the Division to recommend inclusion of negative controls in efficacy studies for new drug products pursuing the indication of Patient Preoperative Skin Preparation in the future; however, the data from the efficacy studies submitted in this NDA were derived from protocols reviewed by the former Microbiology reviewer, Albert Sheldon, Ph.D., which did not include negative controls, but, these protocols were found to be acceptable. Therefore, it would be inappropriate from a regulatory perspective to now reject the data resulting from these studies based on Dr. Coderre's disagreement with the original protocol design; a protocol design that has also been accepted to support the approval of prior NDAs, including Hibiclens®.

Appropriate revisions to the methodology described in the TFM for the Patient Preoperative Skin Preparation indication will be the topic of a future Advisory Committee meeting. A further discussion of inclusion of negative control arms would be appropriate to include in such a venue. Ideally negative controls would consist of: (1) vehicle alone and (2) drug product without vehicle, if it can be formulated. These negative controls would aid in both a determination of the contribution of the active ingredient to the formulation and the contribution of the mechanical action used when applying the vehicle to the skin in the recommended manner.

6.5 Efficacy Conclusions

The Medical Officer concludes that the Applicant has demonstrated that the proposed product, CHG Antiseptic Cloths, is effective for the proposed indication for Patient Preoperative Skin Preparation. As per conditions agreed upon by the Division prior to the Applicant's submission of NDA 21,669, data from the pivotal "efficacy" studies conducted at [redacted] sufficiently support the proposed indication at the abdominal ("dry") site and data from the pivotal "efficacy" studies conducted at [redacted] sufficiently support the proposed indication at the inguinal ("wet") site. No additional information is needed at this time to determine the efficacy of the Applicant's product for the proposed indication.

Under the testing procedures defined in the TFM, CHG Antiseptic Cloths appear to be at least as effective as the positive control product, Hibiclens®, which is already FDA-approved for the indication of Patient Preoperative Skin Preparation.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Applicant has demonstrated that the proposed product, CHG Antiseptic Cloths, is safe for the proposed single use indication of Patient Preoperative Skin Preparation.

Their were two types of subject exposures, involving a total of 417 subjects, in studies submitted to support approval of CHG Antiseptic Cloths for the indication of Patient Preoperative Skin Preparation. A total of 175 subjects received single topical application of the study drug in the four pilot "efficacy" studies [redacted] #01-109628-11, [redacted] #02-120904-103, [redacted] #020418-103, and [redacted] #500-101) and the three pivotal "efficacy" studies [redacted] #01-109381-11, [redacted] #020125-103-01, and [redacted] #500-102). The intended use of the product for Patient Preoperative Skin Preparation is most similar to use in these seven studies (i.e. single application without use of occlusive dressings).

The second type of subject exposure, involving a total of 242 subjects, occurred in the two pivotal "safety" studies (21-Day Cumulative Irritation Test #NWU-515-001 and Repeat Insult Patch Test #SGNC-001). These studies were designed to elicit the maximal irritation and sensitization potential (that is, multiple consecutive applications under occlusive dressing) of CHG Antiseptic Cloths as compared to similar products, a positive control, and negative controls.

Data from all nine studies were reviewed to assess the safety of the Applicant's product. Specifically, case report forms were reviewed for evidence of adverse events, such as skin irritation, and for unexplained subject withdrawal. As is displayed in the following table created by the Medical Officer, from data provided in the NDA, only five adverse events occurred out of the 417 subjects exposed to CHG Antiseptic Cloths. All of the adverse events were manifestations of skin irritation. No adverse events were reported in subjects in any of the other study arms in the nine protocols.

Table 19. Summary Table of All Adverse Events in NDA 21,669 (n=417)

Number (%) of patients	N	%
with one or more AEs	5	1.2
with no AEs	412	98.8
with drug-related AEs*	3	0.7
with serious AEs	0	0
with serious drug-related AEs	0	0
who died	0	0
discontinued due to an AE	2	0.5
discontinued due to a drug-related AE	2	0.5
discontinued due to a serious AE	0	0
discontinued due to a serious drug-related AE	0	0

*Determined by the investigator to be possibly, probably, or definitely drug-related.

Of the five subjects with adverse events, three were considered by the Investigator to be related to treatment with CHG Antiseptic Cloths. Out of these three treatment-related adverse events, only one occurred in a study that simulated the proposed clinical use of CHG Antiseptic Cloths (Subject No. 12 in [redacted] Study No. 500-102). The following table was created by the Medical Officer from data provided in the NDA.

Table 20. Adverse Events In Subjects Exposed to CHG Antiseptic Cloths

(n=417)						
Study	Type of Study	Subject ID (Demographics)	Adverse Event	Severity	Outcome	Treatment Related
Study No. 500-102	Efficacy	No. 12 (47 y.o. Caucasian female)	"Redness" on test site, onset unknown, resolved by 6-hr sampling time point.	Moderate	Subject completed study	Yes
21-Day Cumulative Irritation Study No. NWU-515-001	Safety	No. 24 (27 y.o. Black female)	Day 3-reported "burning" sensation over test site and Day 4 noted "small petechial erosions and/or scabs."	Mild	Subject withdrew from study on Day 5	Yes
*Repeat Insult Patch Test Study No. SGNC-001	Safety	No. 160 (18 y.o. Caucasian-American Indian female)	"Papules" noted within 1st 24hrs of patch placement. Progressed to "moderate erythema, possible presence of mild edema" by Day 18.	None provided	Subject withdrew from study on Day 21. Would have had 18 more days in the study	Yes
*Repeat Insult Patch Test Study No. SGNC-001	Safety	No. 204 (30 y.o. Caucasian female)	Patches "bothering" subject and requests to drop from study	None provided	Subject withdrew	No
*Repeat Insult Patch Test Study No. SGNC-001	Safety	No. 217 (18 y.o. Caucasian female)	Patches "burning", felt "uncomfortable"	None provided	Subject withdrew	No

* Additional subjects considered by Medical Officer to have experienced Adverse Event based on review of Case Report Forms

7.1.1 Deaths

No deaths occurred during the course of this development program.

7.1.2 Other Serious Adverse Events

No non-fatal serious adverse events occurred during this development program. No non-fatal serious adverse events were reported from secondary sources.

7.1.3 Dropouts and Other Significant Adverse Events

The following table created by the Medical Officer, from data in the NDA, provides a listing of reasons why subjects were withdrawn from the Phase 2 pilot "efficacy" studies. Reasons for why subjects were withdrawn from the Phase 3 pivotal "efficacy" studies are provided in the respective subject flow charts found in Figures 1, 2 and 3 of Section 6.3. None of the reasons provided raise concerns that subjects were removed from the studies for reasons related to an adverse event.

Medical Officer's comment: Due to the fact that subjects in the pivotal "efficacy" studies could be withdrawn from a study on one anatomic site and still participate on the other anatomic site, subject flow and withdrawals are more easily illustrated in flow charts as opposed to tables. At the request of the Medical Officer, the Applicant submitted a total of 50 additional pages of flow charts, tables, and text on (1) February 24, 2004 [Serial No. N-000(BZ)] and (2) March 19, 2004 (faxed document) that the Medical Officer used to verify that none of the subjects were removed from the pivotal "efficacy" studies for reasons related to an adverse event.

Table 21. Reasons for Phase 2 Pilot "Efficacy" Study Dropouts

Protocol No.	No. Subjects Dropped (out of) Total Recruited	Low Baseline Bacterial Count	"Personal" - prior to Test Day	"Extra"	Late arrival to Test Center on Day of Test	Refused Pregnancy Test
[redacted]-01-109628-11	9 of 21	0	3	4	2	0
[redacted] 020418-103	1 of 13	0	0	0	0	1
[redacted] 02-120904-106	8 of 18	0	2	5	1	0
[redacted] 500-101	9 of 19	9	0	0	0	0

The two Phase 3 pivotal "safety" studies are entitled, "21-Day Cumulative Irritation Test" and "Repeat Insult Patch Test." These studies do not simulate expected clinical use and are expected to cause skin irritation under the conditions of use in the studies; therefore subjects that reach predefined levels of skin irritation that are required to discontinue therapy by protocol are not generally considered treatment failures or adverse events. These tests are designed to evaluate the irritation and sensitization potential of the proposed product in comparison with other currently marketed potential rival products, as well as, positive and negative control substances. The products are applied under severe conditions, for example, repeatedly under occlusive dressings. The following table created by the Medical Officer, from data in the NDA, provides a listing of reasons why subjects were withdrawn from the Phase 3 "safety" studies.

Table 22. Reasons Phase 3 Pivotal "Safety" Study Dropouts

Protocol	No. Subjects Dropped (out of) Total Recruited^	Withdrew Consent Prior to Study Start	Lost to Follow-up	Unable to Comply with Scheduled Visits	Adverse Event
21-Day Cumulative Irritation Test NWU-515-001	8 of 30	6	1	0	1
Repeat Insult Patch Test SGNC-001	14 of 218	0	0	11	3*

^ Subjects that met predefined protocol irritancy stopping criteria are not included
* The Medical Officer identified three additional subjects that may have discontinued due to adverse events, but relatedness to the drug product could not be determined in two subjects.

An adverse event associated with a dropout was reported by the Applicant and occurred during a special safety study entitled, "21-Day Cumulative Irritancy Testing of Various Skin Care Products in Normal Subjects," No. NWU-515-001. The details of this study are found in volumes 15 and 16 of the Medical Officer's NDA packet. On the third study day, Subject No. 24, a 27 year old Black woman, noted a "burning" sensation over the skin test site. On Day 4, the investigator noted "small petechial erosions and/or scabs." The subject prematurely withdrew from the study on Day 5. The intervention was to leave the skin site "open to air." Time to resolution of the irritation was not noted in the CRF. The investigator marked on the adverse event form that the adverse event was "mild" in intensity and lasted "3 days." The investigator reported that there was a "definite" relationship between the adverse event and the study product.

Medical Officer's comments: The Medical Officer noted three additional adverse events from the "Repeat Insult Patch Test," Study No. SGNC-001, all three were described as skin irritation and resulted in the withdrawal of the three study subjects. The Medical Officer believes that one of the three adverse events was due to the Applicant's product. Subject No. 160, an 18 y.o. Caucasian-American Indian woman, was noted to have "papules" on the skin test site within the first 24 hours of patch placement. The skin irritation progressed to, "moderate erythema, possible presence of mild edema" by Day 18. Subject No. 160 withdrew from study on Day 21. She would have had 18 more days in the study. No substantial evidence exists to implicate CHG Antiseptic Cloths as the cause of the other two adverse events in the "Repeat Insult Patch Test."

Overall, there were too few adverse events to ascribe any relationship to dose-response, time dependency of the dropout, drug-demographic, drug-disease, and drug-drug interactions.

7.1.4 Other Search Strategies

Due to the fact that the safety database is relatively small, only 417 subjects exposed to the Applicant's product, all available subject case report forms were reviewed for evidence of adverse events.

The literature has also been reviewed to define additional potential safety concerns with use of products containing chlorhexidine gluconate. Literature defined safety issues include:

- Deafness as a result of instillation into middle ear[1,3,5]
- Eye injury (corneal opacification) if permitted to enter and remain in the eye[1,5,8,9]
- Excessive irritation when applied to genital areas (mucous membranes)[5]
- Anaphylaxis[10,11]
- Severe skin irritation/ulceration in infants weighing <1000 grams and < 26 weeks gestation[12]
- Direct toxicity to nerve tissue[1,5]

7.1.5 Common Adverse Events

Only five adverse events occurred out of the 417 subjects (1.2%) exposed to the proposed product. All of the adverse events were manifestations of skin irritation. Three of the five adverse events were considered to be related study drug exposure (0.7%); however, only one study drug related adverse event was reported among the 175 subjects in single use studies (0.6%).

Applicant's Approach to Eliciting Adverse Events

Subjects were assessed for adverse events throughout the duration of the studies. In the three Phase 3 pivotal "efficacy" studies, subjects were assessed at a minimum immediately after application of the proposed product, at the ten-minute mark, the thirty-minute mark, and at the six-hour mark. In the Phase 3 pivotal "safety" study entitled, "21-Day Cumulative Irritation Test," subjects were assessed daily for 21 days. In the Phase 3 pivotal "safety" study entitled, "Repeat Insult Patch Test," subjects were assessed three times per week for the first 9 weeks during the induction phase and then at 24 hours and 72 hours after patch removal during the challenge phase. The Phase 2 pilot studies were brief, lasting no more than 10 minutes.

Medical Officer's comment: The Applicant assured the Division that no adverse events occurred during the Phase 2 studies, however the Phase 2 protocols do not delineate at what time points study technicians evaluated study subjects for adverse events.

Additional Analyses and Explorations

There were too few drug-related adverse events to explore associations such as dose dependency, time to onset, adaptation, demographic interactions, drug-disease interactions, and drug-drug interactions.

7.1.6 Less Common Adverse Events

Not applicable. All Adverse Events are described in preceding sections.

7.1.7 Laboratory Findings

The Applicant did not perform laboratory tests on study subjects during the course of the development of this topical antiseptic.

7.1.8 Vital Signs

The Applicant did not perform vital signs on study subjects during the course of the development of this topical antiseptic.

7.1.9 Electrocardiograms (ECGs)

The Applicant did not perform electrocardiograms on study subjects during the course of the development of this topical antiseptic.

Medical Officer's comment: Given that the literature states that topical chlorhexidine gluconate products are poorly absorbed through the skin and gastrointestinal tract[1], it is acceptable to have not conducted safety laboratories and ECG monitoring. In addition, changes in vital signs would be unexpected.

7.1.10 Immunogenicity

The Applicant did not perform specific immunogenicity studies in humans, beyond the Repeat Insult Patch Test (SGNC-001) that is described in detail in Section 7.1.12.2.

7.1.11 Human Carcinogenicity

The Applicant did not perform specific clinical carcinogenicity testing.

7.1.12 Special Safety Studies

The Applicant conducted two special safety studies to assess the cumulative irritancy and contact sensitizing potential of the product. The following summary table was adapted from tables provided by the Applicant. These tables are found on page 006427 of volume 15 of the NDA packet and are entitled, "Table 1: Controlled Safety Studies: Design" and "Table 2: Controlled Safety Studies: Objectives and Results."

Table 23. Pivotal "Safety" Studies: Designs and Results

Study	Principal Investigator	Study Design	Formulation / Dosage	Positive Control CHG Products	Number of Subjects	Age in Years (Evaluables)	Gender (Evaluables)	Duration	Result
21-Day Cumulative Irritation (Protocol No. NWU-515-001)[1]	Dennis West, Ph.D. Northwestern University's Department of Dermatology, Chicago, IL	-Double-blinded -Occluded -Randomized	65 mL bulk drug product applied to 8x8 mm of cloth	• Exidine (2%CHG) ▪ Hibiclens® (4%CHG)	30 (Enrolled) **23 (Evaluable)**	22 - 60	21:2 (F:M)	21 days	CHG Antiseptic Cloths had strong potential for mild to moderate cumulative irritation under the conditions of the study
Repeat Insult Patch Test (Protocol No. SGNC-001)[2]	[redacted]	-Double-blinded -Occluded -Randomized	0.3 mL bulk drug product applied to ¾ x ¾ inches of cloth	• Exidine (2%CHG) ▪ Hibiclens® (4%CHG)	218 (Enrolled) **204 (Evaluable)**	18 - 79	155:49 (F:M)	Induction: 3 weeks Challenge: 72 hours	CHG Antiseptic Cloths exhibited low to moderate irritancy in one-third of the test population. No evidence that it induced allergic reactions on repeated application.

1 Used to determine the skin irritation potential of the test articles when applied daily under occlusion over a 21-day period
2 Used to determine the primary or cumulative irritation potential and/or allergic potential of the proposed product when applied repeatedly

7.1.12.1 Trial Name/Number: "21-Day Cumulative Irritancy Testing of Various Skin Care Products in Normal Subjects"/NWU-515-001.

The details of this study were found in volumes 15 and 16 of the Medical Officer's NDA packet.

Objective/Rationale

The purpose of the study was to evaluate the potential of the Applicant's proposed product's 2% CHG formulation, as a result of repeated applications with occlusion, to induce contact skin irritation in human subjects.

Design

The study was double-blinded and randomized. Twenty-one consecutive daily applications of the test articles contacted the skin under occlusion for approximately 23 hours each day. Scoring for cumulative irritation was done every 24 hours immediately prior to re-application or until excessive irritation was noted at any scoring session.

Protocol

The study was conducted from June 1, 2002 to June 21, 2002 by Dennis P. West, PhD, FCCP and [redacted] at Northwestern University, Dept of Dermatology.

An [redacted] containing 10 individual test articles on individual 8 x 8 mm fabric inserts was uniformly applied to the skin of a subject's left scapular region, removed 1-2 hours prior to scoring and reapplied to the same site for 21 consecutive days. The chamber sites for each test article were randomized for each subject and reapplied in the same chamber each day.

The ten test articles included the following eight drug solutions: CHG Antiseptic Cloths Bulk Solution (with 2% CHG), CHG Antiseptic Cloths placebo solution (without 2% CHG), Hibiclens® (4% CHG) by Astrazeneca, Exidine (2% CHG) solution by Xttrium Laboratories, Calgon Vestal SeptiSoft (mixed according to NoRinse Use instructions), Antibacterial ReadyBath (0.1% BZK) by Medline Industries, Comfort Bath® solution by Sage Products, Inc., and ReadyBath by Medline Industries. In addition, the following two control solutions were used: a positive control (Sodium Lauryl Sulfate 1% solution) and a negative control (Sodium Chloride 0.9% solution).

Each subject was instructed that the patch was to remain in place and kept dry for twenty-three hours +/- one hour daily, at which time the patch was to be removed by the subject prior to the clinic visit. Each subject was instructed to return to the clinic at approximately the same time every day.

The test sites were observed for reaction and each subject asked whether any adverse events or local application site symptoms were experienced during the previous twenty-four hours.

Population, Procedures

Subjects

The investigator wanted to enroll "a sufficient number of subjects" to "assure that a minimum of 25 subjects would complete the study." Subjects could be of either gender and aged 18 years or older.

Inclusion Criteria (taken directly from vol. 15, page 006542)

- Males and females, aged 18 years or older
- Signed informed consent

Exclusion Criteria (taken directly from vol. 15, page 006542)

- Insulin-dependent diabetes
- Mastectomy for cancer involving removal of lymph nodes draining the test site
- Clinically significant skin diseases which may contraindicate participation, including psoriasis, eczema, atopic dermatitis, and active cancer
- Asthma that requires systemic corticosteroid medication
- Immunological disorders such as HIV positive, AIDS, and systemic lupus erythematosus
- Treatment for any type of cancer within the last six months
- Use of any prescribed anti-inflammatory drug (e.g., aspirin, ibuprofen, corticosteroids), immunosuppressive drugs, or antihistamine medication (steroid nose drops and/or eye drops are permitted). Any over-the-counter pain medication that is ingested in quantities exceeding label instructions
- Topical drugs at patch site
- Pregnancy, lactation, or planning a pregnancy
- Medical condition that, in the Investigators' judgment, makes the subject ineligible or places the subject at undue risk
- Participation in any patch test for irritation or sensitization within the last four weeks or known sensitization to adhesives. Current participation in any clinical testing, including other studies being conducted at Northwestern University
- Damaged skin in or around test sites which include sunburn, extremely deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfiguration of the test site

Procedures

Ten test articles were evaluated simultaneously in the study. The study employed reference concentrations and dose quantities of the following ten test articles: CHG Antiseptic Cloths Bulk Solution (with 2% CHG), CHG Antiseptic Cloths placebo solution (without 2% CHG), Hibiclens® (4% CHG) by Astrazeneca, Exidine (2% CHG) solution by Xttrium Laboratories, Calgon Vestal SeptiSoft (mixed according to NoRinse Use instructions), Antibacterial ReadyBath (0.1% BZK) by Medline Industries, Comfort Bath® by Sage Products, Inc., ReadyBath by Medline Industries, physiologic saline (the low irritancy negative control) and sodium lauryl sulfate (high irritancy positive control). Cloth squares, 8 x 8 mm, were saturated with 65 micro liters of each of the test articles and placed into one of ten 9 mm x 9 mm chambers. These cloth squares were made from

100% polyester, the same material as the cloth used to apply the finished CHG Antiseptic Cloths product. The ten-chambered patch was prepared at the time of application and was then affixed to the skin by hypoallergenic non-woven adhesive tape. A series of skin sites on subjects' left scapular regions were utilized for application. In order to eliminate position bias, the chamber sites for each test article were randomized for each subject and reapplied in the same chamber each day.
Individual test articles were applied to assigned sites on the skin for contact periods of approximately 23 hours (+ or – one hour) per application. After 23 hours, subjects removed their patches without supervision. They were to then immediately report to the study site for scoring and reapplication of the patch. The subjects were instructed not to bathe or shower during the time that the patch was removed.

Applications were made every day for 21 consecutive days. All applications for individual test articles were made to the same site unless reactions became so strong as to make this inadvisable. The maximum irritation limits allowed were: (1) any numerical score that was appended with a letter grade of F, G, or H, or (2) a numerical score of "3" or above regardless of the letter grade. When a maximum score was recorded for a test article on a specific panelist, the test article was no longer applied to the panelist. The actual score was recorded for all the remaining patch test sessions. For the purposes of statistical evaluation, this observed score was converted to "3."

Evaluation
Scoring of irritation was conducted using a 100 watt incandescent blue bulb lamp. The scorer was blinded to treatment assignments and any previous scores. All reasonable attempts were made to ensure that the same individual was scoring all reactions during the study.

The irritation scoring systems used by the Applicant follow and are found on pages 006544-006547 of volume 15 of the NDA. The tables are based on scales developed by Berger and Bowman.[2]

Irritation reactions due to test materials were scored as follows:

Table 24. 21-Day Cumulative Irritation: Scoring of Reactions to Test Materials

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

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

Table 25. 21-Day Cumulative Irritation: Scoring of Effects on Superficial Layers of Skin to Test Materials

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

Endpoints
Applications were made every day for 21 consecutive days. All applications for individual test articles were made to the same site unless reactions became so strong as to make this inadvisable. The maximum irritation limits allowed were: (1) any numerical score that was appended with a letter grade of F, G, or H, or (2) a numerical score of "3" or above regardless of the letter grade. When a maximum score was recorded for a test article on a specific panelist, the test article was no longer applied to the panelist. The actual score was recorded for all the remaining patch test sessions. For the purposes of statistical evaluation, this observed score was converted to "3".

Table 26. 21-Day Cumulative Irritation: Composite Score and Resultant Classification of Irritation

Class	Score	Indications from Test
1	0-49	Mild article - no experimental irritation
2	50-199	Possibly mild in normal use
3	200-449	Possibly mild in normal use
4	450-580	Experimental cumulative irritant
5	581-630	Experimental primary irritant

Statistical Considerations
Most of the patch test scores contained a combination of a number and letter grade. The letter grade was converted to a number in the following fashion: A=0, B=1, C=2; and F, G, and H=3. These equivalents were then added to the number grades (for example, 2C=2+2=4). However, an upper limit of "3" was selected since the intent of the test was to compare treatments that were relatively mild. Therefore, for any numerical value greater than "3," a value of "3" was used in the statistical analysis.
According to the Applicant, the test article scores for each test day (and overall total) were analyzed statistically day by day to detect global differences among test articles and controls using the Friedman rank sum test. Then, pair-wise comparisons among test

articles and controls were done using Fisher's Least Significant Difference (LSD) test to identify significant differences between test articles on any particular day and overall.

Medical Officer's comment: A potential flaw of the "21-Day Cumulative Irritation Test" study design is that it assumes that all of the test articles are at most "mildly" irritating. As will be discussed in the Results section of this review, the CHG Antiseptic Cloths Bulk Solution ranked as a Class 4 material. This means that there was evidence of a strong potential for mild to moderate cumulative irritation under the conditions of the study.

Berger and Bowman noted the potential flaw in studies of this design in their 1982 paper entitled, "A Reappraisal of the 21-Day Cumulative Irritation Test in Man,"[2] in which they state "the interpretation and categorization system emphasizes the comparative evaluation of relatively mild test materials" and explain that "...for the calculation of total score, an upper limit of "3" was selected because the intent of this test is to compare treatments that are relatively mild and it would be meaningless in this context to evaluate extreme irritation (scores > 3) in the type of procedure used in this particular study. Thus for any value of > 3, a value of "3" is entered into the formula for calculating total irritation scores. Also following the development of a strong reaction, after application at the reaction site has been terminated, a value of 3 is entered for all scorings for the remainder of the test."

Results

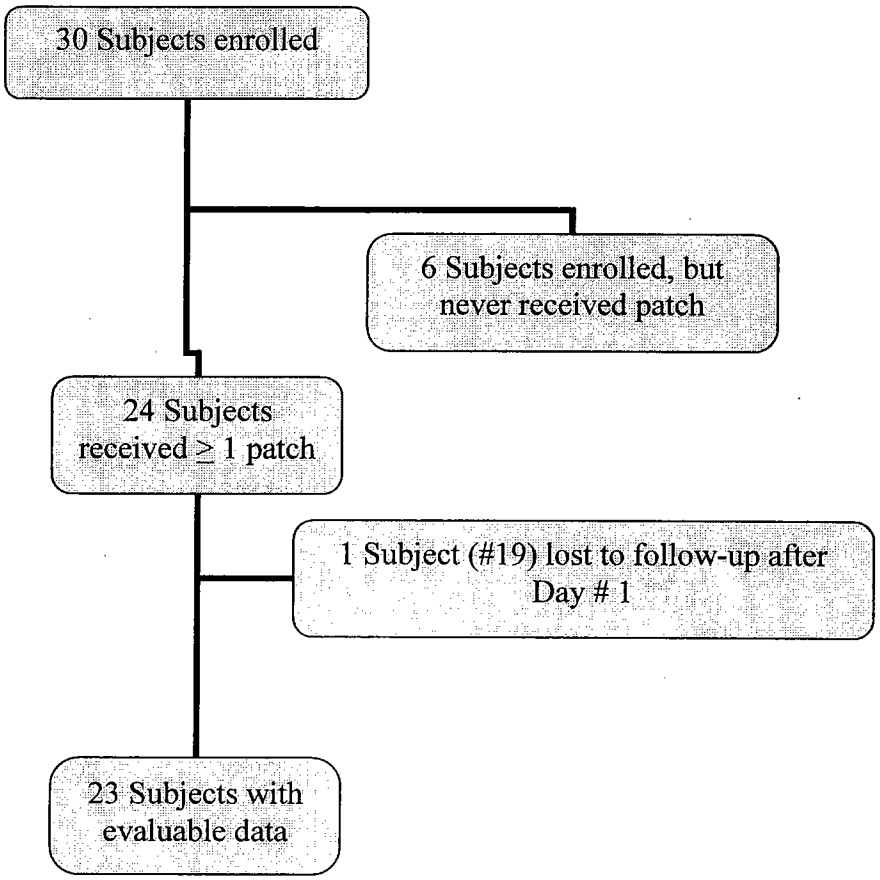
Evaluability

A total of 30 subjects were enrolled. Twenty-three subjects had evaluable data (2 male and 21 female). Six subjects withdrew consent prior to the start of the study. An additional subject withdrew within the first 24 hours of the start of the study. His withdrawal was reportedly not due to an adverse event.

Medical Officer's comment: Due to the nature of the study design, the size of the study population was relatively small. The study enrolled thirty healthy subjects. Subject comparability is limited to the baseline demographic data presented in the "Demographics" section of this review. Based on the limited sample size, the Medical Officer did not detect unusual rates of withdrawal among a particular segment of the study's gender, age, or racial demographic.

The following is a subject flow chart for the "21-Day Cumulative Irritancy Testing of Various Skin Care Products in Normal Subjects"/NWU-515-001. It was created by the Medical Officer from data provided in the NDA.

Figure 4. 21-Day Cumulative Irritation Test: Subject Flow Chart



Demographics
A total of 30 subjects were enrolled. Twenty-three subjects had evaluable data (2 male and 21 female). Subjects ranged in age from 22 to 60 years with a median age of 33 years.

Demographic data are provided in the following table created by the Medical Officer from data provided in the NDA.

Table 27. 21-Day Cumulative Irritation Test: Demographics

	All Enrolled	Subjects Treated with CHG	Evaluable Subjects
Number (%) of Subjects	30[A] (100%)	24[C] (80%)	23[D] (77%)
Median Age (years)	29.5[B]	31.5	33
Age Range (years)	19-60[B]	22-60	22-60
Gender ratio (male:female)	4:25	3:21	2:21
Racial Distribution			
Caucasian	9[B]	8	8
Black	12[B]	10	10
Hispanic	7[B]	6	5
Native American	0	0	0
Asian	0	0	0
Other	0	0	0

[A] The Applicant disclosed that Subject No. 30 was enrolled and randomized, but withdrew prior to Day 1 of the study. No CRF (and no age, race, or gender) was provided for Subject No. 30.
[B] The CRF for Subject No. 10 was inadequate. Age and race of Subject No. 10 were not provided.
[C] Subject No.'s 4, 6, 9, 10, and 14 withdrew consent prior to receiving a single patch.
[D] Subject No. 19, a 22 y.o. Hispanic male, withdrew after one day of exposure to patch. Sponsor states no skin reaction at patch site.
* The information for this table is based on subject CRFs found in vol. 16 and a demographic table on page 010531 in vol. 24 of the Applicant's NDA submission.

Safety Results

Test article #33, CHG Antiseptic Cloths Bulk Solution ranked as a "Class 4" material. This means that there was "evidence of a strong potential for mild to moderate cumulative irritation under the conditions of the study."

Test article #22, Exidine Solution was also ranked as a "Class 4" material.

The positive control, test article #88 – sodium lauryl sulfate 1% solution ranked as a "Class 5" material, that is, it demonstrated "evidence of the potential for primary irritant irritation under the conditions of the test."

Two test articles ranked as "Class 3" materials, that is, "moderate potential for mild cumulative irritation under the conditions of the test." These were test article #11, Medline Antibacterial ReadyBath (0.1% BZK) solution removed from clothes and test article #66, Calgon Vestal SeptiSoft (mixed according to No Rinse Use instructions).

Five test articles, including the negative control, normal saline, ranked as "Class 2" materials, that is, they demonstrated "evidence of a slight potential for very mild cumulative irritation under the conditions of the test."

The following summary table was modified from a table provided by the Applicant and found on page 006503 of volume 15 of the NDA. It was entitled "Formulations Used in the Study.

Table 28. 21-Day Cumulative Irritation: Irritation Scores/Classifications of Test Substances

Test	Formulation	Irritation Score, n=10	Class
00	**Placebo - CHG Antiseptic Cloths solution excluding 2% CHG**	**52**	**2**
11	Medline Antibacterial ReadyBath (0.1% BZK) solution removed from cloths	242	3
22	Exidine Solution	569	4
33	**CHG Antiseptic Cloths Bulk Solution (includes 2% CHG)**	**462**	**4**
44	Comfort Bath solution	57	2
55	Hibiclens Solution	138	2
66	Calgon Vestal SeptiSoft (mixed according to No Rinse Use instructions)	348	3
77	Medline ReadyBath solution removed from cloths	145	2
88	Sodium Lauryl Sulfate 1% solution (positive control)	621	5
99	Sodium Chloride 0.9% solution (negative control)	71	2

Medical Officer's comments: It should be noted that under this protocol, reapplication of test articles was omitted after achieving a level "3" reaction. Therefore, it is possible that test articles may have caused further irritation with additional applications. There were no apparent differences in time to termination of the CHG Antiseptic Cloths Bulk Solution patch between different racial and age groups. The Medical Officer calculates that on average, Caucasian subjects reached level "3" irritation, the threshold level for termination, by 6 days, Hispanic subjects by 7 days, and Black subjects by 8 days. Subjects aged 18 to 40 years reached level "3" irritation by 6 days and subjects aged 41-64 years reached level "3" termination by 10 days. The evaluable population did not contain subjects older than 64 years. The longer time to termination in the group aged 41-64 years appeared to be driven by one 44 year old Hispanic woman who maintained her CHG Antiseptic Cloths Bulk Solution patch for 18 days. If the remaining five subjects are evaluated separately, then, on average, they reached level "3" termination by day 8. This point illustrates that it is difficult to draw

safety conclusions based on demographic differences from this small study of 23 evaluable subjects.

Out of the 23 subjects with evaluable data, 21 were women. Therefore, the Medical Officer cannot draw conclusions about the cumulative irritancy of CHG Antiseptic Cloths Bulk Solution due to gender differences based on the results of this study in which 91% of the participants were women.

Safety Endpoint Outcomes

Safety Comparison of Adverse Events

All Adverse Events

One adverse event occurred during the course of this study. The adverse event form was found on page 007199. Subject No. 24 was a 27 year old Black female who prematurely withdrew from the study on Day 5. On study Day 3 (06/03/02) the subject reported that "the top part of the patch area was burning," and that she had removed the patch early and "placed hydrogen peroxide over test site #88," the area of skin in contact with the positive control. Latter that day, the subject called complaining of continued burning. The subject returned to the center and the technicians removed the polyester squares containing Medline Antibacterial ReadyBath (0.1% BZK) solution, Exidine solution and the sodium lauryl sulfate positive control and replaced those chambers with filter paper without solution. On study day 4 (06/04/02), the CHG Antiseptic Cloths Bulk Solution skin site, #33, reached threshold for removal at level "3" and was noted to have "small petechial erosions and/or scabs." In addition, on the same day a note written on the "Patch Test Reading" form stated that site #'s "88, 77, 33" were left "open to air," and "all three square chambers were cut open." "All other chambers were maintained." The note was initialed "NH" or "HH." The sites left open to air: #88-positive control, #77-Medline ReadyBath solution (without BZK), and #33-CHG Antiseptic Cloths Bulk Solution (proposed product with 2% CHG). On Day 5 (06/05/02), the subject withdrew. The investigator marked on the adverse event (AE) form that the AE was "burning at skin test site," that the AE started "06/03/02," that it was "mild" and lasted "3 days." The investigator reported that there was a "definite" relationship between the adverse event and the study product, and the outcome was the "subject withdrew."

Treatment-Related Adverse Events

As above.

Discontinuations Due to Adverse Events

As above.

Serious Adverse Events

None.

Deaths

None.

Reviewer Conclusions
CHG Antiseptic Cloths Bulk Solution was determined to be a Class 4 Irritant (experimental cumulative irritant) in this study. Both the CHG Antiseptic Cloths Bulk Solution excluding 2% CHG vehicle arm and the Comfort Bath® solution were determined to be Class 2 Irritants (possibly mild in normal use) in this study. Therefore, the excessive irritation seen with CHG Antiseptic Cloths Bulk Solution was most likely either secondary to the chlorhexidine gluconate included in the formulation or as a result of interaction of chlorhexidine gluconate with other components of the bulk solution.

The irritancy potential for the CHG Antiseptic Cloths Bulk Solution was similar to that observed for Exidine Solution (Class 4 Irritant) and greater than that observed for Hibiclens® Solution (Class 2 Irritant) in the population studied.

Based on the results of the 19 subjects with evaluable information who did not drop out of the study unless they had a reaction to the CHG Antiseptic Cloths Bulk Solution, the average length of time that CHG Antiseptic Cloths Bulk Solution was tolerated before the development of a skin reaction was 6.79 days or approximately 1 week. The only products that were tolerated for shorter durations were sodium lauryl sulfate 1% solution (the positive control) and Exidine for which average dropout due to protocol defined irritancy discontinuation criteria occurred at 1.53 days and 3.68 days, respectively.

7.1.13.2 Trial Name/Number: "Exclusive Repeated Insult Patch Test" ("Repeat Insult Patch Test" or RIPT)/Protocol Number: SGNC-001.

The details of this study were found in volume 17 of the medical officer's NDA packet.

Objective/Rationale
To determine by repetitive epidermal contact the primary or cumulative irritation and/or allergic contact sensitization potential of CHG Antiseptic Cloths versus other products on the market.

Design
Randomized and double-blinded safety study.

Protocol
This study was conducted from June 17, 2002 to July 26, 2002 by [redacted]

Eight patches were applied to the backs of 218 healthy subjects. The patches contained eight test products: CHG Antiseptic Cloths Bulk Solution (2% CHG), Placebo - CHG Antiseptic Cloths Bulk Solution (without 2% CHG), Hibiclens® (4% CHG) by Astrazeneca, Exidine (2% CHG) by Xttrium Laboratories, Vestal SeptiSoft (mixed according to NoRinse Use instructions) by Calgon, Antibacterial ReadyBath (0.1% BZK) by Medline Industries, ReadyBath by Medline Industries, Comfort Bath® by Sage Products, Inc. Each subject was instructed that the patch was to remain in place and kept

dry for 23 hours +/- 1 hour daily, at which time the patch was to be removed by the subject prior to the next clinic visit.

The patches were applied using an occlusive dressing that remained in place for 24 hours. The study involved both an induction and challenge phase. The induction phase involved product application three times a week for a total of 9 weeks. Readings occurred 24 hours after patch removal, that is, immediately before reapplication.

If a test site exhibited an evaluation score of "2" during the induction phase, the test patch was moved to an adjacent site. If an evaluation score of "2" was observed on the new site, further applications were discontinued. Evaluation scores of "3" or greater required discontinuation of further applications of that test patch.

Two weeks after the final induction phase patch applications, the subject began the challenge phase of the study. Using an occlusive dressing, the test substances were applied to a new site on each subject's back. The dressings remained occluded for 24 hours. Readings during the challenge phase occurred at 24 and 72 hours post-patch application.

Population, Procedures

Subjects

The investigator planned to enroll approximately 200 male and female subjects aged 18 years or older.

Inclusion Criteria (taken directly from vol. 15, page 006542)

- Males and females, aged 18 years or older
- Absence of any visible skin disease which might be confused with a skin reaction from the test material
- Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation
- Completion of a Medical History form and the understanding and signing of an Informed Consent form
- Considered reliable and capable of following directions

Exclusion Criteria (taken directly from vol. 15, page 006542)

- Ill health
- Under a doctor's care or taking medication(s) which could influence the outcome of the study
- Females who are pregnant or nursing; a urine pregnancy test will be required for females with child bearing potential and those who are peri-menopausal or post-menopausal less than one year
- A history of adverse reactions to cosmetics or other personal care products
- Must not be participating in any other studies

Procedures

Sample Preparation and Dressing

Approximately 0.3 ml of each test solution was measured by a tuberculin syringe, and was applied to a ¾ x ¾ inch absorbent pad center (100% polyester) of a non-porous adhesive dressing (manufactured by [redacted] This was then applied to the appropriate treatment site to form an occluded patch.

Test Procedure

Induction Phase

The patches were applied to the upper back between the scapulae. Each patch was applied to the same site three times per week (Monday, Wednesday, and Friday) for a total of nine applications. Following supervised removal of the first induction patch, participants were instructed to remove the patches at home, 24 hours following all subsequent induction patch applications. Scoring of the test site was made just prior to re-application.

If the subject was unable to report on the assigned day, the subject was allowed one make-up day. A second make-up day was allowed only at the discretion of the study investigator. All make-up days were added to the induction period. If any subject did not report as instructed, the subject was automatically eliminated from the study.

The site was marked with a surgical pen to ensure the continuity of repetitive patch application.

Interim rest periods occurred 24 hours following each Tuesday and Thursday patch removal and 48 hours following each Saturday patch removal.

Challenge Phase

Approximately two weeks following the final induction patch applications, challenge patches were applied to new test sites adjacent to the original induction patch sites, following the same procedure described for induction. The patches were removed and the sites were scored at the clinic 24 hours and 72 hours post-application.

Endpoints

The following table is based on information provided by the Applicant on page 007391 of volume 17 of the NDA, and describes how skin irritation was scored.

Table 29. Evaluation Key for the Repeat Insult Patch Test/Protocol Number: SGNC-001

Score	Clinical Interpretation
0	No visible skin reaction
"+"	Barely perceptible or spotty erythema
1	Mild erythema covering most of the test site
2	Moderate erythema, possible presence of mild edema
3	Marked erythema, possible edema
4	Severe erythema, possible edema, vesiculation, bullae and/or ulceration

Statistical Considerations

Neither the [redacted] ıor Sage Products, Inc. provided a description of the statistical methodology used in this study.

Results

Evaluability

Two hundred eighteen male and female subjects were enrolled in the study. Two hundred four subjects completed the study. According to the Applicant, the remaining fourteen subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

The following table created by the Medical Officer, from data in the NDA, contains the Applicant's reasons for subject discontinuation and the level of irritation noted on the CHG Antiseptic Cloths Bulk Solution skin site at the time of discontinuation.

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Table 30. Reasons for Subject Discontinuation in RIPT Study Provided by CRF and Applicant

Subject ID Numbers	Reason for Discontinuation	Level of Irritation on CHG Antiseptic Cloths Bulk Solution Skin Site
13	6/19/02: "Panelist unable able to comply with schedule."	No visible skin reaction
72	7/2/02: "Panelist unable to comply with schedule."	Dry, but no visible skin reaction
117	6/18/02: "Panelist could not comply with schedule."	No visible skin reaction
131	6/18/02: "Subject was not present for removal of patches." 6/18/02: "Unable to comply with schedule."	No data recorded
137	6/25/02: "Panelist unable to comply with schedule."	No visible skin reaction
164	7/9/02: "Panelist could not comply with procedure."	No visible skin reaction
172	7/2/02: "Panelist unable to comply with schedule."	No visible skin reaction
206	6/24/02: "Panelist could not comply with schedule."	No data recorded
33	6/24/02: "Panelist forgot to come on 6/21 and was out of town on 6/24."	No visible skin reaction
22	No comment in CRF. Applicant added, "Missed two consecutive make-up days."	No visible skin reaction
194	7/5/02: "Panelist had 2M." Applicant added, "Missed two consecutive make-up days."	No visible skin reaction
160*	7/8/02: "Protocol violator." Applicant added, "Not compliant with patch instructions."	Moderate erythema, possible presence of mild edema
204*	6/20/02: "Panelist said patches are bothering her - wants to drop from study."	No data recorded
217*	6/25/02: "Panelist said patches were burning her - she was uncomfortable." 7/02/02: "Due to tape not product related."	No visible skin reaction

*The Applicant did not list the discontinuations of Subject No.'s 160, 204, and 217 as due to possible adverse events.

Medical Officer's comment: The Medical Officer notes that three of the fourteen subjects that discontinued the study prematurely may have had possible adverse events

that were not reported. As noted in the preceding table, upon closer inspection of the subject case report forms (CRFs), Subject No. 160, an 18 year old Caucasian/American Indian woman, had "moderate erythema, possible presence of mild edema" noted at the CHG Antiseptic Cloths Bulk Solution application site on 7/8/02. The CRF for Subject No. 204, a 30 year old Caucasian woman, stated, "panelist said patches are bothering her - wants to drop from study." However, no data was recorded for the level of irritation at the Applicant's proposed product's skin site. On 6/25/02, Subject 217, an 18 year old Caucasian woman, discontinued the study and the CRF noted, "Panelist said patches were burning her - she was uncomfortable." One week later on 7/02/02 another notation in the CRF stated, "Due to tape, not product related." The Medical Officer believes that reports for all three of these cases should be considered adverse events. This information is summarized in Table 20 of this review.

Demographics

Two hundred eighteen male and female subjects were enrolled in the study. The ages of subjects ranged from eighteen to seventy-nine. Two hundred four subjects completed the study. According to the Applicant, the remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Medical Officer's comment: The Medical Officer disagrees with the Applicant's assertion that all 14 of the subjects discontinued the study for reasons unrelated to the Applicant's proposed product. The Medical Officer discussed this in detail in the preceding "Evaluability" section.

Demographic data are provided in the following table created by the Medical Officer from data in the NDA.

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Table 31. Repeat Insult Patch Test: Demographics

	All Enrolled	Subjects that Withdrew Prematurely [A]	Evaluable Subjects
Number (%) of Subjects	218 (100%)	14 (6%)	204 (94%)
Median Age (years)	51	29.5	52.5
Age Range (years)	18-79	18-63	18-79
Gender ratio (male:female)	50:168	1:13	49:155
Racial Distribution			
Caucasian*	180	9	171
Black	9	2	7
Hispanic	24	3	21
Native American	2	0	2
Asian	3	0	3

[A] Please refer to the table entitled "Reasons for Subject Discontinuation in RIPT Study Provided by CRF and Applicant" found in the "Evaluability" section of this review for reasons why subjects withdrew.
*The Applicant counted two Caucasian/American Indian subjects as "Caucasian" for demographic purposes.

Safety Results

The following table created by the Medical Officer, from data in the NDA, summarizes the results of the "Repeat Insult Patch Test."

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Table 32. Repeat Insult Patch Test: Results (n=204 for each product)

Product	No. (%) of subjects with specific level of reaction						
	Induction				Challenge		
	(+)	1	2		(+)	1	2
			Total	Discon-tinued			
CHG Antiseptic Cloths (2% CHG)	13 (6)	12 (6)	42 (21)	17 (8)	4 (2)	9 (4)	5 (2)
Placebo for CHG Antiseptic Cloths	6 (3)	3 (1)	3 (1)	0	0	0	0
Hibiclens® (4% CHG)	14 (7)	6 (3)	6 (3)	0	0	1	0
Exidine (2% CHG)	17 (8)	10 (5)	51 (25)	27 (13)	5 (2)	7 (3)	13 (6)
Vestal SeptiSoft	21 (10)	19 (9)	1	0	1	-	1
Antibacterial ReadyBath(0.1% BZK)	5 (2)	3 (1)	5 (2)	1	-	1	1
ReadyBath	7 (3)	3 (1)	1	1	-	-	1
Comfort Bath®	11 (5)	5 (2)	0	0	-	2 (1)	-

* All percentages are rounded to nearest 1.0.

Medical Officer's comment: This table demonstrates that under the conditions of this special safety study, CHG Antiseptic Cloths (Bulk Solution) caused more irritation during the induction and challenge phases of the study than Hibiclens®. Among the comparator products, only Exidine (2% CHG) caused more irritation than the CHG Antiseptic Cloths during the induction and challenge phases of the test. Of note, the [redacted] produced the bulk 2% CHG solution found in both the CHG Antiseptic Cloths drug product and Exidine drug product used in both the pivotal "safety" studies (Repeat Insult Patch Test and 21-Day Cumulative Irritation Test). This suggests that differences in the finalized formulations of the CHG Antiseptic Cloths and Exidine drug products may result in different levels of irritation.

Safety Endpoint Outcomes

Safety Comparison of Adverse Events

All Adverse Events

See comments made in the preceding "Evaluability" section.

Treatment-Related Adverse Events
As above

Discontinuations Due to Adverse Events
As above

Serious Adverse Events
None.

Deaths
None.

Reviewer Conclusions
According to the Applicant, under the conditions of the "Repeat Insult Patch Test," the CHG Antiseptic Cloths exhibited low to moderate-grade patch test irritant responses in approximately one-third of the test population. There was no evidence of induced allergic contact dermatitis in the population studied.

7.1.13 Withdrawal Phenomena / Abuse Potential

While the Applicant did not perform studies to assess the potential for withdrawal phenomena and abuse potential, there is no expectation that either will be an issue for this topical antiseptic intended for single use application.

7.1.14 Human Reproduction and Pregnancy Data

The Applicant did not submit data on the reproductive toxicity potential of CHG Antiseptic Cloths. However, the Pharmacologist/Toxicologist, Amy Ellis, PhD., noted that there were no concerns with reproductive toxicity related to use of this product based on the summary of literature provided by the Applicant and based on the Agency's prior findings of safety for products containing chlorhexidine gluconate.

7.1.15 Overdose Experience

There are no reports of "overdose" experience with the Applicant's product. Of note, however, chlorhexidine gluconate is poorly absorbed through the skin and gastrointestinal tract[1] making the overdose potential for this antiseptic cloth unlikely.

7.1.16 Post-marketing Experience

There is no post-marketing experience with this product.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Extent and Adequacy of Overall Clinical Experience

A total of 417 subjects were exposed to the proposed drug product. All of the subjects were from the United States.

One hundred and twenty-two of the 417 subjects participated in the three pivotal "efficacy" studies. These studies took place at
In these efficacy studies, exposure on the abdomen consisted of a one-time application to a 5 x 5 inch area (25 in^2 or 161 cm^2). Exposure on the inguinal region consisted of a one-time application to a 2 x 5 inch area (10 in^2 or 65 cm^2). Duration of exposure was six hours. Details of these studies are found in section 6.3 of this review.

Fifty-three of 417 subjects participated in pilot studies at
Exposure consisted of 5 x 5 cm applications of the proposed drug product to one or bilateral inguinal regions. Duration of exposure was 10 minutes.

Twenty-four of 417 subjects participated in the "21-Day Cumulative Irritancy Test." Sixty-five micro liters of bulk drug product were applied to 8 x 8 mm of cloth. Duration of exposure was 21 consecutive daily applications under occlusion for approximately 23 hours each day. This special safety study is described in detail in section 7.1.12 of this review.

Two hundred and eighteen of 417 subjects participated in the "Repeated Insult Patch Test". The quantity of bulk drug product applied to ¾ x ¾ inch of cloth was 0.3 mL. Exposure occurred during an induction phase and a challenge phase. The patches were applied using an occlusive dressing that remained in place for 24 hours. For example, the induction phase involved product application three times a week for a total of nine weeks. Twenty-four hour interim rest periods followed patch removals every Tuesday and Thursday. Forty-eight hour interim rest periods followed patch removals every Saturday. Two weeks after the final induction phase patch applications, the subject began the challenge phase of the study. Using an occlusive dressing, the test substances were applied to a new site on each subject's back. The dressings remained occluded for 24 hours and then were removed. This special safety study is described in detail in section 7.1.12 of this review.

The safety testing was adequate for single use of the proposed product, CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution) for the indication of Patient Preoperative Skin Preparation. Given the lack of systemic absorption,[1] no additional safety evaluation is needed for the single use indication of Patient Preoperative Skin Preparation.

7.2.2 Adequacy of Special Animal and/or *In vitro* Testing

The safety testing was adequate for single use of the proposed topical product, CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution). Given the lack of systemic absorption,[1] no additional pre-clinical safety evaluation is needed for the single use indication of Patient Preoperative Skin Preparation.

consult the Division of Anti-Infective Drug Products regarding the need to perform additional preclinical studies.

7.2.3 Adequacy of Routine Clinical Testing

Not applicable. No routine clinical testing was performed or needed for subjects treated with this topical agent.

7.2.4 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable. Chlorhexidine gluconate is poorly absorbed through the skin and gastrointestinal tract.[1]

7.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by New Drug; Recommendations for Further Study

The Applicant made adequate efforts to identify potential adverse events when their product, CHG Antiseptic Cloths, was used for the single use indication of Patient Preoperative Skin Preparation. The Applicant has adequately studied the potential irritation and sensitization potential of the product.

7.2.6 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of the safety data were adequate to determine the overall safety of the proposed product. However, a few data inconsistencies were found during the review of this NDA:

- Study subjects' case report forms (CRFs) for the [redacted] pivotal "efficacy" study, [redacted] 01-109381-11, did not contain adverse event reporting forms. The study investigator reported that no adverse events occurred during the study and that up to that point in time, forms recording adverse events were only added to subjects' CRFs if an adverse event occurred. The Division of Scientific Investigation has recommended that the study center incorporate adverse event reporting forms into all subject CRFs regardless of whether or not subjects experience an adverse event and document whether or not study personnel observe adverse events.
- The CRFs of twelve out of twelve subjects from the [redacted] Pilot Study No. 020418-103 did not contain the ages of the subjects. No adverse events were reported during this study.

7.3 Summary of Selected Drug-Related Adverse Events

The primary drug-related adverse event identified by studies provided in the NDA is skin irritation, which is not unexpected for chlorhexidine gluconate-containing topical products. Additional potential drug-related adverse events, identified in literature, that should be included in the "problem list" for this chlorhexidine gluconate product include, severe and permanent corneal opacification, deafness, nerve toxicity, severe irritation

with exposure to mucous membranes, anaphylaxis, and severe irritation and ulceration in neonates.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

As was previously noted, there were two types of subject exposures, involving a total of 417 subjects, in studies submitted to support approval of CHG Antiseptic Cloths for the indication of Patient Preoperative Skin Preparation. A total of 175 subjects received single topical application of the study drug in the four pilot "efficacy" studies [redacted] #01-109628-11, [redacted] #02-120904-103, [redacted] #020418-103, and [redacted] #500-101) and the three pivotal "efficacy" studies [redacted] #01-109381-11, [redacted] #020125-103-01, and [redacted] #500-102). The intended use of the product for Patient Preoperative Skin Preparation is most similar to use in these seven studies (i.e. single application without use of occlusive dressings).

The second type of subject exposure, involving a total of 242 subjects, occurred in the two pivotal "safety" studies (21-Day Cumulative Irritation Test #NWU-515-001 and Repeat Insult Patch Test #SGNC-001). These studies were designed to elicit the maximal irritation and sensitization potential (i.e., multiple consecutive applications under occlusive dressing) of CHG Antiseptic Cloths as compared to similar products, a positive control, and negative controls.

It is not unexpected that the majority of adverse events occurred in the pivotal "safety" studies since these are designed to elicit maximal irritation and/or sensitization. The actual adverse event profile with single use in the intended population is more appropriately estimated based on the seven "efficacy" studies in which single applications of test product were applied.

7.4.2 Explorations for Predictive Factors

The following tables created by the Medical Officer, from data in the NDA, provide summaries of the racial and age distribution for all enrolled subjects.

Table 33. Racial Distribution by Study

Race	Pivotal "Efficacy" Studies			Pilot "Efficacy" Studies				Pivotal "Safety" Studies		Total
	[redacted] #01-109381-11	[redacted] #020125-103.01	[redacted] #500-102	[redacted] #01-109628-11	[redacted] #02-120904-106	[redacted] #020418-103	[redacted] #500-101	21-Day Cumulative Irritation	Repeat Insult Patch Test	
Caucasian	49	33	25	11	9	12	15	8	180	342
Black	2	0	3	1	1	0	1	10	9	27
Hispanic	0	1	1	0	0	0	0	6	24	32
Native American	0	1	0	0	0	0	0	0	2	3
Asian	0	0	7	0	0	0	3	0	3	13
Total	51	35	36	12	10	12	19	24	218	417

Table 34. Age Distribution by Study

	Pivotal "Efficacy" Studies			Pilot "Efficacy" Studies				Pivotal "Safety" Studies		Total
Age Group (years)	[redacted] #01-109381-11	[redacted] #020125-103.01	[redacted] #500-102	[redacted] #01-109628-11	[redacted] #02-120904-106	[redacted] #020418-103	[redacted] #500-101	21-Day Cumulative Irritation	Repeat Insult Patch Test	
18-40	8	25	23	1	0	Unknown	10	17	68	152
41-64	26	9	13	5	6	Unknown	9	7	86	161
65-74	17	1	0	6	4	Unknown	0	0	48	76
>74	0	0	0	0	0	Unknown	0	0	16	16
Sub - Total										405
Total	51	35	36	12	10	12*	19	24	218	417*

*Twelve subjects are added to the subtotal from the Pilot Study #020418-103. Individual ages of subjects from the Pilot Study were not provided in submitted CRFs.

The ability to explore the database for patient-predictive factors such as age, sex, and race is limited by the small number of treatment-related adverse events (n=3) that actually occurred, the limited number of non-Caucasian subjects, and the lack of pediatric subjects. It should be noted, however, that all adverse events occurred in female subjects.

The three efficacy studies enrolled subjects up to and including an age of 69 years. Therefore, there is no clinical simulation experience with the use of this product in individuals beyond the age of 69 years. There were no drug-related adverse events among the 92 subjects > 65 years of age exposed to the Applicant's product in either the pivotal "safety" or pivotal "efficacy" studies. No subjects less than 18 years old were exposed to the Applicant's product.

The pivotal "safety" studies demonstrate that the incidence of treatment-related adverse events appears to be strongly related to duration of treatment, particularly if the Applicant's product is applied under an occlusive dressing (Class 4 Irritant).

While the pivotal "safety" studies performed by the Applicant do not mimic expected clinical use of the product as a Patient Preoperative Skin Preparation, the pivotal "safety" studies may provide additional information as to the age groups that may be at risk for adverse events in the general population.

In the "Repeat Insult Patch Test" (RIPT), 17 subjects discontinued the CHG Antiseptic Cloths patches prior to the end of the study due to achieving level "2" irritation ("Moderate erythema, possible presence of mild edema) at two separate skin sites. The average age of the subjects that discontinued treatment prematurely was 60.5 years old. The following table created by the Medical Officer, from data in the NDA, provides the age distribution of these subjects in each of four age strata: 18-40 years, 41-64 years, 65-74 years, and greater than 74 years.

Table 35. Subjects in RIPT that had CHG Antiseptic Cloths Test Patches Discontinued Prematurely (n=218)

Age Range (years)	No. of Subjects Discontinued Prematurely (% total in age group)
18-40	4 (6%)
41-64	4 (5%)
65-74	4 (8%)
>74	5 (31%)

The average age of the 43 subjects that reached level "2" irritation (moderate erythema, possible presence of mild edema) at one site during the induction period of the RIPT study (including the 17 subjects who eventually had to prematurely discontinue treatment) was 55.4 years. The following table created by the Medical Officer, from data in the NDA, demonstrates the number of subjects who reached level "2" in each of four age strata: 18-40 years, 41-64 years, 65-74 years, and greater than 74 years.

Table 36. Subjects in RIPT that had Level 2* Irritation at the CHG Antiseptic Cloths Patch Test Site (n=218)

Age Range (years)	No. of Subjects with Level 2 Irritation (% total in age group)
18-40	10 (15%)
41-64	13 (15%)
65-74	12 (25%)
>74	8 (50%)

* Level 2 = moderate erythema, possible presence of mild edema

Overall, this data suggests that regular or frequent use of the Applicant's product may result in more deleterious effects in older individuals.

7.4.3 Causality Determination

As noted in section 7.3, out of the 417 subjects treated with CHG Antiseptic Cloths, only three treatment-related adverse events occurred. Out of these three treatment-related adverse events, only one occurred in a study that simulated the proposed clinical use of CHG Antiseptic Cloths.

All three adverse events were manifestations of skin irritation and varied in intensity from mild to moderate. Given what is known about chlorhexidine gluconate in the literature,[1] all three adverse events are very likely to be due to the Applicant's product, CHG Antiseptic Cloths.

7.5 Safety Conclusions

Based on the available safety information, the Applicant's proposed product, CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution), is safe for the single use indication of Patient Preoperative Skin Preparation. Given the lack of systemic absorption,[1] no additional safety evaluation is needed for the single use indication of Patient Preoperative Skin Preparation.

The irritancy study conducted by the Applicant demonstrated that CHG Antiseptic Cloths are Class 4 Irritants (experimental cumulative irritant) when repeatedly applied under occlusive dressings. Only the positive control, sodium lauryl sulfate 1% solution, demonstrated a higher irritancy potential in this study.

The Repeat Insult Patch Test conducted by the Applicant did not demonstrate the occurrence of sensitization with repeated application and subsequent re-challenge with CHG Antiseptic Cloths in the population studied. The higher rate of "level 2" irritation and higher rate of discontinuation due to predefined irritancy criteria in subjects greater

than 65 years of age; however, suggests that the Applicant's product may cause greater skin irritation in the elderly population.

There do not appear to be racial differences in the safety profile for the Applicant's product; however, this conclusion is qualified by the fact that the overall number of non-Caucasian subjects that have been exposed to the Applicant's product is relatively few in number.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Applicant's proposed product, CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution) achieved the TFM-required mean $\log_{10}$ reductions of bacteria on the skin as formulated. Data was not provided for other formulations containing differing percents of chlorhexidine gluconate. As is true for other products that have been granted this indication in the past, the Applicant has provided data that supports the conclusion that use of this product results in decreased bacterial counts on the skin; however, the Applicant has not provided direct evidence that supports the conclusion that use of this product [redacted].

The fact that only one adverse event was noted, in the three pivotal "efficacy" studies designed to simulate clinical use (single application), supports the conclusion that toxicity has been adequately minimized with the current formulation of the Applicant's product. Questions related to dose interval, timing of administration (including relation to meals), and importance of any critical interactions are irrelevant for this topical product.

8.2 Drug-Drug Interactions

Not applicable for this topical product as chlorhexidine gluconate is minimally absorbed through the skin in populations with fully keratinized skin (that is, ≥2 months of age).[1]

8.3 Special Populations

At this time, 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 as it does not appear to be absorbed through the skin of the healthy individuals.[1] However, based on the literature, severe skin reactions may occur in infants less than two months of age.[12] Therefore, this product should not be used on infants less than 2 months of age.

8.4 Pediatrics

The Applicant states that the proposed product may be used as a Patient Preoperative Skin Preparation on patients ≥ 2 months of age. The Applicant has provided literature to support this statement. The Applicant requests a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy, and children less than 2 months of age due to the potential for irritation and enhanced absorption.

Medical Officer's comment: The literature submitted by the Applicant on June 14, 2004 supports the Applicant's claim that the proposed product may be used safely in patients ≥ 2 months of age. The Applicant's request for a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy and children less than 2 months of age due to the potential for irritation and enhanced absorption is acceptable. Literature reviewed by the Medical Officer concurs with the Applicant's claim. Garland et al. noted seven cases of severe contact dermatitis in premature and very low birth weight infants.[12] Of note, the pivotal "efficacy" studies were performed in subjects between the ages of 18 and 69 years of age.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

There is extensive literature on clinical experience with chlorhexidine gluconate.

The Applicant provided four articles in the NDA submission.

"Article 1" is **Case DE, McAinsh J, Rushton A, Winrow MJ. "Chlorhexidine: Attempts to detect percutaneous absorption in man." p 367-374 in *Chemotherapy*, Volume 3: "Special Problems in Chemotherapy," 9th Edition, Editor: J.D. Wiliams and A.M. Geddes, Publisher: Plenum Press, London. 1975.**[3] This book section notes that chlorhexidine has been marketed since 1953. Percutaneous absorption of chlorhexidine is minimal. When administered orally, chlorhexidine is poorly absorbed from the gastrointestinal tract, and very small fractions are excreted in the urine and biliary tract. The authors note that, "the compound should not be instilled directly into the middle ear, as deafness may follow."

"Article 2" is **Case DE. "Chlorhexidine: Attempts to detect percutaneous absorption in man." International Congress and Symposium Series, Royal Society of Medicine. No. 23: 45-48, 1980.**[4] Five adult male human subjects had chlorhexidine digluconate applied as a 5% aqueous solution or a 4% formulated hand wash to a 50 cm^2 section of the forearm for three hours. Two of the five subjects had minimal amounts (less than 0.009% of the applied dose) of chlorhexidine detected in their feces in the first 10 days after application, and none in their urine or blood. The remaining three subjects had no chlorhexidine detected in the feces, urine, or blood.

In a repeated application study, 15 clinically healthy adult subjects (8 female and 7 male) used chlorhexidine in a hand scrub regimen carried out five times per day, five days a week, for three weeks. Venous blood was drawn on days 0, 5, 12, 16, and 19. No chlorhexidine was detected in any of the samples.

A third study was carried out among 25 operating room staff from three hospitals. They had to have used chlorhexidine for at least the prior six months as a preoperative

antiseptic for hand disinfection. No detectable levels of chlorhexidine were noted in any of the blood samples.

"Article 3" is **Stuart Pharmaceuticals, Hibiclens® Prescribing Information, In: Physician's Desk Reference, 2000, 551-552.**[5] This reference provides the Hibiclens® entry found in the 2000 Physician's Desk Reference.

Of note, the "Warnings" section states:
"For external use only. Keep out of eyes, ears and mouth. Hibiclens should not be used as a preoperative skin preparation of the face or head. Misuse of Hibiclens® has been reported to cause serious and permanent eye injury when it has been permitted to enter and remain in the eye during surgical procedures. If Hibiclens® should contact these areas, rinse out promptly and thoroughly with water. Avoid contact with meninges. Hibiclens® should not be used by persons who have sensitivity to it or its components. Chlorhexidine gluconate has been reported to cause deafness when instilled in the middle ear through perforated ear drums. Irritation, sensitization and generalized allergic reactions have been reported with chlorhexidine-containing products, especially in the genital areas."

"Article 4" is **Morbidity and Mortality Weekly Report; October 25, 20002; Volume 51; No. RR-16.**[6] This is the 2002 "Guideline for Hand Hygiene in Health-Care Settings," prepared by the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDAS Hand Hygiene Task Force. This guideline supports the use of chlorhexidine (2% and 4% aqueous) for hand hygiene use in healthcare settings.

The Applicant also provided a reference for the methodology used in the "21-Day Cumulative Irritation Test" that the Medical Officer obtained and read. **Berger RS, Bowman JP. A reappraisal of the 21-day cumulative irritation test in man. J. Toxicol. Cut. Ocular Toxicol. 1982;1(2):109-115.**[2]

The Medical Officer also reviewed the following book chapter and six additional articles that highlight safety issues associated with the use of chlorhexidine gluconate.

Denton GW, Ch. 16, "Chlorhexidine" p274-289 in *Disinfection, Sterilization, and Preservation,* 4th Edition, Editor: Seymour S. Block, Ph.D., Publisher: Lea & Febiger, Philadelphia. 1991.[1] This chapter provides extensive information on the chemistry, mechanisms of action, bactericidal activity by test organism, clinical uses, and toxicity of chlorhexidine. With regard to toxicity, long term effects of animal feeding and human topical use demonstrate that absorption from the gastrointestinal tract or through the skin is negligible. There is no evidence for carcinogenicity. The incidence of skin irritation and hypersensitivity is low when applied at recommended concentrations. Chlorhexidine is toxic to nerve tissue and should not contact the brain or meninges. Human patients have developed sensorineural deafness as a result of the use of 0.05% chlorhexidine in 70% alcohol for perioperative disinfection of the middle ear. Concentrations of chlorhexidine greater than 0.05% have been noted to cause ocular damage.

Thornton Spann C, Taylor SC, Weinberg JM. Topical antimicrobial agents in dermatology. Clin Dermatol. 2003 Jan-Feb;21(1):70-7.[7] This review article includes

a comparison of the virtues of chlorhexidine gluconate versus povidone iodine for "presurgical prophylaxis." The authors note that in comparison to povidone iodine, chlorhexidine gluconate may achieve greater reductions in colonizing skin microflora, has a longer residual activity, and is not inactivated by blood or serum proteins.

Hamed LM, Ellis FD, Boudreault G, Wilson FM 2nd, Helveston EM. Hibiclens keratitis. Am J Ophthalmol. 1987 Jul 15;104(1):50-6.[8] The authors discuss the case reports of two patients who sustained severe and permanent corneal opacification after accidental corneal exposure to Hibiclens® (chlorhexidine 4% and detergent). In addition, the authors investigated the gross, microscopic, and histopathologic damage caused when rabbits' eyes were exposed to Hibiclens® for varying time intervals from 5 to 15 minutes. The authors found that severe, irreversible, and progressive corneal damage resulted in all eyes studied.

Tabor E, Bostwick DC, Evans CC. Corneal damage due to eye contact with chlorhexidine gluconate. JAMA. 1989 Jan 27;261(4):557-8.[9] This article provides four cases of patients who suffered irreversible corneal damage after chlorhexidine gluconate was used as a Patient Preoperative Skin Preparation on their faces. Two of the cases were also discussed in the article written by Hamed et al (1987).

Snellman E, Rantanen T. Severe anaphylaxis after a chlorhexidine bath. J Am Acad Dermatol. 1999 May;40(5 Pt 1):771-2.[10] This article discusses 4 cases of anaphylaxis caused by chlorhexidine in Finland. Three of the cases occurred in women after a gynecologic examination in which a lubricant cream containing chlorhexidine had been used. In the forth case, a 49 year old male developed anaphylaxis during a chlorhexidine bath. In all cases, skin prick tests for chlorhexidine were positive.

Okano M, Nomura M, Hata S, Okada N, Sato K, Kitano Y, Tashiro M, Yoshimoto Y,Hama R, Aoki T. Anaphylactic symptoms due to chlorhexidine gluconate. Arch Dermatol. 1989 Jan;125(1):50-2.[11] The authors describe six cases in which Japanese patients developed urticaria, dyspnea, and anaphylactic shock after topical application of chlorhexidine gluconate solution. In five of the six cases, the concentrations of chlorhexidine gluconate ranged from 0.5% to 1%. Allergy to chlorhexidine was confirmed by scratch test, epicutaneous test, or intradermal test. In addition the authors cite a report from the Japanese Ministry of Welfare (Tokyo) that summarizes prior information on adverse reactions to chlorhexidine gluconate in Japan from 1967 to 1984. The report included 22 cases with "fall in blood pressure," 13 with "dyspnea," and 9 with "anaphylactic shock." In the nine cases with "anaphylactic shock," chlorhexidine gluconate was used on mucous membranes (vagina and bladder) at concentrations between 0.02% and 1%. The authors conclude that a concentration of no more than 0.05% chlorhexidine gluconate should be used on wound surfaces and that chlorhexidine gluconate may not be suitable for application on mucous membranes.

Garland JS, Alex CP, Mueller CD, Cisler-Kahill LA. Local reactions to a chlorhexidine gluconate-impregnated antimicrobial dressing in very low birth weight infants. Pediatr Infect Dis J. 1996 Oct;15(10):912-4.[12] This article describes

seven cases of severe contact dermatitis due to a chlorhexidine gluconate-impregnated opaque foam patch (Biopatch®) used as an antimicrobial dressing for central venous catheters in neonates. All of the infants weighed less that 1000 grams and five were < 26 weeks gestational age. Systemic chlorhexidine gluconate concentrations were not measured.

The Medical Officer read the following article to better understand the methodology of the "21-Day Cumulative Irritation Test." **Bowman JP, Berger RS, and Mills OH. The 21-day cumulative irritation test can be reduced to 14 days without loss of sensitivity. J. Cosmet. Sci. 2003 Sept-Oct;54:443-9.**[13]

8.7 Other Relevant Materials

The Medical Officer reviewed the Sage Products, Inc. website, http://www.comfortbath.com/index.cfm, to view descriptions and packaging of other products in their Comfort® Personal Cleansing product line.

9 OVERALL ASSESSMENT

9.1 Conclusions on Available Data

The Medical Officer concludes that the Applicant has demonstrated that the proposed product, CHG Antiseptic Cloths, is effective for the proposed indication for Patient Preoperative Skin Preparation. As per conditions agreed upon by the Division prior to the Applicant's submission of NDA 21,669, data from the pivotal "efficacy" studies conducted at [redacted] sufficiently support the proposed indication at the abdominal ("dry") site and data from the pivotal "efficacy" studies conducted at [redacted] sufficiently support the proposed indication at the inguinal ("wet") site. No additional information is needed at this time to determine the efficacy of the Applicant's product for the proposed indication.

Under the testing procedures defined in the TFM, CHG Antiseptic Cloths appear to be at least as effective as the positive control product, Hibiclens®, which is already FDA-approved for the indication of Patient Preoperative Skin Preparation.

Based on the available safety information, the Applicant's proposed product, CHG Antiseptic Cloths (chlorhexidine gluconate 2% solution), is safe for the single use indication of Patient Preoperative Skin Preparation. Given the lack of systemic absorption,[1] no additional safety evaluation is needed for the single use indication of Patient Preoperative Skin Preparation.

The irritancy study conducted by the Applicant demonstrated that CHG Antiseptic Cloths are Class 4 Irritants (experimental cumulative irritant) when repeatedly applied under occlusive dressings. Only the positive control, sodium lauryl sulfate 1% solution, demonstrated a higher irritancy potential in this study. [redacted]

skin repeatedly, appropriate safety studies that simulate the proposed clinical use would be needed.

The Repeat Insult Patch Test study conducted by the Applicant did not demonstrate the occurrence of sensitization with repeated application and subsequent re-challenge with CHG Antiseptic Cloths in the population studied. The higher rate of "level 2" irritation and higher rate of discontinuation due to predefined irritancy criteria in subjects greater than 65 years of age; however, suggests that the Applicant's product may cause greater skin irritation in the elderly population.

There do not appear to be racial differences in the safety profile for the Applicant's product; however, this conclusion is qualified by the fact that the overall number of non-Caucasian subjects exposed to the Applicant's product is relatively few in number.

9.2 Recommendation on Regulatory Action

From the clinical perspective, based on the studies performed in this NDA, the Applicant's proposed product, CHG Antiseptic Cloths, is safe and effective for the single use indication of Patient Preoperative Skin Preparation. Therefore, the Medical Officer recommends that this new drug application (NDA) be approved provided the Applicant adequately addresses the following deficiencies:

1. Deficiencies described in the Chemistry Reviewer's deficiency letter provided to the Applicant (via fax) on June 3, 2004 and further discussed at a teleconference between the Applicant and Division of Anti-Infective Drug Products (DAIDP) representatives on July 8, 2004.

- Note: According to the Chemistry reviewer, Milton Sloan, Ph.D., information submitted by the Applicant on June 15, 2004 adequately addressed some of the deficiencies. However, a number of deficiencies remain unresolved. For example, (1) identification of [redacted] impurities in the finished product and (2) establishment of cloth-to-cloth content uniformity. (Dr. Sloan addresses these and additional remaining chemistry deficiencies in Part II of his review.)

2. The Applicant provides scientific evidence for the safe and effective use of the proposed product in pediatric populations for the indication of Patient Preoperative Skin Preparation, or indicates the intention to seek a waiver, partial waiver, or deferral from studying CHG Antiseptic Cloths in Pediatric populations.

- Note: Literature submitted by the Applicant in Serial No. 000 (BZ) on June 14, 2004 supports the Applicant's claim that the proposed product may be used in patients $\geq$ 2 months of age. The Applicant's request for a partial waiver for studies on premature or low birth weight infants, infants receiving phototherapy and children less than 2 months of age due to the potential for irritation and enhanced absorption is acceptable.

3. The Applicant addresses the following labeling issues.

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 2

9.5 Comments to Applicant

The following residual issues must be addressed by the Applicant.

a. The following statement found in the "Directions," [redacted] rub skin back and forth…," does not accurately reflect the application technique used in the three pivotal "efficacy" studies.

   i. The Division recommends that the "Directions" state the following: "Vigorously scrub the skin back and forth…" The Division notes on page 009231 of volume 21 of the NDA, the [redacted] "Preoperative Prep Application Procedures" state, "The technician scrubbed the test sites vigorously for three (3) minutes, using a back-and-forth motion." On page 009997 of volume 22, the [redacted] "Treatment-Application Procedures" state under the section entitled, "DS No. 6215 – 2% CHG Impregnated Towelette (Test)," that "Test product will be applied vigorously to each site using a back and forth motion for 3 minutes." The Division notes only the [redacted] efficacy study protocol, on page 008689 of volume 20, states, [redacted] rub skin back and forth..."

10 APPENDIX

10.1 Review of Individual Study Reports

Individual study reports 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 section 9.4 for the Medical Officer's concerns with the Applicant's proposed label, as well as, the labeling review of Michelle Jackson, Ph.D. of the Division of Over-the-Counter Drug Products.

10.3 References

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