CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	207964
Drug Name:	Medline 2% CHG cloth (ReadyPrep CHG)
Indication(s):	Pre-Surgical Skin Preparation
Applicant:	Medline Industries
Date(s):	Receipt date: 10/20/2017 PDUFA Goal date: 11/20/2018
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Biometrics Division:	Division of Biometrics 7
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Keywords: Responder rate, Average Treatment Effect, Log_{10} reduction, Confidence interval, Fisher Exact test, Normal approximation

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LIST OF ABBREVIATIONS

ADAM	Analysis Data Model
AT	As- Treated
mAT	Modified As-Treated
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence Interval
CFU	Colony-Forming Unit
CHG	Chlorhexidine Gluconate
CRF	Case Report Form
CSR	Clinical Study Report
DB7	Division of Biometrics 7
DNDP	Divisison of Nonprescription Drug Products
EDR	Electronic Document Room
FDA	Food and Drug Administration
IND	Investigational New Drug
IR	Information Request
ISE	Integrated Summary of Efficacy
ITT	Intent-To-Treat
LOG10	Base 10 Logarithm
mITT	Modified Intent-To-Treat
NDA	New Drug Application
SDTM	Study Data Tabulation Model
TFM	Tentative Final Monograph

1 EXECUTIVE SUMMARY

This document is a statistical review of two pivotal studies R13-053 and R15-029 submitted by the applicant to support marketing of Medline 2% CHG cloth for patient preoperative preparation. The Applicant has submitted pivotal studies R13-053 and R15-029 to evaluate the antimicrobial efficacy and safety of Medline 2% CHG cloth for patient preoperative skin preparation. All two studies were randomized, vehicle and active controlled studies, evaluator blinded, single center studies in healthy volunteers, who received 2 of 3 study products on the abdomen and/or 2 of 3 possible study products on the groin. The three products in each study were Medline 2% CHG cloth (test product), Dyna-Hex 2 (active control) and Medline placebo solution cloth (vehicle). Bacterial count was measured at baseline, 10 minutes, 6 hours, and 8 hours post-treatment application. Prior to fielding the study, the FDA and the sponsor agreed upon using study design and analysis procedures consistent with the 2015 Proposed Rule.

The primary study objective was to show a 70% responder rate of the test product at 10 minutes (lower bound of the two sided 95% Confidence Interval (CI) of percent responders greater than or equal to 70%). On the abdomen, a responder was defined as a subject with a 2 $\log_{10}/cm^2$ bacterial reduction at 10 minutes. On the groin region, a responder was a subject with a 3 $\log_{10}/cm^2$ bacterial reduction at 10 minutes. In addition to responder rates, this review examines results on mean log bacterial counts in its assessment of efficacy.
Secondary study objectives for the test product were to show:

- A 100% responder rate at 6 hours. At the 6 hours sample, a responder is a subject with skin flora counts at 6 hours below baseline, either in groin or abdomen.
- Statistical superiority to the vehicle.

To check study validity, the active control was also evaluated.

In order to support the efficacy of preoperative skin preparation products, it is expected that data for both abdominal and groin regions from two adequate and well-controlled studies conducted at independent laboratories show substantial evidence of efficacy. From a statistical standpoint, there is sufficient evidence that Medline 2% CHG is effective and adds benefits beyond those of Dyna-Hex 2 and the placebo cloth. Specifically, the table below shows that for both Study R13-053 and Study R15-029:

- Medline cloth meets the effectiveness criteria outlined in the 2015 Proposed Rule, with lower bound of the 95% CI of the responder rate greater than 70% at 10 minutes.
- Medline cloth is statistically superior (based on average treatment effects) to both Dyna-Hex 2 and the vehicle at 10 minutes, in both the body regions and studies.

The sponsor failed to validate the study conduct to assure that the expected results are produced, as Dyna-Hex 2 did not meet the 70% responder rate criteria.

		Study R13-053		Study R15-029	
		Estimate	95% CI	Estimate	95% CI
Abdomen					
Responder Rate	Medline Cloth	93% (235/252)	(89%,96%)	81% (194/241)	(75%,85%)
	Dyna-Hex 2	85% (216/254)	(80%,89%)	72% (181/253)	(66%,77%)
	Vehicle	50% (24/48)	(35%,65%)	50% (25/50)	(36%,65%)
ATE* Difference	Medline Cloth – Dyna-Hex 2	-0.26	(-0.39, -0.13)	-0.34	(-0.52, -0.16)
	Vehicle - Medline Cloth	1.22	(0.99, 1.46)	0.81	(0.50, 1.12)
	Vehicle - Dyna-Hex 2	0.97	(0.74, 1.20)	0.47	(0.17, 0.78)
Groin					
Responder Rate	Medline Cloth	86% (218/254)	(81%,90%)	85% (213/252)	(79%, 89%)
	Dyna-Hex 2	65% (162/249)	(59%,71%)	73% (189/259)	(67%,78%)
	Vehicle	25% (12/48)	(14%,40%)	56% (29/52)	(41%, 70%)
ATE* Difference	Medline Cloth – Dyna-Hex 2	-0.60	(-0.80, -0.41)	-0.90	(-1.12, -0.68)
	Vehicle - Medline Cloth	1.80	(1.45, 2.14)	0.94	(0.55, 1.33)
	Vehicle - Dyna-Hex 2	1.19	(0.85, 1.54)	0.04	(-0.35, 0.42)

*ATE=difference between 2 treatments in estimated mean log bacterial counts at 10minutes; estimated by linear regression of log-bacterial counts at 10 minutes on treatment and baseline log-bacterial counts, in each body region.

At 6 hours, Medline Cloth showed 100% responder rates for each body region in both studies R13-053 and R15-029. Although Dyna-Hex 2 achieved a 100% responder rate in all body regions for Study R13-053, this product only achieved a 100% responder rate at the groin in R15-029.

A few protocol violations were uncovered during the review or inspection of Study R15-029 and unplanned unblinding of the response rates of 6 placebo subjects occurred as a quality control assessment at the early stage of the R15-053 study. However, the main conclusions hold with different post-hoc sensitivity analyses conducted by the reviewer. In addition, the sponsor did not include a statistical analysis plan (SAP), SAP amendments, or raw datasets. Therefore, we have several recommendations for future submissions for this indication (see Section 5.2).

2 INTRODUCTION

2.1 Overview

The sponsor examined the antimicrobial efficacy and/or safety of Medline 2% CHG in 3 pivotal studies (Study R13-052, Study R13-053, and Study R15-029). The sponsor proposed to rely on studies R13-053 and R15-029 for both safety and efficacy. The sponsor additionally proposed to only use the safety data for R13-052, after stating that R13-052 does not meet the criteria of an adequate controlled efficacy study due to concerns related to performance, blinding, and handling of missing data. Table 1 provides the description of the two pivotal phase 3 trials.

Table 1: Description of Efficacy and/or Safety Studies

Study number	Design	Treatment arms/Sample size	Primary endpoint/analysis
R13-053 (Virginia)	Randomized, vehicle and active controlled, evaluator blinded (8 hours of treatment)	Test product: Medline 2% CHG Cloth (groin 254, abdomen 252) Active comparator: Dyna-Hex 2 (groin 249, abdomen 254) Vehicle control: Medline placebo (groin 48, abdomen 48)	(1) Primary endpoint: At 10mns, the responder rate for Medline 2% CHG cloth is significantly higher than 70%. (2) Check for study validity: At 10mns, Dyna-Hex 2 responder rate is significantly higher than 70% and both active substances are statistically superior to the vehicle.
R15-029 (Romania)	Randomized, vehicle and active controlled, evaluator blinded (8 hours of treatment)	Test product: Medline 2% CHG Cloth (groin 252, abdomen 241) Active comparator: Dyna-Hex 2 (groin 259, abdomen 253) Vehicle control: Medline placebo (groin 52, abdomen 50)	(1) Primary endpoint: At 10mns, the responder rate for Medline 2% CHG cloth is significantly higher than 70%. (2) Check for study validity: At 10mns, Dyna-Hex 2 responder rate is significantly higher than 70% and both active substances are statistically superior to the vehicle.

Source: Reviewer Table, derived from R13_053.xpt, R15_029.xpt and Clinical Study Reports for R13-053 and R15-029

2.2 Data Sources

The sponsor submitted electronic documents and datasets for R13-053 and R15-029. These datasets include baseline characteristics, disposition, and study endpoints for all

subjects randomized. Clinical study reports (CSRs) of each individual trial were available.

The following file folders available within the CDER Electronic Document Room (EDR) were used in this review:

- Clinical Study Reports for R13-053 and R15-029, submitted to DARRTS on 02/09/2016: \\cdsesub1\EVSPROD\NDA207964\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pt-pre-op-\5351-stud-rep-contr
- Integrated Summary of Efficacy, submitted to DARRTS on 10/19/17: \\cdsesub1\EVSPROD\NDA207964\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pt-pre-op-\5353-rep-analys-data-more-one-stud\ise
- Clinical Information Amendment, submitted to DARRTS on 03/15/2018: \\cdsesub1\EVSPROD\NDA207964\0023\m1\us
- Clinical Information Amendment, submitted to DARRTS on 05/30/2018: \\cdsesub1\EVSPROD\NDA207964\0026\m1\us
- Clinical Information Amendment, submitted to DARRTS on 06/13/2018: \\cdsesub1\EVSPROD\NDA207964\0028\m1\us
- Datasets used for the analyses, submitted to DARRTS on 06/11/18: \\cdsesub1\EVSPROD\NDA207964\0028\m5\datasets
- Statistical Report Addendum 01 and 02, submitted to DARRTS on 06/12/18: \\cdsesub1\EVSPROD\NDA207964\0028\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pt-pre-op-skin-prep\5351-stud-rep-contr\r15-029-pivotal

Note that several of the documents and datasets referred above are different from the ones submitted in the original submission on 02/29/2016 because of information requests and amendments sent during the review of this NDA. More details on this in Section 3.1.

The format, content, and documentation of the data submitted in support of this application was adequate to conduct our statistical review of the antimicrobial efficacy of Medline 2% CHG cloth for preoperative skin preparation.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor and the investigator were responsible for ensuring proper study conduct with regard to protocol adherence and validity of the data recorded on the Case Report Forms (CRFs). The investigator gave Medline Industries, Inc. study monitor direct access to source documents that supported data on the CRFs and made available such records to authorized Medline Industries, Inc., quality assurance, IRB and regulatory personnel for inspection and/or copying. Note that the source documents are defined as any original documents, data, and records where data are first recorded (e.g. CRF, questionnaire, consent form, laboratory notes).

Medline Industries, Inc. study monitor assessed the progress of the study by performing

the following oversight:
- Periodic on-site review
- Telephone communications and e-mail
- Review of CRFs and source documents

The sponsor reported a few protocol deviations in the February 9, 2016 Clinical Study Reports for R13-053 and R15-029. For R13-053, 7 deviations were listed (3 product application deviations, 3 pregnancy tests not performed, and 1 groin result recorded on the abdomen page). For R15-029, 4 product application deviations, 1 bacterial counting entry data deviation, and many sampling time deviations were listed.

In response to several information requests from DB7 (dated December 21, 2017 and May 16, 2018), the sponsor submitted amendments on March 15, 2018 and May 30, 2018, where they reported a few additional errors. For R13-053, one groin region should have been excluded as a treatment day baseline failure but was not. For R15-029, the sponsor reported 16 subjects with treatment received incorrectly recorded in the dataset (12 and 4 respectively in March and May amendments).

An FDA inspection of the Romania site (Study R15-029), which occurred on March 26, 2018, identified many deviations. Specifically, the inspector stated that 'the site reported many time deviations that did not occur, and did not report many time deviations that did occur'. Note that the site for Study R13-053 was not inspected. For the results of the FDA inspection, we refer to Sharon Gershon's Clinical Inspection Summary submitted to DARRTS on 08/27/2018. Following the inspection, the sponsor reported updated sampling time deviations for R15-029 in an amended clinical study report submitted on June 12, 2018. Overall, deviations in R15-029 are as follows: 160 sampling time deviations, 105 time recording deviations, 23 treatment day baseline count deviations, 17 screening day baseline counts deviations, 13 product application time deviations, 4 sample plating deviations, 2 incubation time deviations. The clinic did not replace the 23 treatment day baseline count deviations. As a result, the statistical analyst (sponsor) excluded these deviations at analysis stage. Table 2 below shows the number of deviations by treatment group and body region for sampling time, time recording, treatment day failures, and screening day failures, which were associated with the largest number of deviations.

Table 2. Percentage of Each Deviation by Treatment Group in R15-029

	Abdominal Regions			Groin Regions		
	Medline 2% CHG (N=311)	Dyna Hex 2 (N=311)	Medline Placebo (N=58)	Medline 2% CHG (N=290)	Dyna Hex 2 (N=294)	Medline Placebo (N=56)
Screening Day Baseline Count Deviation	10 (3.2%)	6 (1.9%)	0	0	1 (0.3%)	0
Treatment Day Baseline Count Deviation	14 (4.5%)	7 (2.3%)	1 (1.7%)	1 (0.3%)	0	0
Product Application Time < 4 min	0	2 (0.6%)	1 (1.7%)	4 (1.4%)	5 (1.7%)	1 (1.8%)
10 Min Sampling Time < 9Min 30 Sec or > 10 Min 30 Sec	17 (5.5%)	34 (10.9%)	4 (6.9%)	22 (7.6%)	25 (8.5%)	6 (10.7%)
6 Hour Sampling Time < 5 Hour 30 Min or > 6 Hour 30 Min	2 (0.6%)	4 (1.3%)	0	1 (0.3%)	5 (1.7%)	0
8 Hour Sampling Time < 7 Hour 30 Min or > 8 Hour 30 Min	8 (2.6%)	12 (3.9%)	0	7 (2.4%)	13 (4.4%)	0
Inconsistent Time Recording at Baseline[1]	4 (1.3%)	5 (1.6%)	2 (3.4%)	3 (1.0%)	10 (3.4%)	2 (3.6%)
Inconsistent Time Recording at 10 Min Sampling[1]	6 (1.9%)	3 (1.0%)	2 (3.4%)	8 (2.8%)	4 (1.4%)	4 (7.1%)
Inconsistent Time Recording at 6 Hour Sampling[1]	5 (1.6%)	5 (1.6%)	0	5 (1.7%)	5 (1.7%)	1 (1.8%)
Inconsistent Time Recording at 8 Hour Sampling[1]	6 (1.9%)	10 (3.2%)	3 (5.2%)	7 (2.4%)	5 (1.7%)	0

Source: Reviewer Table and Calculations based on dataset R15_029.xpt and Statistical Report Addendum 02

Note: This table uses all subjects randomized and treated. Treatment group is based on treatment received.

[1]The recorded receipt time at the microbiology laboratory preceded the recording sampling end time. The time difference was up to 84 minutes and due to a malfunction in the chronometer.

This application was sent in electronic format and submitted via the secure gateway by Global Submit. The submission is well organized and easy to navigate. However, the sponsor submitted only the derived data and did not provide the raw data.

Blinding/unblinded procedures were well documented. In R13-053, the response data for 6 placebo subjects were unblinded as a quality control assessment, because the results of the Neutralization Validation showed a greater than expected antimicrobial activity in the placebo group. This assessment has been referred to as an interim analysis in previous communications between FDA and the sponsor. At the interim, the response rates of the 6 placebo subjects were reviewed by the Investigator and released to the Sponsor and statistical analyst early, after close to 60 subjects had been enrolled. The sponsor proposes that the interim assessment did not affect the conclusions of the study.

The sponsor did not include the statistical analysis plan and any SAP amendments in this submission. However, at the IND stage, FDA statistical reviewers from the Division of Biometrics IV provided comments to a synopsis of the study protocol (see statistical review from Dr. Christopher Kadoorie, submitted to DARRTS on December 15, 2011).

Reviewer Comments:

- *The large number of deviations raises concerns about the quality of study conduct. However, Table 2 suggests that except for sampling time, there is a small difference in the proportions of deviations across treatment groups, which is reassuring. For sampling time, Table 2 generally shows a larger proportion of deviations for Dyna Hex 2 regardless of time point and body region. Note that the staff performing the bacterial sample collections were not blinded.*
- *Although traceability remains an issue with a single dataset per study, the reviewer was able to reproduce the analyses for the primary endpoint (responder rates at 10 minutes) and secondary endpoints (responder rates at 6 and 8 hours) from datasets R13-05.xpt and R15-029.xpt that the sponsor provided.*
- *Unblinding of study R13-053 is problematic, as it could result in issues such as investigator bias. However, the sponsor only unblinded placebo subjects and did not conduct any efficacy comparisons. The FDA reviewer considers that the unblinding was conducted for monitoring purposes, with no plan stop the trial early depending on the results.*

3.2 Evaluation of Efficacy

The efficacy review is based on two pivotal studies, R13-053 and R15-029. The sites for R13-053 and R15-029 were respectively MicroBioTest, Inc. (MBT) in Sterling, Virginia and Evic Romania in Bucharest, Romania.

3.2.1 Study Design and Endpoints

Studies R13-053 and R15-029 were randomized, vehicle and active controlled, third-party blind (staff performing bacterial enumeration), single center studies. Both studies enrolled healthy volunteers who had no dermatological conditions or known history of sensitivity to natural rubber latex, adhesive skin products, or CHG. Both studies included three treatment arms (Medline 2% CHG cloth, Dyna-Hex 2, and Medline placebo solution cloth) and planned a 5:5:1 randomization ratio. A noteworthy

difference in initial inclusion/exclusion criteria was that Study R15-029 allowed subjects 18 or older to participate, whereas R13-053 allowed subjects as young as 16 to enroll.

Additional study design elements are presented below for R13-053 and R15-029. Note that unless specified, the description holds for both studies. For details about the treatment application procedures, we refer to Dr Michelle Jackson's clinical microbiology review.

Study Schedule

Each study consisted of 3 phases: a pre-treatment phase (14-day washout to allow for the removal of any antimicrobial agents from the subject's skin), a screening phase, and a treatment phase (scheduled at least 72 hours after screening baseline collection).

Baseline CFU Criteria

Baseline CFU values were assessed on screening day and on treatment day. Both the screening day criteria and treatment day criteria were baseline counts of at least 1.3×10^3 CFU/cm^2 per abdominal region and/or 1.0×10^5 CFU/cm^2 per groin region.

Randomization and Replacements

The sponsor assigned randomization numbers on treatment day (prior to treatment day baseline sampling and treatment application), using a computer-generated randomization schedule. The randomization was balanced with respect to treatments, left/right body side, and sampling time/sampling area. The treatment assignments were balanced such that the number of readings per anatomical region meets the sample size requirements.

Replacement subjects were to follow the same treatment/randomization schedule as the disqualified subject. Note that enrolled subjects were replaced for one of the following reasons:

- Treatment Day baseline counts less than the minimum baseline requirement for at least one side of the groin and/or abdomen. Note that if a subject failed the treatment day baseline criteria for only one side of a body region, his/her values that passed treatment day criteria and all values of the replacement subject for that body region were used in the analysis.
- Missing data at any sampling interval (treatment day baseline, 10 minute, 6-hour, or 8-hour), which may be due to subject discontinuation, early withdrawal, missed appointment or a lab accident.
- A skin irritation rating of 3 following the application of study treatment
- A serious protocol deviation that compromises the data results

Blinding

For both studies, the sponsor reported that "*The investigator and the staff performing the*

material application or bacterial sample collections were not blinded. This is because the two active substances had different labeled application techniques and the placebo solution was visually differentiable from the active solutions. The study personnel performing the bacterial enumerations were blinded both when generating and when recording the data. The analyst was not blinded."

Endpoints

The primary endpoint is responder rates at 10 minutes post-treatment on the abdominal and groin region. At 10 minutes, a responder on the abdomen had a 2 $\log_{10}/cm^2$ bacterial reduction compared to baseline; a responder on the groin region had a 3 $\log_{10}/cm^2$ bacterial reduction compared to baseline.

Secondary endpoints are responder rates at 6 hours and 8 hours post-treatment on the abdominal and groin sites. At 6 hours and 8 hours, subjects had skin flora counts below baseline at either groin or abdomen.

Additional endpoints assessed in this review are log bacterial counts at 10 minutes.

Reviewer comments:

- *Exclusion of treatment day baseline failures and recruitment of replacement subjects breaks the randomization.*

3.2.2 Statistical Methodologies

Sample Size

For the active substances (Medline 2% CHG and Dyna-Hex 2), assuming a minimum 80% responder rate and alpha 0.0125 (0.05/4 after Bonferroni correction), the sponsor estimated the sample size to be 248 for 90% power. For the placebo, the sponsor states that 'the sample sizes for the placebo group were calculated based on both the pilot study and historical data for placebo applications using similar procedures. Based on this data, all subjects treated with inactive substances are non-responders at 10 minutes for both the abdomen and groin. The 10-minute time point can therefore be distinguished from active products using sample sizes of approximately 10 (possibly fewer) but in order to reduce the burden of multiple comparison adjustments the placebo group power was increased by increasing the sample size to 48.' This meant that a minimum of 272 subjects, (248×2+48)/2, were required. If the required number of subjects was not met, additional volunteers were to be recruited.

Adjustment for Multiplicity

The sponsor pre-specified that the alpha would be $\alpha = 0.05 / 4 = 0.0125$ for both studies, after Bonferroni correction due to four significant comparisons. However, in order to account for the unplanned interim analysis, the sponsor modified the alpha level to be $\alpha = 0.04 / 4 = 0.01$ in R13-053, after 0.01 spent on the interim analysis. Because there is a single product proposed for approval and the interim analysis in R13-053 was conducted

for monitoring purposes with no plan to stop the trial early, FDA deemed these adjustments unnecessary and asked the sponsor to re-analyze the data without adjustment for multiple comparisons.

Main Efficacy Analyses

This subsection presents the main methods used to evaluate the antimicrobial effectiveness of Medline 2% CHG cloth. The pre-specified primary analysis was based on responder rates at 10 minutes and a modified as-treated (mAT) population that used treatment received and included all randomized subjects who met treatment day baseline criteria. Pre-specified secondary analyses were based on responder rates at 6 hours and 8 hours. To further assess efficacy, the FDA reviewer requested that the sponsor also conduct analyses based on average treatment effects (ATE). Below, we provide details about the responder rate analyses and ATE analyses. The analyses presented in this review are the re-analyses by the sponsor with no adjustment for multiple comparisons.

- *Responder Rate Analyses*

The sponsor calculated responder rates and associated 95% confidence intervals (CIs) for each body region and time point. The CIs for all responder rates are based on Fisher exact tests.

- *Analysis based on Average Treatment Effects*

DB7 requested that the sponsor conduct a post-hoc analysis where ATEs and 95% confidence interval were calculated.

The sponsor analysis pooled the two body regions (abdomen and groin), estimated the ATE by linear regression of log-bacterial reductions at 10 minutes on the interaction of treatment and body region, with subject-specific random effects. The sponsor analysis did not adjust for baseline log-bacterial counts. The DB7 statistical reviewer conducted an ATE analysis that adjusted for baseline log-bacterial counts. The DB7 analysis analyzed each body region separately.

Sensitivity Analyses

The main analyses for R13-053 and R15-029 used a mAT population, where subjects with treatment day baseline failures were excluded. As a sensitivity analysis, the DB7 reviewer conducted the following analyses:

- An as-treated (AT) analysis that includes all subjects randomized and uses treatment received.
- A modified intent to treat (mITT) analysis that includes all subjects randomized except for treatment day baseline failures and uses treatment randomized.
- An intent-to-treat (ITT) analysis that includes all subjects randomized and uses treatment randomized.

Criteria for Evaluation

The reviewer will evaluate Medline 2% CHG according to the criteria the applicant was targeting in the planning of the study. That is, meeting the effectiveness criteria outlined in the 2015 Proposed Rule. Based on the 2015 Proposed Rule, the analysis needed to demonstrate the following for the test product:

- A 70% responder rate at 10 minutes (lower bound of the 95% CI of percent responders greater than or equal to 70%) for both the abdomen and the groin.
- A 100% responder rate at 6 hours, for both the abdomen and the groin. The 8 hour sample was also analyzed but has no specific target.
- Superiority to the vehicle.

To validate the study conduct to assure that the expected results are produced, the responder rate for active control was also evaluated using the same thresholds.

Although the sponsor conducted analyses based on difference in responder rates, the reviewer will compare the efficacy of the different treatment arms based on average treatment effects. The reviewer will assess the robustness of the primary analysis to several sensitivity analyses.

Reviewer Comments:
DB7 did not review the sample size calculation, which was provided after study conduct, and the sponsor justification did not provide sufficient information for the reviewer to reproduce the numbers for the placebo arm

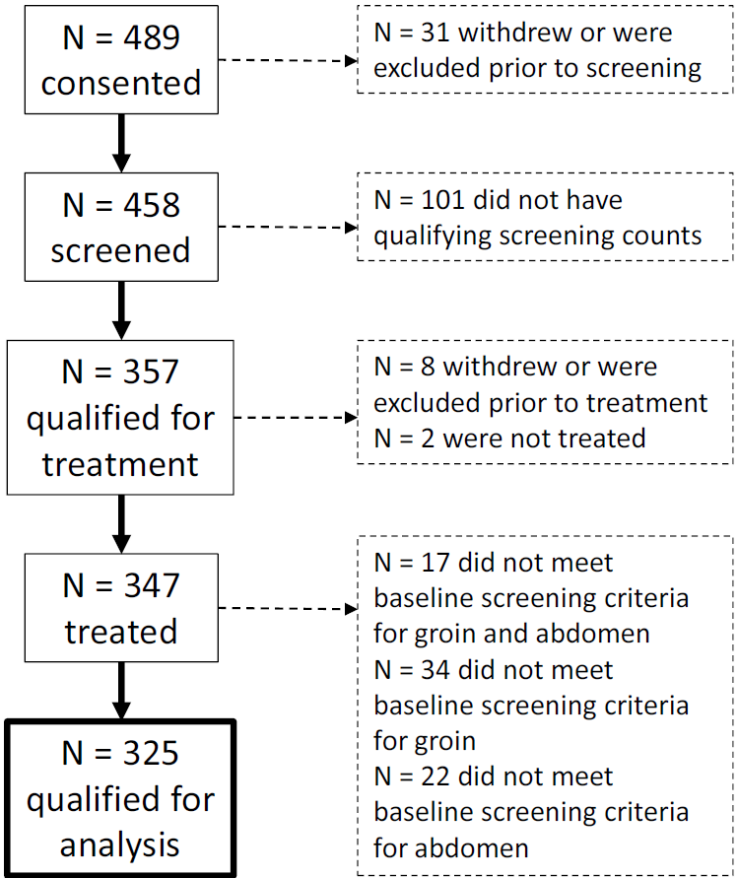
3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

In R13-053, a total of 489 subjects were consented and 458 subjects were screened. Among the screened subjects, 357 passed screening day baseline criteria and 347 were randomized and treated. Among the randomized subjects, 326 passed treatment baseline criteria and were included in the main analyses. For a disposition flowchart, see Figure 1.

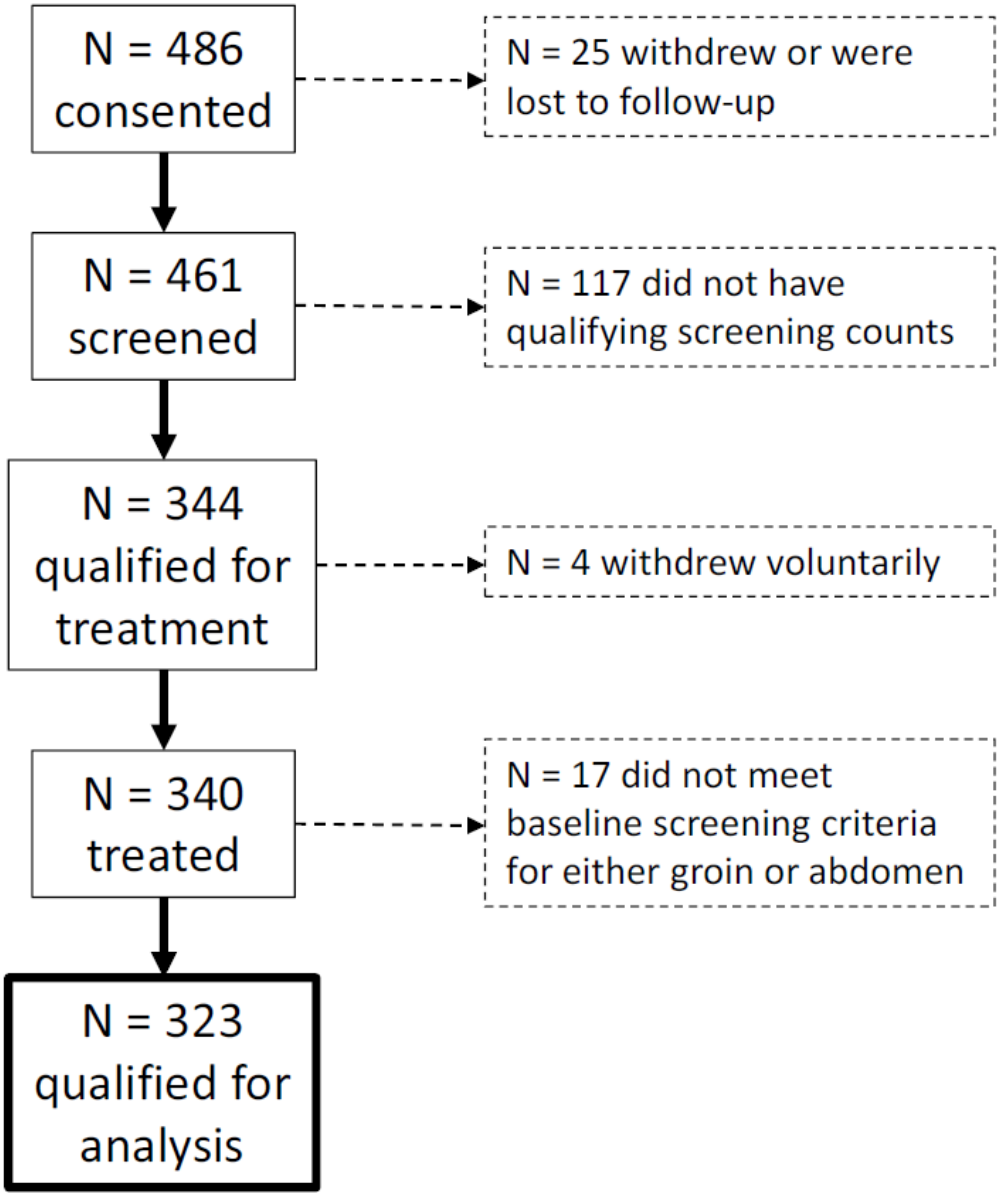
In R15-029, a total of 486 subjects were consented and 461 subjects were screened. Among the screened subjects, 344 passed screening day baseline criteria and 340 were randomized and treated. Among the randomized subjects, 323 passed treatment baseline criteria and were included in the main analyses. For a disposition flowchart, see Figure 2.

Figure 1.Flow Chart of Subject Disposition for Study R13-053



Source: Integrated Summary of Efficacy
Reviewer verified the sample size for subjects randomized and qualified for analysis in R13_053.xpt.
Note that in R13_053.xpt the sample size for subjects qualified for analysis is N=326.

Figure 2. Flow Chart of Subject Disposition for Study R15-029



Source: Integrated Summary of Efficacy
Reviewer verified the sample size for subjects randomized and qualified for analysis in R15_029.xpt.

Sample Size by Treatment Arm and Body Region

For each study, the treatments and number of subjects in the as-treated population are shown in the table below.

Table 3. Number of Applications

	R13-053		R15-029	
Treatment	Abdomen	Groin	Abdomen	Groin
Medline 2% CHG Cloth (test product)	252	254	241	252
Dyna Hex 2 (active control)	254	249	253	259
Medline Placebo Cloth (vehicle control)	48	48	50	52

Source: Reviewer Table, derived from R13_053.xpt, R15_029.xpt
Note that in R13-053 Statistical Report Addendum 01 for Application 207964, SN0028, the sample size for Medline 2% cloth and Dyna-Hex 2 numbers were inadvertently reversed.

Demographic Characteristics

Table 4 below summarizes demographic characteristics in each study, by body region, for subjects analyzed. Within each study and body region, the distributions of age, sex, and race were similar between the three treatment arms. However, there were some differences in demographic characteristics between the two studies, with study R13-053 enrolling younger subjects, more males, and less Caucasians than study R15-029.

Table 4. Demographic Characteristics (by treatment group) at abdomen

		R13-053			R15-029		
		Medline 2% CHG cloth	Dyna-Hex 2	Placebo cloth	Medline 2% CHG cloth	Dyna-Hex 2	Placebo cloth
Abdominal Region							
Number Analyzed		252	254	48	241	253	50
Age	Mean (SD)	35.9 (14.4)	35.5 (14.1)	36.2 (15.4)	51.0 (12.0)	51.1 (11.9)	48.5 (13.1)
	Minimum	16	16	18	18	18	19
	Median	32	32	31.5	54	55	51
	Maximum	79	72	79	69	69	68
Sex	Male	57.9%	59.5%	60.4%	47.7%	49.0%	46.0%
	Female	42.1%	40.5%	39.6%	52.3%	51.0%	54.0%
Race	White/Caucasian	42.9%	41.0%	39.6%	100%	100%	100%
	Black/African American	21.4%	21.6%	10.4%	0	0	00
	Hispanic	10.7%	11.4%	14.6%	0	0	0
	Asian	22.6%	23.6%	27.1%	0	0	0
	Other	2.4%	2.4%	8.3%	0	0	0
Groin Region							
Number Analyzed		254	249	48	252	259	52
Age	Mean (SD)	36.4 (14.7)	35.7 (14.3)	34.7 (16.0)	51.9 (11.6)	51.9 (11.7)	48.6 (13.1)
	Minimum	16	16	16	18	18	19
	Median	32	32	30	56	56	51.5
	Maximum	79	72	79	69	69	68
Sex	Male	63.8%	65.5%	66.7%	45.6%	48.3%	38.5%
	Female	36.2%	34.5%	33.3%	54.4%	51.7%	61.5%
Race	White/Caucasian	44.1%	44.2%	39.6%	100%	100%	100%
	Black/African American	19.3%	19.7%	14.6%	0	0	0
	Hispanic	11.8%	10.4%	14.6%	0	0	0
	Asian	23.2%	23.7%	25.0%	0	0	0
	Other	1.6%	2.0%	6.2%	0	0	0

Source: Reviewer table, derived from R13-053.xpt and R15-029.xpt

3.2.4 Results

Results at 10 Minutes

The following subsections describe the primary analysis consisting of responder rates as well as analyses based on average treatment effects, at 10 minutes.

- Responder Rates at 10 minutes

For each study, responder rates at 10 minutes for each treatment are summarized in Table 5 and Table 6 below. For Medline 2% CHG, the lower bound of the 95% CI for responder rate was greater than 70% for all body regions, in both studies. For Dyna-Hex 2, the lower bound of the 95% CI for responder rate was greater than 70% only in R13-053 at the abdomen.

Table 5 . Study R13-053: Responder Rates at 10 Minutes

Body Area	Treatment	10 Minute Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	85.04% (216 of 254)	0.8005 to 0.8919
Abdomen	Medline Cloth	93.25% (235 of 252)	0.8942 to 0.9602
Abdomen	Vehicle Cloth	50.00% (24 of 48)	0.3523 to 0.6477
Groin	Dyna-Hex 2	65.06% (162 of 249)	0.5879 to 0.7097
Groin	Medline Cloth	85.83% (218 of 254)	0.8092 to 0.8987
Groin	Vehicle Cloth	25.00% (12 of 48)	0.1364 to 0.3960

Source: Table 6 of R13-053 Statistical Report Addendum 01 for Application 207964, SN0028. Reviewer verified the sponsor's results presented in this table.

Table 6. Study R15-029: Responder Rates at 10 Minutes

Body Area	Treatment	10 Minute Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	71.54% (181 of 253)	0.6555 to 0.7702
Abdomen	Medline Cloth	80.50% (194 of 241)	0.7492 to 0.8530
Abdomen	Vehicle Cloth	50.00% (25 of 50)	0.3553 to 0.6447
Groin	Dyna-Hex 2	72.97% (189 of 259)	0.6713 to 0.7828
Groin	Medline Cloth	84.52% (213 of 252)	0.7946 to 0.8876
Groin	Vehicle Cloth	55.77% (29 of 52)	0.4133 to 0.6953

Source: Table 6 of R15-029 Statistical Report Addendum 01 for Application 207964, SN0028. Reviewer verified the sponsor's results presented in this table.

- Average Treatment Effects at 10 Minutes

Average treatment effects at 10 minutes for each treatment comparison are shown in Table 7 and Table 8 below. These tables suggest that Medline 2% CHG cloth is statistically superior to both Dyna-Hex 2 and the vehicle at 10 minutes, in both body regions and studies. Dyna-Hex 2 was statistically superior to the vehicle in both studies at the abdomen, but only in R13-053 at the groin.

Table 7. Study R13-053: Differences in Log10 CFU/cm2 Changes from Baseline at 10 Minutes between Treatments

Body Region	Treatment Comparison	10 Minute log10 CFU/cm2 Reductions	
		Difference	95% Confidence Interval
Abdomen	Medline Cloth – Dyna-Hex 2	-0.26	-0.39 to -0.13
	Vehicle - Medline Cloth	1.22	0.99 to 1.46
	Vehicle - Dyna-Hex 2	0.97	0.74 to 1.20
Groin	Medline Cloth – Dyna-Hex 2	-0.60	-0.80 to -0.41
	Vehicle - Medline Cloth	1.80	1.45 to 2.14
	Vehicle - Dyna-Hex 2	1.19	0.85 to 1.54

Source: Reviewer Table, derived from R13_053.xpt

Table 8. Study R15-029: Differences in Log10 CFU/cm2 Changes from Baseline at 10 Minutes between Treatments

Body Region	Treatment Comparison	10 Minute log10 CFU/cm2 Reductions	
		Difference	95% Confidence Interval
Abdomen	Medline Cloth – Dyna-Hex 2	-0.34	-0.52 to -0.16
	Vehicle - Medline Cloth	0.81	0.50 to 1.12
	Vehicle - Dyna-Hex 2	0.47	0.17 to 0.78
Groin	Medline Cloth – Dyna-Hex 2	-0.90	-1.12 to -0.68
	Vehicle - Medline Cloth	0.93	0.55 to 1.33
	Vehicle - Dyna-Hex 2	0.04	-0.35 to 0.42

Source: Reviewer Table, derived from R15_029.xpt

Results at 6 hours

Responder rates at 6 hours for each treatment are summarized in Table 9 and Table 10 below. While Medline Cloth showed 100% responder rates for each body region at 6 hours in both studies R13-053 and R15-029, Dyna-Hex 2 observed a 100% responder rate at 6 hours in all body regions for Study R13-053 but only at the groin in Study R15-029.

Table 9. Study R13-053: Responder Rates at 6 hours

Body Area	Treatment	6 Hour Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	100.00% (254 of 254)	0.9856 to 1.0000
Abdomen	Medline Cloth	100.00% (252 of 252)	0.9855 to 1.0000
Abdomen	Vehicle Cloth	97.92% (47 of 48)	0.8893 to 0.9995
Groin	Dyna-Hex 2	100.00% (249 of 249)	0.9853 to 1.0000
Groin	Medline Cloth	100.00% (254 of 254)	0.9856 to 1.0000
Groin	Vehicle Cloth	100.00% (48 of 48)	0.9260 to 1.0000

Source: Table 7 of R13-053 Statistical Report Addendum 01 for Application 207964, SN0028. Reviewer verified the sponsor's results presented in this table.

Table 10. Study R15-029: Responder Rates at 6 hours

Body Area	Treatment	6 Hour Responder Rates	
		Rate (%) (counts)	95% Exact Confidence Interval
Abdomen	Dyna-Hex 2	98.81% (250 of 253)	0.9657 to 0.9975
Abdomen	Medline Cloth	100.00% (241 of 241)	0.9848 to 1.0000
Abdomen	Vehicle Cloth	96.00% (48 of 50)	0.8629 to 0.9951
Groin	Dyna-Hex 2	100.00% (259 of 259)	0.9859 to 1.0000
Groin	Medline Cloth	100.00% (252 of 252)	0.9855 to 1.0000
Groin	Vehicle Cloth	100.00% (52 of 52)	0.9315 to 1.0000

Source: Table 7 of R15-029 Statistical Report Addendum 01 for Application 207964, SN0028. Reviewer verified the sponsor's results presented in this table.

Sensitivity Analyses

This section describes results of sensitivity analyses conducted by the reviewer.

The sensitivity analyses that used different analysis sets (AT, ITT, and mITT populations) led to similar conclusions as the primary analysis (mAT population):

- Although the ITT population had a considerably larger sample size (see Table 11) than the primary analysis that excluded treatment day baseline failures, the same conclusion holds: Medline 2% CHG always meets the 70% responder rate criteria, while Dyna-Hex 2 does not (see Table 12).
- The results for the AT analysis were almost identical to the results of the ITT analysis, as the two analysis sets differed only by a few subjects (see Table 11).
- The results between the primary analysis and the mITT analysis were almost identical, as the two analysis sets differed only by a few subjects (see Table 11).

Table 11. Number of Body Regions Analyzed in Different Analyses Populations

Population	R13-053			R15-029		
	Medline 2% CHG Cloth	Dyna Hex 2	Placebo Cloth	Medline 2% CHG Cloth	Dyna Hex 2	Placebo Cloth
Abdomen						
As-Treated	284	283	59	311	311	58
Intent-To-Treat	284	283	59	311	311	58
Modified As-Treated	252	254	48	241	253	50
Modified Intent-To-Treat	252	254	48	241	253	50
Groin						
As-Treated	297	292	59	290	294	56
Intent-To-Treat	297	292	59	291	294	55
Modified As-Treated	254	249	48	252	259	52
Modified Intent-To-Treat	254	249	48	253	259	51

Source: Reviewer Table, derived for R13-053.xpt and R15-029.xpt
Notes:

- As-treated population includes all subjects randomized and analysis uses treated received.
- Modified intent to treat population includes all subjects randomized except for treatment day baseline failures and analysis uses treatment randomized.
- Intent-to-treat population includes all subjects randomized and analysis uses treatment randomized.

Table 12. Responder rates in R13-053 and R15-029 in ITT analysis

	R13-053		R15-029	
	% (counts)	95% CI	% (counts)	95% CI
Abdomen				
Dyna-Hex 2	82% (233 of 283)	(0.77, 0.86)	69% (213 of 311)	(0.63, 0.74)
Medline Cloth	91% (259 of 284)	(0.88, 0.94)	77% (238 of 311)	(0.71, 0.81)
Placebo	42% (25 of 59)	(0.30, 0.56)	52% (30 of 58)	(0.38, 0.65)
Groin				
Dyna-Hex 2	65% (191 of 292)	(0.60, 0.71)	67% (197 of 294)	(0.61, 0.72)
Medline Cloth	87% (257 of 297)	(0.82, 0.90)	80% (233 of 291)	(0.75,0.85)
Placebo	27% (16 of 59)	(0.16, 0.40)	55% (30 of 55)	(0.41, 0.68)

Source: Reviewer Table, derived for R13-053.xpt and R15-029.xpt

3.2.5 Conclusions

The sponsor planned and powered the study to meet the effectiveness criteria outlined in the 2015 Proposed Rule. Based on Study R13-053 and Study R15-029, Medline 2% CHG cloth is effective:

- The lower bound of the 95% CI for responder rate of Medline 2% CHG was greater than 70% for all body regions at 10 minutes, in both studies,
- Medline 2% CHG showed persistent antimicrobial properties (100% responder rates at 6 hour),
- Medline 2% CHG was statistical superior to the placebo cloth in both studies.

However, the sponsor was not able to validate the study, because Dyna-Hex 2 did not always meet the responder rate criteria outlined in the 2015 proposed rule:

- Dyna-Hex 2 did not meet the 70% responder criteria in R13-053 at the groin and in R15-029 at both body regions
- Dyna-Hex 2 did not meet a 100% responder rate at 6 hours at the abdomen in R15-029.

The analyses based on ATE showed similar conclusions:

- Medline 2% CHG cloth was statistically superior to both Dyna-Hex 2 and the vehicle at 10 minutes, in both the body regions and studies.
- Dyna-Hex 2 was not always statistically superior to the vehicle.

Reviewer comments:
From a statistical standpoint, both the analyses of responder rates and average treatment effects show that Medline 2% CHG is effective. However, the active control (Dyna-Hex 2) failed to validate study conduct. Note that although Dyna-Hex 2 has been in the market for many years, it was not approved based on the criteria set forth in the *2015 Proposed Rule.*

3.3 Evaluation of Safety

All treated subjects were evaluated for safety. The main measures of safety were skin irritation scores and incidence of reported adverse events. No skin irritation and no adverse event were observed for any subject in the study. For further evaluation of safety, we refer to the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For preoperative skin preparation simulation studies, the Division of Nonprescription Drug Products does not require subgroup analyses since the clinical simulation studies are conducted on healthy volunteers who are not treated for sickness. However, per DB7 request, the sponsor conducted subgroup analyses of efficacy by race, age, and gender.

Analyses of responder rates and log bacterial counts were conducted for each subgroup, within each study, body region, and timepoint. The results (not shown in this review but provided in Section 3.5 of the Integrated Summary of Efficacy), confirmed that the

efficacy of Medline 2% CHG, Dyna-Hex 2, and the vehicle does not differ across these subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Table 14 summarizes the main findings of efficacy at 10 minutes from Study R15-029 and Study R13-053.

Results based on responder rates show that for Medline 2% CHG cloth, the lower bound of the 95% CI for responder rate was greater than 70% for all body regions at 10 minutes, in both studies. For Dyna-Hex 2, the lower bound of the 95% CI for responder rate was greater than 70% only in R13-053 at the abdomen.

Results based on average treatment effect show that Medline 2% CHG cloth is statistically superior to both Dyna-Hex 2 and the vehicle at 10 minutes, in both body regions and studies. Dyna-Hex 2 was statistically superior to the vehicle in both studies at the abdomen, but only in R13-053 at the groin.

Table 13. Responder Rate and ATE difference at 10 minutes (mAT population)

		Study R13-053		Study R15-029	
		Estimate	95% CI	Estimate	95% CI
Abdominal Region					
Responder Rate	Medline Cloth	93% (235/252)	(89%,96%)	81% (194/241)	(75%,85%)
	Dyna-Hex 2	85% (216/254)	(80%,89%)	72% (181/253)	(66%,77%)
	Vehicle	50% (24/48)	(35%,65%)	50% (25/50)	(36%,65%)
ATE Difference	Medline Cloth – Dyna-Hex 2	-0.26	(-0.39, -0.13)	-0.34	(-0.52, -0.16)
	Vehicle - Medline Cloth	1.22	(0.99, 1.46)	0.81	(0.50, 1.12)
	Vehicle - Dyna-Hex 2	0.97	(0.74, 1.20)	0.47	(0.17, 0.78)
Groin Region					
Responder Rate	Medline Cloth	86% (218/254)	(81%,90%)	85% (213/252)	(79%, 89%)
	Dyna-Hex 2	65% (162/249)	(59%,71%)	73% (189/259)	(67%,78%)
	Vehicle	25% (12/48)	(14%,40%)	56% (29/52)	(41%, 70%)
ATE Difference	Medline Cloth – Dyna-Hex 2	-0.60	(-0.80, -0.41)	-0.90	(-1.12, -0.68)
	Vehicle - Medline Cloth	1.80	(1.45, 2.14)	0.94	(0.55, 1.33)
	Vehicle - Dyna-Hex 2	1.19	(0.85, 1.54)	0.04	(-0.35, 0.42)

Source: Reviewer Table, derived from R13_053.xpt, R15_029.xpt

5.2 Conclusions and Recommendations

From a statistical standpoint, there is sufficient evidence that Medline 2% CHG is effective and adds benefits beyond those of Dyna-Hex 2 and the placebo cloth. Specifically, both R13-053 and R15-029 show that:

- Medline 2% CHG cloth met the effectiveness criteria outlined in the 2015 Proposed Rule (see sections 3.2.4 and 3.2.5), with responder rates greater than 70% at 10 minutes and persistent antimicrobial properties at 6 hours.
- Analyses based on average treatment effects also showed that Medline cloth is statistically superior to both Dyna-Hex 2 and the vehicle at 10 minutes, in both the body regions and studies.

However, the sponsor failed to validate the study conduct to assure that the expected results are produced, as Dyna-Hex 2 (which is an approved product) did not always meet the 70% responder rate criteria.

For better transparency, we recommend the following improvements for future

submissions with the same indication:

- Submission of a SAP and SAP amendments.
- Submission of raw datasets for traceability. The sponsor only submitted derived datasets and did not provide raw datasets that would allow the FDA reviewer to verify the derivation of key variables.
- Plots of log bacterial reductions versus sampling time for all body regions and time points. The data used to generate the plots should include all subjects randomized, regardless of protocol deviations. In this submission, the reviewer noticed a larger proportion of sampling time deviations for Dyna Hex 2. The staff performing the bacterial sample collections were not blinded and it is possible that a longer sampling time could have resulted in higher bacterial reduction.

6 APPENDIX

6.1 Additional Tables for R13-053

Table 14. Mean Log10 CFU Counts and Changes from Baseline in R13-053

Body Area	Treatment	Baseline	10 Minutes		6 Hours		8 Hours	
			Value	Change	Value	Change	Value	Change
Abdomen	Dyna-Hex 2	3.4383	0.5255	2.9128	1.2072	2.2311	1.4097	2.0286
Abdomen	Medline Cloth	3.4586	0.2812	3.1774	0.9456	2.5131	1.0150	2.4437
Abdomen	Vehicle Cloth	3.4852	1.5232	1.9620	1.9811	1.5041	2.0847	1.4005
Groin	Dyna-Hex 2	5.4634	1.7908	3.6726	2.8017	2.6617	2.8821	2.5813
Groin	Medline Cloth	5.4510	1.1753	4.2757	2.3489	3.1021	2.4062	3.0448
Groin	Vehicle Cloth	5.4148	2.9351	2.4797	3.3531	2.0617	3.4139	2.0009

Source: Table 2 of R13-053 Statistical Report Addendum 01 Reviewer verified the sponsor's results presented in this table.

6.2 Additional Tables for R15-029

Table 15. Mean Log10 CFU Counts and Changes from Baseline in R15-029

Body Area	Treatment	Baseline	10 Minutes		6 Hours		8 Hours	
			Value	Change	Value	Change	Value	Change
Abdomen	Dyna-Hex 2	3.7734	1.2200	2.5534	1.0736	2.6998	1.0511	2.7223
Abdomen	Medline Cloth	3.7865	0.8879	2.8987	0.6990	3.0875	0.6846	3.1019
Abdomen	Vehicle Cloth	3.7050	1.6605	2.0445	1.4601	2.2449	1.3808	2.3242
Groin	Dyna-Hex 2	6.1000	2.4330	3.6670	2.1325	3.9675	2.0658	4.0342
Groin	Medline Cloth	6.1210	1.5369	4.5842	1.1404	4.9806	1.2318	4.8892
Groin	Vehicle Cloth	6.1436	2.4806	3.6630	2.3741	3.7695	2.5288	3.6149

Source: Table 2 of R15-029 Statistical Report Addendum 01. Reviewer verified the sponsor's results presented in this table.

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