

A WORK PLAN FOR COMPLETION OF SAFETY AND EFFECTIVENESS STUDIES
SUBMITTED BY



Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial
Drug Products for Over-the-Counter Human Use; Proposed Amendment
of the Tentative Final Monograph; Reopening of Administrative Record;
Docket No. FDA-1975-N-0012, Regulatory Information No. 0910-AF69

September 9, 2016

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September 9, 2016

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Food and Drug Administration
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Attention: Dr. Theresa Michele
(via <http://www.regulations.gov>)

Re: Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record; **Docket No. FDA-1975-N-0012**, Regulatory Information No. 0910-AF69

Dear Dr. Michele:

The American Cleaning Institute (ACI)¹ is pleased to provide this Work Plan in response to letters from the Food and Drug Administration (FDA) dated March 10, 2016 regarding our requests that benzalkonium chloride (BAC), benzethonium chloride (BZT) and chloroxylenol (PCMX) be deferred from inclusion in the final rulemaking for the December 2013 FDA proposed rule for over-the-counter (OTC) consumer antiseptic washes (78 FR 76444). ACI is also pleased to provide a Work Plan specific to ethyl alcohol which is listed as an eligible active in the proposed rule for Health Care Antiseptic Products (May 1, 2015) and the proposed rule for Consumer Antiseptic Hand Rub Products (June 30, 2016). We believe this information is germane to the Agency's request for a Work Plan with respect to the active ingredients for which we have sought the deferral of rulemaking as we are taking an integrated approach among the three proposed rules and associated active ingredients we are supporting. This integrated approach is a key attribute of our strategy for satisfying the Agency's data requirements as it allows for an efficient utilization of both FDA and industry resources. It will minimize the total amount of human and animal testing to only that sufficient for determination of safety and effectiveness, and allow for iterative, tiered learning to inform testing design.

As we noted in our response letters dated May 3, 2016 (benzalkonium chloride), May 4, 2016 (benzethonium chloride) and May 5, 2016 (chloroxylenol), we intend to fill each of the safety and effectiveness data gaps identified in your letters. ACI and its members have been actively engaged in the rulemaking for Consumer Antiseptic Wash Products (December 17, 2013) and Health Care Antiseptic Products (May 1, 2015), and we intend to be actively engaged in the rulemaking for Consumer Antiseptic Hand Rub Products (June 30, 2016) as well. In addition, in June 2014, we petitioned FDA to create a Food Handler Antiseptic Wash Products category among the OTC monographs. Our data generation plan applies an integrated approach to generating safety and effectiveness data across the noted OTC antiseptic product applications and associated

¹ ACI is a trade association for the \$30 billion U.S. cleaning products industry. ACI members include a significant number of manufacturers of retail and institutional consumer antiseptic hand wash products sold in the U.S. that are the subject of the proposed rule and companies that supply active ingredients for these products.

active ingredients for which we have expressed an interest. You will find this integrated approach apparent throughout this Work Plan.

I. Executive Summary

ACI and its members are planning to work over the coming years to generate safety and effectiveness data to support six active ingredients (benzalkonium chloride, benzethonium chloride, chloroxylenol, ethanol, isopropyl alcohol and povidone iodine) across four FDA OTC topical antimicrobial monographs (Consumer Hand Wash products, Consumer Hand Rub products, Food Handler Products and Health Care Products). In response to letters from FDA dated March 10, 2016, we describe our Work Plan for the three active ingredients we are supporting under the Consumer Hand Wash products monograph (benzalkonium chloride, benzethonium chloride and chloroxylenol) including a timeline for completing the studies necessary to support a final determination of safety and effectiveness for those active ingredients (see Tables 3, 4 and 5). In addition, we provided details for safety and effectiveness testing for those active three ingredients and ethanol under the Health Care Antiseptic products monograph.²

In addition, we offer the following table indicating those actives that will be our immediate focus over the next 6 months and the associated submissions we anticipate to FDA.

Table ES-1. ACI OTC topical antimicrobial safety and effectiveness activities 4Q2016-1Q2017.

Activity	Actives	Planned Initiation	FDA Submission
Submit Clinical Outcome Study protocol (ETEC Challenge Study)	BAC, BZT, PCMX	4Q2016	4Q2016
Submit Clinical Outcome Study protocol (Skin Infection Study)	BAC, BZT, PCMX	4Q2016	4Q2016
Submit chloroxylenol ADME protocol	PCMX	4Q2016	4Q2016
Develop and execute observational studies for consumer and health care hand wash practices (MUsT)	BAC, BZT, PCMX	4Q2016	3Q2017†
Initiate <i>in vitro</i> dermal penetration studies (MUsT)	BAC, BZT	4Q2016	3Q2017†
Initiate pilot studies for ETEC Challenge Study	BAC, BZT, PCMX	4Q2016	3Q2017
Complete <i>In-vitro</i> Time-Kill study*	BAC, BZT, EtOH, PCMX	1Q2017	2Q2017
Submit alcohol pilot MUsT protocol**	EtOH	1Q2017	1Q2017
Complete Alcohol Pilot Health Care Personnel Hand Rub Study*	EtOH	1Q2017	2Q2017

BAC = benzalkonium chloride, BZT = benzethonium chloride, EtOH = alcohol (ethanol), PCMX = chloroxylenol

* Protocol previously submitted and revised based on feedback received from FDA

** Pending FDA response to Q42016 GOJO/ACI Meeting Request

† To be submitted with revised MUsT protocol

² We note the Consumer Hand Rub proposed rule indicates that effectiveness data for Health Care Antiseptic products would support the Consumer Hand Rub indication. We anticipate that effectiveness data for Health Care Antiseptic products also would support a Food Handler product monograph that FDA has yet to propose.

Though we have a great deal of activity planned for the coming months, we also are prepared for an extended research commitment that will run for a number of years. We note in particular that development of the research design for the human pharmacokinetic maximal usage trial (MUsT) is something for which the Agency is currently unable to provide us detailed guidance because there is no precedent for such studies under the use conditions of the OTC topical antiseptic products from which to draw. Likewise, design and execution of clinical outcome studies for OTC topical antiseptic products is particularly challenging and there are few such studies which have been successfully conducted and reported in the scientific literature from which to draw. Consequently, we anticipate continued interaction with the agency including a number of public meetings on these and other research challenges over the coming years. We appreciate the agency's guidance and patience as we answer these challenging questions together.

For our part, we anticipate committing on the order of \$10 million to execute safety and effectiveness studies over the next five years. While we hope that will be sufficient to earn GRAS and GRAE findings by FDA for those active ingredients of interest, we are committed to completely satisfying the Agency's data needs in a timely fashion.

II. Introduction

The OTC drug review monograph system is an established and recognized mechanism for manufacturers to market OTC drugs that were on the market in 1972. The process relies on public rulemaking to establish final monographs that identify acceptable ingredients, doses, formulations, and labeling for OTC drugs. The OTC drug review is a crucial regulatory pathway for topical antiseptic ingredients that are used in a wide variety of consumer, food handler, and health care products.

ACI is providing a foundation of scientific and technical support for antiseptic hand hygiene products regulated by the FDA's OTC monographs, including surgical scrubs, hand washes, and hand rubs, formulated with various active ingredients, and intended for use by professional workers or consumers.

To effectively manage the FDA's safety and effectiveness data requirements for active ingredients, the ACI is proposing a strategy that includes study protocols that address the broadest range of product applications, consistent with sound science. Our intent is to use this integrated approach to leverage safety and effectiveness data across multiple monograph categories and product applications, as allowed by regulations. This will allow for efficient utilization of both FDA and industry resources, minimize the total amount of human and animal testing to only that sufficient for determination of safety and effectiveness, and allow for iterative, tiered learning to inform testing design.

III. Intended Uses

ACI and its members have been actively engaged on the rulemaking for Consumer Antiseptic Hand Wash Products (December 17, 2013) and Health Care Antiseptic Products (May 1, 2015). Recently, FDA released a proposed rule for Consumer Antiseptic Hand Rub Products (June 30, 2016). We intend to be fully engaged in this rulemaking as well. In addition, in June

2014, we petitioned FDA to create a Food Handler Antiseptic Wash Products category among the OTC monographs.

Our data generation plan will apply an integrated approach to generating safety and effectiveness data across the noted OTC antiseptic product applications. We note that FDA has acknowledged such an approach in recent meetings with industry as well as in the proposed rule for Consumer Antiseptic Hand Rubs where the Agency states that “the testing costs for this proposed rule are not attributed here because these costs will be realized if manufacturers conduct testing discussed in the proposed rule for health care antiseptics (80 FR 25166) and we do not count costs twice.”³

IV. Active Ingredients

Across the four topical antiseptic monographs that ACI is supporting, we have identified six active ingredients that are of interest to our members. Table 1 below identifies the active ingredients we are currently supporting and the applications of interest.

Table 1. Antiseptic Active Ingredients for Uses Supported by ACI Members

Active Ingredient	Consumer Antiseptic Hand Wash Products	Health Care Antiseptic Products	Consumer Antiseptic Hand Rub Products	Food Handler Antiseptic Products
Alcohol 60 to 95 percent	NE	Y	Y	Y
Benzalkonium chloride (BAC)	Y	Y	Y	Y
Benzethonium chloride (BZT)	Y	Y	NE	Y
Chloroxylenol	Y	Y	NE	Y
Isopropyl alcohol 60 to 91.3 percent	NE	Y	Y	Y
Povidone-iodine 5 to 10 percent	N	Y	NE	N

N – No

NE – Not Eligible

Y – Yes

V. Safety Studies

A. Clinical Safety: Human pharmacokinetic maximal usage trial (MUSt)

1. Introduction

³ 81 FR 42912 at 42931

In the December 2013 Proposed Rule, the Agency indicated that data from a human pharmacokinetic maximal usage trial (MUsT) were necessary for the active ingredients in order to assess the effects of long-term dermal exposure. In the proposed rules and in later communications, the Agency pointed to its guidance⁴ and a scientific publication⁵ which provides some indication of the issues that need to be addressed in conducting a MUsT. In those documents, the Agency states that a MUsT should be conducted in a suitable number of subjects *with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling*. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- Frequency of dosing
- Duration of dosing
- Use of highest proposed strength
- Total involved surface area to be treated at one time
- Amount applied per square centimeter
- Method of application/site preparation
- Sensitive and validated analytical method
- Multiple formulations

We note that topical antiseptic wash products are generally intended to be used by healthy individuals to prevent infections and the spread of infectious pathogens, and, unlike many other topical medicines, the directions for use may simply state “Apply as needed.” Consequently, a number of the MUsT design elements for consumer antiseptic wash products are not defined by specific conditions of use specified on the product label but are determined by the habits and practices of the consumer. Further, given the nature of the monograph process, and the multiplicity of formulations that may be on the market, identifying a formulation that represents the highest systemic exposure needs to be established as well.⁶ It is our intent to use *in vitro* dermal penetration studies to identify the formulas with the highest potential for dermal penetration of active ingredients for use in each MUsT.

ACI and its members have participated in public meetings with FDA on April 24, 2015, May 6, 2015, July 30, 2015, October 20, 2015, and May 25, 2016 where the subject of the MUsT was discussed. During those meetings and in subsequent communications, it was apparent that both FDA and industry have quite limited experience with MUsT design and execution for OTC topical antiseptics as preventative drugs, particularly in establishing what constitutes the maximum

⁴ U.S. Food and Drug Administration, “Guidance for Industry. Acne Vulgaris: Developing Drugs for Treatment,” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071292.pdf>, 2005.

⁵ Bashaw, E.D. et al., “Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products,” *Therapeutic Innovation and Regulatory Science*, 2014. Available at: <http://dij.sagepub.com/content/49/1/108.full.pdf.html>.

⁶ We note that the same is true of some other OTC drugs such as sunscreens.

potential for exposure. Therefore, the Agency has been unable to offer definitive guidance on how to establish the design elements to successfully complete a MUsT for OTC topical antimicrobial products. Consequently, as part of our holistic strategy for generating safety and effectiveness data for a number of active ingredients across four OTC monographs, we propose to conduct research to establish a number of the design elements for a MUsT and focus on a limited but representative selection of active ingredients in order to gain more experience in successfully executing a MUsT. Our current focus is on a single hand wash active ingredient (benzalkonium chloride) and a single hand rub active ingredient (ethanol) given the different use pattern of those products. A description of the related activity is provided below. With the experience gained by successfully executing a MUsT for active ingredients in hand wash (BAC) and hand rub (alcohol) products, we will conduct additional MUsT studies for the remaining active ingredients used in these products.

2. Benzalkonium chloride

A draft protocol for the MUsT of active ingredients⁷ in Consumer Antiseptic Hand Wash products was submitted to FDA in a letter dated December 14, 2014 from Lewis & Harrison (Docket ID FDA-1975-N-0012-0642). A public meeting between FDA and the study sponsor occurred on May 6, 2015 and comments from FDA on the meeting and protocol were received. Appropriate revisions were made to the MUsT protocol and a second draft was submitted in a letter dated July 10, 2015. Comments were again received from FDA in a letter dated October 15, 2015 (Docket ID FDA-1975-N-0012-0642). Additional revisions and supporting data were submitted to FDA and discussed in a public meeting on May 25, 2016 meeting with Lonza, Henkel and FDA. It is our intent to further revise this MUsT protocol, however, it is apparent that additional data need be collected to better understand specific parameters for running such a study including (but not limited to) the formulation with the greatest dermal penetration and the (reasonable) maximum number of hand washes in a high-use setting (e.g., health care emergency care unit, ICU and/or NICU). Consequently, we intend to conduct preliminary research to establish these parameters in the MUsT before submitting the next revision of the protocol.

In its feedback during the May 25, 2016 public meeting and the advice found in the Agency-prepared meeting minutes (Docket ID FDA-1975-N-0012-0648), FDA agreed with the sponsors' proposal to conduct preliminary *in vitro* dermal penetration studies prior to the MUsT to determine the maximum dermal penetration of benzalkonium chloride and benzethonium chloride in at least four currently marketed hand soaps. The results of the dermal penetration studies would inform the selection of the product to be tested in the MUsT. The sponsors are currently working with appropriate laboratories and anticipate initiating those studies during 4Q2016.

In addition, there was agreement that observational studies in a health care setting would be conducted to determine the appropriate number of hand washes in the MUsT. We understand that such data could additionally serve as a maximal level for the MUsT for Consumer Hand Wash. Likewise, ACI is working to develop a protocol to execute such an observational study. We expect

⁷ Though the protocol was submitted with benzethonium chloride as the test material, it is our intent to revise the protocol with benzalkonium chloride as the test material.

to complete such a protocol by 1Q2017 and execute the study in 2Q2017. Consequently, we expect to modify the MUsT protocol and submit it to FDA in 3Q2017.

Also, we understood from the May 25, 2016 meeting that FDA agreed to a protocol element that would allow subjects in the MUsT to leave the laboratory at the end of each day and conduct unsupervised washes to reach the number of washed required each day in the protocol, assuring they have product and diaries for compliance purposes. We intend to modify the MUsT protocol accordingly.

3. Ethanol (alcohol)

Key elements for general MUsT design consideration have been delineated in: “*Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products*” (Bashaw, 2015) and the *Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use* (FDA 2015). For consideration here, we have organized these into the following Elements:

- Element 1: adequate number of subjects (steps should be taken to ensure that the target population (for example, age, gender, race) is properly represented);
- Element 2: frequency of dosing (e.g., number of hand rub applications during the study);
- Element 3: duration of dosing (e.g., dosing to represent an 8- to 12-hour health care worker shift);
- Element 4: use of highest proposed strength
- Element 5: method of application (e.g., hand rub or hand wash)
- Element 6: total involved surface area to be treated at one time
- Element 7: amount applied per square centimeter
- Element 8: sensitive and validated analytical method; and
- Element 9: different formulations

On September 6, 2016, GOJO Industries submitted “*Approach and Plan to Address Key Elements for Maximal Use PK Trial (MUsT) Design*” which details a proposed approach, rationale and general investigational plan for the conduct of a MUsT for ethyl alcohol and provides an approach to defining each of the nine (9) MUsT design elements. With this submission, GOJO has requested specific feedback on the plan from FDA in order to present a detailed pilot protocol for review. The plan presents a model where the overall MUsT is conducted in stages to address the use of ethyl alcohol across two monographs and multiple indications while addressing the influence of formulation. Specific work to defining each of the nine elements has already been completed or is underway. The PK Study (MUsT) will be conducted in three phases in order to achieve a data set for MUsT.

a. Determination of Frequency and Duration of Dosing

In 2015, detailed research was undertaken by Dr. John Boyce to determine an appropriate maximal frequency of dosing for ethyl alcohol-based products. A literature review and an analysis

of recent studies that utilized electronic hand hygiene monitoring systems was conducted to better understand usual and maximal use of alcohol hand rubs by healthcare workers. A manuscript entitled “Frequency of Use of Alcohol-Based Hand Rubs by Nurses: A Systematic Review” was provisionally accepted for publication in *Infection Control & Hospital Epidemiology* on July 7, 2016, pending satisfactory revision and review of final comments. A report summarizing findings and recommendations for Frequency and Duration of Dosing is included in the September 6, 2016 GOJO submission.

To validate the tolerability of the proposed maximal use frequency and duration of dosing for antiseptic hand rubs, GOJO sponsored a preliminary study to assess the tolerability of a hand rub containing the maximum proposed concentration (i.e., 90% v/v ethyl alcohol) when applied at the worst-case frequency and duration of dosing. This study was completed in May of 2016 and the final report is included in the September 6, 2016 GOJO submission to inform MUsT design.

b. Pilot MUsT

Upon receiving feedback from FDA on the MUsT Approach and Plan submitted by GOJO, ACI will submit a meeting request in 4Q2016 (Table 4) to align on the Pilot MUsT protocol which will be included in a Briefing Document. ACI plans to execute the pilot MUsT for ethyl alcohol 3Q2017 and to submit the final report 4Q2017. The purpose of the Pilot MUsT will be to identify the specific application procedure (i.e., indication) to be run in the Pivotal study, address effect of formulation, and determine time to steady state.

c. Pivotal MUsT

Upon the completion of the Pilot Study, ACI will submit a meeting request to FDA for the purpose of presenting the Pilot Study data for the test materials, and to obtain agreement from FDA on the proposed Pivotal MUsT protocol. Approximate timing for protocol submission and study execution for the pivotal study is presented in Table 6.

B. Nonclinical Safety (Toxicology)

1. Benzalkonium chloride

In its letter of March 10, 2016 to Lonza America, Inc., the American Cleaning Institute and Henkel North America granting initial deferral of benzalkonium chloride from inclusion in the final rulemaking for Consumer Hand Wash products, FDA identified data from two (2) nonclinical (animal) studies recommended to fill safety data gaps to allow the GRAS evaluation of benzalkonium chloride: A Dermal Carcinogenicity Study and Dermal ADME Studies. Further, FDA noted that prior to “initiating the dermal carcinogenicity study, animal pharmacokinetic/toxicokinetic and dermal dose range findings will need to be conducted to inform its design.” With respect to the dermal ADME studies, FDA allowed that it would be “acceptable that these dermal exposure data be collected during the required dermal carcinogenicity study.” And, it was recommended that “the dermal dose range finding toxicity studies and the pharmacokinetic/toxicokinetic study in animals” should be run in parallel with the required human

pharmacokinetic maximal use trial (MUsT) since “data generated from the MUsT will be used to select the doses for the dermal carcinogenicity study.”

FDA has recommended that a dose range-finding study be run in parallel with the MUsT. To the contrary, however, FDA correctly notes that “data generated from the MUsT will be used to select the doses for the dermal carcinogenicity study.” It follows that these same data are needed to select appropriate putative doses to be evaluated in the range-finding study.

At the same time, we have available for dose-setting considerable data on the toxicity and safety of benzalkonium chloride, including a 90-day subchronic toxicity study and ADME following oral dosing. With the addition of human pharmacokinetic and systemic exposure data from the MUsT, it may be possible to establish appropriate dose levels for a dermal carcinogenicity study without the need for performing an additional 90-day range finding study. We plan to develop the protocol for the recommended dermal range-finding study, should this be needed, but only as data from the MUsT become available. It is our intention to present this protocol, or our justification for why a dermal range-finding study is not needed to FDA during the latter half of 2017. Should a range-finding study be required, it should begin during the first quarter of 2018.

With respect to the recommended dermal ADME studies, FDA has said both that this study(ies) should be run in parallel with the MUsT and that it will allow these to be “collected during the required dermal carcinogenicity study.” We propose *not* to run the studies concurrently so as not to overly complicate the dermal carcinogenicity study. Instead, we would run these studies along with the dermal range-finding studies, if the range finding study is necessary. If it is determined, and agreed by FDA, that a dermal range-finding study is not necessary to establish appropriate doses for the dermal carcinogenicity study, dermal ADME studies will be run as stand-alone studies during 2018. A protocol for the dermal carcinogenicity study will be submitted in 2018 for FDA concurrence and this study is planned to commence by the end of 2018 and be completed during 2021 or the first half of 2022. We appreciate the references provided by FDA for Guidelines on the conduct of these studies and intend to conform to these.

Lonza, Inc. is committed to conducting studies to fulfill all data needs identified by FDA necessary to inform the GRAS decision for benzalkonium chloride. We feel strongly, however, that the MUsT should be initiated and completed before any of the additional required safety studies are initiated. Our reasons for this are:

- FDA has indicated that the results of MUsT studies will be the primary data for determination of GRAS. However, MUsT studies have not previously been required for monograph actives and neither we nor the FDA are experienced in the design and interpretation of the complex MUsT protocols required to support the use of an active in multiple OTC formulations. To our knowledge, no MUsT studies have been run to date in such a context. Because we lack clearly definitive data on and agreement about frequency of use of hand wash products, the practical aspects of conducting a MUsT meeting FDA criteria are still being defined. Moreover, FDA has not fully explained how the MUsT data will be used in GRAS determination or provided clear indications of how any findings of systemic benzalkonium levels will be interpreted. As both we and the FDA are developing expertise in this area together, we believe that it is prudent to complete, evaluate and understand the proper

utilization of these MUsT data before the additional, recommended safety studies are initiated. We should defer other safety studies both to establish the most appropriate and useful protocols for these other studies and to avoid wasting resources and laboratory animals in conducting studies that are later determined not to be needed.

- Completion of the MUsT prior to initiating the remaining recommended studies will not substantially delay FDA determination of GRASE for benzalkonium chloride. FDA has defined both the safety data and effectiveness data required to determine GRASE. The clinical outcome effectiveness studies to be conducted are expected to extend beyond the completion dates for safety studies in our timeline, even if effectiveness studies are initiated during 2017. Because of this, the time that will be needed for us to generate all data for benzalkonium chloride required by FDA will not be extended by fully completing the MUsT before additional studies are initiated.

2. Benzethonium chloride

In its letter of March 10, 2016 to Lonza America, Inc., the American Cleaning Institute and Henkel North America granting initial deferral of benzethonium chloride from inclusion in the final rulemaking for Consumer Hand Wash products, FDA identified four (4) areas where nonclinical (animal) data are recommended to fill safety data gaps to allow the GRAS evaluation of benzethonium chloride: an Oral Carcinogenicity Study, Oral and Dermal ADME studies, Developmental and Reproductive Toxicity (DART) studies, and a Hormonal Effects study. Further, FDA noted that the need for the oral carcinogenicity study and further DART testing will depend on the results of the human pharmacokinetic maximal use trial (MUsT) and “may be waived if a human MUsT shows low levels of dermal absorption and if no additional safety signals were obtained from the pending toxicological testing program.” With respect to oral and dermal ADME studies, FDA said that it would be “acceptable that oral exposure data be collected during the oral carcinogenicity study, if conducted.” Finally, with respect to hormonal effects, the FDA stated that it “is possible that DART and carcinogenicity studies conducted with appropriate endpoints may suffice to address adverse effects related to hormonal activity for benzethonium chloride.”

As described above, for benzalkonium chloride, we need *in vitro* dermal penetration studies and observational studies to better understand consumer usage of antimicrobial hand wash products before we initiate the MUsT for benzalkonium chloride. A MUsT with benzalkonium chloride is expected to be initiated and largely completed during 2017. Given that we have not previously conducted a MUsT and the size and practical complexity of this protocol, we plan to initiate a MUsT with benzethonium chloride after the completion of the MUsT with benzalkonium chloride. We plan to initiate a MUsT with benzethonium chloride as soon as practicable following the completion of the MUsT with benzalkonium chloride and expect to complete it during 2018. As noted, above, when the timelines for these studies are considered within the context of the likely timeframe necessary for completing the required clinical outcome effectiveness studies, our plan will not adversely delay the ultimate timing of FDA’s determination of GRASE for benzethonium chloride. Because the FDA has indicated that the need for the oral carcinogenicity study and further DART testing may be waived depending upon the results of the MUsT, these studies will be initiated after the MUsT has been completed. We do, however, intend to submit preliminary,

proposed protocols (as much as practical) for these studies to the FDA while the MUSt is being run so that we have FDA acceptance and can initiate these studies as soon as practicable following the completion of the MUSt if they are needed. Should these studies not be waived, we anticipate that they would be initiated in 2019 and completed in line with their required duration; the carcinogenicity study being the longest and expected to be completed in 2022. With respect to the hormonal effects studies, we plan to address these endpoints in the DART and oral carcinogenicity studies. Because of this, hormonal effects studies are not planned until after these studies are completed, if they are not waived. If DART and oral carcinogenicity studies are waived, we feel that the need for oral and dermal ADME data can be reassessed at that time, and if it is still deemed to be needed, to run these both as independent studies at that time (anticipated to be 2020). Protocols for our proposed hormonal effects studies were submitted to FDA prior to our initial March 2015 meeting and it is our understanding they these protocols are acceptable. Finally, with respect to the recommended oral and dermal ADME studies, we plan to run the dermal studies in parallel with the MUSt (during 2019) and to postpone the oral studies to run them as an adjunct to the oral carcinogenicity study, if it is not waived. If the oral carcinogenicity study is waived, the need for oral ADME data will be reassessed with the FDA at that time and, if still required, will be run independently at that time (anticipated to be 2020).

Lonza, Inc. is committed to conducting studies to fulfill all data needs identified by FDA necessary to inform the GRAS decision for benzethonium chloride. We appreciate the references provided by FDA for Guidelines on the conduct of the recommended studies and intend to conform to these. Protocols for all studies that are ultimately conducted will be submitted to the FDA with sufficient time for review and agreement prior to the anticipated dates of study initiation.

3. Chloroxylenol

FDA identified several areas where nonclinical (animal) studies are required to fill safety data gaps for chloroxylenol. The Agency recommended the following studies be conducted:

- Carcinogenicity studies
 - Oral carcinogenicity study
 - Dermal carcinogenicity study
- ADME studies
- Developmental and Reproductive Toxicity (DART) testing
- Hormonal effects study

The Agency proposed that for several of the studies, the need to fill the particular data gap would depend on the results of a human pharmacokinetic maximal use trial (MUSt), in particular, the oral carcinogenicity study and DART testing. In addition, the Agency indicated that DART and carcinogenicity studies conducted with appropriate endpoints may suffice to address adverse effects related to hormonal activity for chloroxylenol. As such, oral carcinogenicity, DART and hormonal effects studies will not be advanced until a MUSt for chloroxylenol is completed.

With respect to a MUSt for chloroxylenol, as, we intend establish experience with the execution of such studies by focusing our resources on other active ingredients, benzalkonium chloride and alcohol in particular, before we develop a study protocol for chloroxylenol.

In the March 10, 2016 letter, the Agency noted that additional ADME data were necessary. In the December 2013 proposed rule, the Agency noted

Overall, these data demonstrate that absorption of chloroxylenol occurs after dermal application in humans and animals. However, the extent of this absorption and the resulting systemic exposure has not been adequately characterized. In the 1994 TFM, FDA stated that data from human studies characterizing the absorption, distribution, and metabolism of chloroxylenol conducted under maximal exposure conditions were needed (59 FR 31402 at 31415). The administrative record for this active ingredient still lacks data to characterize the rate and extent of systemic absorption, the similarities and differences between animal and human metabolism of chloroxylenol under maximal use conditions, and data to help establish the relevance of findings observed in animal toxicity studies to humans.

We believe that the review of the chloroxylenol ADME data in the December 2013 proposed rule point to adequate adsorption, distribution and elimination data by virtue of the Sved study.⁸ However, we note that that Agency has requested additional data to better understand the extent of adsorption. We believe this information is best addressed through the human pharmacokinetic study (MUsT) which we intend to pursue once we have more experience with those studies after having worked with the other active ingredients.

The issue of metabolism and metabolites appears to be an existing data gap for chloroxylenol. We intend to specifically address this area by employing a modified ADME study in rats using radiolabeled chloroxylenol. We are currently working with a test laboratory to develop such a study and intend to submit the associated protocol to the Agency later this fall.

Regarding a dermal carcinogenicity study, the Agency indicated that animal pharmacokinetic/toxicokinetic studies and dermal dose range finding will need to be conducted to inform the design of a dermal carcinogenicity study. We note that a 13-week dermal toxicity study of chloroxylenol (PCMX) in mice was completed and submitted to the docket in 2001. Based on the results of the study and a protocol for a 24-month dermal carcinogenicity study of PCMX in mice, the Agency recommended doses of 0% (acetone), 3%, 10% and 20% PCMX in a dermal carcinogenicity study in mice. It does not appear that a dermal dose range finding study needs to be repeated. However, given the significant activities on safety and effectiveness of chloroxylenol, we are not planning to immediately develop a protocol for a dermal toxicity study. It is our intent to successfully complete our health care effectiveness studies, the ADME study and the MUsT before developing the protocol and initiating a dermal carcinogenicity study for chloroxylenol.

C. Antibiotic Resistance

Based on concerns over the potential impact of widespread antiseptic use on the development of antimicrobial resistance, the Agency has requested data to clarify the effect of antiseptic active ingredients on the emergence of bacterial resistance. In the March 20, 2015 meeting between ACI and FDA, it was agreed that ACI's proposal to "conduct active ingredient-specific reviews of the literature pertaining to antiseptic resistance and antibiotic cross-resistance

⁸ Sved, D.W., "A dermal adsorption study with [14C]-Labeled PCMX in Mice," FDA-1975-N-0012.

as a substitute for studies proposed by the Agency to assess the development of cross-resistance to antibiotics” was an acceptable approach. Subsequent to the March 2015, ACI initiated literature reviews for benzalkonium chloride, benzethonium chloride and chloroxylenol in collaboration with Dr. Christopher Woolverton, an academic expert in this field. Systematic and comprehensive searches of publically available databases have been completed and the evaluation of the output of these searches is underway to determine whether evidence exists for changes in antiseptic or antibiotic susceptibility, the likelihood that changes would occur in healthcare or consumer settings, and whether such changes pose a public health risk. The evaluation is expected to be completed by 1Q2018 and will be submitted to FDA by 2Q2018 (Tables 3-5).

VI. Effectiveness Studies

A. *In Vitro* Studies

FDA proposed that a demonstration of the effectiveness of antiseptic active ingredients would require that data from *in vitro* studies be included in the record. For the Consumer Hand Wash proposed rule, FDA proposed that *in vitro* Time-Kill data combined with Clinical Outcome Studies would be necessary to demonstrate the effectiveness of active ingredients. For the Health Care Antiseptics proposed rule and Consumer Hand Rub proposed rule, the Agency proposed that *in vitro* Time-Kill data and *in vitro* MIC/MBC data, along with *in vivo* clinical simulation studies were required. We propose to conduct a single Time-Kill study for active ingredients that may be used in any OTC antiseptic monograph, and likewise a single MIC-MBC study.

1. Time-Kill study

ACI submitted to FDA for review on January 5, 2016 a draft Time-Kill protocol that would test six active ingredients use in consumer antiseptic hand wash products and health care antiseptic products (*An In-Vitro Time-Kill Evaluation of Six Test Materials When Challenged with Twenty-Eight Bacterial and Yeast Species*; Bioscience Laboratories, Inc. Draft Protocol #150940-201). ACI received comments from the Agency regarding the protocol on March 25, 2016. ACI proposes to test 261 microorganisms as part of a single Time-Kill test including 36 strains of particular organisms based on Agency guidance (see **Table 2 below**).

An additional 225 clinical isolates (25 clinical isolates for each of the following nine organisms identified by FDA in the Consumer Antiseptic Wash proposed rule) would be tested:

- *Enterococcus faecalis*
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Listeria monocytogenes*
- *Campylobacter jejuni*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Salmonella enterica* Serovar *Enteritidis*
- *Shigella sonnei*

Table 2. Proposed Organisms for *In Vitro* Time-Kill Effectiveness Testing for OTC Topical Antiseptic Monographs

Organism	SOURCES				
	American Type Culture Collection Number	Consumer Antiseptic Hand Wash Rule (Dec. 17, 2013)	Health Care Antiseptics Rule (May 1, 2015)	Consumer Antiseptic Hand Rub Rule (June 30, 2016)	Proposed organisms for Food Handler Rule (ACI Experts)
<i>Enterococcus faecalis</i>	19433	X		X	X
<i>Enterococcus faecalis</i>	29212	X	X	X	X
<i>Staphylococcus aureus</i>	6538	X	X	X	X
<i>Staphylococcus aureus</i>	29213	X	X	X	X
<i>Methicillin-resistant S. aureus</i> (MRSA)	33591	X		X	X
<i>Methicillin-resistant S. aureus</i> (MRSA)	33592	X		X	X
<i>Streptococcus pyogenes</i>	14289	X	X	X	X
<i>Streptococcus pyogenes</i>	19615	X	X	X	X
<i>Listeria monocytogenes</i>	7644	X		X	X
<i>Listeria monocytogenes</i>	19115	X		X	X
<i>Campylobacter jejuni</i>	33291	X		X	X
<i>Campylobacter jejuni</i>	49943	X		X	X
<i>Escherichia coli</i>	11775	X	X	X	X
<i>Escherichia coli</i>	25922	X	X	X	X
<i>Pseudomonas aeruginosa</i>	15442	X	X	X	X
<i>Pseudomonas aeruginosa</i>	27853	X	X	X	X
<i>Salmonella enterica</i> Serovar <i>Enteritidis</i>	13076	X		X	X
<i>Salmonella enterica</i> Serovar <i>Typhimurium</i>	14028	X		X	X
<i>Shigella sonnei</i>	9290	X		X	X
<i>Shigella sonnei</i>	25931	X		X	X
<i>Haemophilus influenza</i>	TBD		X	X	
<i>Bacteroides fragilis</i>	TBD		X	X	
<i>Enterobacter species</i>	TBD		X	X	
<i>Burkholderia cepacia</i>	25416			X	
<i>Burkholderia cepacia</i>	25608			X	
<i>Klebsiella pneumoniae</i>	13883		X	X	
<i>Klebsiella pneumoniae</i>	27736		X	X	
<i>Serratia marcescens</i>	8100			X	
<i>Serratia marcescens</i>	14756		X	X	
<i>Streptococcus pneumoniae</i>	6303		X	X	
<i>Streptococcus pneumoniae</i>	49619		X	X	
<i>Acinetobacter baumannii</i>	TBD		X		
<i>Candida albicans</i>	TBD		X		
<i>Candida tropicalis</i>	TBD		X		
<i>Escherichia coli</i> O157:H7	TBD				X
Community Acquired Methicillin-resistant <i>S. aureus</i> †	BAA-1683	X	X	X	

† Proposed organisms to support for Consumer Antiseptic Hand Wash and Consumer Antiseptic Hand Rub products (ACI Experts)

2. MIC/MBC study

ACI proposes to test 900 organisms by the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) methods. We would test 25 strains and 25 clinical isolates of each of the following 18 microorganisms identified by FDA in the Health Care Antiseptic proposed rule and the Consumer Hand Rub proposed rule:

- *Haemophilus influenza*
- *Bacteroides fragilis*
- *Enterobacter species*
- *Burkholderia cepacia*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*
- *Campylobacter jejuni*
- *Salmonella enterica*
- *Shigella sonnei*
- *Enterococcus faecalis*
- *Staphylococcus aureus* (including methicillin-resistant strains (*aka* MRSA))
- *Streptococcus pyogenes*
- *Listeria monocytogenes*
- *Streptococcus pneumoniae*
- *Acinetobacter baumannii*
- *Candida albicans*

ACI submitted to FDA for review on March 21, 2016 a draft MIC/MBC protocol that would test six active ingredients used in consumer antiseptic hand rub products and health care antiseptic products (*Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Six Test Materials*; Bioscience Laboratories, Inc. Draft Protocol #150941-202). ACI received comments from the Agency regarding the protocol on June 28, 2016 and is finalizing the protocol in preparation for execution of the study.

B. In Vivo Studies

1. Background

In the Health Care Antiseptics Proposed Rule and the Consumer Antiseptic Hand Rub Proposed Rule, the Agency proposed that a log reduction standard based on a surrogate endpoint (i.e., number of bacteria removed from the skin) was a suitable approach for the demonstration of general recognition of effectiveness.

2. Rationale

ACI intends to take advantage of a number of standardized methods (ASTM International) for conducting surrogate endpoint testing for antimicrobial effectiveness of active ingredients in topical antimicrobial products.

3. Proposed Studies

a. Health Care Personnel Hand Wash (BAC, BZT, PCMX)

ACI submitted to FDA on April 28, 2016 a draft pilot *in vivo* effectiveness protocol entitled *Pilot Evaluation of the Antimicrobial Effectiveness of Three Test Materials with an Active Control and Inactive Control Based on the ASTM E1174 Standardized Test Method Performed with a Randomized Parallel Design* that would generate data for three antiseptic active ingredients, namely benzalkonium chloride, benzethonium chloride and chloroxylenol, for use in health care personnel hand wash products. The data generated would be used to develop the protocol for the associated pivotal studies. We believe this Pilot Study is responsive to the requirements described in the Health Care Antiseptics Proposed Rule for *in vivo* effectiveness testing of active ingredients. However, we also believe the data generated will be supportive of the Consumer Antiseptic Wash Proposed Rule.

The primary objective of the Pilot Study is to evaluate the antimicrobial effectiveness of the three test materials with active and inactive controls for use as Health Care Personnel Hand Washes following single test material applications. The study will determine the log reduction which can be achieved at a 70% response rate with 95% confidence according to FDA guidelines, when tested according to modifications of ASTM E1174-13 for a single wash, and determine the sample size necessary for the pivotal studies.

Upon the completion of the Pilot Study, ACI will submit a meeting request to FDA for the purpose of presenting *in vitro* data and the Pilot Study data for the test materials, and to obtain agreement from FDA on the proposed study designs and success criteria for the two Pivotal Effectiveness Studies for health care personnel hand wash.

b. Health Care Personnel Hand Rub and Consumer Antiseptic Hand Rub (ethyl alcohol)

ACI submitted to FDA on April 29, 2016 a draft pilot *in vivo* effectiveness protocol entitled *Adaptive Design Pilot Evaluation of the Antimicrobial Effectiveness of an Active Control and Up to Two Test Materials Using the ASTM E2755 Standardized Test Method Performed with a Randomized Parallel Design* (protocol # 150808-101) that will generate data for ethyl alcohol for use in health care personnel hand rub products. The data generated would be used to develop the protocol for the associated pivotal study. We believe this Pilot Study is responsive to the requirements described in both the Health Care Antiseptics and Consumer Antiseptic Hand Rub Proposed Rules for *in vivo* effectiveness testing of active ingredients.

ACI received comments on protocol # 150808-101 from FDA dated August 10, 2016. Based on the comments, ACI believes that FDA agrees in principle with the overall design of the protocol pending appropriate changes requested in the comments. ACI will modify the protocol

in response to FDA comments and plans to then proceed to study execution. As described in Table 6, the pilot study will be initiated and completed in 1Q2017

The primary objective of the Pilot Study is to evaluate the antimicrobial effectiveness of the three test materials with active and inactive controls for use as Health Care Personnel Hand Washes following single test material applications. A secondary objective is to determine whether an FDA approved Active Control can achieve 70% response rate with 95% confidence according to FDA proposed criteria of a 2.5 log reduction when tested according to ASTM E2755-15. The pilot study will be used to determine the sample size necessary for the pivotal studies.

Upon the completion of the Pilot Study, ACI will submit a meeting request to FDA for the purpose of presenting *in vitro* data and the Pilot Study data for the test materials, and to obtain agreement from FDA on the proposed protocol, which will be included a Briefing Document, for the two Pivotal Effectiveness Studies for health care personnel hand rub. Approximate timing for protocol submission and study execution for the two pivotal studies is presented in Table 6.

a. Pre-surgical Hand Rub

ACI submitted to FDA on April 29, 2016 a draft pilot in vivo effectiveness protocol entitled *Pilot Evaluation of the Antimicrobial Effectiveness of Up to Two Test Materials with an Active Control Based on the Surgical Scrub Procedure in the Standardized ASTM E1115-11 Test Method Performed with a Randomized Parallel Design* (protocol # 150807-102) that will generate data for ethyl alcohol for use in surgical hand rub products. The data generated would be used to develop the protocol for the associated pivotal study.

ACI received comments on protocol # 150807-102 from FDA dated August 10, 2016. Based on the comments, ACI believes that FDA agrees in principle with the overall design of the protocol pending appropriate changes requested in the comments. ACI will modify the protocol in response to FDA comments and plans to then proceed to study execution. As described in Table 6, the pilot study will be initiated and completed in 1Q2017

The primary objective of the Pilot Study is to determine the lowest concentration of alcohol that can achieve a 70% response rate with 95% confidence according to the 2015 FDA proposed criteria of $\geq 2 \log_{10}$ reduction. A secondary objective is to determine whether an FDA approved Active Control can achieve 70% response rate with 95% confidence according to the 2015 FDA proposed criteria of $\geq 2 \log_{10}$ within 1 minute after a single scrub, and that microbial populations recovered in the 6-hour samples are less than baseline populations. The pilot study will be used to determine the sample size necessary for the pivotal studies.

Upon the completion of the Pilot Study, ACI will submit a meeting request to FDA for the purpose of presenting *in vitro* data and the Pilot Study data for the test materials, and to obtain agreement from FDA on the proposed protocol, which will be included a Briefing Document, for the two Pivotal Effectiveness Studies for surgical hand rub. Approximate timing for protocol submission and study execution for the two pivotal studies is presented in Table 6.

C. Clinical Outcome Studies

1. Background

FDA has requested clinical outcome studies to support the effectiveness of active ingredients used in over-the-counter consumer antiseptic wash products. Based on feedback from the March 20, 2015 meeting between ACI and FDA, member companies and experts in the area of clinical trials, have been working to prepare two pivotal clinical protocols.

We are proposing to submit protocols for two clinical outcome studies by the end of November 2016 along with two separate meeting requests. The protocols target two different disease outcomes. In order to facilitate constructive discussions and feedback from the Agency, individual meetings will allow for the teams of experts specific to the protocol to attend and answer any questions regarding study design, clinical relevance, execution and timing.

Below is a brief rationale and description of the two clinical protocols developed and the plan to support the effectiveness of antibacterial actives covered in the deferral letter.

2. Rationale

Antiseptic wash products play a role in helping to reduce bacteria on the skin and the potential for cross contamination between people and fomites. While the Agency believes there are differences in health care and consumer settings, we believe these differences are small and that these products provide the same benefit by reducing or killing more germs than plain soap.

We have identified two risks in the consumer setting that are relevant and can demonstrate the link of reducing bacteria to disease reduction. One model addresses the potential reduction in foodborne illness (the Foodborne Induction Model) while the other model looks at the reduction in soft tissue skin infections (Skin Infection Model).

Based on the feedback provided by the FDA during the March 20, 2015 meeting, the Foodborne Induction Model that will be submitted was designed to address the Agency's concern that the "melon ball disease model" did not address the scenario where a consumer would self-inoculate from contaminated hands. In addition, this new model will not rely on dose models to link infection but will measure clinical reduction in disease following hand washing with an antiseptic vs. a non-antiseptic wash.

The Research Study Design for the second Skin Infection Model was submitted to the docket for the Consumer Antiseptic Hand Wash proposed rule (FDA-1975-N-0012) as a summary from Dr. Ronald Turner (University of Virginia) in comments from ACI dated June 16, 2014. The concept has been developed further as a study protocol and now contains the details the Agency was requesting in the March 20, 2015 meeting.

3. Foodborne Induction Model for Consumer Hand Wash Products

In order to properly execute the Foodborne Induction Model study, a pivotal study is proposed along with several preceding pilot studies to validate particular test procedures and test parameters that would be incorporated into the pivotal study.

- a. **Pilot Study:** Pilot Protocol for Evaluation of Palmar Hand Contamination Method Utilizing Enterotoxigenic *Escherichia coli* (ETEC): (H10704)

Prior to initiation of the pivotal study, a pilot study will be required to generate data needed for the final power analysis and study design.

Study Description:

Prior to initiating the pivotal induction study several of the variables associated with incorporating hand inoculation and washing will need to be explored. This pilot work will seek to determine the reproducibility of inoculating the hands of subjects utilizing the ETEC strain (H10407). This study will look at the reproducibility of this organism under the “palmer contamination method” and or other standardized methods of hand inoculation. In addition, this work will also look at the impact of the stripping solution used to remove the bacteria and evaluate if the ingredients are toxic to ETEC strain.

Additional pilot work will be done to understand the log recovery and log reduction of ETEC following hand washing with active. Vs. non active control and determine the conditions of hand washing.

Site: Henkel Consumer Goods – Clinical Testing Lab

Study Initiation: March, 2016

Study Duration: 8 Months

b. **Pilot Study:** Evaluation of ETEC attack rate using hand dosing method

Prior to initiation of the pivotal study, pilot studies will be required to generate data regarding the attack rate of ETEC using a hand dosing method in order to accurately determine the necessary number of subjects for a successful study.

Study Description:

Evaluate attack rate using hand dosing method without hand washing to determine any effects of treatment with stripping solution etc. on the model. Treat a cohort of 10 subjects with no hand washing in order to demonstrate the viability of the pivotal model. We would specifically test the attack rate to insure no alteration of viability as part of the harvest of organism, e.g., by stripping solution. A successful pilot would result in an inoculum of $5-10 \times 10^8$ and a diarrhea attack rate of at least 50%.

Sites: TBD

Study Initiation: Following Henkel Pilot work

Study Duration: 6 months

Principal Investigator

Mitch Cohen, MD

Chair of Pediatrics

University of Alabama at Birmingham School of Medicine

c. **Pivotal Study:** Incidence of clinical illness and colonization after ingestion of enterotoxigenic *Escherichia coli*: effect of hand washing with either plain soap or an antibacterial hand soap

Study Description:

We will administer a wild-type ETEC strain (H10407), for which there is vast clinical experience in 100 volunteers over 3 decades, to induce diarrheal disease among healthy adult subjects. Consenting subjects will be placed in an inpatient Research Isolation Ward under voluntary physical containment and will receive an oral challenge dose harvested from their hands using a standardized process. ETEC will be removed from their hands using a standardized stripping solution with neutralizer to create a modified challenge inoculum. The modified challenge inoculum will be administered with bicarbonate buffer (NaHCO₃) to neutralize gastric acid after overnight fasting. Approximately 18 subjects in each group (total of 90 subjects) will be inoculated with an individualized single oral dose of challenge material, consisting of stripping solution derived from each participant's own contaminated hands, to evaluate the primary outcome measures. Five experimental groups will be evaluated: No hand washing (NH); Plain soap (PS); Antibacterial 1 (AB1); Antibacterial 2 (AB2); and Antibacterial 3 (AB3).

Following challenge, all stools will be graded (grades 1 & 2 are variants of normal and grades 3-5 are increasing degrees of loose stools); all loose stools (grade 3-5) will be weighed and the values recorded. Daily solicited symptoms that will also be collected include: fever, abdominal pain, abdominal cramping, nausea, vomiting, bloating, flatulence, myalgias, chills, anorexia, headache, and malaise. Oral and intravenous rehydration will be provided, as necessary.

Primary Objectives:

- Attack rates will be compared between cohorts who have not washed, washed with plain soap and washed with an antibacterial active.
- To determine the greatest fecal colonization following ETEC strain H10704 ingestion after recovery from infected subject hands. Colonization is determined by quantitative stool culture.
- To determine the effect of hand washing with plain soap vs. antibacterial active on ETEC inoculum size.

Population: Healthy male and female adult subjects aged 18 – 45 years

Sites: TBD – Two or more

Study Duration: Approximately 12 months

Duration of subject participation: Approximately 6 months.

Principal Investigators:

Mitch Cohen, MD
Chair of Pediatrics
University of Alabama at Birmingham School of Medicine

Wilbur H. Chen, MD, MS, FACP
Associate Professor, Department of Medicine
Chief, Adult Clinical Studies section
Director, UMB Travelers' Health Clinic
University of Maryland School of Medicine
Center for Vaccine Development

Louis Bourgeois, MD
Associate Research Professor at the Center for Immunization Research,
Department of International Health at Johns Hopkins Bloomberg School of Public Health

4. Skin Infection Model for Consumer Hand Wash Products

As part of our comments to the December 17, 2013 proposed rule on OTC consumer antiseptic products, we submitted a research study design from Dr. Ronald Turner (University of Virginia; Docket ID FDA-1975-N-0012-0494) describing a study to evaluate the effect of antibacterial soaps for prevention of recurrent staphylococcal infections. A more detailed description of that study is provided below.

Title: Household use of antimicrobial soap for prevention of recurrent staphylococcal infections

Population: Index patients with a history of recurrent staphylococcal skin or soft tissue infection and their household contacts

Number of Sites: Multi-center, number of sites TBD

Study Duration: 3 years (for clinical studies, total study duration is 5 years)

Subject Duration: Each household will participate in the study for 6 months.

Description of Intervention:

The study intervention will be the exclusive use of antibacterial soap in the household during the observation period. The control group will use standard commercially available soap without antibacterial additives. Subjects will be asked to refrain from using other antibacterial products such as antimicrobial laundry products or household cleaners or hand sanitizers in the home for the duration of the observation period.

Objectives:

The purpose of this proposed study is to evaluate the effect of antibacterial soaps for prevention of recurrent staphylococcal infections; either community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) or methicillin-sensitive *Staphylococcus aureus* (MSSA).

Description of Study Design:

This will be a randomized, placebo-controlled double-blinded study of the effect of antibacterial soap on the occurrence of recurrent SSTI. The unit of randomization will be the household with all members of each household using either antibacterial or standard soap. After randomization, households will be contacted weekly to assess the occurrence of skin infections and whether the infection required medical attention. All households will be followed for six months after randomization. The effectiveness of the antibacterial soap will be assessed by comparing the rate of recurrent infection in the treated and control households.

Timeline: Completion of the study described in this proposal would be expected to require approximately 4 years. Potential milestones are described below:

- Initiation to 9 months: Hiring of CRO, identification of study sites, site initiation at each site. Estimated 15-20 sites.

- 9 months to 36 months: Enrollment and completion of 1200 families (300/arm)
- 36 – 48 months: Data checking and analysis, preparation of data submission to FDA

VII. Study Timelines

A. Benzalkonium Chloride

We offer the following anticipated timeline for safety and effectiveness studies for benzalkonium chloride under the Consumer Hand Wash and Health Care Antiseptic products proposed rules. We note that these timelines are estimates and could change based on the feedback and timing of the approval of study designs by FDA.

Table 3. Timeline for Development of Safety and Effectiveness Data for Benzalkonium Chloride

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Study Report Submission to FDA
Consumer Hand Wash	Effectiveness	In-vitro Time-Kill	January 4, 2016	1Q2017	1Q2017	2Q2017
		Clinical - ETEC Challenge Study: pilot studies		4Q2016	3Q2017	3Q2017
		Clinical - ETEC Challenge Study	4Q2016	4Q2018†	1Q2019	3Q2019
		Clinical - Skin Infection Study	4Q2016	2019	2023	2024
Health Care	Effectiveness	<i>In-vitro</i> Time-Kill	January 4, 2016	1Q2017	1Q2017	2Q2017
		<i>In-vitro</i> MIC-MBC	March 21, 2016	2Q2017	2Q2017	3Q2017
		<i>In vivo</i> Hand Wash (HCPHW)				
		Pilot HW Study	April 28, 2016	2Q2017	2Q2017	3Q2017
		Pivotal HW Study #1	4Q2017	2Q2018	3Q2018	3Q2018
		Pivotal HW Study #2	4Q2018	2Q2019	3Q2019	3Q2019
Consumer/Health Care	Clinical Safety	<i>In vitro</i> dermal penetration (MUsT)		4Q2016	1Q2017	3Q2017**
		Hand wash observational study(ies) (MUsT)		1Q2017	2Q2017	3Q2017**
		MUsT	3Q2017*	4Q2017	1Q2018	2Q2018
Consumer/Health Care	Nonclinical (Animal) Safety	ADME	Following evaluation of MUsT data			
		Dermal Carcinogenicity	Following evaluation of MUsT data			
Consumer/Health Care	Nonclinical Safety	Resistance Literature Reviews	Not applicable	4Q2015	1Q2018	2Q2018

† Anticipates extensive pilot work and protocol development with FDA before clinical study with subjects is initiated.

* A MUsT protocol for Benzethonium Chloride was submitted to FDA on December 14, 2014. It is anticipated that a similar protocol will be used for the other consumer antiseptic wash active ingredients.

** To be submitted with revised MUsT protocol

B. Benzethonium Chloride

We offer the following anticipated timeline for safety and effectiveness studies for benzethonium chloride under the Consumer Hand Wash and Health Care Antiseptic products proposed rules. We note that these timelines are estimates and could change based on the feedback and timing of the approval of study designs by FDA.

Table 4. Timeline for Development of Safety and Effectiveness Data for Benzethonium Chloride

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Study Report Submission to FDA
Consumer Hand Wash	Effectiveness	<i>In-vitro</i> Time-Kill	January 4, 2016	1Q2017	1Q2017	2Q2017
		Clinical - ETEC Challenge Study: pilot studies		4Q2016	3Q2017	3Q2017
		Clinical - ETEC Challenge Study	4Q2016	4Q2018†	1Q2019	3Q2019
		Clinical - Skin Infection Study	4Q2016	2019	2023	2024
Health Care	Effectiveness	<i>In-vitro</i> Time-Kill	January 4, 2016	1Q2017	1Q2017	2Q2017
		<i>In-vitro</i> MIC-MBC	March 21, 2016	2Q2017	2Q2017	3Q2017
		<i>In-vivo</i> Hand Wash (HCPHW)				
		Pilot HW Study	April 28, 2016	2Q2017	3Q2017	3Q2017
		Pivotal HW Study #1	4Q2017	2Q2018	3Q2018	3Q2018
		Pivotal HW Study #2	4Q2018	2Q2019	3Q2019	3Q2019
Consumer Hand Wash/ Health Care	Clinical Safety	<i>In vitro</i> dermal penetration (MUsT)		4Q2016	1Q2017	3Q2017**
		MUsT	December 14, 2014 4Q2018 (revision)*	1Q2019	3Q2019	1Q2020
Consumer Hand Wash/ Health Care	Nonclinical (Animal) Safety	ADME	Following evaluation of MUsT data			
		Oral Carcinogenicity	Following evaluation of MUsT data			
		DART	Following evaluation of MUsT and carcinogenicity data			
		Hormonal Effects	January 14, 2015	Following evaluation of MUsT, carc. and DART data		
Consumer/ Health Care	Nonclinical Safety	Resistance Literature Reviews	Not applicable	4Q2015	1Q2018	2Q2018

† Anticipates extensive pilot work and protocol development with FDA before clinical study with subjects is initiated.

* A MUsT protocol for Benzethonium Chloride was submitted to FDA on December 14, 2014. It is anticipated that a similar protocol will be used for the other consumer antiseptic wash active ingredients.

** To be submitted with revised MUsT protocol

C. Chloroxylenol

We offer the following anticipated timeline for safety and effectiveness studies for chloroxylenol under the Consumer Hand Wash and Health Care Antiseptic products proposed rules. We note that these timelines are estimates and could change based on the feedback and timing of the approval of study designs by FDA.

Table 5. Timeline for Development of Safety and Effectiveness Data for Chloroxylenol

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Study Report Submission to FDA
Consumer Hand Wash	Effectiveness	<i>In-vitro</i> Time-Kill	January 4, 2016	1Q2017	1Q2017	2Q2017
		Clinical - ETEC Challenge Study: pilot studies		4Q2016	3Q2017	3Q2017
		Clinical - ETEC Challenge Study	4Q2016	4Q2018†	1Q2019	3Q2019
		Clinical - Skin Infection Study	4Q2016	2019	2023	2024
Health Care	Effectiveness	<i>In-vitro</i> Time-Kill	January 4, 2016	1Q2017	1Q2017	2Q2017
		<i>In-vitro</i> MIC-MBC	March 21, 2016	2Q2017	2Q2017	3Q2017
		<i>In-vivo</i> Hand Wash (HCPHW)				
		Pilot HW Study	April 28, 2016	2Q2017	3Q2017	3Q2017
		Pivotal HW Study #1	4Q2017	2Q2018	3Q2018	3Q2018
		Pivotal HW Study #2	4Q2018	2Q2019	3Q2019	3Q2019
Consumer Hand Wash/ Health Care	Clinical Safety	<i>In vitro</i> dermal penetration (MUsT)		3Q2018	3Q2018	4Q2018**
		MUsT	December 14, 2014* 4Q2018 (revision)	1Q2019	3Q2019	1Q2020
Consumer Hand Wash/ Health Care	Nonclinical (Animal) Safety	ADME	4Q2016	3Q2017	4Q2017	1Q2018
		Dermal Carcinogenicity	3Q2018	2019	2021	2022
		Oral Carcinogenicity	Following evaluation of MUsT data			
		DART	Following evaluation of MUsT and carcinogenicity data			
		Hormonal Effects	Following evaluation of MUsT, carc. and DART data			
Consumer/ Health Care	Nonclinical Safety	Resistance Literature Reviews	Not applicable	4Q2015	1Q2018	2Q2018

† Anticipates extensive pilot work and protocol development with FDA before clinical study with subjects is initiated.

* A MUsT protocol for Benzethonium Chloride was submitted to FDA on December 14, 2014. It is anticipated that a similar protocol will be used for the other consumer antiseptic wash active ingredients.

** To be submitted with revised MUsT protocol

D. Ethyl Alcohol

We offer the following anticipated timeline for safety and effectiveness studies for ethanol under the Consumer Hand Rub and Health Care Antiseptic products proposed rules. We note that these timelines are estimates and could change particularly based on the feedback and timing of the approval of study designs by FDA.

Table 6. Timeline for Development of Safety and Effectiveness Data for Ethanol

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Study Report Submission to FDA
Health Care	Effectiveness	<i>In-vitro</i> Time-Kill	January 4, 2016	1Q2017	1Q2017	2Q2017
		<i>In-vitro</i> MIC-MBC	March 21, 2016	2Q2017	2Q2017	3Q2017
		<i>In-vivo</i> Hand Rub				
		Pilot Hand Rub Study	April 28, 2016	1Q2017	1Q2017	2Q2017
		Pivotal Hand Rub Study #1	2Q2017	4Q2017	4Q2018	1Q2018
		Pivotal Hand Rub Study #2	2Q2017	4Q2017	4Q2018	1Q2018
		Pilot Surgical Hand Rub Study	April 28, 2016	3Q2017	3Q2017	4Q2017
		Pivotal Surgical Hand Rub Study #1	1Q2018	3Q2018	3Q2018	4Q2018
		Pivotal Surgical Hand Rub Study #2	1Q2018	3Q2018	3Q2018	4Q2018
Consumer Hand Rub/ Health Care	Clinical Safety	Pilot MUsT	1Q2017	3Q2017	3Q2017	4Q2017
		Pivotal MUsT	4Q2017	1Q2018	2Q2018	3Q2018

VIII. Regulatory Issues: Food Handler Antiseptic Products

A. Regulatory Uncertainty

Food handler antiseptic products are designed for use by professional workers to minimize transfer of disease organisms associated with food. While the FDA stated it will develop a separate food handler monograph category, it appears that this is in the formative stage and it may be years before a food handler proposed regulation is published.

1. Safety Requirements

The proposed rules for active ingredients used in health care antiseptic hand products, consumer hand washes, and consumer rubs convey the impression that safety studies for an active ingredient can be leveraged across all monograph categories. ACI presumes that safety data being developed for the consumer and health care monographs will also be applicable to a future food handler monograph, as long as maximal usage trial (MUsT) and adsorption, distribution, metabolism and excretion (ADME) studies encompass the variety of product exposure and use patterns.

2. Effectiveness Requirements

It is difficult for the ACI to anticipate the extent to which the FDA's effectiveness requirements for the food handler monograph will vary from requirements in the proposed Health Care and consumer monographs. This uncertainty adversely affects ACI's ability to apply process efficiencies to effectiveness studies currently proposed for the consumer and healthcare monographs.

For hand rubs, effectiveness requirements for active ingredients in the healthcare and consumer monographs are largely harmonized. ACI anticipates that requirements for food handler antiseptic hand rubs will be somewhat similar, and has included foodborne illness strains in the protocol for consumer *in vitro* time kill studies. The strategic intent is to gain economies of scale in the laboratory studies and evaluate the effectiveness of active ingredients against known food disease organisms.

For hand washes, effectiveness requirements for actives have not been harmonized in the healthcare and consumer tentative monographs. This situation creates additional uncertainty for future food handler hand wash requirements.

B. Hand Wash Effectiveness Requirements for Professional Workers

Antiseptic hand washes for food handlers share common traits with antiseptic hand washes used in healthcare settings. These similarities create a logical pairing of the two categories for purposes of approval of actives. Further, economies of scale and process efficiencies in laboratory studies, and the short amount of time available to generate data under the monograph process, are conducive to addressing effectiveness requirements simultaneously for the healthcare and food handler monograph categories. Notable common traits are:

- Reduce transmission of disease organisms: Topical antimicrobial products are used to decrease microorganisms on human skin and reduce the transfer of disease organisms by contaminated hands.
- Commonality of pathogens: while the primary infectious organisms of concern differ between healthcare and food handling settings, there is increasing overlap and convergence of the two. For example, MRSA and *Clostridium difficile* are associated with hogs, and resistant enteric bacteria are important in both settings.
- Public health concern: Transfer of disease organisms by hands can affect large numbers of people in food handling and healthcare settings.
- Public Health Policy: Frequent hand washing and use of sanitizers is promoted by public health agencies as an intervention point to reduce the frequency that patients are exposed to diseases transferred by hands in health care facilities, and to avoid transfer of disease organisms from hands to food in food preparation and food service facilities.

- Professional use: Antiseptic hand washes are used by a trained, professional workforce employed in the food, healthcare, and hospitality industries and governed by industry standards designed to minimize the transmission of micro-organisms by hands.

C. Regulatory Recommendations

ACI urges the FDA to consider the benefits of process efficiencies and early access to effectiveness data that can be catalyzed by harmonizing the effectiveness requirements for active ingredients in hand wash products regulated by the healthcare and food handler monographs.

IX. Conclusions

ACI is pleased to provide this Work Plan to FDA in response to the March 10, 2016 letters from the Agency. We expect that the Work Plan is responsive to the requests in that letter and we also understand that the Agency expects a report describing specific progress of all ongoing studies by February 10, 2017.

We would be happy to provide copies of any of the cited studies and reports upon request. We are willing to meet with you to review them in detail. Please contact me if you have any questions regarding this Work Plan and associated comments.

Sincerely,



Paul C. DeLeo
Associate Vice President, Environmental Safety