american cleaning institute®

October 1, 2021

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Attention: Dr. Theresa Michele

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

Safety and Effectiveness of Health Care 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-2015-N-0101**, Regulatory Information No. 0910-AF69

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-2016-N-0124**, Regulatory Information No. 0910-AF69

Dear Dr. Michele:

The American Cleaning Institute (ACI)[1] is pleased to provide this report describing specific progress on all ongoing studies on benzalkonium chloride (BAC), benzethonium chloride (BZT), chloroxylenol (PCMX) and ethanol (ETOH) as described in the original Work Plan submitted to the FDA on September 9, 2016 and updated in progress reports submitted on February 10, 2017, February 23, 2018; and povidone-iodine (PVP-I) as described in the Work Plan submitted to the FDA on July 19, 2017 and updated in the progress report submitted on December 15, 2017. The submitted progress report dated March 12, 2019 combined updates and progress on the five actives (ETOH, BAC, BZT, PCMX and PVP-I) as granted by FDA in their letter to ACI dated April 12, 2018. As such, this and the previously submitted progress report dated July 14, 2020 have followed the same structure with updates on the five actives. The work

[1] ACI is a trade association for the $60 billion U.S. cleaning products supply chain. ACI members include manufacturers of retail and institutional antiseptic products sold in the U.S. that are the subject of the final and proposed topical antiseptic rules and companies that supply active ingredients for these products.

plans were submitted to facilitate and support the deferral requests from inclusion in the final rulemakings for over-the-counter (OTC) consumer antiseptic washes on September 6, 2016 (effective September 6, 2017), for health care antiseptics on December 20, 2017 (effective December 20, 2018), and for consumer antiseptic hand rubs on April 12, 2019 (effective April 13, 2020).

As noted in our previous Work Plans and progress reports, this progress report is intended as an integration of our data generation activities across multiple active ingredients we are supporting for the regulations FDA has proposed or is contemplating for consumer antiseptic wash products, health care antiseptic products, consumer antiseptic rub products and food handler antiseptic products. Furthermore, ACI and its members have submitted data to FDA and are committed to work over the coming years to generate additional safety and effectiveness data to support the five active ingredients (ETOH, BAC, BZT, PCMX and PVP-I) across the three FDA OTC topical antiseptic monographs.

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security (CARES) Act was signed into law and included provisions for FDA to implement OTC monograph reform. While FDA has yet to provide implementation guidance, the CARES Act replaces the previous rulemaking process used for regulating OTC drugs with a more streamlined administrative order process. Reflecting this change in procedure, rather than issuing a deferral from final rulemaking for the actives that ACI is supporting, FDA wrote in their November 18, 2020 response to our July 14, 2020 progress report that "We, therefore, do not intend to issue a proposed administrative order regarding the safety and effectiveness of these products for one year, ending on October 31, 2021, subject to renewal. Submit an updated report that includes a description of ACI's specific progress for these active ingredients to FDA by October 1, 2021." Though certain topical antiseptics are legally marketed Category III OTC drugs, FDA reiterated their commitment to working with ACI to continue to fill data gaps identified in the previous rulemakings. Likewise, this progress report demonstrates ACI's commitment to fill data gaps while FDA continues to develop and implement processes of OTC monograph reform such as a data submission platform.

The COVID-19 pandemic has continued to cause worldwide disruptions of normal daily business operations. Some of the research facilities and specialized testing laboratories that ACI relies upon have been closed or limited in activities over the past 20 months, and studies have been put on hold or temporarily delayed. This progress report notes specific projects that have been delayed due to these restrictions.

ACI and its members spent significant time and resources in 2019 and 2020 addressing food handler antiseptics in response to FDA's published Request for Data and Information on food handler antiseptic drug products on December 7, 2018[2]. ACI provided a response document on July 22, 2019 (Docket No. FDA-2018-N-3458) and prepared a briefing package and presentation for a March 11, 2020 meeting of the Nonprescription Drug Advisory Committee (NDAC) to discuss food handler antiseptics. This meeting has been postponed indefinitely due to the COVID-19 pandemic. However, ACI has continued to research issues relevant to food handler antiseptics in 2021 and will do so in 2022.

[2] Food Handler Antiseptic Drug Products for Over-the-Counter Human Use; Request for Data and Information. Food and Drug Administration. Federal Register, Vol. 83 No. 235, 63168-63176. December 7, 2018.

A list of safety and effectiveness data generating activities anticipated to occur under "Next Steps" was provided in our July 14, 2020 Progress Report for ETOH, BAC, BZT, PCMX and PVP-I. In Table 1 below, we summarize the status of key milestones identified in the 2020 Progress Report and Work Plan.

Table 1. Summary and Status of Progress Against Milestones from 2020-2021[3]

Active Ingredient(s)	Milestones	Status	Comments
ETOH, PCMX, BAC and PVP-I	Initiate additional Time Kill studies for concentrations of ETOH, BAC and PCMX PVP-I: Complete Time-Kill study and submit report to FDA	Time-Kill testing for additional ETOH, PCMX and BAC concentrations has been initiated. PVP-I: Time-Kill Study was completed 1Q2021.	Time-Kill testing is in process and will continue through 2Q2022. Study report will be submitted to FDA by 3Q2022. PVP-I: Time Kill Study report* will be submitted after meeting with FDA to discuss results and next steps.
ETOH	Complete pilot hand rub efficacy study for 90% ETOH and submit to FDA	Pilot hand rub efficacy for 90% ETOH was initiated in 4Q2020.	The 90% ETOH pilot hand rub efficacy study is on hold and its resumption is pending a favorable result from ongoing Time-Kill study of 90% ETOH. Hand rub study initiation is anticipated to occur in 2Q2022.
ETOH	Submit the protocol for the pivotal hand rub efficacy study for FDA review	Protocol to be developed and submitted upon the identification and contracting of a qualified laboratory.	Candidate laboratories are being evaluated in 2021 and 1Q2022 to serve as a second qualified site for ACI to contract a pivotal study. Identification of a qualified lab is anticipated by 1Q2022[4]
ETOH	Conduct and submit pilot surgical hand rub efficacy study to FDA	Study is completed, but submission is in preparation	ACI submission to FDA is anticipated in 4Q2021*
ETOH	Complete pilot Maximal Usage Trial (MUsT) study for consumer and health care hand rubs and submit to FDA	Pilot MUsT bioanalytical method development and validation has been contracted with Primera Analytical Laboratories; TKL contracted for clinical work	Method development and validation underway; Pilot MUsT to be initiated 4Q2021
BAC, BZT, PCMX	Complete and submit to FDA literature review related to potential for resistance	Literature review has been completed, and it was submitted to FDA on July 28, 2021	

[3] Progress against milestones and next steps in July 14, 2020 Progress Report for ETOH, BAC, BZT, PCMX and PVP-I. Some milestones such as study report submissions and study initiation dates may not be completed until discussions with FDA have taken place.

[4] Previously qualified laboratory is BioScience Laboratories, Inc., Bozeman, Montana.

* Study report will be submitted following a discussion with FDA.

Active Ingredient(s)	Milestones	Status	Comments
BZT	Develop method for recovering BZT in blood plasma	Ongoing	
BAC	Pivotal MUsT (Consumer Wash)	Initiate study in September 2021	Data expected by 1Q2022 and final report 4Q2022
BAC	Pilot health care personnel hand rub study	An internal pre-pilot study was completed to identify optimum volume for test material efficacy. The Pilot study has been initiated.	The results of the pre-pilot study informed the study design of the Pilot Hand Rub Study. Anticipated pilot study report* submission date is 2Q2022
BAC, PCMX, PVP-I	Conduct and submit pilot health care personnel hand wash study to FDA	Study completed. Report finalized in 3Q2021.	Submission to FDA anticipated in 4Q2021*
BZT	Initiate *in vivo* health care personnel hand wash efficacy study	Pending meeting with FDA to discuss pilot health care personnel hand wash study results for BAC, PCMX, and PVP-I	The pivotal health care personnel hand wash study** will be initiated following submission of the pilot study report* to FDA and a discussion of those results.
BAC, PCMX, PVP-I	Initiate pivotal *in vivo* health care personnel hand wash study	Not completed.	Pilot study is completed, but submission* is in preparation. ACI will request meeting with FDA to review pilot study data and plan pivotal study design.
BAC, BZT, PCMX	Feedback meeting with FDA on August 6, 2018 resulted in agreement to identify alternative clinical outcome study designs for consumer antiseptic wash products	Alternative study designs and respective synopses under development	ACI has contracted Ms. Carey Schlett[5] and Drs. Loren Miller[6], Ronald Turner[7], Eugene Millar[8], and Bruce Stouch[9] to develop study synopses. Submission to FDA anticipated 1Q2022

* Submission following a discussion with FDA.
** The pivotal health care personnel hand wash study for BZT may be conducted along with other active ingredients without performing a pilot study for BZT.

[5] Carey D. Schlett, MPH, Independent Consultant
[6] Loren G. Miller, M.D., MPH, Professor of Medicine, David Geffen School of Medicine at UCLA
[7] Ronald B. Turner, M.D., Professor Emeritus of Pediatrics, University of Virginia School of Medicine
[8] Eugene V. Millar, PhD, MHS, Research Area Director, Wound Infections, Uniformed Services University
[9] Bruce C. Stouch, PhD, Director, Biostatistics & Clinical Epidemiology at Philadelphia College of Osteopathic Medicine

Active Ingredient(s)	Milestones	Status	Comments
BAC, BZT, PCMX	Based on FDA's advice letter (April 3, 2017), revise skin infection protocol for clinical study	Draft skin infection protocol is complete but needs discussion with FDA	ACI has contracted Drs. Loren Miller, Eugene Millar, Bruce Stouch, and Ronald Turner, and Ms. Carey Schlett to revise skin infection protocol and incorporate FDA feedback. Further development of the skin infection study protocol will be informed by discussion with FDA upon synopsis and meeting request submission.
ETOH, BAC, BZT, PCMX, PVP-I	Identify, audit and train additional laboratories for *in vivo* efficacy studies	Two candidate laboratories have been identified to conduct the duplicate pivotal studies planned; ACI is currently engaged in ongoing training trials with these laboratories.	A decision to acknowledge the proficiency of the candidate labs to perform ACI-sponsored pivotal hand rub studies is anticipated in 1Q2022. Hand wash study qualification is ongoing.
PCMX	Complete *in vitro* dermal penetration study	Completed	Submission to FDA anticipated 4Q2021 with the pilot MUsT protocol and meeting briefing package
PCMX	Pilot MUsT	Sannova Analytical contracted to perform analytical work; method development complete; method development underway; Clinical site selected and working on executing contract	ACI submitted a meeting request to FDA on May 26, 2021 to discuss Pilot MUsT
PVP-I	Complete *in vitro* dermal penetration study	A 9-month chronic *in vivo* dermal study has been completed in an appropriate non-clinical model.	ACI member companies have been supporting preliminary work for an FDA meeting request to discuss results from the dermal study and seek guidance on next steps.
PVP-I	Submit FDA meeting request to discuss plans for safety and efficacy studies	Meeting request and briefing document will be prepared pending FDA guidance on monograph/OMOR issues	Sponsor is prepared to meet with FDA pending FDA guidance on monograph/OMOR issues

The following is a summary of the work completed for each active ingredient since the last report of progress.

I. Ethanol (ETOH)

A. Safety

1. Human pharmacokinetic maximal usage trial (MUsT)

A protocol, supporting formulation permeation data and additional information on bioanalytical method development were submitted to FDA for review on July 13, 2017. ACI has revised the protocol to address comments received from FDA in an Advice Letter dated August 6, 2018. Lambda Therapeutics (a contract research organization in India) was selected to conduct a pilot MUsT and a contract was executed in 2019, at which time bioanalytical method development was initiated. Bioanalytical method development and validation was nearly complete in early 2020 but placed on hold due to COVID-19 pandemic. In March 2020, ACI was informed by Lambda Therapeutics that the clinical site, which had been retrofitted for the study, would be moving from Mumbai to Mehsana (~375 miles away from the analytical laboratory). ACI made the decision to move the study to an alternate laboratory for various reasons, with the primary reason being the uncertainty of travel restrictions and further delays as a result of the COVID-19 pandemic. Consequently, Primera Analytical Solutions (New Jersey) is now contracted to perform method development and validation, and analytical services for the pilot MUsT study. TKL Research is contracted as the clinical site for the pilot MUsT study, which is anticipated to commence in 4th quarter 2021.

B. Effectiveness Studies

1. *In Vitro* Studies

a) Time-Kill Studies

A time-kill study for the active ingredients BAC, BZT, PCMX and ETOH has been completed (Final Report #150940-201 entitled "An *In-vitro* Time-Kill Evaluation of Four Test Materials When Challenged with Various Bacterial and Yeast Species"). The time-kill study generated data for these active ingredients covered the respective requirements for all of the final, proposed and anticipated rules for topical antiseptics (consumer wash, health care, consumer hand rub, and food handler products). The report from this study was submitted to FDA on April 12, 2018. ACI submitted a response on February 26, 2019 to comments and questions included in an FDA Advice Letter dated July 5, 2018. An additional time-kill study has been initiated at BioScience Laboratories, with testing to be conducted from 3rd quarter of 2021 until the 1st quarter 2022. The purpose of this study is to obtain data for additional active ingredient concentrations within the respective eligibility ranges that ACI is supporting. The concentrations of actives being tested are as follows: 0.5% BAC, 0.3% and 1.0% PCMX and 60%, 70%, 80%, and 90% ETOH. The final report for this study is expected to be issued by Q2 2022, and ACI expects to submit this report to FDA by Q3 2022.

b) Minimum Inhibitory Concentration (MIC) / Minimum Bactericidal Concentration (MBC) Studies

An MIC/MBC study report for the active ingredients BAC, BZT, PCMX, PVP-I and ETOH entitled "Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum

Bactericidal Concentrations (MBC) of Five Test Materials" was submitted to FDA on February 15, 2019. The MIC/MBC study generated data for these active ingredients covering all final, proposed and anticipated rules for topical antiseptics (consumer hand wash, consumer hand rub, health care, and food handler products). FDA confirmed that this study is satisfactory, and the milestone is complete in the August 29, 2019 Advice Letter to ACI.

2. *In Vivo* Studies

a) Qualifying laboratories to conduct *in vivo* efficacy studies

Numerous clinical laboratories located in the United States and Europe have been audited for their capabilities to conduct ASTM *in vivo* efficacy studies. A minimum of two clinical laboratories are needed to meet FDA's requirement that the two pivotal studies for each indication are conducted at different laboratories. Further, multiple laboratories are being sought in order to support the conduct of the full range of pivotal *in vivo* studies contemplated for BAC, PCMX, ETOH and PVP-I. Performance evaluations at candidate laboratories in 2018 failed to identify a second laboratory qualified to conduct the studies. In 2019, two potential laboratories were identified. Training trials in 2020 to develop their proficiency in the *in vivo* efficacy study methods (for hand rub and hand wash studies) as well as to determine their capabilities and qualifications were delayed due to laboratory closures and travel restrictions as a result of the COVID-19 pandemic. Final hand rub training studies by these laboratories to evaluate lab performance will be conducted from 3Q 2021 to 1Q 2022. Results from these studies will allow ACI to decide which labs will receive ACI study contracts for hand rub studies. Qualification for hand wash studies is ongoing.

b) Health Care Personnel/Consumer Hand Rub

A protocol entitled "Pilot Evaluation of the Antimicrobial Efficacy of an Active Control, Negative Control, and Three Test Products Based on the ASTM E2755-15 Standardized Test Method for Determining the Bacteria-Eliminating Effectiveness of Healthcare Personnel Hand Rub Formulations using Hands of Adults, Performed with a Randomized Parallel Design" incorporated modifications based upon feedback from FDA received January 19, 2017. The final report of the study based on the revised protocol was included as part of the Briefing Document for a March 1, 2018 ETOH Efficacy Feedback Meeting with FDA. In 4Q 2020, ACI initiated an additional pilot hand rub efficacy study to test 90% ETOH using the same protocol as was used for the initial pilot hand rub study. 90% ETOH is a higher ETOH concentration than was previously tested, and it is being evaluated to provide data to represent the high end of the ETOH concentration eligibility range that ACI is supporting. The 90% ETOH hand rub study was placed on hold prior to sample testing in 2020. Resumption of this study is anticipated in 2Q 2022 pending receipt of favorable results for 90% ETOH in the ongoing Time Kill study.

A pivotal hand rub efficacy study for ETOH is expected to be conducted, but its implementation is pending the identification of a second clinical laboratory qualified to conduct this study and the outcome of the Time Kill study and pilot 90% ETOH hand rub study. A draft pivotal study protocol has been developed, and the final proposed protocol will be submitted for FDA review prior to study start-up. There is no additional information to

report for this milestone.

c) Surgical Hand Rub

A pilot ETOH surgical hand rub study using the ASTM E1115 standard test method was initiated in 2nd QTR 2019 based on a protocol submitted to FDA on April 28, 2016 and modified based on FDA feedback received on August 10, 2016 and January 19, 2017. A negative control, active control, and 70%, 80%, and 90% ETOH (vol/vol) solutions were evaluated. The pilot study has been completed, the final report has been issued, and will be submitted following a meeting and discussion with FDA. The results of the pilot study will be used to inform the design of a pivotal surgical hand rub protocol. We will be requesting a meeting with FDA to discuss the pilot study results and align on a final pivotal study design.

C. Study Timelines

Please find in Table 2 an update to the anticipated timeline for safety and effectiveness studies for ETOH under the existing and anticipated rules for Consumer Hand Rub, Health Care and Food Handler antiseptic products.

Table 2. Timeline for Development of Safety and Effectiveness Data for Ethanol (ETOH)

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Study Report Submission to FDA
Health Care	Effectiveness	*In vitro* Time-Kill	January 4, 2016	1Q2017	1Q2018	2Q2018
		Additional Time-Kill Study for 90% ETOH	N/A	3Q2021	2Q2022	3Q2022
		In vitro MIC-MBC	March 21, 2016	4Q2017	3Q2018	1Q2019
		In vivo Health Care Personnel Hand Rub				
		Pilot Hand Rub	April 28, 2016	2Q2017	3Q2017	1Q2018
		90% ETOH Pilot Hand Rub	N/A	4Q2020	2Q2022*	3Q2022*
		Pivotal Hand Rub	**	**	**	**
		Pivotal Hand Rub	TBD	TBD	TBD	TBD
		In vivo Surgical Hand Rub				
		Pilot Surgical Hand Rub	April 28, 2016	2Q2019	1Q2021	4Q2021*
		Pivotal Surgical Hand Rub	2023	2023*	2024*	2025*
		Pivotal Surgical Hand Rub		**	**	**
Consumer Hand Rub/ Health Care	Clinical Safety (MUsT)	Pre-Pilot MUsT Tolerability Study	N/A	2Q2016	2Q2016	3Q2016
		In vitro Permeation	N/A	1Q2016	2Q2017	3Q2017
		Bioanalytical Method Development and Validation	N/A	2Q2021	4Q2021	***
		Pilot MUsT	3Q2017	4Q2021	2Q2022	4Q2022
		Pivotal MUsT	2023	2023	2023	2024

N/A – not applicable

* Following meeting with FDA to discuss pilot study results and Time Kill study results.

** Pending identification and qualification of second clinical laboratory.

*** Bioanalytical method development report will be submitted with pilot MUsT study report.

TBD – Pending results from pivotal hand rub study that confirm pilot hand rub study results.

II. Benzalkonium Chloride (BAC)

A. Safety

1. Human pharmacokinetic maximal usage trial (MUsT)

FDA has provided reviews regarding a protocol for a MUsT for BAC in consumer antiseptic wash products. Experience with that protocol will be used to support the development of protocols for BAC-containing health care antiseptic products. To finalize the pivotal test protocol, data are being generated that will inform the appropriate frequency and duration of dosing and an appropriate product formulation for testing is being identified. Efforts to generate these data are described below.

a) Determination of Frequency and Duration of Dosing

Consumer Antiseptic Hand Washes

The ACI Work Plan proposed to develop and execute observational studies of hand wash maximal usage for a consumer setting. Two observational studies were executed in 2017 with the primary objective of learning the handwashing practices of childcare workers. The results of these studies provided substantive data on the number of hand washing events in what is considered a high exposure workplace setting where consumer hand wash products are used. This information will be used to define the maximum number of washes in a proposed pilot MUsT for consumer antiseptic hand wash products containing BAC, BZT, and PCMX. Reports of the observational studies were submitted to FDA for the Feedback Meeting on May 9, 2018 related to BAC and BZT. FDA initially requested the pilot MUsT follow a dosage format of 40 washes per day for 30 seconds per wash (FDA meeting minutes letter, not dated); in response, a 3-day hand wash tolerance study of BAC and BZT was conducted using the FDA recommended dosage format (Letter to FDA April 8, 2019). This resulted in loss of study participants due to dermal effects to the hands. As a result of this exaggerated hand wash study, the pilot MUsT dosage will have a hand wash frequency of 30 washes per day at 30 seconds per wash for 5 days.

Healthcare Antiseptic Frequency of Use

An electronic surveillance study was executed in 2017 with the primary objective of learning the hand hygiene practices for health care workers. The study was reported in a 2018 peer-reviewed publication[10]. This information will be used to define the number of hand hygiene events in a pilot MUsT for health care antiseptic products containing BAC.

b) Determination of Composition of Tested Formulations - *In Vitro* Dermal Penetration Studies with Human Skin

Research has been conducted to: 1) assess whether there are significant dermal absorption differences among the marketed formulas of consumer antiseptic hand wash products, 2) identify a product type having the greatest dermal penetration of the actives BAC and BZT in liquid, bar,

[10] Jessica Albright, Bruce White, Daniel Pedersen, Pete Carlson, Lisa Yost, Cheryl Littau. "Use patterns and frequency of hand hygiene in healthcare facilities: Analysis of electronic surveillance data." American Journal of Infection Control, 46 (2018) 1104-9. https://doi.org/10.1016/j.ajic.2018.04.205

and foaming formulations, and 3) compare skin permeation enhancers in the top selling formulations. A final report for *in vitro* dermal penetration studies of BAC and BZT for consumer uses was submitted to FDA for a May 9, 2018 Feedback Meeting. FDA concurred that one formulation may be selected for use in the pilot MUsT (FDA preliminary response, July 3, 2019). As requested by FDA, an additional *in vitro* dermal penetration study has been completed for consumer uses, and the results were submitted to FDA in the briefing document for the July 30, 2020 meeting. Lonza and Henkel met virtually with the FDA on July 30, 2020 to discuss results of the pilot MUsT and the pivotal MUsT protocol. The FDA provided input on the number of test products, test subject numbers, and the need to evaluate metabolites.

c) Maximal Use Trial (MUsT) Protocol Development

A draft protocol for a pilot MUsT for BAC and BZT was submitted to FDA for review at a meeting on May 9, 2018. FDA provided comments on the pilot MUsT protocol, and revisions were made and resubmitted (May 19, 2019) with the briefing materials for the July 9, 2019 meeting. FDA stated that the previous *in vitro* dermal penetration results (submitted for May 9, 2018 meeting) in combination with the additional *in vitro* dermal penetration testing that was proposed would suffice for selecting a formula for evaluation in the pilot MUsT. FDA also stated that the pilot MUsT protocol appears reasonable (July 3, 2019). The pilot MUsT was completed and the final report submitted to FDA as part of the briefing package for a meeting with FDA scheduled for July 30, 2020. A pivotal MUsT study is expected to be initiated by 3Q2021.

2. Nonclinical Safety (Toxicology)

a) Antibiotic Resistance

In 2016, a systematic search was conducted by reviewing commercially published peer-reviewed and grey literature. Search databases included: Google Scholar, PubMed, PubChem, Science.gov, worldwidescience.org, and the U.S. Patent and Trademark Office. Searches were conducted for BAC, BZT, and PCMX. The biocide names and synonyms were then linked with descriptors such as "biological action, toxicity, bacteria, bacterial resistance, antibiotics, antimicrobial therapy, pathogenicity islands, gene cassette, resistance mechanism, efflux pump," and others, to capture a diverse base of literature.

A detailed review of the retrieved literature was conducted to determine whether there is sufficient evidence to indicate that use of these active ingredients contributes to antibiotic and antimicrobial resistance and cross-resistance in consumer, health care, or food handling settings. Since the 2019 progress report submission, additional work has been conducted to finalize the antibiotic resistance report including an additional review of recent publications (those published from 3rd quarter 2019 – January 2021) and clarification of definitions within the literature review. The review has been completed and a final report was submitted to FDA on July 28, 2021.

B. Effectiveness

1. *In Vitro* Studies

a) Time-Kill Studies

A time-kill study for the active ingredients BAC, BZT, PCMX and ETOH has been completed (Final Report #150940-201 entitled "An *In-vitro* Time-Kill Evaluation of Four Test Materials When Challenged with Various Bacterial and Yeast Species"). The time-kill study generated data for these active ingredients covered the respective requirements for all of the final, proposed and anticipated rules for topical antiseptics (consumer wash, health care, consumer hand rub, and food handler products). The report from this study was submitted to FDA on April 12, 2018. ACI submitted a response on February 26, 2019 to comments and questions included in an FDA Advice Letter dated July 5, 2018. An additional Time-Kill study has been initiated at BioScience Laboratories, with testing to be conducted from 3rd quarter of 2021 until the 1st quarter 2022. The purpose of this study is to obtain data for additional active ingredient concentrations within the respective eligibility ranges that ACI is supporting. The concentrations of actives being tested are as follows: 0.5% BAC, 0.3% and 1.0% PCMX and 60%, 70%, 80%, and 90% ETOH. The final report for this study is expected to be issued by Q2 2022, and ACI expects to submit this report to FDA by Q3 2022.

b) Minimum Inhibitory Concentration (MIC) /
Minimum Bactericidal Concentration (MBC) Studies

An MIC/MBC study report for the active ingredients BAC, BZT, PCMX, PVP-I and ETOH entitled "Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Five Test Materials" was submitted to FDA on February 15, 2019. The MIC/MBC study generated data for these active ingredients covering all final, proposed and anticipated rules for topical antiseptics (consumer hand wash, consumer hand rub, health care, and food handler products). FDA confirmed that this study is satisfactory, and the milestone is complete in the August 29, 2019 Advice Letter to ACI.

2. *In Vivo* Studies

a) Qualifying laboratories to conduct *in vivo* efficacy studies

Numerous clinical laboratories located in the United States and Europe have been audited for their capabilities to conduct ASTM *in vivo* efficacy studies. A minimum of two clinical laboratories are needed to meet FDA's requirement that the two pivotal studies for each indication are conducted at different laboratories. Further, multiple laboratories are being sought in order to support the conduct of the full range of pivotal *in vivo* studies contemplated for BAC, PCMX, ETOH and PVP-I. Performance evaluations at candidate laboratories in 2018 failed to identify a second laboratory qualified to conduct the studies. In 2019, two potential laboratories were identified. Training trials in 2020 to develop their proficiency in the *in vivo* efficacy study methods (for hand rub and hand wash studies) as well as to determine their capabilities and qualifications were delayed due to laboratory closures and travel restrictions as a result of the COVID-19 pandemic. Final hand rub training studies by these laboratories to evaluate lab performance will be conducted from 3Q 2021 to 1Q 2022. Results from these studies will allow

ACI to decide which labs will receive ACI study contracts for hand rub studies. Qualification for hand wash studies is ongoing.

b) Health Care Personnel Hand Wash

Modifications have been incorporated into a protocol for a pilot *in vivo* testing of health care personnel hand washes containing BAC, PCMX and PVP-I based upon feedback from the FDA. The pilot study has been completed and the final report will be submitted to FDA following a meeting to discuss the results. The results of the pilot study will be used to inform the design of a pivotal healthcare personnel hand wash protocol. We will be requesting a meeting with FDA to discuss the pilot study results and align on a final pivotal study design.

c) Health Care Personnel Hand Rub

An internal Pre-pilot study was completed to identify optimum volume for 0.13% BAC test material efficacy. The Pilot study has been initiated in 2nd quarter 2021, and the final report is anticipated for submission to FDA in the 2nd quarter 2022. The results of the pilot study will be used to inform the design of a pivotal hand rub study protocol.

3. Clinical Outcome Studies

a) Proposed Foodborne Induction Model for Consumer Hand Wash Products (ETEC Challenge Study)

ACI submitted a draft protocol for a clinical outcome study entitled *Incidence of clinical illness and bacterial colonization after ingestion of enterotoxigenic Escherichia coli (ETEC): effect of hand washing with either plain soap or an antibacterial hand soap*[11] on November 22, 2016 to the FDA for review. The study would generate data for BAC, BZT and PCMX when used in consumer antiseptic hand wash products. As outlined in our February 10, 2017 progress report, pilot work was being performed to finalize several of the variables that will need to be defined prior to executing a pivotal challenge study. The FDA provided an Advice Letter (April 3, 2017) to ACI regarding the protocol, which was accounted for in designing the preliminary studies.

Preliminary work was completed addressing how the hands would be inoculated using a whole hand contamination method. Additional studies evaluated bacterial removal for no treatment, soap with active ingredients (BAC, BZT, and PCMX) and plain soap. These data demonstrated differences in the amount of bacteria recovered from the hands between active ingredients and plain soap. Neutralization studies were also completed and the standard stripping solution was determined to be effective in inactivating the three actives.

ACI participated in a Feedback Meeting with FDA on August 6, 2018 to review protocol design elements for this study based on the April 3, 2017 Advice Letter and the follow up

[11] Docket ID number: FDA-1975-N-0012-0722

studies. As part of the briefing package for the meeting, the data developed in the preliminary studies and responses were provided to address FDA concerns expressed in the Advice Letter.

At the feedback meeting, the FDA stated[12] "*We acknowledge our prior communication from the March 20, 2015 meeting with ACI and others, whereby we stated that a challenge model may be acceptable and that the appropriateness of the model and relevance to the consumer population would need to be considered. Upon further consideration of the value of using a challenge model to show efficacy of antiseptic hand wash in a consumer setting, we do not believe a challenge model is appropriate."* As a result of this conclusion ACI is researching alternative strategies. As discussed at the meeting, we will need additional time to develop protocols looking at alternative consumer settings to demonstrate a clinical benefit. As discussed at the meeting, "FDA said it would be willing to work with Industry on developing these intervention studies with the understanding that Industry will submit proposed study synopses to FDA for comment with as much detail as possible, and with specific questions for FDA."

Following FDA's feedback at the August 6, 2018, ACI has sought and been in consultation with several potential Principal Investigators to develop protocols and new study designs. ACI contracted experts, Loren Miller, M.D., M.P.H. (Professor of Medicine, David Geffen School of Medicine at UCLA), Ron Turner, M.D. (Professor Emeritus of Pediatrics, University of Virginia School of Medicine), Bruce Stouch (BCS Statistical Solutions, LLC), Eugene Millar (Uniformed Services University), and Carey Schlett (Independent Consultant) to further develop the skin infection protocol along with developing study synopses for alternative settings.

b) Skin Infection Model for Consumer Hand Wash Products

ACI submitted a draft protocol to FDA for a multi-year clinical outcome study entitled *Household Use of Antimicrobial Soap for Prevention of Recurrent Staphylococcal Infection* on December 9, 2016 for FDA review[13]. The study would generate data for the active ingredients BAC, BZT and PCMX when used in consumer antiseptic hand wash products.

The FDA provided ACI with an Advice Letter (April 3, 2017) regarding the protocol. ACI received further feedback on the study design approach in the meeting with FDA on August 6, 2018. ACI has contracted Drs. Loren Miller, Ronald Turner, and Bruce Stouch to revise and refine the study protocol.

The study protocol design is being refined to determine the safety and effectiveness of antimicrobial soap to prevent the recurrence of Staph infections in a household setting. The submission of a Household Setting study synopsis for FDA review is planned for 1Q2022. We will also be requesting a meeting with FDA to discuss the Household Setting study synopsis so as to inform final study design and protocol development.

c) Study Designs in Alternative Consumer Settings

ACI has contracted experts, Drs. Loren Miller, Ronald Turner, Eugene Millar, Bruce

[12] FDA Meeting Minutes for August 6, 2018 meeting with ACI
[13] Docket ID number: FDA-1975-N-0012-0723

Stouch, and Ms. Carey Schlett, to develop study synopses for investigating clinical consumer efficacy in alternative consumer settings.

An alternative study design is currently being developed that is based within a Military setting. Here a military trainee study population will be evaluated to determine the safety and effectiveness of antimicrobial soap on reducing the transmission of methicillin-resistant Staphylococcus aureus (MRSA). The submission of a Military Setting study synopsis for FDA review is planned for 1Q2022. We will also be requesting a meeting with FDA to discuss the Military Setting study synopsis to inform final study design and protocol development.

C. Study Timelines

Please find in Table 3 an update to the anticipated timeline for safety and effectiveness studies for BAC under the existing and proposed rules for Consumer Hand Wash, Consumer Hand Rub, and Health Care, and with potential application to the anticipated rule for Food Handler Antiseptic products.

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

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Report Submission to FDA
Consumer Hand Wash	Effectiveness	*In vitro* Time-Kill	January 4, 2016	1Q2017	1Q2018	2Q2018
		Clinical #1 – Skin Infection Study – Household Setting Study Design†	December 9, 2016	2022*	2026	2026
		Clinical #2 – Develop Alternate Setting study synopses	1Q2022	*	*	*
		Clinical #2 – Develop clinical efficacy draft study protocol	2022	*	*	*
Health Care	Effectiveness	*In vitro* Time-Kill	January 4, 2016	1Q2017	1Q2018	2Q2018
		Additional Time Kill study for 0.5% BAC	N/A	1Q2021	2Q2022	3Q2022
		In vitro MIC-MBC	March 21, 2016	4Q2017	3Q2018	1Q2019
		In vivo Hand Wash (HCPHW)				
		Pilot HW Study	April 28, 2016	3Q2019	2Q2020	**
		Pivotal HW Study #1	**	2023	2023	2023
		Pivotal HW Study #2	N/A	2024	2024	2024
		In vivo Hand Rub				
		Pilot Hand Rub Study	3Q2021£	2Q2021	1Q2022	2Q2022**
		Pivotal Hand Rub Study #1	TBD	2023	2023	2023
		Pivotal Hand Rub Study #2	TBD	2024	2024	2024
Consumer Wash	Clinical Safety (MUsT)	*In vitro* dermal penetration	N/A	4Q2016	1Q2017	2Q2018
		Observational Study – Consumer Wash	N/A	1Q2017	3Q2017	2Q2018
		Bioanalytical method development and validations	N/A	1Q2019	2Q2019	2Q2019
		Pilot MUsT	2Q2018	3Q2019	1Q2020	2Q2020
		Pivotal MUsT	4Q2020	3Q2021	1Q2022	4Q2022***
Health Care	Clinical Safety (MUsT)	Electronic Surveillance study	N/A	2017	2017	1Q2019
		Pilot MUsT	2023	--	--	--
		Pivotal MUsT	--	--	--	--
Consumer/ Health Care	Nonclinical (Animal) Safety	ADME	Following evaluation of MUsT data	--	--	--
		Dermal Carcinogenicity	Following evaluation of MUsT data	--	--	--

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Report Submission to FDA
Consumer/ Health Care	Nonclinical Safety	Resistance Literature Reviews	N/A	1Q2018	1Q2021	3Q2021

* The initiation of this study is contingent on discussion with FDA and approval of the study design, and the COVID-19 pandemic.

** Submission following FDA meeting and discussion.

*** Pending FDA's establishment of submission process and information platform.

† Anticipates extensive pilot work, and submission of a revised protocol before clinical study with subjects is initiated.

£ To be initiated following evaluation of initial study to determine product and volume to use for study.

III. Benzethonium Chloride (BZT)

In its deferral letter dated August 14, 2019, FDA requested a meeting with ACI to discuss health care antiseptic indications for PVP-I and BZT. For BZT discussion, ACI submitted a type C meeting request to FDA on June 10, 2020 with a written-only response. FDA granted the meeting on July 7, 2020 with a goal of providing a written response by September 30, 2020 that will be in FDA dockets FDA-1975-N-0012 and FDA-2015-N-0101 and FDA-2016-N-0124 for public display. FDA provided a written response to the type C meeting request on October 5, 2020 and communicated that ACI has demonstrated "…an ongoing commitment to and progress in conducting the necessary safety and efficacy studies to address existing data gaps for BZT and the health care personnel hand wash indication." FDA concluded that they have no intention issuing a proposed administrative order regarding the safety and efficacy of BZT health care personnel handwashes for one year, subject to renewal.

As previously communicated to FDA, safety testing with BZT will commence following completion of MUsT testing with BAC. The FDA has provided multiple reviews and participated in meetings with sponsors to establish the MUsT protocol used in the recently completed Pilot MUsT with BAC in consumer antiseptic wash products submitted to FDA on June 22, 2020. Experience with this protocol during the Pilot MUsT and from completion of the scheduled Pivotal MUsT testing with BAC is directly applicable to proposed human pharmacokinetic maximal usage trials with BZT in consumer and healthcare antiseptic wash products. To finalize a BZT MUsT test protocol, data are being generated that will inform the appropriate frequency and duration of dosing, and an appropriate product formulation for testing is being identified. Efforts to generate these data are described below.

A. Safety

1. Human pharmacokinetic maximal usage trial (MUsT)

The FDA has provided multiple reviews and participated in meetings with sponsors regarding a protocol for a MUsT for BAC in consumer antiseptic wash products. Experience with that protocol will be used to support development of protocols for BZT in consumer and healthcare antiseptic wash products. To finalize the pivotal test protocol, data are being generated that will inform the appropriate frequency and duration of dosing, and an appropriate product formulation for testing is being identified. Efforts to generate these data are described below.

a) Determination of Frequency and Duration of Dosing

Consumer Antiseptic Hand Washes

The ACI Work Plan proposed to develop and execute observational studies of hand wash maximal usage for a consumer setting. Two observational studies were executed in 2017 with the primary objective of learning the handwashing practices of childcare workers. The results of these studies provided substantive data on the number of hand washing events in what is considered a high exposure work place setting where consumer hand wash products are used. This information will be used to define the maximum number of washes in a proposed pilot MUsT for consumer antiseptic hand wash products containing BAC, BZT, and PCMX. Reports

of the observational studies were submitted to FDA for the Feedback Meeting on May 9, 2018 related to BAC and BZT. FDA initially requested the pilot MUsT follow a dosage format of 40 washes per day for 30 seconds per wash (FDA meeting minutes letter, not dated); in response, a 3-day exaggerated hand wash study was conducted for the FDA recommended dosage format (Letter to FDA April 8, 2019). This resulted in loss of study participants due to dermal effects to the hands. As a result of the exaggerated hand wash study, the pilot MUsT for BAC utilized a hand wash frequency of 30 washes per day at 30 seconds per wash for 5 consecutive days. We anticipate using the same dosage format for BZT.

Healthcare Antiseptic Frequency of Use

An electronic surveillance study was executed in 2017 with the primary objective of learning the hand hygiene practices for health care workers. The study was reported in a 2018 peer-reviewed publication.[14] This information will be used to define the number of hand hygiene events in a pilot MUsT for health care antiseptic products containing BZT.

b) Determination of Composition of Tested Formulations - *In Vitro* Dermal Penetration Studies with Human Skin

Research has been conducted to 1) assess whether there are significant dermal absorption differences among the marketed formulas of consumer antiseptic hand wash products, and 2) identify a product type having the greatest dermal penetration of the actives BAC and BZT in liquid, bar, and foaming formulations. A final report for *in vitro* dermal penetration studies of BZT was submitted to FDA for a May 9, 2018 Feedback Meeting. Based on the submitted *in vitro* dermal penetration data, we will select the formulation with the highest penetration to support both consumer and healthcare uses in the pilot MUsT.

c) Maximal Usage Trial (MUsT) Protocol Development

As communicated to FDA, a pilot MUsT for BZT will be conducted following the pivotal MUsT for BAC. A draft protocol for a pilot MUsT for BAC and BZT was also submitted for FDA review at the meeting on May 9, 2018. FDA provided comments on the pilot MUsT protocol and revisions were made and resubmitted (May 19, 2019) with the briefing materials for the July 9, 2019 meeting. FDA stated that the previous *in vitro* dermal penetration results (submitted for May 9, 2018 meeting) in addition to proposed additional *in vitro* dermal penetration testing would suffice for selecting a formula for evaluation in the BAC pilot MUsT. FDA also stated that the BAC pilot MUsT protocol appears reasonable (July 3, 2019). Currently, a pilot MUsT to support consumer indications for BAC has been completed and the Final Report submitted to FDA. A protocol for the pivotal MUsT was submitted to FDA and discussed during the meeting on July 30, 2020. FDA indicated a method must be developed to recover BZT in blood plasma as a prerequisite for the Pilot BZT MUsT. Development of bioanalytical methods for BZT is ongoing pending finalization of bioanalytical methods for BAC metabolites associated with the pending Pivotal MUsT, described above. We anticipate that this work will

[14] Jessica Albright, Bruce White, Daniel Pedersen BS, Pete Carlson, Lisa Yost, Cheryl Littau. "Use patterns and frequency of hand hygiene in healthcare facilities: Analysis of electronic surveillance data." American Journal of Infection Control, 46 (2018) 1104-9. https://doi.org/10.1016/j.ajic.2018.04.205

resume during Q4 2021.

2. Nonclinical Safety (Toxicology)

a) Antibiotic Resistance

In 2016, a systematic search was conducted by reviewing commercially published peer-reviewed and grey literature. Search databases included: Google Scholar, PubMed, PubChem, Science.gov, worldwidescience.org, and the U.S. Patent and Trademark Office. Searches were conducted for BAC, BZT, and PCMX. The biocide names and synonyms were then linked with descriptors such as "biological action, toxicity, bacteria, bacterial resistance, antibiotics, antimicrobial therapy, pathogenicity islands, gene cassette, resistance mechanism, efflux pump," and others, to capture a diverse base of literature.

A detailed review of the retrieved literature was conducted to determine whether there is sufficient evidence to indicate that use of these active ingredients contributes to antibiotic and antimicrobial resistance and cross-resistance in consumer, health care, or food handling settings. Since the 2019 progress report submission, additional work has been conducted to finalize the antibiotic resistance report including an additional review of recent publications (those published from 3rd quarter 2019 – January 2021) and clarification of definitions within the literature review. The review has been completed and a final report was submitted to FDA on July 28, 2021.

B. Effectiveness

1. *In Vitro* Studies

a) Time-Kill Studies

A time-kill study for the active ingredients BAC, BZT, PCMX and ETOH has been completed (Final Report #150940-201 entitled "An *In-vitro* Time-Kill Evaluation of Four Test Materials When Challenged with Various Bacterial and Yeast Species"). The time-kill study generated data for these active ingredients covering all the final, proposed and anticipated rules for topical antiseptics (consumer wash, health care, consumer hand rub and food handler products). The report from this study was submitted to FDA on April 12, 2018. ACI submitted a response on February 26, 2019 to comments and questions included in an FDA Advice Letter dated July 5, 2018. In FDA's Advice Letter posted to the docket on August 9th 2019, FDA stated that no additional concentrations need to be proposed for time-kill studies with BZT because of the narrow eligible concentration range for BZT.

b) Minimum Inhibitory Concentration (MIC) /
Minimum Bactericidal Concentration (MBC) Studies

An MIC/MBC study report for the active ingredients BAC, BZT, PCMX, PVP-I and ETOH entitled "Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Five Test Materials" was submitted to FDA on February 15, 2019. The MIC/MBC study generated data for these active ingredients covering all final,

proposed and anticipated rules for topical antiseptics (consumer hand wash, consumer hand rub, health care, and food handler products). FDA confirmed that this study is satisfactory, and the milestone is complete in the August 29, 2019 Advice Letter to ACI.

2. *In Vivo* Studies

a) Health Care Personnel Hand Wash

A pilot health care personnel hand wash study has not yet been initiated for BZT. Since a pilot study has been completed for BAC, PCMX and PVP-I, the pivotal health care personnel hand wash study for BZT may be conducted along with these other active ingredients without performing a pilot study for BZT. The final report for the health care personnel hand wash pilot study will be submitted following a meeting with FDA to discuss these results, and will inform development of the pivotal study protocol.

3. Clinical Outcome Studies

a) Proposed Foodborne Induction Model for Consumer Hand Wash Products (ETEC Challenge Study)

ACI submitted a draft protocol for a clinical outcome study entitled *Incidence of clinical illness and bacterial colonization after ingestion of enterotoxigenic Escherichia coli (ETEC): effect of hand washing with either plain soap or an antibacterial hand soap*[15] on November 22, 2016 to the FDA for review. The study would generate data for BAC, BZT and PCMX when used in consumer antiseptic hand wash products. As outlined in our February 10, 2017 progress report, pilot work was being performed to finalize several of the variables that will need to be defined prior to executing a pivotal challenge study. The FDA provided an Advice Letter (April 3, 2017) to ACI regarding the protocol, which was accounted for in designing the preliminary studies.

Preliminary work was completed addressing how the hands would be inoculated using a whole hand contamination method. Additional studies evaluated bacterial removal for no treatment, soap with active ingredients (BAC, BZT, and PCMX) and plain soap. These data demonstrated differences in the amount of bacteria recovered from the hands between active ingredients and plain soap. Neutralization studies were also completed and the standard stripping solution was determined to be effective in inactivating the three actives.

ACI participated in a Feedback Meeting with FDA on August 6, 2018 to review protocol design elements for this study based on the April 3, 2017 Advice Letter and the follow up studies. As part of the briefing package for the meeting, the data developed in the preliminary studies and responses were provided to address FDA concerns expressed in the Advice Letter.

At the feedback meeting, the FDA stated[16] "*We acknowledge our prior communication from the March 20, 2015 meeting with ACI and others, whereby we stated that a challenge model may be acceptable and that the appropriateness of the model and relevance to the*

[15] Docket ID number: FDA-1975-N-0012-0722
[16] FDA Meeting Minutes for August 6, 2018 meeting with ACI

consumer population would need to be considered. Upon further consideration of the value of using a challenge model to show efficacy of antiseptic hand wash in a consumer setting, we do not believe a challenge model is appropriate." As a result of this conclusion ACI is researching alternative strategies. As discussed at the meeting, we will need additional time to develop protocols looking at alternative consumer settings to demonstrate a clinical benefit. As discussed at the meeting, "FDA said it would be willing to work with Industry on developing these intervention studies with the understanding that Industry will submit proposed study synopses to FDA for comment with as much detail as possible, and with specific questions for FDA."

Following FDA's feedback at the August 6, 2018, ACI has sought and been in consultation with several potential Principal Investigators to develop protocols and new study designs. ACI contracted experts, Loren Miller, M.D., M.P.H. (Professor of Medicine, David Geffen School of Medicine at UCLA), Ron Turner, M.D. (Professor Emeritus of Pediatrics, University of Virginia School of Medicine), Bruce Stouch (BCS Statistical Solutions, LLC), Eugene Millar (Uniformed Services University), and Carey Schlett (Independent Consultant) to further develop the skin infection protocol along with developing study synopses for alternative settings.

b) Skin Infection Model for Consumer Hand Wash Products

ACI submitted a draft protocol to FDA for a multi-year clinical outcome study entitled *Household Use of Antimicrobial Soap for Prevention of Recurrent Staphylococcal Infection* on December 9, 2016 for FDA review.[17] The study would generate data for the active ingredients BAC, BZT and PCMX when used in consumer antiseptic hand wash products.

The FDA provided ACI with an Advice Letter (April 3, 2017) regarding the protocol. ACI received further feedback on the study design approach in the meeting with FDA on August 6, 2018. ACI has contracted Drs. Loren Miller, Ronald Turner, and Bruce Stouch to revise and refine the study protocol.

The study protocol design is being refined to determine the safety and effectiveness of antimicrobial soap to prevent the recurrence of Staph infections in a household setting. The submission of a Household Setting study synopsis for FDA review is planned for 1Q2022. We will also be requesting a meeting with FDA to discuss the Household Setting study synopsis so as to inform final study design and protocol development.

c) Study Designs in Alternative Consumer Settings

ACI has contracted experts, Drs. Loren Miller, Ronald Turner, Eugene Millar, Bruce Stouch, and Ms. Carey Schlett, to develop study synopses for investigating clinical consumer efficacy in alternative consumer settings.

An alternative study design is currently being developed that is based within a Military setting. Here a military trainee study population will be evaluated to determine the safety and effectiveness of antimicrobial soap on reducing the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA). The submission of a Military Setting study synopsis for FDA

[17] Docket ID number: FDA-1975-N-0012-0723

review is planned for 1Q2022. We will also be requesting a meeting with FDA to discuss the Military Setting study synopsis so as to inform final study design and protocol development.

C. Study Timelines

Please find in Table 4 an update to the anticipated timeline for safety and effectiveness studies for BZT under the existing and proposed rules for Consumer Hand Wash, Health Care, and with potential application to the anticipated rule for Food Handler antiseptic products.

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

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	1Q2018	2Q2018
		Clinical #1 – Skin Infection Study-Household Setting Study Design †	December 9, 2016	2022*	2026	2026
		Clinical #2 – Develop Alternate Setting study synopses	1Q2022	*	*	*
		Clinical #2 – Develop clinical efficacy study protocol	2022	*	*	*
Health Care	Effectiveness	*In vitro* Time-Kill	January 4, 2016	1Q2017	1Q2018	2Q2018
		In vitro MIC-MBC	March 21, 2016	4Q2017	3Q2018	1Q2019
		In vivo Hand Wash				
		Pilot HW Study **	April 28, 2016	--	--	--
		Pivotal HW Study #1	**	2023	2023	2023
		Pivotal HW Study #2 **	N/A	--	--	--
Consumer and Health Care Hand Wash	Clinical Safety (MUsT)	*In vitro* dermal penetration	--	4Q2016	1Q2017	3Q2017
		Observational Study – Consumer Wash	--	1Q2017	3Q2017	2Q2018
		Development and validation of bioanalytical methods	--	4Q2021	2Q2022	3Q2022
		Electronic Surveillance study	N/A	2017	2017	1Q2019
		Pilot MUsT***	2Q2018	2023	2023	2023
		Pivotal MUsT	Following evaluation of pilot MUsT data	2024	2024	2024
Consumer Hand Wash/ Health Care	Nonclinical (Animal) Safety	ADME	Following evaluation of MUsT data	--	--	--
		Oral Carcinogenicity		--	--	--
		DART		--	--	--
		Hormonal Effects	Following evaluation of MUsT, carcinogenicity and DART data	--	--	--
Consumer/ Health Care	Nonclinical Safety	Resistance Literature Reviews	N/A	1Q2018	1Q2021	3Q2021

† Anticipates extensive pilot work and submission of a revised protocol before clinical study with subjects is initiated.

*The initiation of this study is contingent on FDA approval of the study design and the COVID-19 pandemic.

**The pivotal health care personnel hand wash may be conducted along with other active ingredients without performing a pilot study for BZT.

***As communicated to FDA, a pilot MUsT for BZT will be conducted following the pivotal MUsT for BAC.

N/A = Not Applicable

IV. Chloroxylenol (PCMX)

A. Safety

1. Clinical Safety: Human pharmacokinetic maximal usage trial (MUsT)

With respect to a MUsT for PCMX, our Work Plan dated September 9, 2016, stated we intend to establish experience with the execution of MUsT studies for ETOH and BAC before we develop a study protocol for PCMX. Development work has been undertaken to define the design elements for a MUsT for PCMX and further work has been initiated, as follows. Discussions with two candidate laboratories were conducted in regard to development, optimization and validation of a bioanalytical method for PCMX and to conduct the pilot MUsT. Consequently, Sannova Analytical, Inc. has been contracted to conduct the pilot MUsT. ACI submitted a meeting request to the FDA on May 26, 2021 to discuss the Pilot MUsT protocol for PCMX.

a) Determination of Frequency and Duration of Dosing

Consumer Antiseptic Hand Washes

The ACI Work Plan proposed to develop and execute observational studies of hand wash maximal usage for a consumer setting. Two observational studies were executed in 2017 with the primary objective of learning the handwashing practices of childcare workers. The results of these studies provided substantive data on the number of hand washing events in what is considered a high exposure workplace setting where consumer hand wash products are used. This information will be used to define the maximum number of washes in a proposed pilot MUsT for consumer antiseptic hand wash products containing BAC, BZT, and PCMX. Reports of the observational studies were submitted to FDA for the Feedback Meeting on May 10, 2018 related to BAC and BZT. FDA initially requested the pilot MUsT follow a dosage format of 40 washes per day for 30 seconds per wash (FDA meeting minutes letter, not dated); in response, a 3-day exaggerated hand wash study was conducted using the FDA recommended dosage format (Letter to FDA April 8, 2019), this resulted in loss of study participants due to dermal effects to the hands. As a result of the exaggerated hand wash study, the pilot MUsT dosage will have a hand wash frequency of 30 washes per day (10 hrs per day) for 4 days.

Healthcare Antiseptic Frequency of Use

An electronic surveillance study was executed in 2017 with the primary objective of learning the hand hygiene practices for health care workers. The study was reported in a 2018 peer-reviewed publication.[18] This information will be used to define the number of hand hygiene events in a pilot MUsT for health care antiseptic products containing PCMX.

[18] Jessica Albright, Bruce White, Daniel Pedersen BS, Pete Carlson, Lisa Yost, Cheryl Littau. "Use patterns and frequency of hand hygiene in healthcare facilities: Analysis of electronic surveillance data." American Journal of Infection Control, 46 (2018) 1104-9. https://doi.org/10.1016/j.ajic.2018.04.205

b) Determination of Composition of Tested Formulations - *In Vitro* Dermal Penetration Studies

A laboratory was retained to carryout bioanalytical method verification and *in vitro* dermal penetration (IVDP) studies with human skin in 2019. In 2018, ACI initiated a market-based research initiative to inform product selection based on the range of antiseptic concentrations and inert ingredients that may act as penetration enhancers for products containing PCMX. The intent was to identify the PCMX-containing formulation that demonstrates the greatest penetration through human skin. Subsequently, the formulation(s) will be used in the MUsT in support of PCMX under the anticipated rules for consumer, health care, and food handler antiseptic products. ACI has completed an *in vitro* dermal penetration study in which a range of PCMX products were evaluated for the permeation of PCMX. ACI submitted a meeting request to the FDA on May 26, 2021 to discuss the IVDP results, product selection, and the pilot MUsT protocol. Sannova Analytical, Inc. has been contracted for analytical method development, validation, and pilot MUsT sample analysis.

c) Sensitive and validated analytical method

ACI has contracted Sannova Analytical, Inc. for method development and validation, and pilot MUsT sample analysis for PCMX in human plasma. Sannova has successfully completed a feasibility study demonstrating the capability of detecting PCMX at 0.5 ng/ml.

2. Nonclinical Safety (Toxicology)

a) Antibiotic Resistance

In 2016, a systematic search was conducted by reviewing commercially published peer-reviewed and grey literature. Search databases included: Google Scholar, PubMed, PubChem, Science.gov, worldwidescience.org, and the U.S. Patent and Trademark Office. Searches were conducted for BAC, BZT, and PCMX. The biocide names and synonyms were then linked with descriptors such as "biological action, toxicity, bacteria, bacterial resistance, antibiotics, antimicrobial therapy, pathogenicity islands, gene cassette, resistance mechanism, efflux pump," and others, to capture a diverse base of literature.

A detailed review of the retrieved literature was conducted to determine whether there is sufficient evidence to indicate that use of these active ingredients contributes to antibiotic and antimicrobial resistance and cross-resistance in consumer, health care, or food handling settings. Since the 2019 progress report submission, additional work has been conducted to finalize the antibiotic resistance report including an additional review of recent publications (those published from 3rd quarter 2019 through January 2021) and clarification of definitions within the literature review. The review has been completed and a final report was submitted to FDA on July 28, 2021.

B. Effectiveness

1. *In Vitro* Studies

a) Time-Kill Studies

A time-kill study for the active ingredients BAC, BZT, PCMX and ETOH has been completed (Final Report #150940-201 entitled "An *In-vitro* Time-Kill Evaluation of Four Test Materials When Challenged with Various Bacterial and Yeast Species"). The time-kill study generated data for these active ingredients covered the respective requirements for all of the final, proposed and anticipated rules for topical antiseptics (consumer wash, health care, consumer hand rub, and food handler products). The report from this study was submitted to FDA on April 12, 2018. ACI submitted a response on February 26, 2019 to comments and questions included in an FDA Advice Letter dated July 5, 2018. An additional Time-Kill study has been initiated at BioScience Laboratories, with testing to be conducted from 3rd quarter of 2021 until the 1st quarter 2022. The purpose of this study is to obtain data for additional active ingredient concentrations within the respective eligibility ranges that ACI is supporting. The concentrations of actives being tested are as follows: 0.5% BAC, 0.3% and 1.0% PCMX and 60%, 70%, 80%, and 90% ETOH. The final report for this study is expected to be issued by Q2 2022, and ACI expects to submit this report to FDA by Q3 2022.

b) Minimum Inhibitory Concentration (MIC) /
Minimum Bactericidal Concentration (MBC) Studies

An MIC/MBC study report for the active ingredients BAC, BZT, PCMX, PVP-I and ETOH entitled "Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Five Test Materials" was submitted to FDA on February 15, 2019. The MIC/MBC study generated data for these active ingredients covering all final, proposed and anticipated rules for topical antiseptics (consumer hand wash, consumer hand rub, health care, and food handler products). FDA confirmed that this study is satisfactory and the milestone is complete in the August 29, 2019 Advice Letter to ACI.

2. *In Vivo* Studies

a) Qualifying laboratories to conduct *in vivo* efficacy studies

Numerous clinical laboratories located in the United States and Europe have been audited for their capabilities to conduct ASTM *in vivo* efficacy studies. A minimum of two clinical laboratories are needed to meet FDA's requirement that the two pivotal studies for each indication are conducted at different laboratories. Further, multiple laboratories are being sought in order to support the conduct of the full range of pivotal *in vivo* studies contemplated for BAC, PCMX, ETOH and PVP-I. Performance evaluations at candidate laboratories in 2018 failed to identify a second laboratory qualified to conduct the studies. In 2019, two potential laboratories were identified. Training trials in 2020 to develop their proficiency in the *in vivo* efficacy study methods (for hand rub and hand wash studies) as well as to determine their capabilities and qualifications were delayed due to laboratory closures and travel restrictions as a result of the COVID-19 pandemic. Final hand rub training studies by these laboratories to evaluate lab

performance will be conducted from 3Q 2021 to 1Q 2022. Results from these studies will allow ACI to decide which labs will receive ACI study contracts for hand rub studies. Qualification for hand wash studies is ongoing.

b) Health Care Personnel Hand Wash

Modifications have been incorporated into a protocol for a pilot *in vivo* testing of health care personnel hand washes containing BAC, PCMX and PVP-I based upon feedback from the FDA. The pilot study has been completed and the final report is anticipated for submission to FDA following a meeting to discuss the results. The results of the pilot study will be used to inform the design of a pivotal healthcare personnel hand wash protocol. We will be requesting a meeting with FDA to discuss the pilot study results and align on a final pivotal study design.

3. Clinical Outcome Studies

a) Proposed Foodborne Induction Model for Consumer Hand Wash Products (ETEC Challenge Study)

ACI submitted a draft protocol for a clinical outcome study entitled *Incidence of clinical illness and bacterial colonization after ingestion of enterotoxigenic Escherichia coli (ETEC): effect of hand washing with either plain soap or an antibacterial hand soap*[19] on November 22, 2016 to the FDA for review. The study would generate data for BAC, BZT and PCMX when used in consumer antiseptic hand wash products. As outlined in our February 10, 2017 progress report, pilot work was being performed to finalize several of the variables that will need to be defined prior to executing a pivotal challenge study. The FDA provided an Advice Letter (April 3, 2017) to ACI regarding the protocol, which was accounted for in designing the preliminary studies.

Preliminary work was completed addressing how the hands would be inoculated using a whole hand contamination method. Additional studies evaluated bacterial removal for no treatment, soap with active ingredients (BAC, BZT, and PCMX) and plain soap. These data demonstrated differences in the amount of bacteria recovered from the hands between active ingredients and plain soap. Neutralization studies were also completed and the standard stripping solution was determined to be effective in inactivating the three actives.

ACI participated in a Feedback Meeting with FDA on August 6, 2018 to review protocol design elements for this study based on the April 3, 2017 Advice Letter and the follow up studies. As part of the briefing package for the meeting, the data developed in the preliminary studies and responses were provided to address FDA concerns expressed in the Advice Letter.

At the feedback meeting, the FDA stated[20] "*We acknowledge our prior communication from the March 20, 2015 meeting with ACI and others, whereby we stated that a challenge model may be acceptable and that the appropriateness of the model and relevance to the consumer population would need to be considered. Upon further consideration of the value of*

[19] Docket ID number: FDA-1975-N-0012-0722
[20] FDA Meeting Minutes for August 6, 2018 meeting with ACI

using a challenge model to show efficacy of antiseptic hand wash in a consumer setting, we do not believe a challenge model is appropriate." As a result of this conclusion ACI is researching alternative strategies. As discussed at the meeting, we will need additional time to develop protocols looking at alternative consumer settings to demonstrate a clinical benefit. As discussed at the meeting, "FDA said it would be willing to work with Industry on developing these intervention studies with the understanding that Industry will submit proposed study synopses to FDA for comment with as much detail as possible, and with specific questions for FDA."

Following FDA's feedback at the August 6, 2018, ACI has sought and been in consultation with several potential Principal Investigators to develop protocols and new study designs. ACI contracted experts, Loren Miller, M.D., M.P.H. (Professor of Medicine, David Geffen School of Medicine at UCLA), Ron Turner, M.D. (Professor Emeritus of Pediatrics, University of Virginia School of Medicine), Bruce Stouch (BCS Statistical Solutions, LLC), Eugene Millar (Uniformed Services University), and Carey Schlett (Independent Consultant) to further develop the skin infection protocol along with developing study synopses for alternative settings.

b) Skin Infection Model for Consumer Hand Wash Products

ACI submitted a draft protocol to FDA for a multi-year clinical outcome study entitled *Household Use of Antimicrobial Soap for Prevention of Recurrent Staphylococcal Infection* on December 9, 2016 for FDA review.[21] The study would generate data for the active ingredients BAC, BZT and PCMX when used in consumer antiseptic hand wash products.

The FDA provided ACI with an Advice Letter (April 3, 2017) regarding the protocol. ACI received further feedback on the study design approach in the meeting with FDA on August 6, 2018. ACI has contracted Drs. Loren Miller, Ronald Turner, and Bruce Stouch to revise and refine the study protocol.

The study protocol design is being refined to determine the safety and effectiveness of antimicrobial soap to prevent the recurrence of Staph infections in a household setting. The submission of a Household Setting study synopsis for FDA review is planned for 1Q2022. We will also be requesting a meeting with FDA to discuss the Household Setting study synopsis so as to inform final study design and protocol development.

c) Study Designs in Alternative Consumer Settings

ACI has contracted experts, Drs. Loren Miller, Ronald Turner, Eugene Millar, Bruce Stouch, and Ms. Carey Schlett, to develop study synopses for investigating clinical consumer efficacy in alternative consumer settings.

An alternative study design is currently being developed that is based within a Military setting. Here a military trainee study population will be evaluated to determine the safety and effectiveness of antimicrobial soap on reducing the transmission of methicillin-resistant Staphylococcus aureus (MRSA). The submission of a Military Setting study synopsis for FDA

[21] Docket ID number: FDA-1975-N-0012-0723

review is planned for 1Q2022. We will also be requesting a meeting with FDA to discuss the Military Setting study synopsis so as to inform final study design and protocol development.

C. Study Timelines

Please find in Table 5 an update to the anticipated timeline for safety and effectiveness studies for PCMX under the final and proposed Consumer Hand Wash and Health Care Antiseptic rules, and with potential application to the anticipated Food Handler antiseptic products proposed rule.

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

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	1Q2018	2Q2018
		Additional Time-Kill Studies for 0.3% and 1.0% PCMX	N/A	1Q2021	2Q2022	3Q2022
		Clinical #1 – Skin Infection Study – Household Setting Study Design †	December 9, 2016	2022*	2026	2026
		Clinical #2 – Develop Alternate Setting study synopses	1Q2022	*	*	*
		Clinical #2 – Develop clinical study efficacy protocol	2022	*	*	*
Health Care	Effectiveness	*In vitro* Time-Kill	January 4, 2016	1Q2017	1Q2018	2Q2018
		Additional Time-Kill Studies for 0.3% and 1.0% PCMX	January 4, 2016	1Q2021	2Q2022	3Q2022
		In vitro MIC-MBC	March 21, 2016	4Q2017	3Q2018	1Q2019
		In vivo Hand Wash				
		Pilot HW Study	April 28, 2016	3Q2019	2Q2020	**
		Pivotal HW Study #1	**	2023	2023	2023
		Pivotal HW Study #2	N/A	2024	2024	2024
Consumer Hand Wash/ Health Care	Clinical Safety (MUsT)	Observational Study – Consumer Wash	N/A	1Q2017	3Q2017	2Q2018
		Electronic Surveillance study	N/A	2017	2017	1Q2019
		In vitro dermal penetration	N/A	3Q2019	4Q2019	***
		Development and validation of bioanalytical methods	N/A	4Q2020	4Q2021	***
		Pilot MUsT	N/A§	3Q2021	3Q2022	1Q2023
		Pivotal MUsT	2023	2023	2023	2023
Consumer Hand Wash/ Health Care	Nonclinical (Animal) Safety					
		Dermal Carcinogenicity	Following evaluation of MUsT data	--	--	--
		Oral Carcinogenicity		--	--	--

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Study Report Submission to FDA
		DART	Following evaluation of MUsT and carcinogenicity data	--	--	--
		Hormonal Effects	Following evaluation of MUsT, carcinogenicity and DART data	--	--	--
Consumer Hand Wash/ Health Care	Nonclinical Safety	Resistance Literature Reviews	N/A	1Q2018	1Q2021	3Q2021

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

§ A MUsT protocol for BAC 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.

* The initiation of this study is contingent on FDA approval of the study design and the COVID-19 pandemic.

** Submission following FDA meeting and discussion.

*** To be submitted with pilot MUsT protocol.

N/A = Not Applicable

V. Povidone Iodine (PVP-I)

In its advice letter dated September 30, 2020, FDA responded to ACI's inquiry regarding meeting requests for "the status and milestones for some of the *in vivo* efficacy studies for the active ingredients povidone-iodine and benzethonium chloride for certain health care antiseptic indications". The advice letter states the FDA agrees there is no need to submit a meeting request to discuss *in vivo* efficacy for PVP-I at this time. The following sections detail data being developed for PVP-I as an active ingredient in health care antiseptics. The PVP-I group is pursuing pre-operative indications.

A. Safety

With respect to a MUsT for PVP-I, our Work Plan dated July 19, 2017, stated we intend to establish experience with the execution of MUsT studies for ETOH and BAC before we develop a study protocol for PVP-I. However, preliminary development work has been undertaken to define the design elements for a MUsT for PVP-I and further work has been initiated, as follows.

1. Clinical Safety: Human Pharmacokinetic Maximal Usage Trial (MUsT)

a) Determination of Frequency and Duration of Dosing

Healthcare Antiseptic Frequency of Use

An electronic surveillance study was executed in 2017 with the primary objective of learning the hand hygiene practices for health care workers. The study was reported in a 2018 peer-reviewed publication.[22] This information will be used to define the number of hand hygiene events in a pilot MUsT for health care antiseptic products containing PVP-I.

b) Determination of Composition of Tested Formulations – *In Vitro/In Vivo* Dermal Penetration Studies

ACI has collected information on marketed topical products that contain PVP-I as the active ingredient. An *in vivo* 9-month dermal safety study of PVP-I in an appropriate non-clinical model was completed in 3rd quarter 2021, with a final report targeted for 4th quarter 2021. We plan on requesting a meeting with FDA to discuss the results of this study and seek guidance on next steps. The final report will be submitted following the meeting.

B. Effectiveness Studies

1. *In Vitro* Studies

a) Time-Kill Study

[22] Jessica Albright, Bruce White, Daniel Pedersen BS, Pete Carlson, Lisa Yost, Cheryl Littau. "Use patterns and frequency of hand hygiene in healthcare facilities: Analysis of electronic surveillance data." American Journal of Infection Control, 46 (2018) 1104-9. https://doi.org/10.1016/j.ajic.2018.04.205

The study has been completed per FDA requirements. We plan on meeting with FDA to discuss the results of this study and seek guidance on next steps. The final report will be submitted following the meeting.

b) Minimum Inhibitory Concentration (MIC) / Minimum Bactericidal Concentration (MBC) Studies

An MIC/MBC study report for the active ingredients BAC, BZT, PCMX, PVP-I and ETOH entitled "Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Five Test Materials" was submitted to FDA on February 15, 2019. The MIC/MBC study generated data for these active ingredients covering all final, proposed and anticipated rules for topical antiseptics (consumer hand wash, consumer hand rub, health care, and food handler products). FDA confirmed that this study is satisfactory and the milestone is complete in the August 29, 2019 Advice Letter to ACI.

2. *In Vivo* Studies

a) Qualifying laboratories to conduct *in vivo* efficacy studies

Numerous clinical laboratories located in the United States and Europe have been audited for their capabilities to conduct ASTM *in vivo* efficacy studies. A minimum of two clinical laboratories are needed to meet FDA's requirement that the two pivotal studies for each indication are conducted at different laboratories. Further, multiple laboratories are being sought in order to support the conduct of the full range of pivotal *in vivo* studies contemplated for BAC, PCMX, ETOH and PVP-I. Performance evaluations at candidate laboratories in 2018 failed to identify a second laboratory qualified to conduct the studies. In 2019, two potential laboratories were identified. Training trials in 2020 to develop their proficiency in the *in vivo* efficacy study methods (for hand rub and hand wash studies) as well as to determine their capabilities and qualifications were delayed due to laboratory closures and travel restrictions as a result of the COVID-19 pandemic. Final hand rub training studies by these laboratories to evaluate lab performance will be conducted from 3Q 2021 to 1Q 2022. Results from these studies will allow ACI to decide which labs will receive ACI study contracts for hand rub studies. Qualification for hand wash studies is ongoing.

b) Health Care Personnel Hand Wash

Modifications have been incorporated into a protocol for a pilot *in vivo* testing of health care personnel hand washes containing BAC, PCMX and PVP-I based upon feedback from the FDA. The pilot study has been completed, and the results will be used to inform the design of a pivotal healthcare personnel hand wash protocol. We will be requesting a meeting with FDA to discuss the pilot study results and align on a final pivotal study design, and the final report will be submitted following the meeting.

C. Study Timelines

Please find in Table 6 an update to the anticipated timeline for safety and effectiveness studies for PVP-I under the final Health Care Antiseptic rule.

Table 6. Timeline for Development of Safety and Effectiveness Data for Povidone-Iodine (PVP-I)

Monograph	Data Need	Study	Submission of protocol to FDA for review	Study Initiation	Study Completion	Final Study Report Submission to FDA
Health Care	Effectiveness	*In vitro* Time-Kill	January 4, 2016	2Q2020	3Q2021	4Q2021**
		In vitro MIC-MBC	March 21, 2016	4Q2017	3Q2018	1Q2019
		In vivo Hand Wash (HCPHW)				
		Pilot HW Study	April 28, 2016	3Q2019	2Q2020	**
		Pivotal HW Study #1	**	2023	2023	2023
		Pivotal HW Study #2	N/A	2024	2024	2024
		Pre-Op Skin Prep Study #1	2Q2022	2Q2022	4Q2022	2023
		Pilot Surgical Scrub	N/A	2023	2024	2024
Health Care	Clinical Safety (MUsT)	*In vivo nonclinical* dermal safety study	N/A	2020	2021	2022**
		Development and validation of bioanalytical method	N/A	2020*	2021*	2022**
		Electronic Surveillance study	N/A	2017	2017	1Q2019
		Pilot MUsT	Pending FDA Feedback from Meeting	--	--	--
		Pivotal MUsT	Pending FDA Feedback	--	--	--
Health Care	Nonclinical (Animal) Safety	Dermal Carcinogenicity	Pending FDA Feedback	--	--	--

* Pending FDA feedback from meeting.

** Submission following FDA meeting and discussion.

N/A = Not Applicable

VI. Completed Milestones

Please find in Table 7, a summary of completed milestones.

Table 7. Summary of Completed Milestones as Required by Final Monographs

Active Ingredient(s)	Milestones	Status	Comments
BAC, BZT	Complete *in vitro* dermal penetration studies for BAC and BZT-containing consumer antiseptic hand wash products	*In vitro* screening study on dermal penetration was completed and submitted to FDA (April 9, 2018). Additional *in vitro* dermal penetration study for BAC (Consumer)	Provided FDA (briefing document May 9, 2019) with follow-up material and information in the briefing document for the feedback meeting held on July 9, 2019 At FDA's request, completed and submitted an additional *in vitro* dermal penetration study in Lonza and Henkel Briefing Document, June 17, 2020
BAC, BZT, PCMX, ETOH and PVP-I	Complete MIC/MBC study and submit report to FDA	MIC/MBC study completed and final report submitted to FDA 1Q2019	FDA concurs that this milestone is complete (Advice Letter from FDA, August 29, 2019)
BAC, BZT, PCMX	Complete and submit to FDA an observational study for childcare workers to support development of pilot consumer hand wash MUsT protocol	Observational study for childcare workers completed and submitted 2nd QTR 2018	Observational study submitted to FDA for Feedback Meeting on May 9, 2018; follow-up Advice Letter from FDA concludes number of washes necessary (July 3, 2019)
BAC, BZT, PCMX	Complete and submit to FDA literature review related to potential for resistance	Literature review was completed, and it submitted to FDA 3Q2021	
BAC, BZT, PCMX, PVP-I	Submit to FDA a report of observational study for health care products to support development of pilot health care hand wash MUsT protocols	Electronic surveillance study was published in the American Journal of Infection Control in 2018	Manuscript was referenced and submitted in ACI's response to FDA's request for data and information on food handler antiseptic drug products for OTC human use on July 22, 2019
BAC	Pilot MUsT	Pilot MUsT completed. Henkel and Lonza met virtually with FDA on July 30, 2020 to discuss result and pivotal MUsT protocol.	

Active Ingredient(s)	Milestones	Status	Comments
BAC	Complete bioanalytical method development	Completed and accepted by FDA for pilot MUsT	

VII. Next Steps

We anticipate achieving the following new milestones before the next progress report (anticipated to be in October 2022):

- Submit report for additional time Time-Kill studies for concentrations of BAC, ETOH, and PCMX
- Submit pilot *in vivo* health care personnel hand wash efficacy study report for products containing BAC, PCMX and PVP-I to FDA*
- Submit study synopses for clinical outcome studies for consumer antiseptic hand wash products containing BAC, BZT and PCMX; meet and discuss with FDA, and align on study protocols prior to initiation of studies
- Select one or more qualified laboratories to conduct ACI-sponsored *in vivo* efficacy studies
- Initiate ETOH Pilot Hand Rub study* for 90% (v/v), pending the results of Time Kill
- Submit pilot Surgical Hand Rub *in vivo* efficacy study final report* for ETOH to FDA
- Complete bioanalytical method validation for ETOH for Pilot MUsT
- Complete and submit ETOH Pilot MUsT study
- Complete bioanalytical method development and validation for BZT
- Initiate pivotal MUsT for BAC
- Complete bioanalytical method validation for PCMX
- Complete the pilot MUsT for PCMX
- Submit pilot healthcare personnel hand rub study for BAC*
- Continue to support the development of a food handler monograph by FDA for the 5 active ingredients that are eligible for consumer and health care indications. PVP-I options are under consideration.
- Request a meeting with FDA to discuss results from the PVP-I *in vivo* non-clinical dermal safety study and seek guidance on next steps.
- Submit Time-Kill study report* for PVP-I to FDA
- Submit PVP-I non-clinical dermal safety study report* to FDA
- Initiate pre-operative skin preparation study for PVP-I

* Submission of study report or initiation of study is dependent on meeting and discussion with FDA

V. Conclusion

ACI is pleased to provide this Progress Report to the Work Plans for BAC, BZT, PCMX and ETOH (submitted to FDA on September 9, 2016 and updated in progress reports submitted on February 10, 2017 and February 23, 2018), and for PVP-I (as described in the original Work Plan submitted to the FDA on July 19, 2017), and updated in the most recent progress reports covering all 5 actives (submitted on March 12, 2019 and July 14, 2020). We would like to note that the commitments we are making to fill the safety and efficacy data gaps are long term and resource intensive in labor and expenditures to conduct the studies requested by FDA. In order for industry to continue to make such investments, we again state that it is imperative that FDA provide assurances for longer term market access (deferral of rulemaking) and we request FDA

provide a multi-year deferral for each of the topical antiseptic rules with the understanding that we will continue to make progress and provide regular Progress Reports on our activities.

We would appreciate confirmation from FDA that the deferrals of BAC, BZT, PCMX, ETOH and PVP-I from rulemaking under the final rules for consumer antiseptic wash products (78 FR 76444; 81 FR 61106), consumer rub products (81 FR 42912; 84 FR 14847), and health care antiseptics (80 FR 25166; 82 CFR 60474) are being extended.

Please contact me if you have any questions regarding this Progress Report or if you desire more detailed information regarding the work we are conducting. We would be pleased to participate in a face-to-face meeting with FDA staff to discuss our Work Plan, if you would find that useful.

Sincerely,

James Kim, PhD, DABT
Vice President, Science & Regulatory Affairs