



american cleaning institute®

# **Food Handler Antiseptic Drug Products for Over-the-Counter Human Use**

**Request for Data and Information  
Docket No. FDA-2018-N-3458**

**Submitted by:  
American Cleaning Institute**

**July 22, 2019**

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Food Handler Antiseptic Drug Products for Over-the-Counter Human Use;  
Request for Data and Information; Docket No. FDA-2018-N-3458

The American Cleaning Institute (ACI)<sup>1</sup> appreciates this opportunity to provide comments and information in response to the Food and Drug Administration's (FDA's) request for data and information on food handler antiseptic drug products for over-the-counter (OTC) human use.<sup>2</sup>

We submit these comments to inform FDA's ongoing review of OTC antiseptic drug products intended for use in food handler settings. Some of the information that we are providing has been previously submitted to other dockets for OTC antiseptic drug products:

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 FDA 1975-N-0012)

Safety and Effectiveness for Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use (Docket FDA-2015-N-0101)

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 FDA-2016-N-0124)

ACI has organized this submission according to the questions for public input that FDA has put forward: Definition of Food Handler Antiseptics, Active Ingredients for Food Handler Antiseptic Products, Safety, and Effectiveness. As pointed out within this response document, there are opportunities to gather and provide additional data and information (*e.g.*, market volume estimates; frequency, type, and level of soil on hands in various food handler settings; frequency of food handler antiseptic use; test methods) to fill information gaps. We request to work in collaboration with FDA to gather the additional information and data needed prior to the issuance of an Advanced Notice of Proposed Rulemaking.

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<sup>1</sup> ACI is a trade association for the \$60 billion U.S. cleaning products industry. ACI members include a significant number of suppliers of active ingredients and manufacturers of food handler antiseptic products sold in the U.S. that are the subject of this RFI.

<sup>2</sup> 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.

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## Request for Data and Information

### A. Definition of Food Handler Antiseptics

#### A1. What are the categories of workers who might use these products?

Food handler antiseptics could be used by professional workers that handle food in a wide variety of commercial and regulated environments.

#### A2. In what settings are food handler antiseptics used?

A2a. What should be the boundaries (e.g., growth, harvest, production, manufacturing, processing, packaging, transportation, storage, preparation, service, and consumption) of regulated use of food handler antiseptics?

Antiseptics can be used in all food handler settings, including settings such as growth, harvest, production, manufacturing, processing, packaging, transportation, storage, preparation, service, and consumption of food. The boundaries of regulated uses of food handler antiseptics should encompass this full range of settings.

A2b. Are there any additional details and information to be considered related to scope-of-use settings of food handler antiseptics?

ACI recommends that the food handler monograph category be aligned with the scopes of the Food Safety Modernization Act (FSMA; US FDA 2011) and the US Food Code (US FDA 2017).

FSMA regulations require food safety evaluation and intervention throughout the supply chain, including the growth, harvest, production, manufacturing, processing, packaging, transportation, storage, preparation, service, and consumption of food. Food safety interventions include proper employee health and hygiene, of which hand washing and sanitization is a critical component.

The US Food Code states that employees are to wash their hands before working in food preparation and after any activity that contaminates hands. Food preparation and service settings, including cafeterias, restaurants, delis, bakeries, and ready-to-eat food processing facilities, have a high potential for hands to contact and contaminate food.

A3. What types of antiseptic products are used by food handlers and what terms are used in the food industry to describe such products (e.g., wash, or leave-on products)?

Food handler products include antiseptic washes and leave-on rubs including hand wipes.

#### A4. How frequently are food handler antiseptics used?

There are a limited number of published field studies that have included observations of employee hand washing practices in the institutional food service, restaurant, and retail grocery store facilities. However, none of these studies address the specific frequency question and all of these have limitations that impact their ability to provide a combined meta data set which could be assessed to determine the actual handwashing frequency, as it exists in the commercial and regulated environments where food handling occurs today.

Key limitations include:

- (1) A focus on hand hygiene opportunities and compliance rate, not on actual measured handwashing events;
- (2) The observation periods were short, mostly ranging from 55 minutes (Green et al. 2006) to a few hours (Allwood et al. 2004, Clayton and Griffith 2004, do Prado et al. 2015, Strohbehn et al. 2008, York et al. 2009). The extrapolation of washes per hour, based on these short observation windows, may not be representative of the actual frequency of use over an entire shift or workday;
- (3) The observed data were not reported on an individual basis, but instead were aggregated across the entire facility (Allwood et al. 2004, Clayton and Griffith 2004, do Prado et al. 2015, Strohbehn et al. 2008); thus the data were not specific enough to calculate an individual's exposure to topical antiseptic ingredients;
- (4) The innate error of several observation studies, all performed by different groups of observers with different study criteria, make it impossible to merge the results into a meaningful meta data set.

To address these shortcomings, the 1<sup>st</sup> phase of a project to research the actual frequency of hand washing in the food service industry was undertaken. In this phase, a direct observational screen was initiated, focusing on individual food handlers' frequency of use across multiple full-service and quick service restaurants in the greater Toledo, Ohio area during October and November 2018. Two hundred food handling staff from 6 full-service restaurants and 11 quick service restaurants were monitored. These observations were made over a four-hour continuous period during peak customer times for one or two days per restaurant. The average hourly hand washing occurrences per employee, in full-service restaurants and quick service restaurants, ranged between 1.68 and 2.33 washings per hour.

The 2<sup>nd</sup> phase of the hand hygiene frequency study, utilizing electronic data collection on individual food handlers' hand wash frequency, similar to a study conducted in healthcare facilities by Albright et al. (2018), is currently underway.

Industry believes these data can provide a solid basis to understand how frequently these products are used by food handlers. A study report including both the direct observational data and electronically monitored data will be submitted to FDA.

## **B. Active Ingredients for Food Handler Antiseptic Products**

ACI is concerned that FDA may be taking an unduly restrictive approach to assessing the monograph eligibility of active ingredients intended for food handler antiseptic drug products. FDA's Request for data and Information (RFI) states:

FDA's recognition of the potential eligibility of food handler antiseptic products for evaluation under the OTC Drug Review is relatively new. We expect that many of the antiseptic active ingredients found in products currently used by food handlers may not have been on the U.S. market when the OTC Drug Review was first established, or that it may be difficult to establish eligibility based on use at that time (Food Handler Antiseptic Drug Products for Over-the-counter Human Use; Request for Data and Information, FDA 2018)

However, in January 1972, before the inception of the OTC drug review, FDA announced that it was convening an advisory panel on "all antibacterial ingredients used in OTC drugs for repeated daily consumer use as prophylaxis against minor skin infections or transmission of disease" (National Archives and Records Administration. 37 FR 195, Jan.7, 1972) In this notice, FDA specifically identified "food handlers" as among those who "may benefit from the antibacterial action of these products" (National Archives and Records Administration. 37 FR 195, Jan.7, 1972). This language is consistent with the recognition that antiseptics, with broad claims to prevent transmission of disease, were already in use and of benefit to food handlers. Therefore, the potential eligibility of antiseptics for food handler use has been clear from the beginning of the OTC drug review.

In 1994, FDA recognized that, historically, hand sanitizers have been marketed for use by food handlers as hand cleansers with general drug claims such as "antibacterial handwash," "kills germs and bacteria on contact," or "effectively reduces bacterial flora of the skin" (US FDA, 1994). In fact, in the 1994 tentative final monograph (US FDA 1994) for antiseptic drugs, FDA stated that the agency had reviewed the labeling of such products intended for food handlers and concluded that hand sanitizer products for food handlers were intended as drugs. Therefore, it would be unreasonable for FDA to require, as a condition of monograph eligibility, the submission of labeling specific to food handler use when it is well known that such products, with more general antiseptic claims, were historically used by food handlers. It should be sufficient for determining monograph eligibility to show that the ingredients were intended for antiseptic use broad enough to cover food handling, rather than requiring food handler specific labeling.

### **B1. What are the active ingredients currently used in food handler antiseptic products?**

The active ingredients currently used by ACI members in food handler antiseptics include benzalkonium chloride (BAC), benzethonium chloride (BZT), chloroxylenol (PCMX), and ethanol (EtOH). Povidone-iodine (PVP-I) inclusive of iodine complexes has been

historically used by food handlers as evidenced by EPA's Reregistration Eligibility Decision (EPA 2006) and historical labels.<sup>3</sup>

**B2. How long and to what extent (e.g., number of units or volume sold) have currently marketed active ingredients been in the marketplace inside and/or outside of the U.S. market?**

In the 1994 preamble to the tentative final monograph for health care antiseptic drug products (US FDA 1994), FDA acknowledged that food handler antiseptics had been under the jurisdiction of the United States Department of Agriculture (USDA 1979). ACI has identified publications by the USDA indicating that food handler antiseptics were in use prior to 1972, which are summarized below.

Until 1998, the USDA Compounds and Packaging Branch annually published a list of hand sanitizing substances in "Miscellaneous Publication No. 1419, List of Proprietary Substances and Nonfood Compounds." Earlier versions of this list were titled "List of Chemical Compounds Authorized for Use Under USDA Inspection and Grading Programs." The USDA list included the following categories that align with antiseptic drug products (USDA 1979):

- Handwashing and sanitizing compounds: The compounds must be dispensed from adequate dispensers located a sufficient distance from the processing line to prevent accidental product contamination. The hands need not be washed prior to the use of the compounds. After the use of the compounds, the hands must be thoroughly rinsed with potable water.
- Hand sanitizing compounds: The hands must be washed and thoroughly rinsed prior to sanitizing with the compound. The hands need not be rinsed following the use of the compound.

These hand wash products were intended "for use in slaughtering and processing plants operating under the U.S. Department of Agriculture Poultry, Meat, Rabbit, Shell Egg Grading and Egg Products Inspection Programs" and thus would appear to qualify as food handler antiseptic products. Unfortunately, although the publication lists manufacturers and trade names for products corresponding to the hand wash categories listed above, it does not disclose the active ingredients in these products.

ACI members report that they have been marketing hand hygiene products with EtOH, BAC, BZT, PVP-I, and PCMX for over 30 years that have been used by the food handling industry. It is difficult to estimate the number of units or volume sold of currently marketed active ingredients inside and outside of the U.S. market. Additional research would be needed to obtain these figures.

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<sup>3</sup> FDA Docket 75N-183H, Book III OTC Vol. 23001. Relevant pages are extracted and presented in Attachment 1.

In addition to the information from USDA, there are currently over 160 products listed by NSF International with either “handwashing and sanitizing compound” or “hand sanitizing compound” certifications. The product listings can be viewed at the White Book™ - Nonfood Compounds Listing Directory at <http://info.nsf.org/USDA/psnclistings.asp>. NSF is an independent accredited organization that facilitates the development of standards and tests and certifies products. NSF assumed responsibility for the review of hand wash products in 1998 from USDA and the White Book lists nonfood compounds for use in Federally Inspected Meat and Poultry plants.

**B3. What active ingredients were in products on the market for food handler use prior to 1972, and what evidence of eligibility for evaluation for use in food handler antiseptic products under the OTC Drug Review is available for these active ingredients?**

ACI has identified a number of advertisements for food handler products dating back prior to 1972 (Attachment 2). In particular, ACI has identified advertisements for Roccal Brand Sanitizing Agent from 1949, 1953, and 1954. This product is advertised as a “quaternary ammonium germicide” for use by the food industry in “wash rooms,” “as a hand rinse for help,” and as “hand and teat wash.” A journal publication from 1952 on organic chemicals in the food industry suggests that the quaternary ammonium in use at the time was benzalkonium chloride (Coppock 1952), which is in use today as an active ingredient for food handler antiseptic products.



## C. Safety

C1. Should the data required to demonstrate the safety of active ingredients intended for use in food handler antiseptic products be the same as the safety criteria for active ingredients intended for use in consumer antiseptic and health care antiseptic products?

We expect that the new data which are being generated to support the safe use of EtOH, BAC, BZT, PVP-I, and PCMX in consumer and health care antiseptic products, including those intended to address human exposure, will also be sufficient to meet the safety data needs for food handler products.

C2. If antiseptic hand rubs or leave-on products are used, the presence of residual antiseptic products on the hands of food handler professionals may result in indirect consumer exposure (*i.e.*, ingestion of residual antiseptic due to transfer of such residues from food handlers to food contact surfaces and/or food). Are additional studies required to address this concern?

For active ingredients in the food handling environment for professional use, the quantity of active ingredient expected to transfer to food are estimated to be minimal. Surface transfer coefficient models exist for modeling transfer of pesticides to surfaces of agricultural goods and these calculations may be used to model the transfer rates from hand to foodstuffs. In this way, these models can be extended to assess the migration and dietary concentration of the active ingredients in food. We expect these levels to be below the threshold of regulation (TOR) for substances used in food contact articles (US FDA 2018).

Food handling in food-service environments for the highest exposure risk category, ready-to-eat foods (RTE), requires the use of gloves to prevent microbial contamination (US FDA 2017b). This glove barrier will also prevent active ingredient transfer from the hands.

Considering these factors and the safety data from the MUsT studies, which are part of the GRAS data package being developed, ACI anticipates there will be sufficient data to complete an assessment of the potential safety impact of residue transfer to food, and is not expected to be an area that will need additional data development.

C3. If additional studies are required to address indirect consumer exposure to antiseptic ingredients, what should they be?

Based on our answer to Question C2, no additional studies should be required to address indirect consumer exposure to antiseptic ingredients from food handler uses.

C4. On a daily basis, how frequently do food handlers use food handler antiseptic products in the workplace?

There are a limited number of published field studies that have included observations of employee hand washing practices in the institutional food service, restaurant, and retail grocery store facilities. However, none of these studies address the specific frequency question and all of these have limitations that impact their ability to provide a combined meta data set which could be assessed to determine the actual handwashing frequency, as it exists in the commercial and regulated environments where food handling occurs today.

Key limitations include:

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[C4a. Are there any requirements related to the frequency of using food handler antiseptics in the workplaces where food is handled \(e.g. produce safety standards\)?](#)

There are common practices and/or requirements related to the frequency of using food handler antiseptics in food handling settings. For instance, specific requirement of use applies when switching between food types, as well as working continuously or during intermittent breaks. Specific practices of hand washing are also required, as in the US Food Code (U.S. FDA 2017b). Other requirements may also exist and be specific to processing plants, corporate policies, food establishments, etc.

**C5. What data are available to support the long-term safety of the active ingredients of these products (e.g. oral and dermal carcinogenicity studies)?**

The data available and being developed to support the long-term safety of the active ingredients EtOH, BAC, BZT, PVP-I, and PCMX in consumer and/or health care antiseptic products are expected to sufficiently support the long-term safety of the same ingredients used in food handler products.

**C6. How should the potential for antimicrobial resistance to these active ingredients be assessed?**

We strongly believe the approach taken to assess the potential for antimicrobial resistance to active ingredients intended for use in health care antiseptic products can be utilized for food handler products, namely a comprehensive literature review of pertinent research in the area of antimicrobial resistance, which ACI is sponsoring for submission to FDA.

One primary contributing factor likely to reduce risk of antimicrobial resistance development, is the use of biocidal (not biostatic) concentrations of active ingredients. This means that is unlikely that food handlers will be exposed to a theoretically selective environment of sub-cidal concentrations, as is typically studied in academia (see response to question C7).

**C7. What data are available regarding antimicrobial resistance for these products, and how should the potential of food handler antiseptics' use with potential emergence of antimicrobial resistance be assessed?**

The most relevant data on the potential for the development of antimicrobial resistance to active ingredients used in food handler topical antiseptic products are being assessed and summarized in a report ACI intends to submit to FDA under its work plans for BAC, BZT, and PCMX (see response to question C6). The aim of the assessment is to understand the impact of these active ingredients, if any, on the development of bacterial resistance or decreased susceptibility.

**C8. What other issues should be taken into consideration to support evaluation of the safety of food handler antiseptic products?**

We strongly believe answers to the above questions are able to fully support the safety evaluation of food handler antiseptic products, with no other issues anticipated.

## D. Effectiveness

Responses to FDA's questions related to effectiveness are discussed below. Questions have been reordered to facilitate discussion. While our answers represent a deep knowledge of the food handler industry, the science of antiseptic actives, and available test methods, we recognize that gaps remain which preclude design of specific testing and efficacy criteria for antiseptic actives. Industry is committed to working in collaboration with the FDA to address these scientific gaps prior to development of proposed GRAE requirements. The development of test methods and guidelines is an iterative process. We look forward to working with FDA to define the requirements.

**D1. How are food handler antiseptics used in food handler settings? Are they used according to the manufacturer's directions of use or according to establishment-based standard operating procedures?**

The process of hand washing is typically guided by manufacturer instructions.

Individual establishments will create standard operating procedures that address when hands must be washed. The procedures established within these facilities will account for the types of food being handled and all precautionary measures employed within that facility (such as the use of gloves). For foodservice establishments, general guidance regarding when handwashing should occur is provided in the US Food Code (US FDA 2017b) (as summarized below).

FOOD EMPLOYEES shall clean their hands and exposed portions of their arms as specified under § 2-301.12 immediately before engaging in FOOD preparation including working with exposed FOOD, clean EQUIPMENT and UTENSILS, and unwrapped SINGLE-SERVICE and SINGLE-USE ARTICLES and:

- (A) After touching bare human body parts other than clean hands and clean, exposed portions of arms;
- (B) After using the toilet room;
- (C) After caring for or handling SERVICE ANIMALS or aquatic animals as specified in ¶ 2-403.11(B);
- (D) Except as specified in ¶ 2-401.11(B), after coughing, sneezing, using a handkerchief or disposable tissue, using tobacco, eating, or drinking;
- (E) After handling soiled EQUIPMENT or UTENSILS;
- (F) During FOOD preparation, as often as necessary to remove soil and contamination and to prevent cross contamination when changing tasks;
- (G) When switching between working with raw FOOD and working with READY-TO-EAT FOOD;
- (H) Before donning gloves to initiate a task that involves working with FOOD; and

(I) After engaging in other activities that contaminate the hands.

Food production and harvesting settings/facilities are governed by FSMA (US FDA 2011). FSMA does not contain the same guidelines as the US Food Code (US FDA 2017b) for when to wash hands. However, under FSMA's required preventive controls, known by the acronym HARPC (Hazard Analysis and Risk-based Preventive Controls), manufacturers must create and maintain a thorough hygiene discipline throughout their facilities. Specifically, the law says "*management of covered facilities must ensure that all employees who manufacture, process, pack or hold food have the necessary education, training, and/or experience and ensure they receive training in the principles of food hygiene, food safety, and employee health and hygiene.*" Such training includes thorough and regular briefings on proper hand hygiene protocols, as well as hand hygiene records available for FDA inspection.

### In Vitro

The following are ACI's response to FDA's request for information as it relates to the following questions on *in vitro* testing:

#### D2. How should the products demonstrate effectiveness *in vitro*?

The most appropriate *in vitro* method for assessing the biocidal activity of topical antiseptics is the Time-kill assay (ASTM 2016). This is because the Time-kill assay measures rapid biocidal activity at active concentrations and exposure times that closely simulate in-use conditions.

#### D3. What *in vitro* test methods should be used, e.g., minimal bactericidal concentration and Time-kill Assay?

We believe that the *in vitro* test methods utilized to support the efficacy of antiseptic active ingredients for the Health Care Antiseptic monograph, as well as the Consumer Hand Wash and Consumer Hand Rub monographs, are appropriate for use in any additional testing which may be needed to support the use of active ingredients under the Food Handler monograph. The time-kill (ASTM 2016) and MIC/MBC (CLSI 2015) methods are accepted standards and have been required by the FDA as a portion of the historical Health Care Topical Antiseptic supporting data set. The FDA determined these tests are part of the required data to support the topical active ingredients in a GRAE determination. The FDA has deemed these well-established, standard test methods to be suitable for use in the pivotal time kill and MIC/MBC studies sponsored by ACI (Bioscience Laboratories, Inc. 2018a, 2018b). Food handler organisms were included in these studies in anticipation of this RFI and a subsequently expected Food Handler proposed monograph. Both studies have been submitted to FDA in support of the *in vitro* activity of the eligible antiseptic ingredients being sponsored by ACI.

D4. What organisms should food handler antiseptics be required to demonstrate effectiveness against? Should viruses and other organisms (e.g., protozoa) be tested as well as bacteria?

FDA provided a list of organisms that they deemed relevant to the consumer and health care settings as outlined in the issued proposed monographs.

The pivotal time kill study included 270 strains of Gram negative and Gram-positive bacteria. The MIC/MBC study included 1251 microorganism strains – 51 strains of *Escherichia coli*, as well as 50 strains of each of the following organisms: *Acinetobacter baumannii*, *Bacteroides fragilis*, *Burkholderia cepacia*, *Campylobacter jejuni*, *Candida albicans*, *Enterobacter* species, *Enterococcus faecalis*, *Enterococcus faecium* (including Vancomycin-Resistant *Enterococcus* [VRE]), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Micrococcus luteus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Serratia marcescens*, *Shigella* species (including *Shigella sonnei*), *Staphylococcus aureus* (including Methicillin-Resistant *Staphylococcus aureus* [MRSA]), *Staphylococcus epidermidis* (including Methicillin-Resistant *Staphylococcus epidermidis* [MRSE]), *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus saprophyticus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

ACI included additional organisms in the pivotal time kill study and MIC/MBC study that are known to be relevant to food handler settings. The organisms identified as relevant to food handler settings are listed in the table below.

The list of organisms was derived from governmental reference sources such as the CDC, CFSAN and Industry Food Safety publications as well as industry experts to construct a representative list of organisms known to cause foodborne or associated outbreaks. Additional resources such as FDA’s website (<https://www.fda.gov/food/outbreaks-foodborne-illness/foodborne-pathogens>), FDA reports (i.e., Pathogens and Filth in Spices, US FDA 2017a), and the US Food Code (US FDA 2017b) provide the rationale for the selection.

<b>Gram Negative Bacteria</b>	<b>Tested in Pivotal Time Kill</b>	<b>Tested in MIC/MBC</b>
<i>Campylobacter jejuni</i>	ATCC #33291 and ATCC #49943	50 Strains
<i>Escherichia coli</i>	ATCC #11229	50 strains
<i>Escherichia coli</i> O157:H7	ATCC #35150	No
<i>S. enterica</i> serotype Typhi	ATCC #6539	No
<i>Salmonella enterica</i>	ATCC #10708	50 strains
<i>Shigella sonnei</i>	ATCC #9290 and ATCC #25931	50 strains
<b>Gram Positive Bacteria</b>		
<i>Enterococcus faecalis</i>	ATCC #19433 and ATCC #29212	50 strains
<i>Enterococcus faecium</i>	ATCC #51575	50 strains
<i>Listeria monocytogenes</i>	ATCC #7644	50 strains
<i>Staphylococcus aureus</i>	ATCC #6538	50 strains

The pivotal time kill and MIC/MBC studies provide significant evidence of rapid broad-spectrum germicidal activity of 5 antiseptic ingredients against organisms relative to the food handler settings. The generated data provided to FDA should be used as support for the efficacy of antiseptic active ingredients used in food handler settings<sup>4</sup> (Bioscience Laboratories, Inc. 2018a, 2018b).

While viruses and protozoa are important microorganisms in food handling settings, FDA has not typically allowed claims for these microorganisms for monograph products and has consistently communicated that such claims are only allowable in New Drug Applications. ACI, therefore, recommends that testing against viruses and protozoa be optional and not be a requirement for establishing effectiveness (*i.e.*, GRAE status). Industry requests a dialog with FDA on this point prior to development of proposed GRAE requirements.

**D5. Should the (*in vitro*) test methods address the effects of organic load (*i.e.*, high fat content, blood, or other materials) and dirt or soil on the effectiveness of food handler antiseptics?**

Best practices for safe harvesting, processing, storage and handling of food have evolved in recent years, resulting in these areas being far more regulated than ever before. Hand wash training and reinforcement programs, glove use and minimal bare hand contact with RTE food have led to a diminished role of soil in these environments (US FDA 2017b).

ACI acknowledges that there are no comprehensive studies examining soil across the food industry. ACI is willing to work with FDA to assess the types of soils and their frequency of occurrence in food handler environments and, if appropriate, their impact on efficacy.

**D6. What other variables could impact the effectiveness of food handler antiseptics besides organic load, and how should the effect of such variables be taken into consideration during testing?**

Previous studies have shown that product dose (*i.e.*, application volume), wash time, formulation composition, active concentration, and drying with paper towels can impact the efficacy of hand washes (Jensen et al. 2015; 2017a; 2017b). Furthermore, the efficacy of alcohol hand rubs is affected by application volume and product drying or contact time (Macinga et al. 2011; 2015; Suchomel 2018). The same is expected for food handler antiseptic products.

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<sup>4</sup> Submission to Docket FDA-2015-N-0101, Re: 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, RIN 0910-AF69. Report on the “Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Five Materials.” Final Report No. 150941-202.



D7. How quickly must these products demonstrate effectiveness?

D8. At what specific time point(s) should effectiveness be measured?

For antiseptic hand wash products, a 30 second time point is typically used to demonstrate rapid germicidal properties. The exception to this is some leave-on, no-rinse antiseptic products, like those containing ethanol, are tested at both 15 and 30 second time points. The pivotal time kill data submitted to the FDA dockets utilized 30 seconds and 1 minute for actives found in hand wash products, while ethanol was tested at 15 and 30 seconds.

### *In Vivo*

To assess the effectiveness criteria for food handler antiseptic active ingredients, as well as the testing methods necessary to demonstrate effectiveness, FDA is interested in gathering information on the following questions related to *in vivo* testing:

D9. Should effectiveness be established through clinical outcome study (e.g., show a statistically significant reduction in food-borne illness associated with the use of a food handler antiseptic in comparison to vehicle or washing with plain soap and water)?

We believe that clinical outcome studies and the complexities they encompass are unnecessary to prove the effectiveness of Food Handler antiseptics. Taken together, *in vitro* and *in vivo* clinical simulation data are sufficient to characterize the efficacy of food handler topical antiseptics. *In vivo* clinical simulation tests can be better controlled to evaluate specific factors relevant to the food handler use patterns while avoiding the downsides and possible risks of conducting clinical outcome studies (US FDA 2019, US FDA 2017).

To further investigate this question, industry has researched and prepared a detailed evaluation of the utility and advisability of conducting clinical outcome studies to establish the efficacy of food handler antiseptics, provided in Attachment 3. The evaluation indicates that controlled clinical outcome studies of food handler topical antiseptics will require impracticably large study populations to yield statistically meaningful results, and that the inclusion of control treatments in such studies may raise ethical issues and/or incur unnecessary risks to public health.

The primary factors supporting this conclusion (discussed at length in Attachment 3) include the following:

- The process of delivering safe to eat food is complex. Food can become contaminated from a multitude of vectors, including the hands of food workers. Conducting a well-controlled clinical outcome study capable of determining the effectiveness of any hand hygiene intervention, would require controlling an impossibly large environment, the handling, storage and processing of the food as well as ensuring consistent human behavior throughout the process.



- To overcome the complexities of the food chain and the impossibility of consistently controlling all of the above variables, it is estimated that very large populations would be required to generate statistically meaningful results within the context of a clinical study. Attachment 3 describes the design of two clinical outcome studies that could theoretically evaluate the efficacy of food handler topical antiseptics for reducing foodborne illness. Based upon the information available, it is estimated that even narrowly defined clinical studies focused on the efficacy of food handler antiseptics at the point-of-service only (e.g. restaurants or cafeterias) would need to incorporate more than 14,000 study sites and require participation of more than 361,000 study subjects in order to be adequately powered. With this large test population, multiple illness vectors, identification parameters and clinical culture confirmation will be necessary. The analytical and microbiological laboratory capacity to process the anticipated sample load, much less the CRO management capacity for this magnitude of a study, does not currently exist.
- It is anticipated that conducting studies of this size would be confounded by several logistical challenges including identification and onboarding of sites willing to participate in the study, obtaining adequate informed consent from study participants and others who may be impacted by foodborne illness during the study, ensuring and documenting protocol compliance, and the timely monitoring of potential adverse events.
- Conducting such clinical outcome studies would have ethical implications and public health consequences. Food handler compliance with standard hygiene requirements is already relatively low, and poor food handler hygiene is a known contributor to foodborne illness that could impact study participants and potentially be spread to other individuals not directly involved in the study. As such, there are serious questions regarding whether or not it would be ethical to conduct a large, controlled clinical outcome studies for food handler antiseptics, particularly given that there are other experimental frameworks, most notably clinical simulation studies, which could safely yield efficacy data sufficient to support a robust efficacy evaluation (see additional discussion below).

FDA does not require clinical outcome studies to evaluate the efficacy of professional-use healthcare topical antiseptic hand washes nor are they required for consumer topical antiseptic hand rubs. Although distinct from healthcare topical antiseptics, the public health and ethical challenges associated with conducting placebo-controlled clinical trials are also applicable to the food handler topical antiseptic use pattern. These factors, as well as the other issues discussed above and detailed in Attachment 3, provide a decision-making framework that indicates clinical outcomes studies should not be used to evaluate the efficacy of food handler topical antiseptics and clinical simulation studies are the most executable choice to establish efficacy.

#### D10. What studies should be used for a demonstration of efficacy *in vivo*?

To demonstrate *in vivo* efficacy, studies should be designed to focus on clinical simulation studies. *In vivo* human clinical simulation studies are a valid and feasible way to determine efficacy for an antiseptic ingredient. Simulation studies have been used in the past to

demonstrate the efficacy of antiseptic products since the publication of the 1978 ANPR. The previous tentative monographs for antiseptics relied on surrogate endpoint measurements to support the efficacy of these active ingredients, as have the Final Monographs for Health Care Antiseptics and Consumer Antiseptic Hand Rubs. Primary factors to consider include the use of relevant organisms regularly encountered in food handling settings, and evaluation of active ingredients in products under realistic use conditions.

There are currently four standardized *in vivo* test methods designed to evaluate the reduction of transient bacterial flora on hands by topical antiseptics. These methods may be used as a model or starting point for the design of studies to evaluate the *in vivo* effectiveness of antiseptic active ingredients. Two of these methods (ASTM E1174 and ASTM E2755) are utilized to provide efficacy documentation associated with the existing health care antiseptic monograph. Historically, ASTM E1174 is the method from which all the other methods have been derived (ASTM 2013a).

ASTM E 1174: Evaluation of the Effectiveness of Healthcare Personnel Handwash Formulations. This method is designed to evaluate topical hand wash formulations after contamination with a challenge microorganism. Log reduction of the challenge organism is determined after a single wash and optionally after ten consecutive washes. Test organisms used are *E. coli* (ATCC 11229) or *Serratia marcescens* (ATCC 14756) with inoculum levels ranging from  $5 \times 10^8$  to  $1 \times 10^9$ . The option to use *E. coli* as a test organism is more relevant in food handling environments than *S. marcescens*. (ASTM 2013a)

ASTM E2755: Determining the Bacteria Eliminating Effectiveness of Healthcare Personnel Hand Rub Formulations using Hands of Adults. This method is designed to test the efficacy of antiseptic hand rubs (aka hand sanitizers) against transient microorganisms on hands. The method accommodates the use of either a Gram-positive (*Staphylococcus aureus*) or Gram-negative (*S. marcescens*) challenge organism and uses a low volume, low soil inoculum which simulates the usage conditions for hand rub formulations. (ASTM 2015a)

ASTM E2946: Determining the Bacteria Reducing Effectiveness of Food Handler Handwash Formulations using Hands of Adults. This method evaluates hand wash efficacy in the presence of moderate or heavy food soil. The challenge microorganism, *Escherichia coli*, is added to a surrogate food soil. Beef broth is used to simulate moderate soil and hamburger is used to simulate heavy soil. Although E2946 is designed for evaluating hand washes, it has been used successfully to test both hand washes and hand rubs (Edmonds et al. 2010, Edmonds et al. 2012). (ASTM 2013b)

ASTM E2784-10: Standard Test Method for Evaluation of the Effectiveness of Handwash Formulations Using the Paper Towel (Palmar) Method of Hand Contamination. This procedure has been designed to evaluate hand wash products using a palmar surface only contamination method. Test organisms which may be used are *Serratia marcescens*, *Escherichia coli*, *Shigella flexneri*, and *Staphylococcus aureus*. This method has been used in conjunction with methods to evaluate microbial transfer to food. (ASTM 2015b)

### Choice of microorganisms

Ideally a test organism should be relevant to food handler settings, known to transmit via the hands, be stable on the hands, amenable to standard microbiological procedures, and safe for application to the hands of human test subjects at high titers. In practice, it may be difficult to satisfy all of these requirements.

Alternative test organisms that may be appropriate for Food Handler testing may be evaluated within ASTM E1174 to provide a consistent approach with the Health Care monograph.

Bacterial pathogens most important in food handling settings are listed in the FDA's "*Bad Bug Book: Handbook of Foodborne Pathogenic Microorganisms and Natural Toxins*" (<https://www.fda.gov/media/83271/download>). Several of these microorganisms are challenge microorganisms in the aforementioned ASTM methods, including *E. coli*, *S. aureus*, and *S. flexneri*. Each of these microorganisms is known to be transmitted via the hands and have been validated for at least one of the clinical simulations studies listed above, making them candidates for efficacy studies to demonstrate the effectiveness of food handler antiseptics.

### Soil load

Historically, FDA has demonstrated a concern with soil loading and effects on antiseptic efficacy. In the published studies where soils have been evaluated, the effect of soil loading was minimal to moderate (Larson et al. 1992, Pickering et al. 2011, Racicot et al. 2013). In the Health Care Antiseptic monograph addressing professional-use products, there has been no requirement to perform efficacy studies under moderate or heavily soiled conditions. There are a number of factors that lead us to believe that soil should not be part of the efficacy requirement for GRAE status of Food Handler Antiseptics either.

- 1) In the farm to fork landscape of food handler facilities the heaviest soils are likely to be encountered on the farm or in meat processing plants. Such heavy soil loading already requires specialized instructions in order to clean skin and allow antiseptics to prevent cross contamination, especially following bathroom usage. Employees in these types of facilities receive training, instructions (including visual aids and multilingual wall charts), as well as tools (nail brushes, etc.) to reinforce correct procedures. Developing enhanced procedures to ensure hands are adequately decontaminated is consistent with other hygiene paradigms. Both EPA and FDA promote sanitization procedures for hard surfaces that require a pre-cleaning/removal step in the presence of excess soil to allow

for effective cidal activity (U.S. EPA 2012, US FDA 2017b). This model can be translated to a prescribed label direction or training instruction for heavy soil scenarios.

- 2) In retail and restaurant food establishments the evolution of regulated glove use and regulations to prevent bare hand contact with RTE underscores that soil is not a primary factor in these areas (US FDA 2017b).
- 3) The inclusion of soil has been incorporated in ASTM E1174 method by the inocula in combination with the growth media which are applied to the hands. This a significant soil load, innate to the method, which may adequately address the typical soil that may be encountered by a professional food handler.

ACI acknowledges that there are no comprehensive studies examining soil across the food industry. ACI is willing to assess the frequency and types of soil encountered in food handler environments and, if appropriate, their impact on efficacy.

**D11. If the bacterial log reduction method for assessing effectiveness is used, what should be the required log reduction criteria for food handler antiseptics and what are the data that support such log reduction criteria?**

We are currently unaware of existing data linking log reduction data to specific risk reductions of foodborne illness. We point out that this is also the case for log reduction criteria proposed in the Health Care Antiseptics Final Monograph. There are a number of different approaches that could be taken to set log reduction criteria. These are discussed below.

#### Comparison to active and negative controls

The Final Rule for Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use proposes an efficacy analysis to assess whether the average treatment effects (ATE) across subjects meet indication-specific conditions of superiority and non-inferiority. Specifically, the antiseptic should be superior to a negative control and non-inferior to an FDA approved active control by specified margins. The proposed margins were derived from review and analysis of existing data and FDA notes that these may be revised as data gaps on deferred antiseptic ingredients are filled. The following are comments on identified approaches:

- 1) We agree with the general approach FDA has taken to establish efficacy of health care antiseptics and that this is a potentially viable option for food handler antiseptics. There are, however, several obstacles to this approach.
  - To our knowledge, there are no FDA approved products with a food handler antiseptic indication.
  - We are also unaware of studies that demonstrate effectiveness of FDA approved health care antiseptics using food handler specific methods or test conditions (*e.g.*, in

the presence of food handler specific soils). In the absence of such data, it is not possible at this time to identify appropriate non-inferiority and superiority margins (if they exist).

## 2) Link log reduction requirements to established food safety quality criteria

An alternative approach for establishing log reduction criteria could be to link the reduction of microorganisms on the hands of food handlers and subsequent handling of food to established microbial food quality standards.

Guidelines for determining the microbial quality of RTE foods may be used as a starting point for establishing such maximum allowable limits on the hands of food handlers. At least twenty-two countries have basic guidelines or recommendations on maximum allowable microbial limits in foods, including ready-to-eat foods. A comprehensive listing of microbial food limits is provided for reference in Attachment 4.

## 3) Microbial Transfer Methods

Another approach for establishing log reduction criteria is to link the reduction of microorganisms on the hands of food handlers and subsequent handling of food to established dose response modeling curves (Schaffner et al. 2014, Boyce et al. 2012, Fischler et al. 2007). Though data of this type were submitted to the FDA in response to the Consumer Antiseptic Monograph (ACI/PCPC, 2014) and determined by FDA to not be appropriate, a second look at its relevance and merit in the Food handler setting is warranted.

**D12. Do the data support use of a simulation model as a surrogate for effectiveness, such as bacterial log reduction on the hands of a food handler or on food following use of the product? What data can be used to link a simulation model to clinical outcomes related to food-borne illness (i.e., model validation)?**

Data can be generated to validate a simulation model for Food Handler Antiseptics. The most direct method to evaluate effectiveness of these products is by measuring log reduction of organisms on the hands of food handlers.

**D13. Are there any other criteria, such as reduction of transmission of microorganisms after use of food handler antiseptics that should be considered to determine the effectiveness of food-handler antiseptics?**

Measuring the reduction of transmission of microorganisms, including after use of food handler antiseptics, is a technically feasible component of validating a food safety model (Chen et al. 2001). However, the primary mode of risk reduction for food workers should focus on the direct log reduction from topical antiseptics on hands.

D14. The Health Care Antiseptics Final Rule requires that for surgical hand scrub and patient preoperative skin preparation indications, the antiseptic activity of the product must be both immediate and persistent (82 FR 60474 at 60488). The effectiveness criteria for such products require that, in addition to the immediate antibacterial activity demonstrated by log reduction, bacterial growth is also suppressed for 6 hours after product use. Should food handler antiseptics' action be persistent?

Persistent effects should not be required (and can even be counterproductive) if hygiene is practiced at the key moments of risk. Surgical scrub is a special case in which the contamination/infection risk is ongoing through the course of an operation and in which there is a risk of one person's native skin flora becoming a pathogen when introduced internally to another person's bloodstream. To our knowledge, that scenario is not a risk in food or gut transmission where potential pathogens (Salmonella, Listeria, etc.) are not "native skin flora" – i.e. once disinfected properly, repopulation should not occur without re-contamination.

D15. Given the importance of a consistently effective product, should the dose of a food handler antiseptic vary with the product or should a standard dose be required?

As discussed in section D6, the efficacy of hand rubs are directly dependent on the dose, and the efficacy of antiseptic hand washes appears to be influenced by doses as well. Because product efficacy can be influenced by formulation, the dose used for efficacy testing of formulated products may vary but should be consistent with label claims.

D16. For the same reasons noted earlier, should the recommended length of time and/or frequency of use of the antiseptic product be consistent and standardized for all food handler antiseptics?

ACI believes frequency of use of topical antiseptic products is dependent on food handler activities. The duration of hand washing or application of hand rubs should be based on product performance in simulated use studies.

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## **List of Attachments**

Attachment 1: Labels extracted from Book III OTC Vol. 230001 of FDA Docket 75N-183H

Attachment 2: Historical Advertisements

Attachment 3: Clinical Outcome Paper

Attachment 4: Food Safety Criteria

Attachment 5: References for RFI Submission

Attachment 6: References for Clinical Outcome Paper

- Attachment 6.1: 6 CCR 1010-2 through CDC, 2019
- Attachment 6.2: CSPI, 2015 through FDA, 2017
- Attachment 6.3: FDA, 2018a through Sickbert-Bennett, 2004
- Attachment 6.4: Todd, 2007 through Young, 2017