

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

Briefing Document

Meeting of the Nonprescription Drugs Advisory Committee

March 11, 2020

Docket No. FDA-2020-N-0418

**Submitted by:
American Cleaning Institute**

February 7, 2020



american cleaning institute®

Table of Contents

Executive Summary	ES-1
I. Scope and importance of skin antiseptics in food handling settings	1
II. The Clinical Benefit and Efficacy of Food Handler Antiseptic Drug Products	5
III. The Safety of Food Handler Antiseptic Drug Products	9
IV. Viruses	11
V. References	13
VI. List of Attachments	18
Attachment 1: Historical Use of Antibacterial Active Ingredients in Food Handler Hand Hygiene Products and FDA, USDA, and NSF Oversight	19
Attachment 1-1: Historical Advertisements	22
Attachment 1-2: Labels extracted from Book III OTC Vol. 230001 of FDA	28
Attachment 2: Challenges, Practices and Requirements Related to Hand Hygiene in Food Handling Settings	53
Attachment 3: In Vitro Testing	55
Attachment 4: In Vivo Testing	58
Attachment 4-1: Topical Food Handler Antiseptic Drug Products: Clinical Study Considerations	65
Attachment 5: Studies of the Frequency of Use of Food Handler Products	103

List of Figures

Figure 1. Increased U.S. expenditure on food prepared away from home (USDA 2018)	2
Figure 2. Professional Food Worker Workforce Segments (14.6 million total)	2
Figure 3. CDC Reported Locations of Foodborne Outbreaks (CDC 2016)	3
Figure 4. Contributing risk factors for foodborne illness outbreaks	4

Acronyms and Abbreviations

ACI	American Cleaning Institute
ASTM	ASTM International
BAC	Benzalkonium chloride
BZT	Benzethonium chloride
CDC	Centers for Disease Control
CFSAN	Center for Food Safety and Applied Nutrition
EPA	United States Environmental Protection Agency
EtOH	Ethanol
FDA	United States Food and Drug Administration
FSIS	Food Safety and Inspection Service
FSMA	Food Safety Modernization Act
HARPC	Hazard Analysis and Risk-based Preventive Controls
MIC/MBC	Minimum Inhibitory Concentration/Minimum Bactericidal Concentration
MUsT	Maximal Use Trial
NSF	National Science Foundation
OTC	Over-the-counter
PCMX	Chloroxylenol
PVP-I	Povidone-iodine
QMRA	Quantitative microbial risk assessment
RTE	Ready-to-eat
U.S.	United States
USDA	United States Department of Agriculture
WHO	World Health Organization
WTO	World Trade Organization

Executive Summary

On February 5, 2020, the United States Food and Drug Administration (FDA) announced a meeting of the Nonprescription Drugs Advisory Committee (NDAC) to provide advice and recommendations regarding food handler antiseptic drug products (FDA, 2020). According to FDA's announcement, the NDAC will review information previously submitted in response to a 2018 Request for Data and Information (FDA 2018a) "on the current use of over-the-counter (OTC) antiseptics in the food handler setting and the recommended testing criteria to establish the safety and effectiveness of these products" (FDA, 2020). The American Cleaning Institute (ACI)¹ recognizes and appreciates that FDA is in the process of establishing a GRAS/GRAE framework for food handler antiseptic drug products in order to establish an OTC monograph for these products.

ACI is pleased to provide this briefing package in response to the FDA's notice. This briefing package builds upon ACI's responses (ACI 2019) to FDA's Request for Data and information for "Food Handler Antiseptic Drug Products for Over-the-counter Use" (FDA 2018a).

ACI intends to support the following active ingredients for use in food handler antiseptic products: benzalkonium chloride (BAC), benzethonium chloride (BZT), chloroxylenol (PCMX), ethanol (EtOH), and povidone-iodine (PVP-I). Food handler topical antiseptic product types currently on the market include antiseptic hand washes and leave-on hand rubs. BAC, BZT, PCMX, and EtOH are active ingredients currently used by ACI members in the food handler antiseptic products. PVP-I inclusive of iodine complexes has been historically used by food handlers (United States Environmental Protection Agency [EPA] 2006).

Hand hygiene products containing BAC, BZT, PCMX, EtOH, and PVP-I marketed by ACI members have been used by the food handling industry for over 30 years. FDA has been interested in the antibacterial benefits of these products since 1972, with the United States Department of Agriculture (USDA) and the National Science Foundation (NSF) playing various roles over the intervening years. Attachment 1 provides a summary of the historical information on use of topical antiseptic products in the food handler industry and FDA, USDA and NSF oversight of these products.

The boundaries of regulated uses of food handler topical antiseptic products should encompass the full range of settings FDA has identified where professional workers handle food in commercial and regulated environments, including growth, harvest, production, manufacturing, processing, packaging, transportation, storage, preparation, service, and consumption of food (FDA 2018b). To that end, ACI recommends that the food handler monograph category be

¹ The American Cleaning Institute® (ACI – www.cleaninginstitute.org) is the Home of the U.S. Cleaning Products Industry® and its members include the manufacturers and formulators of soaps, detergents, and general cleaning products used in household, commercial, industrial and institutional settings; companies that supply ingredients and finished packaging for these products; and chemical distributors. ACI serves the growth and innovation of the U.S. cleaning products industry by advancing the health and quality of life of people and protecting our planet. ACI achieves this through a continuous commitment to sound science and being a credible voice for the cleaning products industry.

aligned with the scopes of the Food Safety Modernization Act (FSMA) (FDA 2011) and the US Food Code (FDA 2017a).

FSMA regulations require food safety evaluation and intervention throughout the supply chain, including the full range of settings listed above (FDA 2011). Food safety interventions include proper employee health and hygiene, of which hand washing and sanitization is a critical component.

Additionally, the US Food Code states that employees are to wash their hands before working in food preparation and after any activity that contaminates hands (FDA 2017a). 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.

The following are the key conclusions presented in this briefing document:

1. **An OTC monograph is needed for topical antiseptics used by food handlers.** Foodborne illnesses are a significant burden to the U.S. health care system, from both the perspective of patient outcome and economic consequences. The use of topical antiseptics is a critical risk reduction practice that reduces microorganisms on the skin, helps prevent the spread of pathogenic organisms and, in the case of topical food handler products, decreases the occurrence of foodborne illnesses. This necessitates an OTC monograph category covering these products to protect public health.
2. **Efficacy criteria should mirror the approach for health care topical antiseptic drug products.** The framework for determining the efficacy of topical antibacterial active ingredients (GRAE status) used in professional food handler settings should include both *in vitro* testing and *in vivo* human simulation studies that mirror the approach for health care topical antiseptic drug products. Studies to support the efficacy of these ingredients under the health care antiseptic drug framework are ongoing.
3. **Long-term safety of these ingredients is in the process of being demonstrated.** New data being generated to assess the human exposure and safe use of EtOH, BAC, BZT, PVP-I, and PCMX in consumer and health care antiseptic products will sufficiently support the long-term safety of the same ingredients used in food handler antiseptic products.
4. **FDA should establish a separate indication for viruses.** ACI recommends that the effectiveness of food handler antiseptics against viruses be recognized as a separate indication. Anti-viral claims should be investigated collaboratively with industry, while proceeding first towards a final monograph for activity of food handler antiseptics against bacteria.

The following sections provide data and background information considered in arriving at these conclusions.

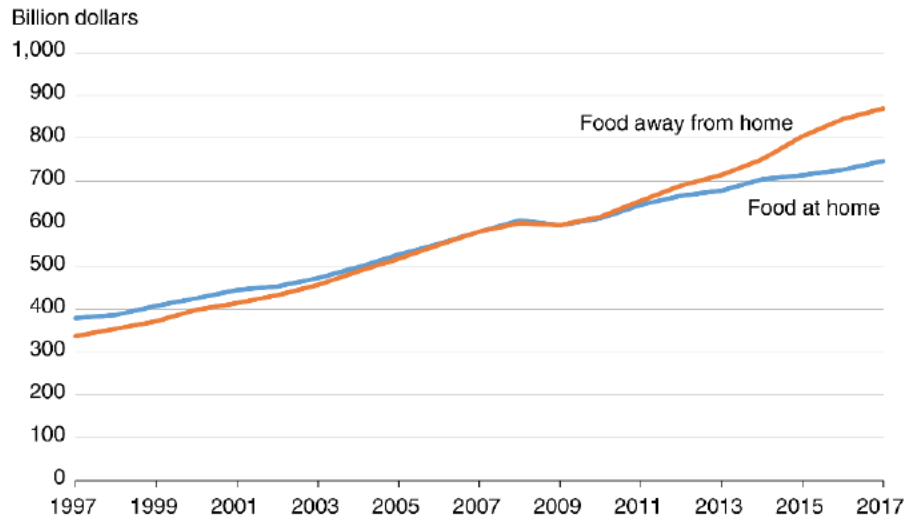
I. Scope and importance of skin antiseptics in food handling settings

Foodborne illnesses are a significant burden to the United States (U.S.) health care system, from both the perspective of patient outcome and economic consequences. The use of topical antiseptics is a critical risk reduction practice for professional food handler hygiene programs that reduces microorganisms on the skin, helps reduce the risk of food contamination and foodborne illnesses. This necessitates an OTC monograph category covering these products to protect public health.

The overall purpose of topical antiseptics is to reduce the level of microorganisms on the skin to help prevent the spread of pathogenic organisms and, in the case of topical food handler products, the occurrence of foodborne illnesses. Foodborne illnesses are a significant burden to the U.S. health care system, from both the perspective of patient outcome and economic consequences. Food handler antiseptic drug products are an established and vital component of infection control programs in U.S. facilities that handle food and play a critical role in reducing the overall burden of foodborne illnesses.

The following paragraphs summarize data from publicly available statistics that illustrate the scope and importance of food handler skin antiseptics. Trends in food consumption behaviors, the size and complexity of the professional food-handling workforce, outbreak numbers and outbreak attribution information all build a case for consideration of an OTC category for topical antiseptic products for food handlers as a public health necessity. These factors led ACI to submit a Citizen Petition to U.S. FDA in 2014 that requested the agency create a food handler category to address the safety and effectiveness of this category of products (ACI 2014).

A growing multitude of food choices from fast food to fine dining, existence of foods that are ‘natural’ rather than highly processed, and other factors have resulted in increased spending on food prepared away from home (Figure 1). It is estimated that 94 billion meals prepared away from home are consumed by the U.S. public each year (U.S. Department of Agriculture [USDA] 2018; U.S. Census Bureau 2018). This number does not take into consideration the number of meals and meal components that have in some way been handled by a professional food worker.



Source: USDA, Economic Research Service, Food Expenditure Series.

Figure 1. Increased U.S. expenditure on food prepared away from home (USDA 2018)

Much of the food that ends up on the average American's plate has either been harvested, processed, prepared, cooked or served by a professional food handler. The Bureau of Labor Statistics estimates that there are 430,000 farm workers, 800,000 food manufacture workers and 13.4 million food preparation and service workers in the U.S. (Figure 2) (Bureau of Labor Statistics 2018). This adds up to an approximate 14.6 million workforce across the food industry, which is nearly the 16.5 million level in the health care industry (Bureau of Labor Statistics 2019).

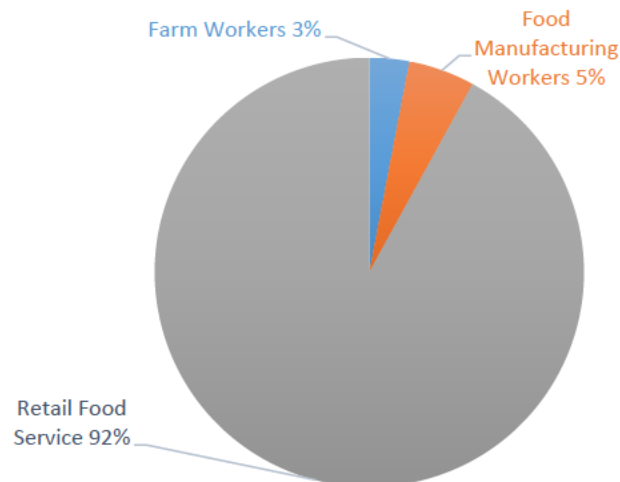


Figure 2. Professional Food Worker Workforce Segments (14.6 million total)

Similar to health care infection programs, improvements continue to be made in surveillance and the development of strong multi-faceted food safety programs. These include hand hygiene programs and the use of antiseptics to help interrupt the chain of foodborne pathogen infection. However, the Centers for Disease Control (CDC) estimates 48 million incidents of foodborne disease and 3000 associated deaths still occur each year in the U.S. (Scallan et al. 2011). Locations where reported outbreaks occurred are overwhelmingly associated with food that was prepared outside of the home (Figure 3).

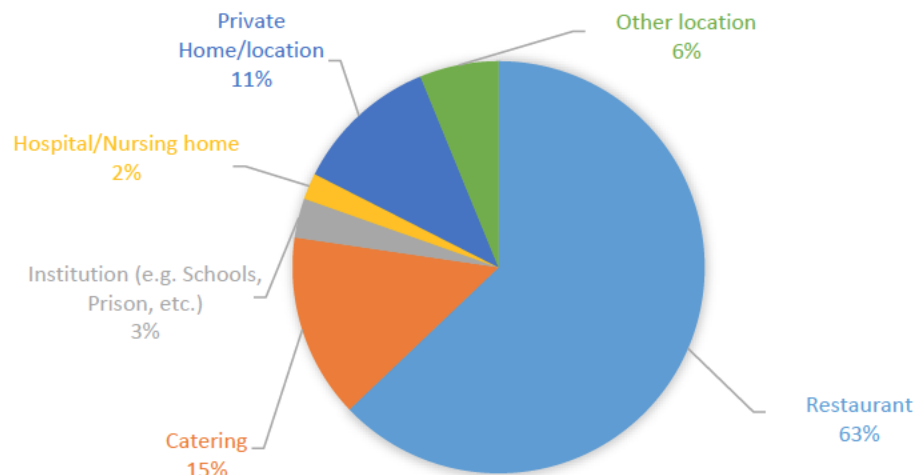


Figure 3. CDC Reported Locations of Foodborne Outbreaks (CDC 2016)

Food prepared outside the home resulted in more than ten times as many foodborne illness outbreaks than food prepared in the home. Further, food prepared outside the home resulted in an almost 40% more illnesses per outbreak than food prepared in the home (CDC 2017; CDC 2019).

The CDC also tracks when a risky food safety practice has been attributed to a particular outbreak, allowing us to understand the most common contributing factors to these events. Figure 4 charts the most common factors that contribute to outbreaks of foodborne illness, with improper personal hygiene being a contributing risk factor in 25% of foodborne illness outbreaks and contaminated surfaces in 13% of the outbreaks (Figure 4, CDC 2016). The latter is cited in recognition that cross contamination between hands, surfaces and foods can be reduced by robust hand hygiene programs including the proper use of skin antiseptics.

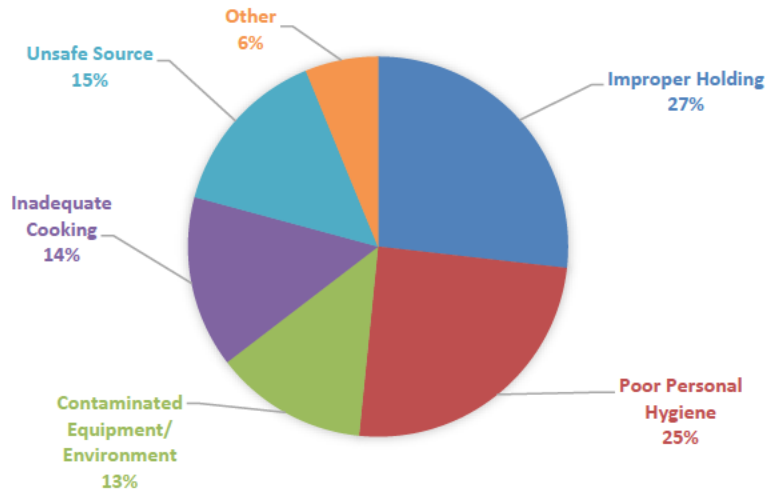


Figure 4. Contributing risk factors for foodborne illness outbreaks

The primary target of food handler skin antiseptics are bacteria, which account for 44% of all reported foodborne outbreaks (CDC 2016). This proportion includes foodborne outbreaks attributable to *Salmonella*, the bacterial pathogen that results in more hospitalizations and deaths than any other foodborne pathogen (Scallan et al. 2011). Combined, bacterial pathogens cause 64% of foodborne illness deaths in the US (Scallan et al. 2011). On a cost per case level, the USDA-Economic Research Service has estimated that a single *Salmonella* illness costs the U.S. \$3,568 in lost workdays and health care costs, compared to \$413 for Norovirus, indicating that bacterial foodborne infections pose a disproportionate burden on the public health system compared to viral infections (USDA 2019).

Safe production, distribution and preparation of food impacts every person in the U.S., young, old, healthy and sick alike. U.S. food safety agencies (FDA-Center for Food Safety and Applied Nutrition [CFSAN] and USDA-Food Safety and Inspection Service [FSIS]) continue to make strides to ensure a modern and safe food supply through the Food Safety Modernization Act regulations, Hazard Analysis Critical Control Point regulations, the Food Code, surveillance and inspection. Attachment 2 provides a summary of common challenges, practices and requirements related to the hand hygiene in food handling settings. The food industry follows these foundational guideposts for proactive and systematic approaches, implementing valid preventive interventions and technologies to protect consumers and workers from foodborne illness. Today, these programs include skin antiseptics and should continue this practice as a critical component of comprehensive and proactive food safety management and risk reduction.

II. The Clinical Benefit and Efficacy of Food Handler Antiseptic Drug Products

The framework for determining the efficacy of topical antimicrobial active ingredients (GRAE) used in food handler settings against bacteria should mirror the approach for health care topical antiseptic drug products, including both *in vitro* testing and *in vivo* clinical simulation studies. Further discussion of the points outlined can be found below and in Attachment 4.

Topical antiseptics in the food handling environment are intended to protect both workers handling food and consumers of food from exposure to potential pathogens resulting from the presence of contaminated food or infectious agents brought into the food worker's environment.

The hands of workers in a food handler environment are exposed to and colonized by pathogens that cause infections through contact with food entering and being stored in a facility. The extent of the contamination can be impacted by factors such as dermatitis, length of exposure and type of food handling activities.

ACI acknowledges that, similar to the healthcare environment, food handlers experience a wide array of situations where exposure to a variety of soils and infectious agents may occur. Like healthcare workers, food handlers follow infection prevention protocols designed to keep both workers and the food they handle, safe. ACI is aware the FDA may be interested in discussing whether the food handler monograph category could consist of more than one monograph and/or indication; we believe this should be established using a situational risk approach considering the following factors:

- A. **Pathogen variability:** Similar to the health care environment, food handlers may encounter different pathogens. In the 1994 Tentative Final Monograph for Health Care Topical Antiseptics, one portion of FDA's definition of topical antiseptics was that they must demonstrate broad-spectrum activity. Industry has generated a substantial amount of data in time kill and Minimum Inhibitory Concentration/Minimum Bactericidal Concentration (MIC/MBC) studies (Bioscience Laboratories, Inc. 2018a, 2018b; additional studies in-progress) which support describing topical antiseptics as broad-spectrum for bacterial pathogens.
- B. **Glove use:** Like health care infection prevention programs, many companies in the food supply chain have implemented the use of gloves as part of their infection prevention programs (King and Michaels 2019). There is significant variability in the implementation of glove use in food establishments. The types of gloves used from manufacturing/processing to retail food settings vary greatly and are not held to the same quality and performance standards as those used in health care settings. Additionally, there is increasing awareness that use of gloves may also create unique challenges in preventing foodborne illness due to lack of vigilance in engaging in hand hygiene, not changing gloves with adequate frequency, and failure to promptly identify holes in glove.

King and Michaels (2019) describe the need for antimicrobial hand hygiene products to clean and sanitize food handler hands in retail sales and foodservice and the role of gloves in these settings.

- C. **Soils and soil loading on professional food handler hands:** ACI is unaware of any comprehensive studies examining soil across the food industry. However, there are observations of soils in food handling settings that affect worker practices, as illustrated in King and Michaels (2019) for retail sales and foodservice settings. Recognizing that soils are present in food handler settings, it is worthwhile noting that health care workers also encounter numerous soils and the health care monograph does not have unique effectiveness testing requirements based on soil loading or soils encountered. Given the use of gloves in the food handler setting and the breadth and complexity of roles and responsibilities within the food handling setting it may be unclear in some settings what role soils may play. As such, 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 the effectiveness of food handler antiseptics.

FDA's OTC Drug Review for topical antiseptic indications in health care settings is based on a combination of *in vitro* studies to assess the spectrum of antibacterial activity and speed of kill, and pivotal clinical simulation studies based on *in vivo* surrogate endpoints. Substantial progress has been made in developing *in vitro* and *in vivo* data using methods advised by FDA that are directly applicable to or which could inform testing of antiseptics used in food handler products, as noted below. The following are key points ACI raises in support of this recommendation followed by elaborations on their implications for studies to substantiate the GRAE status of food handler antiseptics:

- Accepted test methods already exist for establishing the effectiveness of topical antiseptics which can be adapted as needed to food handler antiseptics (Attachments 3 and 4).
- Pivotal *in vitro* data utilizing test methods developed upon the advice of FDA are already available for antiseptics used in food handler products
 - The pivotal time kill and MIC/MBC studies ACI is sponsoring (Attachment 3) provide significant evidence of rapid broad spectrum germicidal activity of four antiseptic ingredients being sponsored by ACI, including against organisms relevant to food handler settings (i.e., 3-Log₁₀ or greater reductions for 100% of all tested microorganisms exposed to benzalkonium chloride [BAC], benzethonium chloride [BZT], and ethanol [EtOH] and 99% of all tested microorganisms exposed to chloroxylenol [PCMX]). The generated data provided to FDA should be used as support for the efficacy of antiseptic active ingredients used in food handler settings (Bioscience Laboratories, Inc. 2018a, 2018b; additional studies in-progress). Time Kill testing for povidone-iodine (PVP-I) is currently underway.
- *In vivo* clinical simulation studies are being applied to topical antiseptics. Attachment 4 elaborates the following points:
 - *In vivo* human clinical simulation studies are a valid and feasible way to determine efficacy for antiseptic ingredients. 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 need to be modified to specifically meet the needs for food handler settings. ACI is committed to working with FDA to define relevant design criteria.

- Controlled clinical outcome studies are not appropriate to establish GRAE status for food handler topical antiseptics. The inclusion of control treatments in such studies may raise ethical issues by incurring unnecessary risks to public health, as well as require impracticably large study populations (e.g., >361,000 study participants across 14,000 study sites) to yield statistically meaningful results due to the infeasibility of consistently controlling variables that affect food contamination (e.g., handling, storage and processing of the food; human behavior). Additionally, there is great complexity of the delivery and distribution of food within the farm-to-fork food chain as contamination may occur from a multitude of vectors; there would be significant challenges in identifying a single point of pathogen transfer (Attachment 4-1).
- Choice of microorganisms
 - Ideally, a test organism used in *in vivo* studies 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. Relevant food handler setting organisms that are currently listed in all/some of the referenced standardized test methods include: *E. coli*, *S. aureus*, and *S. flexneri*.
- Soil Load
 - As noted above, ACI acknowledges food handlers will encounter soils which may contact hands. We are not aware of data measuring quantity or types of soil that would constitute a real-world, relevant scenario for assessing the performance of topical antiseptics used in food handler settings. Additionally, we are not aware of comprehensive studies which have assessed how workers respond to heavy soil loading events (e.g., do workers wash more than once if hands are heavily soiled or do workers avoid these events by wearing gloves). There are not comprehensive studies which define a specific need for hand hygiene products to be active in the presence of these soils.
 - Health care workers also encounter a variety of potentially infectious soils in day-to-day activities. Health care workers and food handlers are trained professionals who should follow infection control and mitigation strategies. It should be noted that soils were not an issue of particular consideration for the health care monograph.

ACI recognizes that even with the applicable studies completed and underway additional information gaps may exist which preclude design of specific test methods and efficacy criteria for antiseptic actives used in food handler settings and, as such, ACI is committed to working in

collaboration with the FDA to address these scientific gaps prior to development of proposed GRAE requirements.

III. The Safety of Food Handler Antiseptic Drug Products

New data being generated to assess the human exposure and safe use of EtOH, BAC, BZT, PVP-I, and PCMX in consumer and health care antiseptic products will sufficiently support the long-term safety of the same ingredients used in food handler antiseptic products.

ACI and its members supplying antiseptic actives and formulating OTC antiseptic products are working to generate safety data on EtOH, BAC, BZT, PVP-I, and PCMX required for their determination of GRAS/E for consumer and health care applications (of washes and rubs) using protocols designed on the advice from FDA Center for Drug Evaluation and Research (FDA 2019b). This work, especially with respect to the monograph for health care antiseptic OTC products, provides a model for assessing the safety of the proposed active ingredients for food handler antiseptic products, and will generate the data needed to establish GRAS status.

These antiseptic actives are the same as proposed for use in food handler products. We expect the range of concentrations of these actives across products in the consumer and health care categories will overlap those anticipated for food handler products to a large extent and that new data being generated to support the safe use of EtOH, BAC, BZT, PVP-I, and PCMX in consumer and health care antiseptic products addressing human exposure (Maximal Use Trials; MUSt) will sufficiently support the long-term safety of food handler antiseptic products. While the frequency of use practices by food handlers are anticipated to be within the range of maximal uses observed in health care, confirming studies are underway (Attachment 5). The MUSt studies planned and underway will follow study protocols reviewed by and found acceptable to the FDA Center for Drug Evaluation and Research.

In addition, for active ingredients present in topical antiseptics used by food handling professionals, minimal quantities of active ingredient are expected to transfer to food. Surface transfer coefficient models (Durkin et al. 1995) exist for modeling transfer of pesticides to surfaces of agricultural goods. These calculations may be used to model the transfer rates from hand to food. In this way, these models can be used to assess the migration and dietary concentration of the active ingredients in food. We expect these levels to be below the threshold of regulation for substances used as indirect food additives in food contact articles (FDA 2018b).

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

Considering these factors and the safety data from the ongoing and contemplated MUSt studies, which are part of the GRAS data package being developed by ACI for other topical antiseptic monographs, ACI anticipates there will be sufficient data for assessing potential safety impact of residue transfer to food. Additional data development on transfer is not expected to be necessary.

ACI is unaware of any reports of antimicrobial resistance in real world food handler settings attributed to the use of food handler antiseptic drugs. With regard to EtOH (and PVP-I) specifically, FDA concluded in its final antiseptic consumer rubs (FDA 2019b) and health care

rules (FDA 2017b) that “sufficient data has been provided to assess the risk of antiseptic resistance and antibiotic cross-resistance.” For PVP-I, the agency has determined that resistance to PVP-I occurs infrequently in the laboratory setting while noting that “observations made in the laboratory setting are not necessarily replicated in the real world setting” and “Clinical studies assessing bacterial resistance to povidone-iodine were primarily negative” (FDA 2017b). The agency concluded there is sufficient information to determine that exposure to PVP-I does not lead to the development of bacterial resistance (FDA 2017b).

ACI is sponsoring a comprehensive literature review of pertinent research on antimicrobial resistance for the active ingredients BAC, BZT, and PCMX. FDA reviewed and accepted this approach as an initial step to assess the potential for antimicrobial resistance for these three active ingredients intended for use in consumer and health care antiseptic products (FDA 2015, 2017b). This literature review will be submitted to FDA. This same approach can be applied to food handler products. The assessment will address the impact of BAC, BZT, and PCMX, if any, on the development of bacterial resistance or decreased susceptibility. ACI anticipates the report will provide adequate data for the FDA to assess the potential for these ingredients to contribute to antimicrobial resistance through their use in food handler products.

In summary, no additional safety studies should be required to address the safety of antiseptic ingredients for food handler products, either in use or from indirect consumer exposure to antiseptic ingredients from food handler uses.

IV. Viruses

ACI recommends that the effectiveness of food handler antiseptics against viruses be recognized separately under the OTC monograph review process and that separate conditions establishing GRAE status for anti-viral antiseptics be investigated collaboratively with industry, while allowing monograph conditions for activity of food handler antiseptics against bacteria to proceed and be finalized.

Viruses are important microorganisms in food handling settings, as evidenced by the 51% of outbreaks in food handling settings that are attributed to viruses, primarily norovirus and hepatitis A (CDC 2016; CDC 2018; Fiore and Acheson 2004). FDA has not yet established requirements or methods for broad anti-viral claims under the OTC Drug Review process, and while the existence of infections due to viruses in the health care settings was acknowledged, the review focused on effectiveness against bacteria in the recent monographs. Specifically, FDA stated the following in a 2010 response (FDA 2010) to a Citizen Petition (ACI 2014) related to anti-viral indications for topical hand hygiene products:

“An evaluation of the effectiveness of OTC topical antimicrobial drug products for an antiviral indication has not been part of the OTC Drug Review.”...

“Since the publication of the Antimicrobial I Panel's recommendations in September 1974 (Federal Register 1974), two proposed rules for OTC topical antimicrobial products have been published. The first of these was published in January of 1978 (Federal Register 1978). Then, in June of 1994, an amended proposed rule was published (Federal Register 1994). Neither of these proposed rules addresses the effectiveness of OTC antiseptic active ingredients against viruses. All effectiveness determinations for the antiseptic active ingredients in these proposals are based on a demonstration of effectiveness against bacteria.”...

“However, we now recognize that viral pathogens are emerging as an important cause of nosocomial infection in health care facilities. Developing effectiveness standards for the demonstration of antiviral activity could be an important component of OTC drug development in the future.”

FDA did not mention viruses in either the health care antiseptics proposed or final rule (FDA 2015; 2017b). Thus, while data suggest that establishing a pathway towards acceptance of specific antiviral claims is relevant to foodborne illness risk reduction and potentially more manageable in design, and these claims may be more meaningful, these efforts should be accomplished separately in conjunction with industry so as to not delay review of efficacy and safety pertaining to an antibacterial monograph.

ACI has discussed pathways toward acceptance of general anti-viral claims with the FDA. While a significant effort would lie ahead to develop an understanding of the settings for viral infections in those environments, the food supply chain may provide a narrower scope because the majority of reports of viral infections leading to foodborne illness have been attributed to a very limited set of viruses (e.g. norovirus, hepatitis A). Nevertheless, testing would be needed to establish their GRAE status and should be considered separately.

That being said, the industry fully recognizes the significance of viral infections acquired through food handler settings and considers it an important, yet challenging, opportunity to develop topical products that could play a role in mitigating the public health risk associated with foodborne illnesses attributable to viruses. Recognizing that a monograph supporting anti-bacterial claims for food handler products could follow the frameworks put forward for previous monographs (e.g., monograph for health care antiseptic ingredients) leading to expeditious development of a food handler monograph for anti-bacterial indications, ACI recommends that FDA develop monograph conditions for acceptance of anti-viral claims as a separate indication, and not integrate requirements for anti-viral claims with requirements for anti-bacterial antiseptics. ACI would welcome a dialog with FDA on this point prior to development of proposed GRAE requirements for anti-viral products.

V. References

- Albright, J., B. White, D. Pedersen, P. Carlson, L. Yost and C. Littau. 2018. Use patterns and frequency of hand hygiene in health care facilities: Analysis of electronic surveillance data. *Am. J. of Infect. Control* 46: 1104 – 1109
- Allwood, P.B., T. Jenkins, C. Paulus, L. Johnson, C.W. Hedberg. 2004. Hand washing compliance among retail food establishment workers in Minnesota. *J. of Food Prot.* 67: 2825 – 2828.
- American Cleaning Institute/Personal Care Products Council (ACI/PCPC). 2014. Comments on Proposed Rule to the tentative final monograph for over-the- counter (OTC) antiseptic drug products for human use (Consumer Antiseptics), 78 Fed. Reg. 76,444. <https://www.cleaninginstitute.org/sites/default/files/assets/1/Page/ACI-PCPC-comments-to-FDA-06162014.pdf>
- American Cleaning Institute. 2019. American Cleaning Institute, Comment response on the Food Handler Antiseptic Drug Products for Over-the-Counter Human Use; Request for data and information Docket No. FDA-2018-N-3458
- American Society for Testing Materials (ASTM). 2013a. E1174-13, Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel Handwash Formulations, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E1174.htm>
- American Society for Testing Materials (ASTM). 2013b. ASTM E2946-13, Standard Test Method for Determining the Bacteria-Reducing Effectiveness of Food-Handler Handwash Formulations Using Hands of Adults, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E2946.htm>
- American Society for Testing Materials (ASTM). 2015a. ASTM E2755-15, Standard Test Method for Determining the Bacteria-Eliminating Effectiveness of Health care Personnel Hand Rub Formulations Using Hands of Adults, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E2755>.
- American Society for Testing Materials (ASTM). 2015b. ASTM E2784-10, Standard Test Method for Evaluation of the Effectiveness of Handwash Formulations Using the Paper Towel (Palmar) Method of Hand Contamination, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E2784>.
- American Society for Testing Materials (ASTM). 2016. Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure, E2783-11 <https://www.astm.org/Standards/E2783.htm>
- Bioscience Laboratories, Inc. 2018a. An In-Vitro Time-Kill Evaluation of Four Test Materials When Challenged with Various Bacterial and Yeast Species [BAC, BZT, PCMX, ethanol]. 26 February 2018. <https://www.regulations.gov/document?D=FDA-1975-N-0012-0736>

- Bioscience Laboratories, Inc. 2018b. Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Five Test Materials [BAC, BZT, PCMX, ethanol, PVP-I]. 12 November 2018. <Submission awaiting docket posting>
- Boyce, J.M., H.L. DuPont, J. Massaro, D. Sack, D.W. Schaffner. 2012. An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial handwash products. *Am. J. of Infect. Control* 40: 742 – 749.
- Bureau of Labor Statistics 2018. National Occupational Employment and Wage Estimates. Accessed 25 January 2020. United States https://www.bls.gov/oes/current/oes_nat.htm#35-0000.
- Bureau of Labor Statistics. 2019. Health Care Employment. Accessed 25 January 2020. <https://www.bls.gov/iag/tgs/iag62.htm>
- Centers for Disease Control (CDC) 2016. Foodborne disease surveillance data. Accessed 25 January 2020. https://www.cdc.gov/fdoss/pdf/2016_FoodBorneOutbreaks_508.pdf
- . 2017. Surveillance for Foodborne Disease Outbreaks: Annual Report. Atlanta, Georgia: U.S. Department of Health and Human Services. Accessed 04 February 2020. <https://www.cdc.gov/fdoss/annual-reports/2017-report-highlights.html>
- . 2018. Burden of Norovirus Illness in the U.S. Accessed 03 February 2020. <https://www.cdc.gov/norovirus/trends-outbreaks/burden-US.html>
- CDC NEARS [Centers for Disease Control & Prevention, National Environmental Assessment Reporting System (NEARS)]. 2019. Foodborne Illness Outbreaks at Retail Establishments- National Environmental Assessment Reporting System, 16 State and Local Health Departments, 2014-2016. MMWR 68(1):1-8. Surveillance Summary. Available at: <https://www.cdc.gov/mmwr/volumes/68/ss/ss6801a1.htm> Accessed 30 January 2020.
- Chen, Y., K.M. Jackson, F.P. Chea and D.A. Schaffner. 2001. Quantification and variability analysis of bacterial cross-contamination rates in common food service tasks. *J. Food Protect.* 64: 72 - 80.
- Clayton, D. A. and C.J. Griffith. 2004. Observation of food safety practices in catering using notational analysis. *Brit. Food J.* 106:211 - 227.
- Clinical and Laboratory Standards Institute. 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard Tenth Edition.
- Coppock, J. 1952. Analytical and pharmacological problems arising from the use of organic chemicals as processing aids and hygiene aids in the food industry. *J. Sci. Food and Agric.* 3: 115-122.
- do Prado, D.B., A.P. Bettoni, V.A. Correa, B.A. de Abreu Filho, L.B. Garcia, M.C.B. Tognim and C.L. Cardoso. 2015. Practice of hand hygiene in a university dining setting. *Food Control* 57: 35 – 40

- Durkin, P.R., L. Rubin, J. Withey, and W. Meylan. 1995. Methods of assessing dermal absorption with emphasis on uptake from contaminated vegetation. *Tox Ind Health*. 11 (1): 63-79.
- Fiore and Acheson. 2004. Hepatitis A transmitted by food. *Food Safety*. 38. 705-715.
- Fischler, G.E., J.L. Fuls, E.W. Dail, M.H. Duran, N.D. Rodgers and A.L. Waggoner. 2007. Effect of hand wash agents on controlling the transmission of pathogenic bacteria from hands to food. *J. Food Protect.* 70: 2873 – 2877.
- Green, L.R., C.A. Selman, V. Radke, D. Ripley, J.C. Mack, D.W. Reimann, T. Stigger, M. Motsinger, and L. Bushnell. 2006. Food worker hand washing practices: An observation study. *J. Food Protect.* 69: 2417 -2423.
- King, H. and Michaels, B. 2019. The Need for a Glove-Use Management System in Retail Foodservice. *Food Safety Magazine*. <https://www.foodsafetymagazine.com/magazine-archive1/junejuly-2019/the-need-for-a-glove-use-management-system-in-retail-foodservice/>
- Scallan, E., R. M. Hoekstra, F.J. Angulo, R.V. Tauxe, M. Widdowson, S.L. Roy, J.L. Jones, and P.M. Griffin. 2011. Foodborne Illness Acquired in the United States—Major Pathogens. *Emerg. Infect. Dis.* 17(1), 7-15.
- Schaffner, D.W., J.P. Bowman, D.J. English, G.E. Fischler, J.L. Fuls, J.F. Krowka, and F.H. Kruszewski. 2014. Quantitative microbial risk assessment of antimicrobial hand hygiene products on risk of Shigellosis. *J. Food Protect.* 77:574 – 582.
- Strohbehn, C., J. Sneed, P. Paez and J. Meyer. 2008. Hand washing frequencies and procedures used in retail food service. *J. Food Protect.* 71: 1641 - 1650.
- United States Census Bureau. 2018. Household population 2014 – 2018. Accessed 25 January 2020. <https://www.census.gov/quickfacts/fact/table/US/HSD410218>
- United States Department of Agriculture (USDA). 1979. List of Chemical Compounds Authorized for Use under USDA inspection and Grading Programs. Miscellaneous Publication Number 1373. Accessed 25 January 2020. https://archive.org/details/listofchemicalco1373unit_3
- . 2018. America’s Eating Habits: Food Away from Home. Accessed 25 January 2020. <https://www.ers.usda.gov/webdocs/publications/90228/eib-196.pdf>
- . 2019. Cost Estimates of Foodborne Illnesses. Accessed 25 January 2020. <https://www.ers.usda.gov/data-products/cost-estimates-of-foodborne-illnesses.aspx>
- United States Environmental Protection Agency (EPA). 2006. Reregistration Eligibility Decision on Iodine and Iodophor Complexes. EPA-HO-OPP-2006-0599. Accessed 25 January 2020. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_G-90_27-Jul-06.pdf

- . 2012. Product Performance Test Guidelines OCSPP 810.2300: Sanitizers for Use on Hard Surfaces – Efficacy Data Recommendations. EPA 712-C-07-091. January 2012. <https://nepis.epa.gov/Exe/ZyPDF.cgi/P100IJAU.PDF?Dockkey=P100IJAU.PDF>
- United States Food and Drug Administration (US FDA). 1972. National Archives and Records Administration. Federal Register: 37 FR 195. Accessed 25 January 2020. www.loc.gov/item/fr037004
- . 1974. Proposal to Establish a Monograph for Over-the-Counter Topical Antimicrobial Products. National Archives and Records Administration. 39 FR 33103. Accessed 30 January 2020. <https://www.loc.gov/item/fr039179/>
- . 1978. Over-the-Counter Drugs Generally Recognized as Safe, Effective, and Not Misbranded. National Archives and Records Administration. 43 FR 1210. Accessed 30 January 2020. <https://www.loc.gov/item/fr043004/>
- . 1994. Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products. National Archives and Records Administration. 59 FR 31402. Accessed 25 January 2020. <https://www.govinfo.gov/app/details/FR-1994-06-17/94-14503/summary>
- . 2010. Letter to The Soap and Detergent Association (now the American Cleaning Institute) and the Personal Care Products Council. March.
- . 2011. Food Safety Modernization Act. Periodical Retrieved from <https://www.govinfo.gov/content/pkg/PLAW-111publ353/pdf/PLAW-111publ353.pdf>
- . 2015. 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. 80 FR 25165. Accessed 30 January 2020. <https://www.federalregister.gov/documents/2015/05/01/2015-10174/safety-and-effectiveness-of-health-care-antiseptics-topical-antimicrobial-drug-products-for>
- . 2017a. United States Food Code. Accessed 30 January 2020. <https://www.fda.gov/media/110822/download>
- . 2017b. Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use. 82 FR 60474. Accessed 30 January 2020. <https://www.federalregister.gov/documents/2017/12/20/2017-27317/safety-and-effectiveness-of-health-care-antiseptics-topical-antimicrobial-drug-products-for>
- . 2017c. Risk Profile: Pathogens and Filth in Spices. Center for Food Safety and Applied Nutrition. <https://www.fda.gov/media/108126/download>
- . 2018a. Docket No. FDA–2018–N–3458, Food Handler Antiseptic Drug Products for Over-the-Counter Human Use; Request for Data and Information. 83 FR 63168. Accessed 5 February 2020. <https://www.federalregister.gov/documents/2018/12/07/2018-26561/food-handler-antiseptic-drug-products-for-over-the-counter-human-use-request-for-data-and>

- . 2018b. Threshold of regulation for substances used in food-contact articles. 21 C.F.R. 170.39. Accessed 25 January 2020. https://www.ecfr.gov/cgi-bin/text-idx?SID=4f9481dc0dcea1ce37a7dd56e8202d14&mc=true&node=pt21.3.170&rgn=div5#se21.3.170_139.
- . 2019a. Current Good Manufacturing Practice, Hazard Analysis, and Risk-based Preventive Controls for Human Food. Subpart B - Current Good Manufacturing Practice. 21 CFR Vol. 117. No. 10. Accessed 30 January 2020. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=117>
- . 2019b. Safety and Effectiveness of Consumer Antiseptic Rubs: Topical Antimicrobial Drug Products for Over-the-Counter Human Use. 84 FR 14847. Accessed 25 January 2020. <https://www.federalregister.gov/documents/2019/04/12/2019-06791/safety-and-effectiveness-of-consumer-antiseptic-rubs-topical-antimicrobial-drug-products-for>
- . 2020. Docket No. FDA–2020–N–0418, Nonprescription Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments. 85 FR 6565. Accessed 5 February 2020. <https://www.federalregister.gov/documents/2020/02/05/2020-02244/nonprescription-drugs-advisory-committee-notice-of-meeting-establishment-of-a-public-docket-request>
- York, V.K., L.A. Brannnon, C.W. Shanklin, K.R. Roberts, B.B. Barrett, and A.D. Howells. 2009. Intervention improves restaurant employees' food safety compliance rates. *Intl J of Contemp Hosp Manag*. 21: 459 – 478

VI. List of Attachments

- **Attachment 1:** Historical Use of Antibacterial Active Ingredients in Food Handler Hand Hygiene Products and FDA, USDA, and NSF Oversight
 - *Attachment 1-1:* Historical Advertisements
 - *Attachment 1-2:* `Labels extracted from Book III OTC Vol. 230001 of FDA Docket 75N-183H
- **Attachment 2:** Challenges, Practices and Requirements Related to Hand Hygiene in Food Handling Settings
- **Attachment 3:** *In vitro* Testing
- **Attachment 4:** *In vivo* Testing
 - *Attachment 4-1:* Topical Food Handler Antiseptic Drug Products: Clinical Study Consideration
- **Attachment 5:** Studies of the Frequency of Use of Food Handler Products

Attachment 1: Historical Use of Antibacterial Active Ingredients in Food Handler Hand Hygiene Products and FDA, USDA, and NSF Oversight

In January 1972, before the inception of the over-the-counter (OTC) drug review, the United States Food and Drug Administration (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” (FDA 1972). In this notice, FDA specifically identified “food handlers” as among those who “may benefit from the antibacterial action of these products” (FDA 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 use of antiseptics for food handler use has been clear from the beginning of the OTC drug review process.

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” (FDA 1994). In fact, in the 1994 tentative final monograph for antiseptic drugs (FDA 1994), 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.

In the 1994 preamble to the tentative final monograph for health care antiseptic drug products (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. Until 1998, the USDA Compounds and Packaging Branch annually published a list of hand sanitizing compounds 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 hand washing and hand sanitizing compounds categories that align with antiseptic drug products (USDA 1979). These hand wash products were intended “for use in slaughtering and processing plants operating under the USDA Poultry, Meat, Rabbit, Shell Egg Grading and Egg Products Inspection Programs” and thus 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 the products.

American Cleaning Institute (ACI) members have determined 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.

In addition to the information from USDA, there are currently over 160 products listed by the National Sanitation Foundation (NSF International) with either “handwashing and sanitizing compound” or “hand sanitizing compound” certifications (NSF 2020). 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.

Further, ACI has identified a number of advertisements for food handler products dating back prior to 1972 (Attachment 1-1) and a journal publication from 1952. 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 “washrooms,” “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.

In addition, labels for historical products that had been purportedly used in food handler settings are presented in Attachment 1-2.

ACI expects that it may be difficult to establish use in food handling settings prior to 1972 based on product labels specifying use for food handling purposes (US FDA 2018a) given the passage of time and the resulting loss of records prior to 1972. It would be unreasonable for FDA to require, as a condition of monograph eligibility, the submission of labeling specific to food handler use in light of the absence of labeling records prior to 1972 and the aforementioned references to antiseptic food handler products under FDA, USDA and NSF programs, as well as manufacturers’ experiences regarding the use of their antiseptic products by food handlers. It should be sufficient for determining monograph eligibility by showing that the ingredients were intended for antiseptic use broad enough to cover food handling, rather than requiring food handler specific labeling be demonstrated prior to 1972.

References

- Coppock, J. 1952. Analytical and pharmacological problems arising from the use of organic chemicals as processing aids and hygiene aids in the food industry. *J. Sci. Food and Agric.* 3: 115-122.
- NSF International. 2020. NSF the White Book™ - Nonfood Compounds Listing Directory. Accessed 04 February 2020. <http://info.nsf.org/USDA/psnclistings.asp>
- United States Department of Agriculture (USDA). 1979. List of Chemical Compounds Authorized for Use under USDA inspection and Grading Programs. Miscellaneous Publication Number 1373. Accessed 25 January 2020. https://archive.org/details/listofchemicalco1373unit_3
- United States Food and Drug Administration (US FDA). 1972. National Archives and Records Administration. Federal Register: 37 FR 195. Accessed 25 January 2020. www.loc.gov/item/fr037004
- . 1994. Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products. National Archives and Records Administration. 59 FR 31402. Accessed 25 January 2020. <https://www.govinfo.gov/app/details/FR-1994-06-17/94-14503/summary>

———. 2018. Docket No. FDA–2018–N–3458, Food Handler Antiseptic Drug Products for Over-the-Counter Human Use; Request for Data and Information, Federal Register, Vol. 83, No. 235, December.

Attachment 1-1: Historical Advertisements

Attachment 1-1: Historical Advertisements

Food Industries (1949)



Laboratory Tested and Controlled

TO DO A BETTER SANITIZING JOB EVERY TIME

The ORIGINAL Quaternary Ammonium Germicide



243189R

This Control No. Guarantees POTENCY UNIFORMITY QUALITY

Insist on getting only GENUINE Roccal BRAND SANITIZING AGENT

USES IN FOOD INDUSTRY

To Sanitize:

- STORAGE BINS
- FREEZING UNITS
- REFRIGERATORS
- CONVEYORS
- TANKS
- PROCESSING EQUIPMENT
- PACKAGING EQUIPMENT
- TRUCKS
- WALLS AND FLOORS
- WASH ROOMS
- AND AS A HAND RINSE FOR HELP

In the Food Industry, the importance of using only the best in sanitizing methods cannot be over-emphasized. In Roccal, the original quaternary ammonium germicide, the food industry is offered a sanitizing agent that is laboratory controlled and tested. The uniform quality of Roccal means uniformly good results in doing a proper sanitizing job.

Roccal is a powerful germ-killer. In recommended dilutions, it is non-poisonous, virtually odorless and tasteless. It is non-irritating to the skin and no more corrosive than plain water.

Roccal can be used for every sanitizing job in processing and packaging in the following food industries: milk, cream, ice cream, butter, cheese, egg breaking, sugar, fish, poultry, fresh frozen vegetables and fruits, meat products, cereal products, candy and beverage, wherever the product comes in contact with equipment. Also to keep walls and floors sanitary.

Start using Roccal today—you'll find that better sanitation is good business.

Fortify all your milk with DELTAXIN® — The purest known form of Vitamin D₂

SPECIAL MARKETS—INDUSTRIAL DIVISION

Winthrop-Stearns, INC.

179 VARICK STREET, NEW YORK 13, N. Y., Dept. W-99

174 (Vol. p. 1326)

tion IV of the Federal Catalog is a publication revised to Jan. 1, 1949. It contains the following: 1. United States Standards (including \$1.50 (subscription supplements). 2. Index of Specifications. 3. Index of Specifications. Navy Department, 1949 (Revised to NAVSANDA Publications for copies direct Bureau of Supplies, Navy Department, D. C. This index.

MAKING AMERICAN OF UNIFORMITY (by PASTEURIZED MILK, et al. Bureau of BDIM-Inf-73. Micro-densed summary of laboratory procedure from through packaging of

DRIED ICE-CREAM H. Williams and Bureau of Dairy Inf-74. Mimeographed summary of the type formulas and type

DIRECTIONS FOR TITRATION SIZE OF APPROPRIATE SPRAYS. By J. E. of Entomology and ET-267. Mimeographed of methods of experiment.

DEVELOPING & SELLING By Gustav E. Lorne Commerce. Price 25¢ book for manufacturers "reduce the risk in development and sale of

MARKET DISCOUNTS BY RETAILERS-POULTRY, et al. Department of Miscellaneous Publications eographed.

PRICE PROBLEMS OF THE SECTOR OF AGRICULTURE by H. W. Henderson Agriculture. Price 25¢ an analysis of problems of methods in

The above documents the prices indicated by the Department of Agriculture, Printing Office, Washington. When no price is indicated, the price is free and the price is from the Bureau of issue.

WH
for C

If your steam k
steam kept in int
from air, you are
every hour.
Worse yet, you
rejects, if your eq

AUTOS

PLASTICS

GREENHOUSE

SA
SAVES
IMPRO
FOOD INDUSTRI

Journal of Milk and Food Technology (1949)

JOURNAL of MILK and FOOD TECHNOLOGY
(including MILK AND FOOD SANITATION)
Official Publication of the
International Association of Milk and Food Sanitarians, Inc.
(Association Organized 1911)
Designated Official Organ of Other Dairy Products Organizations

Office of Publication 374 Broadway, Albany, N. Y.
Entered as second class matter at the Post Office at Albany, N. Y., March 4, 1942, under the Act of March 3, 1879.
Published bimonthly beginning with the January number.
Subscription rate, \$2.00 per volume. Single copy, 50 cents.

(For complete Journal Information, see page 56)

Volume 12 January-February Number 1

CONTENTS

	Page No.
Editorials	
Message of the President.....	1
Biography of Abraham Wallerstein Fuchs.....	2
Facts Versus Opinions.....	3
Sympathetic Consideration to "Milk and Food Sanitation: One Field, One Organization".....	4
Missouri Association of Milk and Food Sanitarians.....	4
Merit and Shortcomings of Various Procedures for Making Sediment Tests—A. G. Weckel.....	5
The Use of Patent Information by Sanitarians—A. Appleby.....	9
Sanitary Standards Covering Homogenizers and High Pressure Pumps of the Plunger Type.....	11
Quaternaries Vs. Chlorine in Bacteria Control—E. M. Foster.....	13
Progress Report of the Committee on Professional Status of Sanitarians of the International Association of Milk and Food Sanitarians—H. B. Robinson, <i>Chairman</i>	19
New Approach to Food-Handler Training—J. L. Rowland and J. H. Fritz.....	23
Homogenized Milk—Chart Showing Percentage Difference in Fat Between Top Portion of Milk and Remainder After Forty-eight Hours Storage—E. Kaplan.....	31
Quality Control in the Milk Industry—H. F. Judkins.....	34
Sanitary Technology in the Ice Cream Industry—F. E. Uetz.....	41
Grading Milk with the Resazurin Test—N. S. Golding.....	48
The Qualifications of a Quality Fieldman—F. M. Birch.....	52
New Books and Other Publications.....	54
Information Concerning Journal of Milk and Food Technology.....	56
Affiliates of International Association of Milk and Food Sanitarians, Inc.....	57
Association News.....	58
Industrial Notes.....	62
Fieldmen's Conference at University of Wisconsin.....	63
New Members.....	64
Index to Advertisers.....	XII

Copyright, 1949, International Association of Milk and Food Sanitarians

337826

ADVERTISEMENTS VII

Insist on—

GENUINE Roccoal

BRAND

THE ORIGINAL Quaternary Ammonium Germicide

SANITIZING AGENT

TO DO A BETTER SANITIZING JOB EVERY TIME

Laboratory tested and Controlled

243189R
This Control No. Guarantees
**POTENCY
UNIFORMITY
QUALITY**

In the Dairy Industry, more than any other industry, the importance of using only the best in sanitizing methods cannot be over-emphasized.

In Roccoal, the original quaternary ammonium germicide, the dairy industry is offered a product that is laboratory controlled and tested. The uniform quality of Roccoal means uniformly good results in doing a proper sanitizing job.

Roccoal is a powerful germ-killer. In recommended dilutions, it is non-poisonous, virtually odorless and tasteless. It is non-irritating to the skin and no more corrosive to equipment than plain water.

In the dairy, Roccoal can be used for every sanitizing job. For tank trucks, weigh tanks, pasteurizers, separators, bottle filling and capping machines, to keep walls and floors sanitary.

Try Roccoal for just one week and watch your bacteria counts go down... down... down!

Write us for new booklet describing Roccoal's uses in the dairy plant and on the producing farm.

USES IN DAIRY INDUSTRY

To Sanitize:

- MILKING MACHINES
- TEAT CUPS
- COOLING TANKS
- TANK TRUCKS
- MILK CANS
- WEIGH TANKS
- PASTEURIZERS
- SEPARATORS
- BOTTLE FILLING MACHINES
- AND AS HAND and TEAT WASH

SPECIAL MARKETS INDUSTRIAL DIV.
Winthrop Stearns Inc.
170 VARICK ST. N. Y. 13, N. Y. DEPT. F-19

Fortify all your milk with **DELTAXIN**® The purest known form of Vitamin D₂

When writing to advertisers, say you saw it in this Journal

American Journal of Public Health (1953)

American Journal of Public Health and THE NATION'S HEALTH	
Official Monthly Publication of the American Public Health Association, Inc.	
Volume 43	November, 1953
CONTENTS	
Hygeia: Service with Spirit and Ideals	Wilton L. Halverson, M.D., Dr.P.H.
Principles of Immunization as Applied to Poliomyelitis and Influenza	Jonas E. Salk, M.D.
Prediction and Possible Prevention of Coronary Disease	Ancel Keys, Ph.D.
Local Health Hazards Among U. S. Army Troops Returning from Korea	George W. Hunter, III, Colonel, MSC
Mounting Incidence of Psittacosis	M. Michael Sigel, Ph.D., L. S. Cole, and O. Hunter
Animal Diseases Transmissible to Man	Oscar Sussman, D.V.M., M.P.H.
Continued on page vi	
Expressions of opinion and statements of supposed facts are published on authority of the writer and whose name they appear. These are not to be regarded as expressing the views of the American Public Health Association, Inc., unless formally adopted by vote of the Association.	
Contents of previous issues of the American Journal of Public Health and The Nation's Health can be found by consulting the International Index in your Library.	
Published by the American Public Health Association, Inc., at 374 Broadway, Albany 7, N. Y. Executive Office, 1790 Broadway at 58th St., New York 19, N. Y.	
NOTICE:—Subscription \$10.00 per year for United States, Cuba and Mexico, South and Central America \$10.50 for Canada; and \$11.00 for other countries. Single copies \$1.00 postpaid.	
Copyright, 1953, by American Public Health Association, Inc.	
Address correspondence regarding editorial contents and manuscripts to C.-E. A. Winslow, Editor, 1790 Broadway, New York 19, N. Y.	
Address correspondence regarding subscriptions, advertising, reprints, etc., to American Public Health Association, Inc., 374 Broadway, Albany 7, N. Y., or 1790 Broadway at 58th St., New York 19, N. Y.	
Entered as second-class matter at the Post Office at Albany, N. Y., September 17, 1932, under the Act of March 3, 1879.	
Acceptance for mailing at the special rate of postage provided for in Section 1103, Act of October 3, 1917.	

Roccal

SANITIZING AGENT

Measures up in every way as the quaternary of choice

The sanitizing properties of quaternary ammonium compounds are so well known to public health officials that little could be said about them that you do not know. Almost everybody in public health work has added the "quats" to the armamentarium he uses in his war on disease.


The question then is, "Which 'quat'?" Are they all alike? Which one can I depend on to do the job expected of it every time?

In Roccal, the original quaternary ammonium germicide, you are offered a product that is always uniform in quality because it is made under the most rigid controls. Every batch must pass the comprehensive laboratory tests of one of the world's leading pharmaceutical manufacturers. You can depend on Roccal to do a better sanitizing job every time!

When you specify a "Quat" be sure it's Genuine Roccal

In recommended dilutions Roccal is:

- ✓ POTENT
- ✓ NON-POISONOUS
- ✓ TASTELESS
- ✓ ODORLESS
- ✓ STAINLESS
- ✓ NON-IRRITATING
- ✓ NON-CORROSIVE
- ✓ STABLE



Insist on Genuine Roccal

SANITIZING AGENT

Sterwin Chemicals, Inc.
SUBSIDIARY OF STERLING DRUG INC.
1450 Broadway, New York 18, N. Y.

11

A.J.P.H., JUNE 1954



GENUINE
Roccoal
SANITIZING AGENT

TO DO A BETTER
SANITIZING JOB EVERY TIME

**LABORATORY TESTED
AND CONTROLLED**

S112KB
This Control No. Guarantees
POTENCY • UNIFORMITY • QUALITY

The sanitizing properties of quaternary ammonium compounds are so well known to public health officials that little could be said about them that you do not know. Almost everybody in public health work has added the "quats" to the armamentarium he uses in his war on disease.

The question then, is which "quat"? Are they all alike? Which one can I depend on to do the job expected of it every time?

In Roccoal, the original quaternary ammonium germicide, you are offered a product that is always uniform in quality because it is made under the most rigid controls. Every batch must pass the comprehensive laboratory tests of one of the world's leading pharmaceutical manufacturers. You can depend on Roccoal to do a better sanitizing job every time!

**When you specify a "quat"
BE SURE IT'S GENUINE ROCCAL**

Sterwin Chemicals, Inc.
Subsidiary of Sterling Drug Inc.
1450 Broadway,
New York 18, N. Y.

Offices in Principal Cities
Throughout The U.S.A.

AUGUST 1954, A.J.P.H.

XVII



Roccoal
SANITIZING AGENT

**Measures up in every way as
the quaternary of choice**

1. POTENT
2. NON-POISONOUS
3. TASTELESS
4. ODORLESS
5. STAINLESS
6. NON-IRRITATING
7. NON-CORROSIVE
8. STABLE

The sanitizing properties of quaternary ammonium compounds are so well known to public health officials that little could be said about them that you do not know. Almost everybody in public health work has added the "quats" to his armamentarium in the war on disease.

The question then is, "Which 'quat'?" Which one can I depend on to do the job expected of it every time?

Roccoal, the original quaternary ammonium germicide, is always uniform in quality because it is made under the most rigid controls. Every batch must pass the comprehensive laboratory tests of one of the world's leading pharmaceutical manufacturers. You can depend on Roccoal to do a better sanitizing job every time!

**When you specify a "Quat"
BE SURE IT'S
GENUINE ROCCAL**

Sterwin Chemicals, Inc.
Subsidiary of Sterling Drug Inc.
1450 Broadway, New York 18, N. Y.

Offices in principal
cities throughout
the United States

**Attachment 1-2: Labels extracted from Book III OTC Vol. 230001 of FDA
Docket 75N-183H**

Labeling DuraPrep

New Ref. 8

8630

3M

NDC 17518-011-01

DURA PREP SURGICAL SOLUTION

IODOPHOR (0.5%
AVAILABLE IODINE),
ISOPROPYL ALCOHOL
(70% W/W),
24 ML SELF-DISINFECTING
SOLUTION

*Long
lasting
antimicrobial
film*

WARNINGS/DIRECTIONS
FOR USE ON INSIDE

STERILE CONTENTS:

- 1 Applicator
- 2 Cotton-Tipped Swabs
- 1 Hospital Wrap

Sterility of sterile contents guaranteed unless envelope is damaged or open.

Store below 74°F

Made in U.S.A. by
Medical-Surgical Products
3M Health Care
St. Paul, MN 55144-1000

Package Insert

DURAPREP[™] SURGICAL SOLUTION

DESCRIPTION: DuraPrep surgical solution (0.5% available iodine, isopropyl alcohol 70% w/w) is a film-forming iodophor complex. The DuraPrep kit includes a bottle containing 24 ml of DuraPrep surgical solution, a sponge applicator head and two swabs within a hospital wrap.

INDICATIONS: DuraPrep surgical solution is indicated for topical use as a long-lasting preoperative skin preparation with fast, broad spectrum antimicrobial activity.

WARNINGS: DuraPrep surgical solution contains alcohol which is flammable. Until dry, do not use around spark or flame (i.e., electrocautery). Use in well-ventilated area. Do not use in or near eyes. Isopropyl alcohol is a moderate eye irritant. If product gets into eyes, flush immediately with water. For external use only.

PRECAUTIONS: Avoid using in ears or on mucous membranes. Not recommended for use on patients with known sensitivity to iodine. Not recommended for use on infants of less than one year of age. For professional use only.

DIRECTIONS FOR USE

PRIOR TO PROCEDURE: When hair removal is necessary, the preferred procedure is to use a surgical clipper on the morning of the surgery. If a wet shave is used, be sure to thoroughly remove all soap residue. DuraPrep surgical solution should be applied to clean, dry, residue-free intact skin.

PROCEDURE:

- 1.) Place kit on table and upon hospital wrap.
- 2.) Remove screw cap on bottle of DuraPrep surgical solution but do not remove foil top. DuraPrep surgical solution is water insoluble, therefore avoid contact with reusable items (i.e., basins, instruments).
- 3.) To assemble, hold the applicator with the sponge head up and screw foil-topped bottle into applicator, thus rupturing foil.
- 4.) Invert applicator. With sponge head down, prep will flow into sponge.
- 5.) Clean umbilicus with swabs when applicable (moisten swabs by pressing against prep-soaked sponge applicator).
- 6.) Use sponge applicator to paint operative site. Begin when fluid level reaches indicator line on the applicator barrel. If is not necessary to scrub. (Simply paint a single uniform application.)
- 7.) If pooling occurs, immediately blot with sponge applicator and continue to apply a uniform application.
- 8.) Once a uniform coating is applied, allow DuraPrep surgical solution to dry thoroughly (approximately 2-3 minutes) before incision or use of electrocautery. Use gauze flat to wick any pooling (i.e., umbilicus); do not blot the entire prepped operative site with a towel.

AFTER DURAPREP SOLUTION IS DRY:

- If incise drapes are used, apply directly to dry prep. On completion of surgical procedure, removal of incise drape will remove DuraPrep film.
- Normally DuraPrep solution is left on the skin and gradually wears away over several days. Depending on skin type and level of patient activity, it may last longer.
- If desired, prep can be removed with alcohol-saturated gauze flats.

PATIENT TAKE HOME INSTRUCTIONS

Regarding your antimicrobial (bacteria-killing) pre-operative skin preparation:

Your surgeon used DuraPrep[™] surgical solution because it is a fast-acting, long-lasting antimicrobial preparation which effectively kills bacteria and can reduce anesthesia time.

After the surgical procedure, it is recommended that DuraPrep solution remain on the skin as it continues to kill bacteria for up to 12 hours. DuraPrep solution gradually wears away over several days.

If removal is required: soak gauze with 70% Isopropyl alcohol and place on surgical site for at least 40 seconds. Lightly scrub to remove solution.

3M-7030 3470 1

Solution, U.S. Patent # 3,884,192

©3M, 1981

Made in U.S.A. 60

Medical-Surgical Products
3M Health Care

11-0001 04/81 101 100



Package Insert



HAN SAN I
SANITIZING HAND CLEANER
With Patented Free Iodine Technology

Authorized by USDA for use in federally inspected
meat and poultry plants

KEEP OUT OF THE REACH OF CHILDREN
CAUTION

If eye contact occurs, flush eyes with plenty of
water. If ingested, call a physician immediately.

Avoid prolonged storage above 90°F.
SOLD BY

► ECCO CHEMICALS INC. ► 8505 Directors Row ► Dallas, TX 75247 ►

FOR INDUSTRIAL AND INSTITUTIONAL USE ONLY

HAN SAN I is a superior hand washing and sanitizing compound for use in food processing plants, food handling establishments, veterinary clinics and animal handling facilities. This iodine based hand cleaner effectively kills germs and bacteria on contact. Its pH balanced formula contains cosmetic grade detergents and foam stabilizers which generate a thick, luxurious lather. Han San I contains no added fragrances, colors or phosphates. Routine use of Han San I prior to handling food or food processing equipment, and before and after handling animals, will reduce bacterial contamination on hands.

DIRECTION FOR USE:

Hand Washing and Sanitizing

Apply a generous amount of Han San I to hands. Lather hands and arms, thoroughly cleaning between fingers, around cuticles and under finger nails. Rinse with water. Repeat if necessary.

NET CONTENTS:

GAL.

LOT NO.

EXPIRATION DATE:

➤ ECCO CHEMICALS INC. ➤ 8505 Directors Row ➤ Dallas, TX 75247 ➤

KLENZ GEL BLU

**ONE-STEP HAND CLEANER / SANITIZER
FOR INDUSTRIAL USE ONLY**

USDA E-2 AUTHORIZED

AUTHORIZED BY U.S.D.A. FOR USE IN FEDERALLY
INSPECTED MEAT AND POULTRY PLANTS

KEEP OUT OF REACH OF CHILDREN

CAUTION:

Avoid contact with eyes. In case of eye contact, flush eyes thoroughly. If irritation develops, get medical attention.

KLENZ GEL BLU is a mild cleansing lotion combined with active antimicrobial ingredients which are direct food additives. It cleans and sanitizes in one step. KLENZ GEL BLU incorporates many of the same ingredients found in facial cleansers and moisturizers, to assure a safe product which is gentle to your hands.

Manufactured by
Kenside, Division of ECOLAB INC.
Ecolab Center, St. Paul, MN 55102

USE DIRECTIONS:

Wet hands, apply generous amount of KLENZ GEL BLU. Lather and scrub in a normal manner. Rinse thoroughly.

Use KLENZ GEL BLU when hands become soiled, when entering processing area, or when returning from a break or the lavatory.

This product is authorized by the USDA as an E-2 hand washing and sanitizing compound. It must be dispensed a sufficient distance from the processing line to prevent accidental product contamination. Hands need not be washed prior to using KLENZ GEL BLU. After use, hands must be rinsed well with potable water.

NET CONTENTS:

E-2

**HAND-CLEAN
PRODUCTS**

E - 2 SANITIZING HAND SOAP

**ONE-STEP
ANTIBACTERIAL HANDWASHING AND SANITIZING COMPOUND**

Authorized for Use Under USDA Poultry
and Meat Inspection Programs

Recommended for use by food plant personnel prior to
handling food or food processing equipment.

CAUTION:

Keep Out of Reach of Children. See side panel for additional
precautionary statements.

NET CONTENTS: 128 FL OZ (1 Gal)

HAND-CLEAN PRODUCTS, INC.

301 SWING ROAD - P.O. BOX 988
GREENSBORO, N.C. 27402

DIRECTIONS FOR USE

Meat, Food Plants and Restaurants

E-2 Sanitizing Hand Soap is an effective sanitizing hand soap which
has been authorized by USDA for use in federally inspected meat
and poultry processing plants. It is also recommended for use in
food processing plants and restaurants by personnel prior to
handling food and/or food processing equipment.

This formulation effectively reduces bacterial flora of the skin.
Hands need not be washed prior to using this product. For one-
step hand washing and sanitizing, place approximately 5cc in palm
of hand, add 15cc of water, lather and wash in normal manner.
After use, hands must be thoroughly rinse with potable water.
Repeat whenever re-entering production area. This product must
be dispensed from an adequate dispenser located a sufficient
distance from the processing line to prevent accidental production
contamination.

CAUTION:

Do not get in eyes. Harmful if swallowed. Avoid contamination of
food. Remove and wash contaminated clothing.

In case of contact, immediately flush eyes, call a physician.
Remove and wash all contaminated clothing before reuse. If
swallowed, drink egg whites or gelatin solution, or if these are not
available, drink large quantities of water. Call a physician.

**DO NOT CONTAMINATE WATER, FOOD, OR FEED BY STORAGE
AND DISPOSAL.**

KEEP OUT OF REACH OF CHILDREN

17-2

DIRECTIONS:

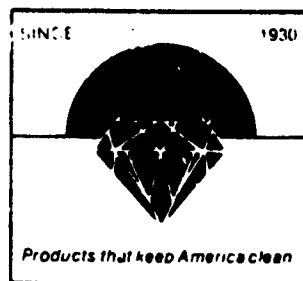
HANDI-KLEEN is an effective sanitizing soap. It is recommended for use in food processing plants and restaurants by personnel prior to handling food and/or food processing equipment.

This formulation effectively reduces bacterial flora of the skin. Hands need not be washed prior to using this product.

For one step hand washing and sanitizing, place approximately 5cc in palm of hand, add 15cc of water, lather and wash in normal manner. After use, hands must be thoroughly rinsed with potable



HANDI-KLEEN



**DIAMOND
CHEMICAL
COMPANY
INC.** Page & Schuyler Avenue
Lyndhurst, N.J. 07071

CAUTION

Do not get in eyes. Harmful if swallowed.
Avoid contamination of food.
Remove and wash contaminated clothing.

In case of contact, immediately flush eyes, call a physician.
Remove and wash all contaminated clothing before use.
If swallowed, drink egg whites or gelatin solution, or
if not available, drink large quantities of water.
Call a physician.

DO NOT CONTAMINATE WATER, FOOD, OR FEE
STORAGE AND DISPOSAL

KEEP OUT OF REACH OF CHILDREN

NET CONTENTS:

15-15-15

EXPOSURE

This product is an irritant. Ingestion may cause nausea, vomiting, and diarrhea.

SAFETY C.UTION

Refer to M.S.D.S. for additional safety information.

FIRST AID STATEMENTS

Inhalation: Move to fresh air. Consult physician if symptoms persist. Skin: Rinse with water. Eyes: Flush eyes with large quantities of water for 15 minutes, lifting the eyelids occasionally. Get medical attention. Ingestion: Give large quantities of water then several glasses of milk. Induce vomiting. Get medical attention immediately.

STORAGE

Store in a cool dry place. Keep container closed when not in use.

THIS PRODUCT IS DESIGNED EXCLUSIVELY FOR INDUSTRIAL AND INSTITUTIONAL USE BY TRAINED PERSONNEL. THIS PRODUCT IS SOLD "AS IS" AND THE MANUFACTURER MAKES NO WARRANTY, EXPRESS OR IMPLIED, OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR OTHERWISE. Manufactured By AERO Chemical Company, Inc., 8570 Jamieson Rd., Morrow, GA 30260, 404-688-9222, 512-051382.

HMIS Rating: Health:0, Flammability:0, Reactivity:0

CONTROL
NUMBER

NET CONTENTS
GALLONS

AERO

Handy Quat

SANITIZING HAND SOAP

CAUTION
KEEP OUT OF REACH OF CHILDREN

DESCRIPTION

This product is an effective one-step cleaner/sanitizer for use in food processing plants and restaurants by personnel prior to handling food and/or food-processing equipment. Based on quaternary ammonium chlorides, this viscous formulation is more cost-efficient than traditional PCMX-based products. This formulation effectively reduces the bacterial flora of the skin. When tested via the "Modified Available Chlorine Germicidal Equivalent Concentration Test" it demonstrates equal sanitizing activity to 50 ppm of free chlorine against *Staphylococcus aureus* and *Salmonella typhimurium*. Formulated with skin conditioners for extra mildness.

DIRECTIONS

Hands need not be washed prior to using this product. For one-step hand washing and sanitizing, place approximately 5 cc in palm of hand, add 15 cc of water, lather and wash in normal manner. After use, hands must be thoroughly rinsed with potable water.

Manufactured For:

AERO
CHEMICAL COMPANY
Atlanta, GA / Dallas, TX

ONE-STEP CLEANING AND DISINFECTING:

This product may be used to clean and disinfect operating areas, patient rooms, floors, walls, counter tops, rest rooms, shower areas, refuse containers, bed frames, morgues, laboratories, cafeterias, commercial freezers, animal rooms, cages and other hard, non-porous surfaces. Before applying disinfecting solution, food products and packaging materials must be removed from the room or carefully protected. Remove heavy soil deposits before applying the disinfecting solution. Using a solution of 3 ounces ZZZ DISINFECTANT per 5 gallons of warm water (68° to 20° C or warmer), immerse objects in disinfecting solution, or apply solution with mop, sponge or brush. Where appropriate, use a mechanical sprayer. Allow a 10 minute contact time with disinfecting solution. All food contact surfaces must be rinsed with potable water before reuse. Floors, walls and all other non-food contact surfaces may drain dry without rinsing.

NOTE: When mixing ZZZ DISINFECTANT with cold water (as low as 41° F, 5° C), increase use to 6 oz. per 5 gallons water.

TO CLEAN AND DISINFECT TOILET BOWLS AND URINALS: Flush toilet. Add 1 ounce of ZZZ DISINFECTANT directly to water in toilet bowl. Brush to cover all bowl surfaces including under the rim. Allow disinfectant to remain for at least 10 minutes. Flush toilet. Rinse metal parts with water after disinfecting to prevent corrosion.

USE DILUTION TABLE	
ZZZ DISINFECTANT	WATER
1 oz to 5	gallons water
3 oz to 5	gallons water
6 oz to 5	gallons water

TITRATABLE IODINE
25 ppm
75 ppm
150 ppm

NET CONTENTS: 1 Gallon
LOT NO.:

Made in USA

011-0005-A0191

FOR INDUSTRIAL AND INSTITUTIONAL USE ONLY

WESTAGRO ZZZ DISINFECTANT

CONCENTRATED BROAD SPECTRUM IODOPHOR FOR USE AS A
1 STEP CLEANER-DISINFECTANT AND NO-RINSE SANITIZER.

Authorized by USDA for use in federally inspected meat, poultry and egg processing plants.

ACTIVE INGREDIENTS:

Iodine* 1.75%

INERT INGREDIENTS: 98.25%

Total 100.00%

*From alpha-(p-terphenyl)-omega-hydroxy-poly(oxyethylene)-iodine complex

PRECAUTIONARY STATEMENTS: HAZARD TO HUMANS AND DOMESTIC ANIMALS

KEEP OUT OF THE REACH OF CHILDREN

DANGER. CORROSIVE. Causes irreversible eye damage. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Wear goggles or face shield. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

EPA Reg. No. 4995-16
EPA Est. No.: 4995-IL-01

ENVIRONMENTAL HAZARDS This product is toxic to fish. Keep out of lakes, ponds or streams. Do not contaminate water by cleaning of equipment or disposal of wastes. Do not discharge into lakes, streams, ponds or public waters unless in accordance with a NPDES permit. For guidance, contact the regional office of EPA.

STATEMENT OF FIRST AID / PRACTICAL TREATMENT
In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes. For ingestion, call a physician. If swallowed, promptly drink a large quantity of water. Do not induce vomiting. Avoid alcohol. Get medical attention. Remove and wash contaminated clothing before reuse.
NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage. Measures against circulatory shock, respiratory depression and convulsions may be needed.

STORAGE AND DISPOSAL

Keep container closed when not in use. Do not store below 25° F or above 100° F for extended periods.

PROHIBITIONS: Do not contaminate water, food or feed by storage or disposal. Open dumping is prohibited.

PESTICIDE DISPOSAL: Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, spray mixture or rinsate is a violation of Federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance.

CONTAINER DISPOSAL: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or incinerator, or, if allowed by State or local authorities, burn container. If burned, stay out of smoke.

DIRECTIONS FOR USE:

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.
Not for Residential Use.

The color of a ZZZ DISINFECTANT solution is proportional to the available iodine concentration. Prepare a fresh solution daily, or when there is a noticeable change in its rich amber color, or more often if the solution becomes diluted or soiled. Used as directed, ZZZ DISINFECTANT is effective in hard water (up to 400 ppm CaCO_3) and in 5% organic serum load against listed bacteria and pathogenic fungi.

SANITIZING PREVIOUSLY CLEANED FOOD CONTACT SURFACES:
Sanitize previously cleaned and rinsed hard, non-porous surfaces such as glass, metal, plastic, and porcelain, with a solution containing 1 ounce of ZZZ DISINFECTANT per 5 gallons of water. Spray or immerse equipment with sanitizing solution and allow 1 minute contact time. Drain solution from equipment; do not rinse. ZZZ DISINFECTANT used at 1 ounce per 5 gallons of water contains 25 ppm available iodine and does not require a final rinse with potable water in accordance with Federal Food Additive Regulation 178.1010.

HAND SANITIZING IN FOOD PROCESSING PLANTS: Thoroughly wash and rinse hands before sanitizing. Dip or rinse hands in a solution containing 1 ounce of ZZZ DISINFECTANT per 5 gallons of water. ZZZ DISINFECTANT may be injected directly into wash or rinse water at a rate of 1 ounce per 5 gallons of water. A final potable water rinse is not required.

Manufactured by:

WESTAGRO

11110 N. Congress Avenue / Kansas City, Missouri 64153
The oldest name in new technology.™

SC-764

SANITIZING HAND CLEANER WITH PATENTED FREE IODINE TECHNOLOGY

A one step, cleaning and sanitizing handsoap formulated with effective, low levels of active iodine. Contains emollients and viscosity enhancers.

ACTIVE INGREDIENT: Iodine

KEEP OUT OF REACH OF CHILDREN CAUTION

If eye contact occurs, flush eyes with plenty of water. If ingested, call a physician immediately.

Store at room temperature (59°F - 86°F). Keep from freezing.

Sold By:

SHRADER CHEMICAL CO., INC.
Compton, CA 90221

FOR INDUSTRIAL AND INSTITUTIONAL USE ONLY

SC-764 is a superior hand washing and sanitizing compound for use in FOOD PROCESSING PLANTS, FOOD HANDLING ESTABLISHMENTS, RESTAURANTS AND OTHER FOOD SERVICE ESTABLISHMENTS, PUBLIC RESTROOMS, VETERINARY CLINICS and ANIMAL FACILITIES. This iodine based hand cleaner effectively kills germs and bacteria on contact. Its pH balanced formula contains cosmetic grade detergents and foam stabilizers which generate a thick, luxurious lather. SC-764 contains no added fragrances, colors or phosphates. Routine use of SC-764 prior to handling food or food processing equipment, and before and after handling animals, will reduce bacterial contamination on hands.

DIRECTIONS FOR USE:

Hand Washing and Sanitizing

Apply a generous amount of SC-764 to hands. Lather hands and arms, thoroughly cleaning between fingers, around cuticles and under finger nails. Rinse with water. Repeat if necessary.

U.S. Patent Number 4,271,149

NET CONTENTS:

LOT. NO.:

EXPIRATION DATE:

E-3

E-3

(Klenzade logo)

TOPAX 91

Deodorizer - Sanitizer

ACTIVE INGREDIENTS:

n-Alkyl (60% C₁₄, 30% C₁₆, 5% C₁₂, 5% C₁₈) Dimethyl Benzyl
Ammonium Chlorides.....5%
n-Alkyl (68% C₁₄, 32% C₁₆) Dimethyl Ethylbenzyl
Ammonium Chlorides.....5%
INERT INGREDIENTS.....90%

EPA Reg. No. 1677-148

EPA Est. 1677-IL-2 (J), 1677-NJ-1 (W), 1677-TX-1 (D),
1677-GA-1 (M), 1677-CA-1 (S), 1677-MN-1 (P),
1677-PR-1 (B), 1677-IA-1 (H)

Superscript refers to first letter of date code.

KEEP OUT OF REACH OF CHILDREN

DANGER

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

DANGER: CORROSIVE. CAUSES EYE DAMAGE AND SKIN IRRITATION. DO NOT GET IN EYES, SKIN, OR CLOTHING. PROTECT EYES AND SKIN WHEN HANDLING. HARMFUL IF SWALLOWED. AVOID CONTAMINATION OF FOOD. QUORUM CLEAR IS A CONCENTRATE AND SHOULD BE DILUTED BEFORE USING. WASH THOROUGHLY WITH SOAP AND WATER AFTER HANDLING.

STATEMENT OF PRACTICAL TREATMENT

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH PLENTY OF WATER FOR AT LEAST 15 MINUTES. FOR EYES, CALL A PHYSICIAN. REMOVE AND WASH CONTAMINATED CLOTHING BEFORE REUSE. IF SWALLOWED, DO NOT INDUCE VOMITING. DRINK PROMPTLY A LARGE QUANTITY OF EGG WHITE, GELATIN SOLUTION OR, IF THESE ARE NOT AVAILABLE, DRINK LARGE QUANTITIES OF WATER. CALL A PHYSICIAN IMMEDIATELY.

NOTE TO PHYSICIAN: PROBABLE MUCOSAL DAMAGE MAY CONTRAINDICATE THE USE OF GASTRIC LAVAGE.

FOR EMERGENCY MEDICAL INFORMATION, CALL TOLL-FREE: 1-800-328-0026

Manufactured by KLENZADE, Division of Ecolab Inc., Ecolab Center, St. Paul, Minnesota 55102 c, 1991

NET CONTENTS: 55 U.S. GALS. (208.2 l)

21591

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. Prior to use of this product, remove gross food particles and soil with a pre-flush, or pre-scrape, and, when necessary, pre-soak treatment from all surfaces, then wash with detergent or other cleaning solution followed by a thorough potable water rinse.

FOOD PROCESSING EQUIPMENT: Clean equipment with a good detergent and follow with water rinse prior to sanitizing. For sanitization of pre-cleaned food processing equipment and utensils, dilute 1 ounce Topax 91 per minute contact time. At this level, no potable water rinse is required, providing the sanitizing solution is adequately drained. A fresh sanitizing solution should be prepared daily for mechanical as well as manual applications and should not be re-used, except for cleaning or pre-flush of dirty equipment.

MEAT AND POULTRY PLANTS: For sanitizing cleaned food processing equipment or utensils in federally inspected meat and poultry processing plants, dilute 1 ounce Topax 91 per 4 gallons of water (200 ppm). At this concentration, no potable water rinse is required after thorough draining of the sanitizing solution.

MUSHROOM FARMS: To sanitize mushroom equipment, first clean and rinse equipment thoroughly. Then apply sanitizing solution containing 1 ounce Topax 91 to 4 gallons of water (200 ppm). At this level, no potable water rinse is required after complete draining. The Topax 91 can also be used to disinfect floors, walls and inanimate hard surfaces on the mushroom premises only in areas where compost and mushrooms are not present.

AUTHORIZATIONS

Topax 91 is authorized by the U.S. Department of Agriculture for use in Federally inspected meat and poultry products plants. **HAND**

SANITIZING: After hands have been washed and rinsed, dip in a 1 oz per 5 gal solution of Topax 91 (150 ppm active quaternary). **SANITIZING**

SHELL EGGS INTENDED FOR FOOD: To sanitize previously cleaned food-grade eggs in shell egg and egg product processing plants, spray with a solution of 1 oz product in 4 gal of warm water (200 ppm quat). The solution should be warmer than the eggs, but not to exceed 130°F. Wet eggs thoroughly and allow to drain. Eggs sanitized with this product shall be subjected to a potable water rinse only if they are broken immediately for use in the manufacture of egg products. Eggs should be reasonably dry before casing or breaking. The solution should not be reused for sanitizing eggs.

OTHER USES: For other specialized cleaning, sanitizing and disinfecting operations consult your Klenzade Representative.

ENVIRONMENTAL HAZARDS:

This product is toxic to fish. Keep out of lakes, streams or ponds. Treated effluent may not be discharged into lakes, streams, ponds or public waters without a valid discharge permit. For guidance, contact the regional office of the Environmental Protection Agency.

STORAGE AND DISPOSAL

**Keep container closed and store in a cool place when not in use.
DO NOT CONTAMINATE WATER, FOOD OR FEED BY STORAGE OR DISPOSAL**

PESTICIDE DISPOSAL:

Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, spray mixture or rinsate is a violation of Federal Law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency or the Hazardous Waste representative at the nearest EPA Regional Office for guidance.

CONTAINER DISPOSAL: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by incineration, or, if allowed, by state and local authorities, by burning. If burned, stay out of smoke.

APR 16 '91

(Klenzade 1090)

TOPAX 99

Chlorinating Bactericide Disinfectant & Deodorant

ACTIVE INGREDIENTS:

Sodium hypochlorite.....5.25%
INERT INGREDIENTS.....94.75%

EPA Reg. No. 1677-144

EPA Est. 1677-IL-2 (J), 1677-NJ-1 (W), 1677-TX-1 (D),
1677-GA-1 (M), 1677-CA-1 (S), 1677-MN-1 (P),
1677-PR-1 (B), 1677-IA-1 (H)

Superscript refers to first letter of date code.

FOR INDUSTRIAL USE ONLY
DO NOT SPILL TOPAX 99 ON CLOTHING

KEEP OUT OF REACH OF CHILDREN
DANGER

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

DANGER: CAUSES IRRITATION. HARMFUL IF SWALLOWED. AVOID CONTACT WITH EYES, SKIN AND CLOTHING. WASH THOROUGHLY WITH SOAP AND WATER AFTER HANDLING. IN CASE OF EYE CONTACT, IMMEDIATELY FLUSH EYES WITH PLENTY OF WATER FOR AT LEAST 15 MINUTES. CALL A PHYSICIAN. IF SWALLOWED, DRINK LARGE QUANTITIES OF WATER. DO NOT GIVE VINEGAR OR OTHER ACIDS. DO NOT INDUCE VOMITING. GET PROMPT MEDICAL ATTENTION. FLUSH SKIN WITH WATER. DO NOT USE WITH OTHER ACID TYPE CLEANERS, SANITIZERS OR AMMONIA SINCE HAZARDOUS GASES WILL BE RELEASED.

FOR EMERGENCY MEDICAL INFORMATION, CALL TOLL-FREE: 1-800-328-0026

Manufactured by KLENZADE, Division of Ecolab Inc., Ecolab Center, St. Paul, Minnesota 55102 c, 1991

NET CONTENTS. 5.0 U.S. GALS. (190.7 L)

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

SANITIZATION OF NONPOROUS FOOD CONTACT SURFACES (MEAT & FOOD PLANTS)

Before treating utensils and equipment to kill many (or most) bacteria, rinse thoroughly with cold water, then wash with warm solution of cleanser followed by a thorough potable water rinse. Apply Topax 99 to all utensils just before using. Allow 2 minutes exposure time.

FOOD PLANT EQUIPMENT: Flow Method: Prepare 100 ppm in weigh vat and pump through filler. Drain solution through valves. Test solution to maintain strength above 50 ppm. Spray Method: Prepare 200 ppm solution and spray surfaces.

BOTTLES: To treat to kill many (or most) bacteria. Hand Washed: Wash using hand or motor driven brush, rinse thoroughly with potable water, and then immerse in 200 ppm. Remove, invert in cases to drain and dry. Machine Washed: Use Topax 99 for chlorinating device and adjust dispensing mechanism so that the final rinse water contains 50 ppm. Test rinse water frequently to determine if this strength is maintained.

DISINFECTION OF EMERGENCY DRINKING WATER

Farms, Institutions, Camps, Home Water Supplies: To disinfect water whose source is from unprotected supplies, such as cisterns, wells, springs and lakes, add 1/4 ounce Topax 99 to each 100 gallons of water or two drops to each gallon of water and let it stand for 15 to 30 minutes. This is a strength of about 1 part available chlorine per million parts water. The water may be kept in the refrigerator for cooling at the same time if desired.

POULTRY USES

Drinking Water: For fountains, use 25 ppm. For open vessels, use 25 ppm. Change water daily. Place fountains where they will not be contaminated with droppings.

FOOD EGG SANITIZATION

Thoroughly clean all eggs. Thoroughly mix 5 ounces of this product with 10 gallons of warm water to produce 200 ppm available chlorine solution. The sanitizer temperature should not exceed 130°F. Spray the warm sanitizer so that the eggs are thoroughly wetted. Allow the eggs to thoroughly dry before casing or breaking. Do not apply potable water rinse. The solution should not be re-used to sanitize eggs.

FRUIT & VEGETABLE WASHING

Thoroughly clean all fruits and vegetables in a wash tank. Thoroughly mix 10 ounces of this product in 200 gallons of water to make a sanitizing solution of 25 ppm available chlorine. After draining the tank, submerge fruit or vegetables for 2 minutes in a second wash tank containing the recirculating sanitizing solution. Spray rinse vegetables with the sanitizing solution prior to packaging. Rinse fruit with potable water only prior to packaging.

SANITIZING OF HANDS

A 50 ppm available chlorine hypochlorite solution may be used for sanitizing hands. The hands must be washed and thoroughly rinsed prior to sanitizing with this compound. The hands need not be rinsed following sanitizing.

DILUTION TABLE

AVAILABLE CHLORINE	AMOUNT OF TOPAX 99
100	1/2-oz. Topax 99 per 2 gals. water
200	1 oz. Topax 99 per 2 gals. water

PHYSICAL AND CHEMICAL HAZARDS

Strong oxidizing agent: Mix only with water according to label directions. Mixing this product with gross filth such as feces, urine, etc., or with ammonia, acids, detergents or other chemicals may release hazardous gases irritating to eyes, lungs and mucous membranes.

ENVIRONMENTAL HAZARDS

This product is toxic to fish. Keep out of lakes, streams or ponds. Treated effluent may not be discharged into lakes, streams, ponds or public waters without a valid discharge permit. For guidance, contact the regional office of the Environmental Protection Agency.

STORAGE AND DISPOSAL

Store this product in a cool, dry area, away from direct sunlight and heat to avoid deterioration. In case of fire, flood the area with large quantities of water.

PESTICIDE DISPOSAL: Product or rinsates that cannot be used should be diluted with water and disposed in a sanitary sewer. Do not contaminate food or feed by storage, disposal or cleaning of equipment.

CONTAINER DISPOSAL: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or incineration, or, if allowed by state and local authorities, by burning. If burned, stay out of smoke.

GENERAL INFORMATION

IODIP, No. 577 is a hand dip sanitizer specially designed for use in food processing areas for people who handle food products and food processing equipment. IODIP, No. 577 is to be used at 25 ppm active iodine. ppm means parts per million.

PRECAUTIONARY STATEMENTS

KEEP OUT OF REACH OF CHILDREN

DANGER:

Corrosive, concentrated product causes eye and skin damage. May cause blindness. Harmful or fatal if swallowed. Do not get in eyes, on skin, or on clothing. Avoid breathing mist. Wear goggles or face shield with goggles, rubber apron and rubber gloves when handling concentrated product. Remove contaminated clothing and wash before reuse.

FIRST AID:

EXTERNAL AND EYES: In case of contact, immediately flush eyes with plenty of water for 15 minutes. Hold eyelids open while flushing with water. CALL A PHYSICIAN IMMEDIATELY. For skin contact, remove contaminated clothing. Wash with soap and water. If irritation persists, get medical attention.

INTERNAL: If swallowed, DO NOT induce vomiting. Give large quantity of water. NEVER give anything by mouth to an unconscious victim. CALL A PHYSICIAN IMMEDIATELY.

IN CASE OF FIRE: Evacuate area. Fire fighters should wear protective gear including approved respirator.

IN CASE OF SPILL: If concentrated product is spilled, evacuate unprotected personnel from area. Provide maximum ventilation. Wear chemical goggles, face shield, rubber gloves and rubber apron and NIOSH-approved respirator. Contain spill and place into drums for proper disposal. Flush remaining residue with water, neutralize with soda ash, sodium bicarbonate, or lime, and dispose of properly.

HYDRITE CHEMICAL CO.

IODIP
No. 577

Hand Dip Sanitizer

DANGER:

CONCENTRATE CAUSES SEVERE BURNS
TO SKIN AND EYES.

HARMFUL OR FATAL IF SWALLOWED.
CONTAINS PHOSPHORIC ACID.
SEE SIDE PANELS FOR ADDITIONAL
PRECAUTIONARY STATEMENTS.

24 HOUR EMERGENCY NUMBER:

414/277-1311

or CHEMTREC: 800/424-9300

College Grove, WI 53227 LaCross, WI 54603 Milwaukee, WI 53223 Oshkosh, WI 54901 Waterloo, IA 50703
(608) 237-5892 (608) 784-8024 (414) 354-3730 (908) 243-8370 (319) 237-9731

DIRECTIONS

READ & UNDERSTAND LABEL AND MATERIAL SAFETY DATA SHEET BEFORE PRODUCT USE.

1. Add 1 ounce IODIP, No. 577 per 5.5 gallons water (25 ppm iodine).
2. Thoroughly wash and rinse hands before sanitizing.
3. Dip hands into solution.
4. Remove hands from solution and allow to remain wet for at least 60 seconds.
5. A water rinse is not necessary after hands have been sanitized.

Do not mix with chlorine solutions or compounds, lye, washing powders, or household chemicals. Not for use on galvanized surfaces, or concrete or terrazzo floors.

FREIGHT CLASSIFICATION: Compound, Cleaning Liquid.

U.S.C. SHIPPING CLASSIFICATION: Compound, Cleaning, Liquid (Contains Phosphoric Acid), CORROSIVE, NA1760.

FOR INDUSTRIAL USE ONLY.

STORAGE AND DISPOSAL: Store in a cool, well-ventilated area, away from heat or flame. Do not contaminate water, food or feed by storage or disposal. Do not store in open, unlabeled, or mislabeled containers. Triple rinse container thoroughly when empty. Return container for recycling or dispose in manner consistent with local, state and federal regulations. Do not use this container for any other product than what is shown on this label.

(CRC)(R)

NET CONTENTS:

U.S. GALLON
(3.79 Liters/Gal.)

11-3

CAUTION:

Do not get in eyes. Severe eye irritant. Harmful if swallowed. Do not take internally. Remove and wash contaminated clothing before reuse.
DO NOT CONTAMINATE WATER, FOOD, OR FEED BY STORAGE AND/OR DISPOSAL.

In case of contact, immediately flush eyes with plenty of water and call a physician. Remove and wash contaminated clothing before use. If swallowed, drink egg whites, gelatin solution or if these are not available, drink large quantities of water. Avoid alcohol. Contact a physician immediately.

INGREDIENTS: Contains 100 Quaternary Ammonium Compounds, Water.

**390
HANDISAN
HAND SANITIZER SOLUTION**

FOR COMMERCIAL USE ONLY
KEEP OUT OF REACH OF CHILDREN
See side panel for precautionary statement



Manufactured By:
Colonial Chemical Corporation
720 E. MANSION JACKSON, MICHIGAN 49203
PHONE : (617) 700-5151

DIRECTIONS:

This hand sanitizer solution is an effective hand dip sanitizer authorized by the USDA for use in Federally inspected meat, poultry & food processing plants.

Prepare a 200ppm active quaternary solution by adding 1 oz. of hand sanitizer solution to 4 gallons of water.

Thoroughly wash and rinse hands prior to sanitizing with the solution. Dip hands into sanitizing solution and allow to remain wet for at least 60 seconds.

A potable water rinse is not necessary after the hands have been sanitized.

E-3

Monarch[®]

SK 0360

I-Bac

Iodine Detergent Sanitizer

**DIRECTIONS
FOR USE**

IT IS A VIOLATION OF FEDERAL LAW TO USE THE PRODUCT IN A MANNER INCONSISTENT WITH ITS LABELING.

HAL is a concentrated product and must be diluted before using. Not recommended for use on pre-cleaned, hard non-porous environmental surfaces in food processing, meat manufacturing and dairy farms.

PREPARATION: Remove gross soils by flushing with water, scraping or brushing. Pre-clean all surfaces. Rinse thoroughly with potable water. **SANITIZING HARD NON-POROUS SURFACES** (glass or stainless, filters, pipelines, silos, processing vats, hull tanks and utensils): To sanitize previously cleaned equipment and utensils, dip, brush or spray equipment with a solution of I-BAC at 1 ounce to 5 gallons of water. Provides 25 ppm titratable iodine. Allow at least 2 minutes contact time. Allow equipment to drain well. Rinse and dry. Do not rinse.

FOR HAND SANITIZING ONLY: Wash hands thoroughly with soap and water. Rinse hands thoroughly. Dip hands in a solution containing I-BAC at the rate of 1 ounce per 5 gallons of water. This solution provides 12% ppm titratable iodine. In a concentration of not less than 12 ppm or not more than 25 ppm titratable iodine.

EGG SANITIZING: Eggs must first be washed with an approved cleaning compound, followed by a potable water rinse. Washed and rinsed eggs shall be spray rinsed with a solution of I-BAC at 1 ounce to 5 gallons of water. Provides 25 ppm titratable iodine. Never reuse towels or dip a used towel back into solution. Always use freshly prepared solutions and non-corrodible utensils.

EGGS FOR POOKING: Washed and rinsed eggs shall be spray rinsed with a solution of I-BAC at 1 ounce to 5 gallons of water. Provides 25 ppm titratable iodine. Never reuse towels or dip a used towel back into solution. Always use freshly prepared solutions and non-corrodible utensils.

UNDER WASHING: Approximately one minute before applying milking unit, wash and massage teats with a clean paper towel wetted with a solution of I-BAC at 1 ounce to 5 gallons of water at 110°F. Provides 25 ppm titratable iodine. Never reuse towels or dip a used towel back into solution. Always use freshly prepared solutions and non-corrodible utensils.

HAL is authorized by U.S.D.A. for use in federally inspected meat and poultry plants. **IMPORTANT:** Our only obligation shall be to replace or pay for any material proven defective. Beyond the purchase price of materials supplied by us, we assume no liability for damages of any kind and the user accepts the product "as is" and without warranties, expressed or implied. The suitability of the product for an intended use shall be solely up to the user.

ACTIVE INGREDIENTS: Iodine
Phosphoric Acid
INERT INGREDIENTS

1.75%
16.00%
82.25%
100.00%

EPA Reg. No. 4524-30
EPA Est. No. 4524 MN 1

EPA Reg. No. 4524-30
EPA Est. No. 4524 NY 1

EPA Reg. No. 4524-30
EPA Est. No. 4524 CA 2

EPA Reg. No. 4524-30
EPA Est. No. 4524 NC 1

DANGER:

KEEP OUT OF REACH OF CHILDREN

Precautionary Statements: Hazards to Humans and Domestic Animals

CORROSIVE — CAUSES SEVERE EYE AND SKIN DAMAGE

Do not get in eyes, on skin or on clothing. Wear goggles and rubber gloves when handling. Harmful if swallowed. Prevent contamination of food. Prevent breathing spray mist.

CONSULT MATERIAL SAFETY DATA SHEET FOR ADDITIONAL INFORMATION. FOR INDUSTRIAL USE ONLY

Medical personnel familiar with this product are available 24 hours a day, 7 days a week. Toll-free medical emergency number 1/800-228-5635. **STATEMENT OF PRACTICAL TREATMENT:** In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes. For eyes call a physician. Remove and wash contaminated clothing before reuse. If swallowed, drink large quantities of water. Do not induce vomiting. Avoid alcohol. Call a physician immediately.

NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage. Measures against circulatory shock, respiratory depression and convulsion may be needed.

**STORAGE AND
DISPOSAL**

STORAGE: Store away from heat and flames. Protect from freezing. **PROHIBITIONS:** Do not contaminate water, food or feed by storage or disposal. Open dumping is prohibited. **PESTICIDE DISPOSAL:** Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, spray mixture, or rinsate is a violation of Federal law. If these wastes cannot be disposed of by the manufacturer's instructions, contact your State Pesticide and Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance. **CONTAINER DISPOSAL — PLASTIC CONTAINERS:** Triple rinse (or equivalent), then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or incineration, or in other approved manner. Do not burn. Do not pour into sewer. **GENERAL:** Consult Federal, State or local disposal authorities for approved alternative procedures.

KEEP FROM FREEZING. MIX ONLY WITH WATER — DO NOT MIX WITH SOLUTIONS CONTAINING ALKALINE

H.B. Fuller Company
Monarch Division

NET CONTENTS

Labeling for Hand
Sanitizers

TAB A

(REF. 1)

2K-V

**SANITIZING HAND CLEANER
WITH PATENTED FREE IODINE TECHNOLOGY**

ACTIVE INGREDIENT: Iodine

**KEEP OUT OF REACH OF CHILDREN
CAUTION**

If eye contact occurs, flush eyes with plenty of water. If ingested, call a physician immediately.

Store at room temperature (59°F - 86°F). Keep from freezing.

Sold By: **WEST AGRO, INC.**
Kansas City, MO 64153

0000-A0402

**FOR INDUSTRIAL AND INSTITUTIONAL USE
ONLY**

2K-V SANITIZER'S HAND CLEANER is a one-step, cleaning and sanitizing handsoap formulated with effective, low levels of active iodine. Contains emollients and viscosity enhancers.

DIRECTIONS FOR USE:

Hand Washing and Sanitizing
Apply a generous amount of 2K-V SANITIZER'S HAND CLEANER to hands. Lather hands and arms, thoroughly cleaning between fingers, around cuticles and under finger nails. Rinse with water. Repeat if necessary.

U.S. Patent 4,271,100

NET CONTENTS:

LOT. NO.:

EXPIRATION DATE:

USDA-FSIS

Jan 27 '92



**ONE-STEP
ANTIBACTERIAL HANDWASHING AND SANITIZING COMPOUND**

Authorized for Use Under USDA Poultry
and Meat Inspection Programs

Recommended for use by food plant personnel prior to
handling food or food processing equipment.

Active Ingredients

Chlorhexidine Gluconate	1.00%
Didecyl dimethyl ammonium chloride	0.50%

Inert Ingredients

Water, Detergents	98.50%
-------------------	--------

CAUTION:

Keep Out of Reach of Children. See side panel for additional
precautionary statements.

NET CONTENTS: 128 FL. OZ. (1 GAL)

ODORCON SANITATION SERVICES

P.O. BOX 998
GREENSBORO, N.C. 27402

DIRECTIONS FOR USE

Meat, Food Plants and Restaurants

ODORCON CHLORSAN HAND SOAP effectively re-
duces the bacterial flora of the skin. Hands need not be
washed prior to using CHLORSAN. For one-step
handwashing and sanitizing, place approximately 5cc in
palm of hand, add 15cc of water and wash thoroughly in a
normal manner.

Rinse hands thoroughly with potable water after washing
with CHLORSAN.

CAUTION

KEEP OUT OF REACH OF CHILDREN

Do not swallow. If contents come in contact with eyes, flush
with water for at least 15 minutes and get medical attention.
Do not allow concentrate to come in contact with food.
Rinse empty container with water and discard it.

E-2



**LEANSING
SANITIZER**



STOCK NO.

5000 ML NET 1.3 GAL. (168 FL. OZ.)

Must be washed before or chlorine
dipped after using

- Designed for use in hard or soft water
- Cleaning: no irritating fragrance

Directions: For one step handwashing and
sanitizing rub together two (2) parts
of water and one (1) part soap
and wash with potable water.
Rinse well. Dry completely.



CONTAINS: Water, Alkyl Polyglycoside,
Myristalkonium Chloride, Quaternium 14
Hydroxyethyl Cellulose, PEG-6 cocamide,
Glycol Distearate, Citric Acid

CAUTION: KEEP OUT OF EYES. In case of accidental eye contact,
flush eyes thoroughly with water. If condition worsens or irritation
persists, consult a physician. If swallowed, consult a physician or
poison control center. **FOR EXTERNAL USE ONLY**
KEEP OUT OF REACH OF CHILDREN

GOJO INDUSTRIES, INC.
P.O. Box 991
Akron, Ohio 44309-0991
©1991 All rights reserved

USA-FSIS

Jun 11 '92

Attachment 2: Challenges, Practices and Requirements Related to Hand Hygiene in Food Handling Settings

There are substantial requirements related to the hand hygiene in food handling settings and food handler hygiene practices are significantly influenced by these requirements. 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 U.S. Food Code (FDA 2017a). Other requirements may also exist and be specific to processing plants, corporate policies, food establishments, etc.

The process of hand washing is typically guided by product manufacturer instructions. However, individual establishments will create standard operating procedures that address when hands must be washed, accounting 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 (FDA 2017a), summarized as follows:

- 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;
- D) 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 Food Safety Modernization Act (FSMA) (FDA 2011). FSMA does not contain the same guidelines as the US Food Code (FDA 2017a) 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.

Particularly relevant, the FSMA regulations address hand washing and sanitizing:

“The management of the establishment must take reasonable measures and precautions to ensure the following:

...

(b) *Cleanliness*. All persons working in direct contact with food, food-contact surfaces, and food-packaging materials must conform to hygienic practices while on duty to the extent necessary to protect against allergen cross-contact and against contamination of food. The methods for maintaining cleanliness include:

...

(3) Washing hands thoroughly (and sanitizing if necessary, to protect against contamination with undesirable microorganisms) in an adequate hand-washing facility before starting work, after each absence from the work station, and at any other time when the hands may have become soiled or contaminated.

...

(5) Maintaining gloves, if they are used in food handling, in an intact, clean, and sanitary condition” (FDA 2019a).

References

United States Food and Drug Administration (US FDA). 2017a. United States Food Code. Accessed 30 January 2020. <https://www.fda.gov/media/110822/download>

———. 2011. Food Safety Modernization Act. Periodical Retrieved from <https://www.govinfo.gov/content/pkg/PLAW-111publ353/pdf/PLAW-111publ353.pdf>

———. 2019a. Current Good Manufacturing Practice, Hazard Analysis, and Risk-based Preventive Controls for Human Food. Subpart B - Current Good Manufacturing Practice. 21 CFR Vol. 117. No. 10. Accessed 30 January 2020. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=117>

Attachment 3: In Vitro Testing

The pivotal time kill and Minimum Inhibitory Concentration/Minimum Bactericidal Concentration (MIC/MBC) studies that American Cleaning Institute (ACI) is sponsoring provide significant evidence of rapid broad-spectrum germicidal activity of the five antiseptic ingredients being sponsored by ACI against organisms relevant to food handler settings. The generated data provided to United States Food and Drug Administration (FDA) should be used as support for the efficacy of antiseptic active ingredients used in food handler settings (Bioscience Laboratories, Inc. 2018a, 2018b; studies in-progress).

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 International 2016) and MIC/MBC (Clinical and Laboratory Standards Institute 2015) methods are accepted testing standards and have been required by the FDA as a portion of the historical Health Care Topical Antiseptic supporting data set. This Time-kill assay, in particular, measures rapid biocidal activity at active concentrations and exposure times that closely simulate in-use conditions. 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.

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 already completed for benzalkonium chloride (BAC), benzethonium chloride (BZT), chloroxylenol (PCMX), and ethanol (EtOH) 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*), *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*), *Staphylococcus epidermidis* (including Methicillin-Resistant *Staphylococcus epidermidis*), *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 in anticipation of FDA's rulemaking for antiseptic food handler products. The organisms identified as relevant to food handler settings are listed in the table below. The list of organisms was derived from government reference sources, such as the CDC and Center for Food Safety and Applied Nutrition (CFSAN), and industry food safety publications, as well as industry experts, to represent organisms known to cause foodborne or food-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, FDA 2017c), and the US Food Code (FDA 2017a) provide the rationale for the selection.

	Tested in Pivotal Time Kill	Tested in MIC/MBC
Gram Negative Bacteria		
<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
Gram Positive Bacteria		
<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

Results for the time kill studies for BAC, BZT, PCMX, and EtOH demonstrate broad-spectrum, and rapid microbicidal efficacy of these ingredients versus a large variety of Gram-negative and Gram-positive bacteria and two yeast species, including many clinical and/or multi-drug resistant strains. The test materials produced 3-Log10 or greater reductions for 100% of all tested microorganisms exposed to BAC, BZT and EtOH and 99% of all tested microorganisms exposed to PCMX. Time Kill testing for PVP-I is currently underway.

References

- American Society for Testing Materials (ASTM). 2016. Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure, E2783-11 <https://www.astm.org/Standards/E2783.htm>
- Bioscience Laboratories, Inc. 2018a. An In-Vitro Time-Kill Evaluation of Four Test Materials When Challenged with Various Bacterial and Yeast Species [BAC, BZT, PCMX, ethanol]. 26 February 2018. <https://www.regulations.gov/document?D=FDA-1975-N-0012-0736>

- Bioscience Laboratories, Inc. 2018b. Determination of the Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of Five Test Materials [BAC, BZT, PCMX, ethanol, PVP-I]. 12 November 2018. <Submission awaiting docket posting>
- Clinical and Laboratory Standards Institute (CLSI). 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard Tenth Edition.
- United States Food and Drug Administration (US FDA). 2019. Foodborne Pathogens. Accessed 30 January 2020. <https://www.fda.gov/food/outbreaks-foodborne-illness/foodborne-pathogens>
- United States Food and Drug Administration (US FDA). 2017a. United States Food Code. Accessed 30 January 2020. <https://www.fda.gov/media/110822/download>
- . 2017c. Risk Profile: Pathogens and Filth in Spices. Center for Food Safety and Applied Nutrition. <https://www.fda.gov/media/108126/download>

Attachment 4: In Vivo Testing

- **Data from *in vivo* clinical simulation studies in combination with data from *in vitro* studies are sufficient to characterize the efficacy of food handler topical antiseptics.**

Controlled clinical outcome studies should not be undertaken to establish GRAE status for food handler topical antiseptics. A combination of well-designed *in vitro* and *in vivo* clinical simulation data are appropriate 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 risks of conducting clinical outcome studies (FDA 2017a; 2019). This approach is currently being used to establish efficacy for topical antiseptic new drugs (CHG, and CHG-Alcohol handwash products) and to establish GRAE status of health care antiseptics and consumer hand rubs which include the same active ingredients used in the food handling industry. Hand hygiene in food handling settings is similar to health care as they both have:

- high impact to public health,
- specific use patterns and use environments by trained employees, and
- ethical considerations, if these products were removed from the market.

The most viable and appropriate means for assessing GRAE status of these materials is through the use of controlled simulated use clinical trials. ACI is committed to working in collaboration with the FDA to address any scientific gaps prior to development of proposed GRAE requirements. The development of test methods and guidelines is an iterative process and we look forward to working with FDA to define the requirements

ACI supported a detailed evaluation of the utility and advisability of conducting clinical outcome studies to establish the efficacy of food handler antiseptics (provided in Attachment 4-1). The evaluation indicates that controlled clinical outcome studies of food handler topical antiseptics would 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 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 handling and distribution chain (as highlighted in the CDC contributing factor data) and the infeasibility of consistently controlling all of the above variables, it is estimated that very large populations (>361,000 study participants across 14,000 study sites) would be required to generate statistically meaningful results within the context of a clinical study for food handler antiseptics.

- It is anticipated that conducting studies of this size would be impractical and confounded by several logistical challenges including identification of sites willing to participate in the study, obtaining informed consent from study participants and others who may be impacted by foodborne illness during the study, ensuring protocol compliance.
- Conducting such clinical outcome studies would have ethical implications and public health consequences.

In addition, FDA does not require clinical outcome studies to evaluate the efficacy of professional-use health care topical antiseptic hand washes nor are they required for consumer topical antiseptic hand rubs.

Clinical simulation data should be sufficient to characterize the *in vivo* efficacy of food handler antiseptics under conditions which can be better controlled to evaluate specific factors relevant to the food handler use pattern (e.g. types and amounts of soil) while avoiding the aforementioned downsides of conducting clinical studies

Although distinct from health care 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 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.

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 used in topical antiseptic food handler products. 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 Health care 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 5×10^8 to 1×10^9 . 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 Health care 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

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*" (FDA 2012). 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.

Use of a simulation model as a surrogate for effectiveness

The most direct method to evaluate effectiveness of these products is by measuring log reduction of organisms on the hands of food handlers following hand hygiene procedures using antiseptic soaps. A comprehensive approach may also include a Quantitative microbial risk assessment (QMRA) by using a simulation model for Food Handler Antiseptics; this is well established scientific field that integrates microbial hazards, exposure and dose response relationships into a risk characterization. FDA CFSAN (2005; 2013; Dennis et al. 2002), USDA FSIS (2019; Crouch

et al. 2009), EPA (2017; Whelan et al. 2014), Codex Alimentarius (1999), the World Health Organization (WHO) (2016) and WHO and the Food and Agriculture Organization (2008; 2009), and the World Trade Organization (WTO) (1998) all either specifically endorse and use QMRA for food safety decision-making or endorse the risk assessment framework generally for decision making. Published research utilizing QMRA to assess the effect of topical antiseptics on the risk of shigellosis provides an example of how QMRA could be applied as an alternative means of assessing effectiveness of food handler antiseptics (WTO 1998). Data could be generated to validate a simulation model for food handler antiseptics in the various use settings.

Soil load

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 (FDA 2017b).

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 any 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 (EPA 2012; 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 (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.

References

- American Society for Testing Materials (ASTM). 2013a. E1174-13, Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel Handwash Formulations, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E1174.htm>
- American Society for Testing Materials (ASTM). 2013b. ASTM E2946-13, Standard Test Method for Determining the Bacteria-Reducing Effectiveness of Food-Handler Handwash Formulations Using Hands of Adults, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E2946.htm>
- American Society for Testing Materials (ASTM). 2015a. ASTM E2755-15, Standard Test Method for Determining the Bacteria-Eliminating Effectiveness of Health care Personnel Hand Rub Formulations Using Hands of Adults, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E2755>.
- American Society for Testing Materials (ASTM). 2015b. ASTM E2784-10, Standard Test Method for Evaluation of the Effectiveness of Handwash Formulations Using the Paper Towel (Palmar) Method of Hand Contamination, ASTM International, West Conshohocken, PA, <https://www.astm.org/Standards/E2784>.
- Codex Alimentarius Commission. 1999. Principles and guidelines for the conduct of microbiological risk assessment. Accessed 28 January 2020. <http://www.fao.org/3/y1579e/y1579e05.htm>.
- Crouch E.A., D. Labarre, N.J. Golden, J.R. Kause, and K.L. Dearfield. 2009. Application of quantitative microbial risk assessments for estimation of risk management metrics: *Clostridium perfringens* in ready-to-eat and partially cooked meat and poultry products as an example. *J Food Prot.* 72(10):2151-61.
- Dennis, S.B., R.L. Buchanan, and A.J. Miller. 2002. Microbial Risk Assessment: Achievements and Future Challenges. *Food Safety Magazine*. Accessed 28 January 2020. <https://www.fda.gov/media/78197/download>
- Edmonds, S.L., J. Mann, R.R. McCormack, D.R. Macinga, C.M. Fricker, J.W. Arbogast, and M.J. Dolan. 2010. SaniTwice: A Novel Approach to Hand Hygiene for Reducing Bacterial Contamination on Hands When Soap and Water Are Unavailable. *J. Food Protect.* 73:2296-2300.
- Edmonds, S., R. McCormack, S. Zhou, D.R. Macinga, C. Fricker. 2012. Hand Hygiene Regimens for the Reduction of Risk in Foodservice Environments. *J. Food Protection.* 75:1303-1309.
- Food and Agriculture Organization and World Health Organization. 2008. Exposure assessment of microbiological hazards in food. Accessed 28 January 2020. <http://www.fao.org/3/a0251e/a0251e00.htm>.

- Food and Agriculture Organization and World Health Organization. 2009. Risk Characterization of Microbiological Hazards in Food: Guidelines. Accessed 28 January 2020.
<http://www.fao.org/3/i1134e/i1134e00.htm>.
- Larson, E. and L. Bobo. 1992. Effective Hand Degerming in the Presence of Blood. *J. Emergency Medicine*. 10:7-11.
- Pickering A.J., J. Davis, and A.B. Boehm. 2011. Efficacy of alcohol based hand sanitizer on hands soiled with dirt and cooking oil. *J Water Health*. 9 (3): 429-433.
- Racicot, M., A. Kocher, G. Beauchamp, A. Letellier, and J.P. Vaillancourt. 2013. Assessing most practical and effective protocols to sanitize hands of poultry catching crew members. *Prev Vet Med*. 111: 92-99.
- Schaffner D.W., J.P. Bowman, D.J. English, G.E. Fischler, J.L. Fuls, J.F. Krowka, and F.H. Kruszewski. 2014. Quantitative microbial risk assessment of antibacterial hand hygiene products on risk of shigellosis. *J Food Prot*. 77:574-582.61
- United States Department of Agriculture, Food Safety and Inspection Service (USDA FSIS). 2019. Risk Assessments. Accessed 28 January 2020.
<http://www.fsis.usda.gov/wps/portal/fsis/topics/science/risk-assessments>
- United States Environmental Protection Agency (EPA) 2012. Product Performance Test Guidelines OCSPP 810.2300: Sanitizers for Use on Hard Surfaces – Efficacy Data Recommendations. EPA 712-C-07-091. January 2012.
<https://nepis.epa.gov/Exe/ZyPDF.cgi/P100IJAU.PDF?Dockey=P100IJAU.PDF>
- . 2017. Quantitative Microbial Risk Assessment Tutorial – Primer. Accessed 28 January 2020.
https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NERL&TIMSType=&count=10000&dirEntryId=337765&searchAll=&showCriteria=2&simpleSearch=0
- United States Food and Drug Administration (US FDA). 2012. Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins. Second Edition.
- . 2017a. Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use. 82 FR 60474. Accessed 30 January 2020.
<https://www.federalregister.gov/documents/2017/12/20/2017-27317/safety-and-effectiveness-of-health-care-antiseptics-topical-antimicrobial-drug-products-for>
- . 2017b. United States Food Code. Accessed 30 January 2020.
<https://www.fda.gov/media/110822/download>
- . 2019. Safety and Effectiveness of Consumer Antiseptic Rubs: Topical Antimicrobial Drug Products for Over-the-Counter Human Use. 84 FR 14847. Accessed 25 January 2020.
<https://www.federalregister.gov/documents/2019/04/12/2019-06791/safety-and-effectiveness-of-consumer-antiseptic-rubs-topical-antimicrobial-drug-products-for>

- United States Food and Drug Administration Center for Food Safety and Applied Nutrition (US FDA CFSAN). 2005. Quantitative Risk Assessment on the Public Health Impact of Pathogenic *Vibrio parahaemolyticus* in Raw Oysters. Accessed 28 January 2020. <https://www.fda.gov/food/cfsan-risk-safety-assessments/quantitative-risk-assessment-public-health-impact-pathogenic-vibrio-parahaemolyticus-raw-oysters>
- . 2013. Completed and Ongoing Risk Assessment Projects at CFSAN. Accessed 28 January 2020. <http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/ucm247806.htm>
- Whelan, G., K. Kim, M. Pelton, J. Soller, K. Castleton, M. Molina, Y. Pachepsky, and R. Zepp. 2014. An integrated environmental modeling framework for performing Quantitative Microbial Risk Assessments. *Env. Mod. Soft.* 55:77-91
- World Health Organization (WHO). 2016. Quantitative microbial risk assessment. Accessed 28 January 2020. https://www.who.int/water_sanitation_health/publications/qmra/en/
- World Trade Organization (WTO). 1998. Understanding the WTO Agreement on Sanitary and Phytosanitary Measures. Accessed 28 January 2020. http://www.wto.org/english/tratop_e/sps_e/spsund_e.htm

Attachment 4-1: Topical Food Handler Antiseptic Drug Products: Clinical Study Considerations

TITLE

Topical Food Handler Antiseptic Drug Products: Clinical Study Considerations

AUTHORS

Brian (Shawn) Eblen, M.S.; Darci Ferrer, M.S.; Taryn Horr, M.S.; Nelson Pace, Ph.D., S.M.;
Arthur Miller, Ph.D., CFS; J. Ian Van Trump, Ph.D.

DATE COMPLETED

July 19th, 2019

PROJECT NUMBER

1902802.000

SPONSORED BY

American Cleaning Institute (ACI)
1331 L Street NW, Suite 650
Washington, DC 20005

Table of Contents

1.	<u>Executive Summary</u>	4
2.	<u>Introduction</u>	5
3.	<u>Definitions</u>	6
3.1	Food Handler	6
3.2	Food Handler Antiseptics	6
4.	<u>Regulatory History</u>	7
4.1	Review of Available Clinical Outcome Data for Related Products	7
4.2	Decisions Regarding Clinical Outcome Study Requirements	7
4.3	Relationship to the Food Handler Antiseptic RFI	9
5.	<u>Complexity Factors</u>	9
5.1	Category 1: Food	10
5.2	Category 2: Biological Hazards	12
5.3	Category 3: Food Handler Antiseptic	13
5.4	Category 4: Food Handler	13
5.5	Category 5: Consumers	14
6.	<u>Impact of Complexity</u>	15
6.1	General Design Considerations	15
6.2	Study Scenario 1: Narrow CRCT Focused on Point of Service	16
6.3	Study Scenario 2: Broader CRCT Evaluation of Multiple Food Handling Steps	22
6.4	Alternative Study Designs	23
6.5	Summary	25
7.	<u>Logistical Challenges</u>	25
7.1	Study Bounding	25
7.2	Anticipated Study Size	26
7.3	Establishment Participation	26
7.4	Informed Consent	27
7.5	Protocol Compliance and Documentation	27
7.6	Medical Monitoring	29
7.7	Analytical Resources	29
8.	<u>Ethical Considerations</u>	30

8.1	Public Health Implications of Poor Food Handler Hygiene	30
8.2	Ethics of Vehicle Control.....	30
8.3	IRB Approval.....	31
9.	<u>Professional Considerations</u>	31
9.1	Food Code.....	32
9.2	Retail Food Protection: Employee Health and Personal Hygiene Handbook.....	32
9.3	Impacts to Study Feasibility.....	32
10.	<u>Alternatives to Clinical Studies and Endpoints</u>	33
11.	<u>Conclusions</u>	34
12.	<u>References</u>	35

List of Tables

Table 1: Complexity Factor Categories

Table 2: Scenario 1 CRCT Study Design

Table 3: Key Study Parameters – CRCT

Table 4: Required Sample Size for Scenario 1 CRCT

Table 5: Key Study Parameters – Multi-stage CRCT

Table 6: Scenario 2 CRCT Study Design

List of Figures

Figure 1: Representation of Potential Interactions between Complexity Factor Categories

Figure 2: Scenario 1 - Evidence-Based Estimate, Total No. of Clusters by Power

Topical Food Handler Antiseptic Drug Products: Clinical Study Considerations

1. Executive Summary

On December 7th, 2018 the United States Food and Drug Administration (FDA) published a request for data and information (RFI) regarding food handler topical antiseptic drug products for over-the-counter (OTC) human use (food handler antiseptics). One of the questions asked in the RFI was whether or not the efficacy of food handler antiseptics should be evaluated using controlled clinical outcome studies. The purpose of this document is to provide FDA with information regarding the feasibility and utility of conducting clinical outcome studies to evaluate the effectiveness of food handler antiseptic products.

The information presented in this document indicates that controlled clinical outcome studies of food handler antiseptic efficacy will require impracticably large study populations (likely greater than 361,000 participants) 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 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. The food handling and distribution chain includes several interrelated steps and variables that may be impactful to foodborne illness transmission and/or the efficacy of food handler antiseptics.
- To overcome the complexities of the food handling and distribution chain and the infeasibility of consistently controlling all of the above variables, it is estimated that very large study populations would be required to generate statistically meaningful results in a clinical outcome study for food handler antiseptics. 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 more than 361,000 study participants in order to be adequately powered.
- It is anticipated that conducting studies of this size would be impracticable and confounded by several logistical challenges including identification and willingness of sites to participate in the study, obtaining adequate informed consent from study participants and others who may be affected by foodborne illness during the study, ensuring and documenting protocol compliance, the timely documenting and monitoring of potential adverse events, and the availability of sufficient analytical resources (e.g. contract laboratories for microbiological analysis).
- Conducting clinical outcome studies would have ethical implications and public health consequences. Food handler compliance with standard regulatory hygiene regimes (e.g. the FDA Food Code) is 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 if 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 *in vivo* efficacy evaluation.

Clinical simulation data should be sufficient to characterize the *in vivo* efficacy of food handler antiseptics under conditions which can be better controlled to evaluate specific factors relevant to the food handler use pattern (e.g. types and amounts of soil) while avoiding the aforementioned downsides of conducting clinical studies. Such an approach would be consistent with the underlying rationales FDA utilized to determine that the *in vivo* efficacy of related antiseptic products (specifically, consumer antiseptic hand rubs and healthcare antiseptics) should be evaluated using data from clinical simulation studies rather than clinical outcome studies (84 FR 14847, 82 FR 60474).

2. Introduction

In recent years, FDA has initiated rulemaking intended to facilitate finalization of the tentative final monograph (TFM) for a variety of OTC topical antiseptic drug products, including consumer-use antiseptic washes (81 FR 61106), consumer-use antiseptic rubs (84 FR 14847), and healthcare topical antiseptic products (including healthcare personnel handwashes and hand rubs, surgical hand scrubs and rubs, and patient antiseptic pre-injection and pre-surgical skin preparations) utilized by professionals in the healthcare industry (82 FR 60474).

On December 7th, 2018 the FDA published an RFI regarding food handler antiseptic drug products for OTC human use (83 FR 63168). Food handler topical antiseptic drug products, also known as “food handler antiseptics,” have historically been classified as a separate category of antiseptic drug products, distinct from both consumer and healthcare professional products (for example, see 8 FR 76444 at 76446; 80 FR 25166 at 25168; 81 FR 61106 at 61109; 82 FR 60474 at 60483). This distinction is appropriate for several reasons, including the specific use patterns and use environments for food handler antiseptics, the microorganisms of public health concern applicable to food handlings scenarios, the potential of food handler hygiene to impact public health, and the fact that such products are utilized by trained professional personnel.

The food handler antiseptic RFI solicited data and information for food handling antiseptic drug products with respect to a variety of broad issues intended to help FDA make decisions regarding how to finalize the TFM for this category of antiseptic products. Among these issues, FDA requested information regarding how the effectiveness for food handler antiseptics should be assessed, and by what criteria effectiveness should be evaluated. One key question raised by FDA within this topic area is if clinical outcome studies of food handler antiseptic products are necessary to evaluate their effectiveness.

The purpose of this document is to provide FDA with information regarding the feasibility and utility of conducting clinical outcome studies to evaluate the effectiveness of food handler antiseptic products. The available data suggest that conduct of clinical outcome studies for this use pattern may be impracticable given the complexities described in this report. Such complexities, in conjunction with logistical challenges of conducting large clinical outcome studies, also suggest that execution of a robust and valid clinical study design may be difficult or impossible. Furthermore, the conduct of controlled

clinical outcome studies within the context of food handling raises ethical concerns and introduces the potential for public health risks that may be unacceptable or unnecessary to determine the effectiveness of food handler antiseptic products. Alternative study methodologies, most notably clinical simulation studies, could be used to evaluate the efficacy of food handler antiseptics in a more controlled and reliable manner and without incurring the public health risks or ethical concerns which may be associated with the conduct of clinical outcome studies.

3. Definitions

Both “food handler” and “food handler antiseptics” are broad terms that could theoretically encompass a wide variety of workers and antiseptic products present within regulated food handling environments. As part of the food handler RFI, FDA requested additional information on how these terms should be defined for regulatory purposes (83 FR 63168). Although not intended as a formal proposal for the regulatory definition of these terms, for the purposes of this document “food handler” and “food handler antiseptics” are defined below.

3.1 Food Handler

In this document, “food handlers” are broadly defined as professional workers that handle food in commercial and associated regulated environments. Food handlers may work in a wide variety of different environments where food is grown, harvested, produced, manufactured, processed, packaged, transported, stored, prepared, served, or consumed. Each of these broad environmental categories encompass many different settings where food handlers may contact food. For example, food handlers working in “food preparation and service” settings could theoretically work in many different types of commercial establishments including cafeterias, restaurants, delis, bakeries, ready-to-eat food processing facilities, etc. In contrast, farm workers will experience a host of different food contact environments and situations. All of these food handling settings have a high potential for hands to contact and contaminate food; however, each setting also has unique factors that may impact either (a) the ability of a food handler to contaminate food and/or (b) the efficacy of a food handling antiseptic product used within that environment.

Because food handler antiseptics currently play a role in the hygiene practices of professional workers throughout the professional food handling and distribution chain, the broad definition of “food handler” as noted above is considered appropriate for examining the potential role of clinical outcome studies in evaluating the efficacy of food handler antiseptics.

3.2 Food Handler Antiseptics

In this document, the term “food handler antiseptics” refers to antiseptic hand wash and leave-on hand rub (including hand wipe) products specifically intended for use by food handlers within commercial and regulated environments where food handling may occur.

4. Regulatory History

The food handler antiseptic RFI was promulgated within the context of recent rule making conducted for related topical antiseptic products including consumer antiseptic hand washes, consumer antiseptic hand rubs, and healthcare antiseptics. Many of the factors requiring consideration for these related products, including the decision of whether or not to require clinical outcome studies in order to conduct Generally Recognized as Effective (GRAE) evaluation, are also applicable to questions raised in the food handler antiseptic RFI. Decisions made for those similar OTC products, as well as the rationale behind those decisions, can therefore provide a general framework to help inform the efficacy data requirements that would be appropriate for a GRAE evaluation of food handler antiseptics.

4.1 Review of Available Clinical Outcome Data for Related Products

Prior to rule making, FDA reviewed all submitted information, as well as the available published scientific literature, regarding the efficacy of consumer handwash, consumer hand rub, and healthcare antiseptic products. In general, and with a few notable exceptions, FDA's review did not yield clinical outcome data for any of these drug categories which it considered sufficient to evaluate product efficacy vis-à-vis clinical endpoints.

Clinical outcome studies of consumer hand wash, hand rub, and healthcare antiseptic products revealed a number of shared deficiencies, including (a) lack of appropriate control/placebo and active controls, (b) insufficient study size to support a determination of statistical significance, or insufficient statistical evaluations, (c) lack of randomization/blinding, (d) inadequate statistical power, (e) inadequate descriptions of study methodologies or data collection methods, and (f) failure to document protocol compliance for antiseptic use or other study components. In almost all cases, FDA identified other issues with available clinical outcome studies even when the aforementioned issues were not applicable. For example, the Lennell et al., 2008 study (as discussed in 81 FR 42912 at 42920) did not admit of the deficiencies noted above but had other limitations identified by FDA including (a) no clinical or microbiological evaluation of illness, (b) no specific infection studies, and (c) lack of an objective (i.e. non-subjective) primary study endpoint and no statistical evaluation of how variability of the subjective endpoint studied could impact study results¹.

Although acceptable clinical outcome data was not identified for consumer hand wash, consumer hand rub, or healthcare antiseptic products, FDA nevertheless made different decisions regarding which of these product categories would require the conduct of clinical outcome studies to support a GRAE evaluation. The rationale for these differing decisions is discussed below in order to provide regulatory context for similar decision-making as it relates to food handler antiseptics.

4.2 Decisions Regarding Clinical Outcome Study Requirements

FDA concluded as part of the 2016 Final Rule that clinical outcome studies would be required to support a GRAE evaluation for consumer-use antiseptic hand washes (81 FR 61106). This decision differed from

¹ Primary study endpoint was illness absenteeism from the childcare center where the study was employed. The degree and variability of illness and symptoms necessary for parents to keep children home from daycare was not statistically evaluated in the study.

the cases of consumer hand rubs and healthcare antiseptics, where FDA opted to not require clinical outcome studies even though acceptable clinical outcome data was not identified for these product categories either (84 FR 14847, 82 FR 60474). The differential treatment for consumer hand washes appears to have been based upon several factors, including:

Availability of Non-Antiseptic Alternative Products: According to FDA, consumer antiseptic hand washes are typically used in situations where regular (non-antiseptic) soap and water could theoretically be utilized as an alternative hand hygiene measure. However, in the case of consumer antiseptic hand rubs FDA observed (a) that antiseptic hand rubs are typically utilized in situations where regular soap and water are not readily available, (b) that no commercially available alternative hygiene products exist for hand rubs in situations where hand rubs would otherwise be used, and (c) that given the difference in use pattern, regular soap and water may not be an appropriate control for clinical outcome studies evaluating the efficacy of hand rub products (81 FR 42912). In light of these factors, a controlled clinical study for hand rubs would presumably require study participants to simply not clean their hands in situations where they otherwise could use a hand rub product.

The difference in the availability of alternative non-antiseptic products influenced FDA's decision to establish different efficacy study requirements between consumer hand washes and consumer hand rubs:

"In contrast to consumer washes, for which we are asking for clinical outcome data to support the benefit of these products, given the easily available alternative of washing with soap and water, there is no similar readily available alternative for consumer antiseptic rubs. A clinical outcome trial comparing the use of consumer antiseptic rubs to standard hand washing with soap and water has less applicability given that consumer antiseptic rubs are not generally used in situations in which soap and water are a readily available alternative. Therefore, we are currently recommending the use of clinical simulation studies because they are a practical means to assess the general effectiveness of consumer antiseptic rubs." (81 FR 42912 at 42919)

Ultimately, FDA recommended that the efficacy of consumer hand rubs be evaluated using a log reduction standard and noted that *"although a lower number of bacteria on hands may not directly translate into a reduced chance of infection, a reduced bacterial load does decrease the opportunity for infection when used in situations with no other options for hand cleansing"* (81 FR 42912 at 42919).

Public Health/Ethical Considerations: In the 2013 Proposed Rule for consumer hand washes, FDA noted the existence of two clinical outcome studies in the published literature whose design was considered generally acceptable and which demonstrated that clinical outcome studies could ethically be conducted for these products using non-antiseptic products as vehicle controls (78 FR 76444). However, FDA expressed both public health and ethical concerns regarding the conduct of controlled clinical studies for healthcare antiseptic products.

With respect to healthcare antiseptics, FDA noted, *"the use of antiseptics by health care providers in the hospital setting is considered an essential component of hospital infection control measures"* (80 FR 25166 at 25175). As such, FDA acknowledged that the use of vehicle controls for clinical outcome studies of these products in the healthcare environment could *"pose an unacceptable health risk to study*

subjects (hospitalized patients and health care providers)” and that it would be “*generally considered unethical*” to perform a placebo-controlled study of these products within a hospital setting (80 FR 25166 at 25176). The feasibility and ethical concerns associated with the potential use of non-antiseptic products as study vehicle controls are particularly important given FDA’s perspective that the hospital setting has an “*already elevated risk of infections*” (80 FR 25166 at 25176). In addition to these factors, FDA noted that performing a placebo-controlled clinical outcome trial for healthcare antiseptics in hospital settings may not be practicable in light of (a) Centers for Disease Control and Prevention hand hygiene guidelines and hospital accreditation requirements, and (b) the Nonprescription Drugs Advisory Committee’s finding that an institutional review board (IRB) would be unlikely to approve the conduct of such a study (80 FR 25166 at 25176).

4.3 Relationship to the Food Handler Antiseptic RFI

FDA’s different decisions regarding the need for clinical testing of consumer hand washes, consumer hand rubs, and healthcare antiseptics, as well as the scientific rationales underpinning those decisions, provide a general framework by which this same issue can be considered for food handler antiseptics.

Decisions regarding the need for clinical outcome testing for food handler antiseptics should be evaluated with respect to both (a) factors specific to the food handler use pattern (e.g. study complexity and practicability), and (b) the rationales upon which this same question was resolved for consumer hand wash, consumer hand rub, and healthcare antiseptic products (e.g. availability of alternative products and the public health/ethical implications of conducting or requiring clinical outcome studies).

Food handler antiseptics are similar to healthcare products as both are being used by professionally trained staff and the products are utilized as part of an infection control program. Additionally, both food handlers and healthcare professionals serve large populations and have the ability to significantly impact public health. There are serious questions regarding if 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 *in vivo* efficacy evaluation.

5. Complexity Factors

As discussed above, the use pattern for food handler antiseptics is broad and encompasses a wide variety of workers, work environments, tasks, food items, organisms of concern, etc. Therefore, a variety of complexity factors need to be considered in order to assess if a clinical outcome study for food handler antiseptics can reasonably be performed and/or will yield interpretable results.

A non-exhaustive discussion of complexity factors which may impact the efficacy of food handler antiseptics and which may need to be accounted for (i.e. controlled for) in order to obtain useful results from a clinical outcome study is provided below. A controlled evaluation of the most important of these factors may be important even outside the context of clinical outcome studies, since their individual

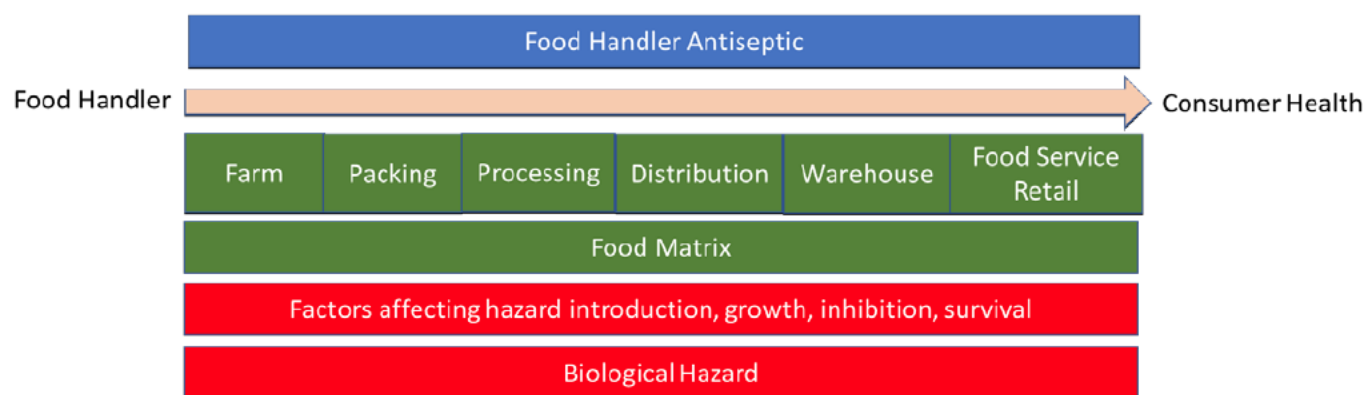
impact on efficacy may be important to decision-making regarding how and where food handler antiseptic products should be used.

For simplicity, these complexity factors have been organized into five categories (food factors, the biological hazard, hand sanitizing agent, the food handler, and the consumer). Table 1 lists the identified categories, while Figure 1 illustrates how these various categories may interact.

Table 1: Complexity Factor Categories

#	Category	Complexity Factors
1	Food	1. Stage/segment of food production continuum 2. Microbiological growth/inhibition factors 3. Ready-to-eat (RTE) vs Non RTE
2	Biological Hazard	1. Pathogen of concern 2. Pathogenicity/Infectious dose
3	Food Handler Antiseptic	1. Active ingredient 2. Application method 3. Efficacy as affected by soil type and level
4	Food Handler	1. Compliance and personal hygiene
5	Consumer	1. Illness outcome 2. Inclusion of secondary illnesses 3. Subjective/survey-based endpoints

Figure 1: Representation of Potential Interactions Among Complexity Factor Categories



5.1 Category 1: Food

Accounting for the impacts of food itself on food handler antiseptic efficacy is important to understanding the general efficacy characteristics of these products. Accounting for the complexities associated with food itself may be difficult in the context of clinical outcome studies and may preclude the generation of definitive data useful for evaluating efficacy unless adequate controls are included in the study design.

There are countless foods that are manipulated by food handlers from farm-to-fork (Green, Figure 1). The food matrix itself has several intrinsic and extrinsic variables that will affect the potential adherence, transfer, survival and/or growth of any biological agent. Intrinsic factors are those that are inherent to the foods, including surface features, size, water activity, pH, nutrient content, and presence of preservatives, etc. (Montville and Matthews, 2007). Extrinsic factors include packaging, time/temperature, holding and storage conditions and specific effects of processing steps (Montville and Matthews, 2007). It is well documented that microorganisms may survive in biofilms on food and in the food environment that serve as a protective cover against the action of antimicrobial agents, including food handler antiseptics.

Ready-to-eat (RTE) foods, such as fresh produce, deli meats, and cheese are normally eaten without further processing by the consumer. RTE foods that are contaminated by food handlers after the final kill step have no means of microbiological reduction outside of the intrinsic factors of the food itself and the concentration of the biological hazard could increase depending on the time and temperature conditions prior to consumption by consumers. Non-RTE foods require the food handler or consumer to apply a lethality step, usually heating, that should eliminate or reduce microbiological hazard concentrations prior to consumption, reducing the risk of an adverse health outcome.

While restaurants and catering settings are where most food worker associated outbreaks originate (Foddai et al., 2016), all stages of food production can potentially introduce or contribute and/or limit the survival and/or growth of the biological hazard prior to effecting consumer health (Red, Figure 1). Examples of factors that may impact the biological hazard include, but are not limited to, the following:

(1) Farms/Packing

- i) Direct or indirect contact with soil or other environmental vectors may carry biological hazards onto food.
- ii) Harvesting and sorting is often performed by hand when transfer of biological hazards can occur, either from product to food handler or vice versa.
- iii) RTE products may receive no or very little downstream processing (kill steps) to reduce microbiological contamination.
- iv) Food handler hygiene

(2) Production/Manufacturing

- i) Raw materials may contain biological hazards. Alternatively, hand contact through sorting or other manual manipulations may transfer hazards to food handlers' hands or ill workers may transfer disease-causing microorganisms to food.
- ii) Processing typically includes preventive controls (kill steps) to reduce or eliminate microbiological contamination. However, post process recontamination is common.
- iii) Extended storage times (transportation/shipping, warehouse storage, retail storage, etc.) provide an opportunity for microbiological growth or decline.
- iv) Food handler hygiene

(3) Food Service/Retail

- i) Food preparation and opportunities for cross contamination.
- ii) Food handler hygiene
- iii) Contamination occurring after a kill step and before serving.

- (4) Other – including farmers markets and temporary food service establishments (i.e. fairs, concession stands, church picnics, etc.).
 - i) Food preparation and opportunities for cross contamination.
 - ii) Contamination could occur after a kill step and before serving.
 - iii) Food handler hygiene

5.2 Category 2: Biological Hazards

Exposure to a specific biological hazard is a key factor to determine the likelihood, symptomology, and severity of potential health effects to a consumer. Therefore, controlling for the specific biological hazard at play will be important to understanding the overall efficacy characteristics of food handler antiseptics. This complexity factor may be challenging to evaluate or control in the context of a clinical outcome study for various reasons, including those discussed in detail below. If not controlled, this factor may confound the interpretation of results obtained from a clinical outcome study or preclude the ability to make informed regulatory decisions regarding under what situations food handler antiseptics should be used.

At the retail level, the FDA deemed six communicable infectious foodborne pathogens to be of most concern for food handlers. These include norovirus, non-typhoidal *Salmonella*, *Salmonella* Typhi, Shiga toxin-producing *Escherichia coli*, *Shigella* species and Hepatitis A virus (FDA, 2018a; ServSafe, 2014). These pathogens were selected due to their low infectious doses, ability to adhere to the gastrointestinal tract, and capacity to shed in high numbers in feces. As described by the FDA, these pathogens can easily be transmitted to consumers by food handlers “even when good handwashing practices are used” (FDA, 2018a). Nevertheless, a survey of 816 foodborne disease outbreaks between 1927 and 2007, where the food workers were reported as instrumental or contributory to the outbreak, identified 14 different microorganisms as the causative agents (Greig et al., 2007). Each microbiological pathogen may replicate, spread and/or infect differently depending on the antiseptic agent used (Category 3), the food handler’s health and behavior (Category 4), the food matrix it contaminates (Category 1) and the person consuming it (Category 5).

The infectious dose of pathogens varies widely and can depend on the health status of the exposed individual (Category 5). Healthy adults tend to require higher levels of infectious agents to cause illness and some may be asymptomatic carriers (Todd et al., 2008). One study showed the breadth of ranges required to cause diarrheal infection, stating that 200 cells of *Shigella* spp., 10^5 cells of *Salmonella* Typhi, and 10^7 cells of *Vibrio cholerae* were sufficient for symptom induction for 20 to 30% of participants, but also stated that the pH of the inoculum affected the infectious dose (Hornick et al., 1970; Todd et al., 2008). Low detected levels of pathogens found in food leftover from outbreaks suggest that very low levels can cause illness, though it is impossible to know retrospectively exactly how much food was consumed (Todd et al., 2008). For example, *E. coli* O157:H7 has been estimated to cause illness at dose levels as low as 10 colony-forming units (CFU) following ingestion of contaminated food (Todd et al., 2008). Generally, it is expected that pathogens with low infectious doses are more easily transmitted (Todd et al., 2008). However, extended time and temperature abuse of foods may permit the growth of pathogens requiring high infectious doses.

5.3 Category 3: Food Handler Antiseptic

Variation among different food handler antiseptic active ingredients, use patterns, and use scenarios are important to evaluating the efficacy of food handler antiseptics as a general drug category. This variation may be evaluated more easily in the context of non-clinical *in vivo* studies than in clinical outcome studies.

Topical antiseptic drug products (consumer hand washes, consumer hand rubs, healthcare antiseptics, and food handler antiseptics) contain a wide variety of active ingredients and come in a number of different formulations associated with different application use patterns. These active ingredients have a range of effectiveness depending on the biological agent (Category 2) and other factors.

The use of different experimental methodologies is problematic for comparison of multiple studies that evaluated the removal from, or inactivation of, pathogens on human hands difficult (Foddai et al., 2016). However, Sickbert-Bennett et al. (2004) reviewed Medline articles concerning hand hygiene, antisepsis and disinfection and determined that the important variables affecting a hand hygiene agent's efficacy included the concentration of the active ingredient, volume of the agent used, and the application time. In general, increased concentrations, volumes and application times of the hygiene agents had increased efficacy (Sickbert-Bennett et al., 2004).

Additionally, the type and degree of soil on the food handler's hands is considered the main factor affecting inactivation rates of hand hygiene products (Foddai et al., 2016). Moderate and heavy soiling is generally considered to reduce antiseptic efficacy, leading to 1-2 log₁₀ less of microbial bioburden reduction (Foddai et al., 2016; Edmonds et al., 2010; Edmonds et al., 2012). When used in combination with soap and water, hand antiseptics can reduce bacteria loads by over 5 logs (Edmonds et al., 2010). This highlights that frequent handwashing by the food handler (Category 4) reduces the amount of soil on hands and reduces the concentration of a causative agent on their hands and can therefore skew health outcome studies.

5.4 Category 4: Food Handler

When evaluating the effectiveness of food handler antimicrobial hand sanitizer use, the food handlers themselves must be considered. Unless adequately controlled for, impacts of food handler variability on antiseptic efficacy may be difficult to ascertain within the context of clinical outcome studies. It is anticipated that adequately controlling for this variability would be challenging, especially for large studies performed outside of a highly controlled clinical environment (e.g. studies conducted at food point-of-service establishments) which may not be familiar with how clinical studies should be conducted (monitoring adequate protocol compliance, documenting protocol compliance, etc.).

The manner and concentration in which food becomes contaminated by food handlers is affected by many factors including, but not limited to, their general personnel hygiene and their compliance with hand hygiene protocols. The 2017 FDA Food Code (the "Food Code"; FDA, 2017) lists the following nine reasons to wash hands throughout the course of a day:

- (1) Touching bare human body parts
- (2) Using the toilet
- (3) Handling animals
- (4) Coughing, sneezing, eating, drinking, etc.
- (5) Handling dirty equipment/utensils
- (6) During food prep as often as necessary to remove soil and prevent cross contamination
- (7) Going from raw to RTE foods
- (8) Before donning gloves
- (9) After engaging in other activities that contaminate the hands

However, in the most recent FDA report on the occurrence of foodborne illness factors in fast food and full-service restaurants (2013-2014) published in 2018, 65.64% of Fast Food Restaurants and 82.40% of Full-Service Restaurants were out of compliance for proper handwashing practices (FDA, 2018b). For larger industrial food manufacturing facilities, anecdotal evidence suggests good compliance with hand hygiene protocols; however, minimal hand washing was observed after breaks or between glove usages (Todd et al., 2010). One study indicated that hand washing by vendors at farmers markets was extremely low at only 4% prevalence (Young et al., 2017). Some specific reasons for not washing hands when needed were identified as laziness, time pressure, inadequate washing facilities or supplies, lack of accountability, and lack of company support for proper hand washing (Todd et al., 2010). These low levels of compliance for handwashing at multiple stages of production suggest that similar levels of compliance for use of food handler antiseptic products may also exist, making the ability to measure their effectiveness difficult. Anticipated difficulties with respect to protocol compliance are evaluated further in Section 7.5.

5.5 Category 5: Consumers

Variability in how different consumers are impacted by exposure to foods that may have been contaminated due to poor food handler hygiene may also make the results of a clinical trial of food handler antiseptics difficult to interpret. It is anticipated that controlling for this variability, as part of a clinical outcome study, would be challenging.

Foodborne illness outcomes can range from mild to severe depending on many complexity factors (Table 1). The most common foodborne illness symptoms include upset stomach, stomach cramps, nausea, vomiting, diarrhea and fever (CDC, 2019). However, some foodborne illnesses present with non-gastrointestinal symptoms, including dehydration, muscle weakness, weight loss, paralysis, brain and nerve damage, kidney failure and sometimes death (CDC, 2019). The wide range of symptoms and their degree of severity depends on the multiple complexity factors discussed and raises the concern of patients potentially experiencing serious adverse health consequences (see discussion in Section 8.1 and Section 8.2). Another key element is if the clinical outcomes rely on patients to self-report illness and symptoms via survey or a journal. This could skew results due to the subjective nature of common symptoms.

The main factor determining the health outcome is the specific pathogen causing the illness (Category 2). However, the likelihood and severity of illness can also be influenced by the pathogen levels in the food, the amount of food consumed as well as consumer's age, gender, diet, and health status. Infants and individuals that are immunocompromised, elderly or pregnant can be more susceptible to illness/infection.

Additionally, the incubation time and onset of foodborne illness symptoms can range from 30 minutes to four weeks, again depending on the causative agent, their virulence factors and levels, and host factors (CDC, 2019). When symptoms take multiple days to develop, it becomes increasingly difficult to distinguish between a primary case and what food caused that case and a secondary case. One survey of 936 household gastroenteritis infections determined 8.8% of those cases were secondary cases (Perry, et al., 2005). This could lead to a skewed number of illnesses attributed to food handlers.

6. Impact of Complexity

As discussed in Section 5, clinical outcome studies conducted for food handler antiseptics would need to account for a variety of complexity factors that could impact both the experimental system and the efficacy of a given food handler antiseptic active ingredient. In the discussion below, the complexity of the food handler use pattern is translated into quantitative terms by evaluating the number of participants that would likely be required to conduct a clinical outcome study intended to evaluate the efficacy of a generic food handler antiseptic compared to a control (e.g., a non-antiseptic product or no treatment). The general study designs discussed below are theoretical and are only intended to allow for an estimation of the study size that would be required to conduct an adequately powered clinical outcome study for food handler antiseptics.

As discussed in detail below, obtaining adequate study power would require a very large number of participants and may be impracticable or unadvisable for reasons discussed in Section 7 through Section 9. Should the study be underpowered, it is unlikely to yield definitive results for a GRAE evaluation.

When data from the scientific literature is used to set key values in the study design, a study size range of approximately 361,000 to 1.5 million participants is estimated to be necessary to yield informative results for a clinical outcome study of food handler antiseptics.

6.1 General Design Considerations

Throughout the rule-making process for consumer antiseptic hand washes, consumer antiseptic hand rubs, and healthcare antiseptic products, FDA has defined the critical elements required in a complete clinical outcome study to appropriately evaluate the efficacy of these products (78 FR 76444, 81 FR 42912, 80 FR 25166). For example, the evaluation of a valid clinical or microbiological indicator of foodborne illness was identified as a critical element (see discussion of Lennell et al., 2008 in Section 4.1). The clinical outcome studies discussed below were intentionally designed in an attempt to meet FDA's expressed expectations for such studies while avoiding deficiencies that FDA identified during its review of clinical outcome studies available in the academic literature for topical antiseptic products (see Section 4.1).

Two different cluster randomized clinical trial (CRCT) outcome study designs were considered. Scenario 1 was intended to model a relatively narrow experimental test system focused on evaluating the efficacy of food handler antiseptics at one step of the food handling and distribution chain. Scenario 2 was intended to encompass a broader study design evaluating three different steps in the food handling and distribution chain.

6.2 Study Scenario 1: Narrow CRCT Focused on Point of Service

Scenario 1 details the study design and considerations necessary to conduct a clinical outcome study examining the impact of food handlers' use of a food handler antiseptic as compared to a non-antiseptic control at the point-of-service, i.e., food service facilities, including restaurants and cafeterias. This more narrowly focused study design considers only the point-of-service and does not encompass other stages of the food handling chain such as harvesting and packaging.

6.2.1 Primary Objective

The primary objective of the Scenario 1 CRCT would be to examine whether food handler antiseptic use by food handlers reduces the incidence of foodborne illness in food consumers compared to a control treatment. Testing the efficacy (i.e. superiority) of a food handler antiseptic compared to a non-antiseptic control in the prevention of foodborne illness in a relatively straightforward manner would require CRCT with two treatment arms (1. antiseptic (A) and 2. control (B)) evaluating a binary health endpoint, foodborne illness (yes/no).

6.2.2 Study Design

Study Scenario 1 is envisioned as a multi-center, cluster-randomized, parallel-group trial conducted at multiple food service facilities in the United States with a follow-up of 1 year.² The general design of a two-level CRCT with a binary outcome is that customers (food consumers) are nested (i.e. clustered) within each food service facility (i.e., restaurant or cafeteria). Food service facilities would be randomized two at a time in equal proportions (1:1 ratio) to either food-handler antiseptic treatment (A – 50%) or a control (B – 50%).

The information on the outcome (clinical diagnosis of foodborne illness) would be captured at the customer level via three methods (a) daily self-report surveys (reported via computer, telephone, or smartphone app-based) of foodborne illness symptoms, (b) medical records, and (c) measurement of biomarkers when illness is reported. Self-report of foodborne illness symptoms would be followed by a request for biomarker measures. Medical records and/or biomarker measures would be used confirm a potential foodborne illness. The statistical analysis would evaluate the difference in foodborne illness incidence between study arms at regular intervals with the primary analysis focusing on foodborne illness incidence over the full 12 months. The estimated number of clusters, cluster size, and total sample size of enrolled and followed participants are presented according to a variety of different assumptions in Section 6.2.7 (Sample Size Estimation).

Table 2 shows basic cluster randomized treatment assignment for food service facilities one through i being randomly assigned to either A (antiseptic) or B (control). The actual number “i” would be determined by number of participants recruited per cluster and additional factors determining the frequency of illness. Table 3 indicates key parameters included in the CRCT study design.

² Follow-up is considered to a one-year minimum to provide adequate time to observe a sufficient number of foodborne illness cases.

Table 2: Scenario 1 CRCT Study Design

Location (cluster, n= <i>i</i>)		Treatment	
Food service facility (restaurant/cafeteria)		A. Antiseptic	B. Control
Facility 1		A	B
Facility 2		A	B
Facility 3		A	B
Facility 4		A	B
Facility 5		A	B
Facility 6		A	B
Facility 7		A	B
...	
...	
Facility <i>i</i>		A	B

Table 3. Key Study Parameters – CRCT

Treatment:	Antiseptic (A), Control (B)
Primary health outcome of interest:	Clinical diagnosis of a Foodborne illness (Yes/No)
Unit of randomization:	Food service facility (restaurant, cafeteria)
Unit of analysis:	Individual participant (food consumer)
Study Period:	One year

6.2.3 Intervention

The intervention would comprise provision of dispensers containing the treatment, food-handler antiseptic or control, according to randomized assignment. These dispensers would replace all other previously present hand cleaning materials. Poster placards providing instructions for application of the treatment would be placed near the dispensers at each study location. To evaluate compliance, managers would report weekly use of the treatment. As discussed in Section 7.5, such measures may or may not be sufficient to establish compliance with the study protocol.

6.2.4 Inclusion Criteria

Food Service Facility: Eligible restaurants or cafeterias would need to voluntarily participate in the study in agreement with company leadership and local management, as applicable. The facilities would need to allow the replacement of prior personnel hygiene supplies with the treatment designated according to the randomized allocation of the study intervention, and to use only those supplies provided by the study. Participating facilities would agree to recruitment of study participants at the point of service or via listservs used by the company to contact food consumers. Monitoring compliance with these requirements may be difficult.

Individual Participants (Food Consumers): Eligible participants would need to be aged 18 to 65 years at the start of the study, eat frequently (once per week or more) at a specific food service facility, and grant written informed consent to complete weekly update surveys regarding symptoms (and submit an updated survey within 24 hours when symptoms of diarrhea or nausea first occur), provide access to relevant medical records during the duration of the study, and submit biomarker samples when foodborne illness symptoms are reported. Participants would be requested not to eat at other participating food service facilities during the course of the study.

6.2.5 Study Incentives

There would likely need to be incentives provided to participating food service facilities and customers to encourage enrollment. Incentives could include meal vouchers for food consumers. By purchasing these vouchers directly from each food service facility, study investigators would provide an incentive for facility-level participation.

6.2.6 Data Collection and Outcomes

After inclusion, the participants would complete a baseline questionnaire relating to health, hygiene practices, food consumption, and basic demographic factors. Weekly update surveys regarding illness would also be completed via computer or phone. Any indication of illness would be followed up with the request for recent medical records/test results, if applicable, and a request to submit biomarker. At enrollment, study participants would be sent materials and instructions to take and ship non-invasive biomarker samples (e.g., a stool sample) for testing of the presence of foodborne pathogens. Updates on study compliance from food service facilities on the use of assigned intervention will be requested weekly.

6.2.7 Scenario 1 Sample Size Estimation

Sample sizes determination for adequate study power for a CRCT is dependent upon a number of factors. The following standard assumptions were made to estimate the required sample size for the hypothesized study under Scenario 1: power of 80% or greater, α -level of 0.05 (corresponding to 95% confidence intervals and p -value <0.05 for statistical significance), one-to-one randomization of treatments, and an interclass correlation coefficient (ICC) of 0.05 (a conservative though reasonable estimate). These assumptions are based upon our understanding of what FDA would expect from a clinical outcome study intended for use in a GRAE evaluation.

Potential Study Size Range: To obtain a range of study sizes, a range of assumptions were used for a number of other factors including (a) baseline incidence of foodborne illnesses (all pathogens vs. bacteria-only), (b) risk of foodborne illness depending on location of consumption (restaurant vs. any location), (c) percent of illness due to food workers, and (d) percent of illness prevented by the antiseptic relative to control. The resultant sample size estimates with varying levels of these factors are presented in Table 4.

Using this approach, a realistic minimum sample size can be estimated based on relatively extreme but plausible assumptions that are designed to decrease the required sample size, namely, (a) the baseline incidence of foodborne illness against which the antiseptic is effective against is 3.14% (Scallan et al.,

2011), (b) restaurant food consumption doubles the risk of foodborne illness compared to consumption in any location overall, (c) 100% of foodborne illnesses originate from food handlers, and (d) the antiseptic use compared to control results in a 50% reduction in foodborne illness) would be 2,080 participants in 208 clusters averaging 10 participants each. While these assumptions are theoretically possible, they are far from probable. The evidence-based sample size is a more scientifically informed estimate of what study size would be required to adequately power a CRCT (see discussion below).

Evidence-Based Estimate: An evidence-based estimate for sample size was also calculated using the available scientific literature to inform key study assumptions. Specifically, the baseline incidence of foodborne illness (a) is assumed to be 1.22% per year, which is the incidence for bacterial foodborne illness reported in Scallan et al. 2011. The risk of foodborne illness in restaurants (b) is anticipated to be 1.6 fold (60% greater than) that in all locations of food consumption overall (CSPI, 2015), and the percent of illnesses due to food workers (c) is estimated to be 58.6% (Lipcsei et al., 2019). For estimation purposes, a reduction on illness (d) of 10% was selected as a clinically meaningful difference.

From all these factors, the evidence-based sample size assuming 100 participants per cluster would be 7,421 clusters (i.e., restaurants) in each study arm (14,842 total clusters). This would result in an effective sample size of 1,484,200 study participants to achieve 80% power and detect a 10% difference in foodborne illness over 1 year. With an average of 10 instead of 100 participants per cluster, 18,084 clusters would be needed per study arm (36,168 total clusters), with 361,680 total study participants. A graphical representation of the relationship between power and number of clusters for the two different cluster sizes (n=100 or 10) is provided in Figure 2. Figure 2 shows that power increases with increasing number of clustered and a smaller number of clusters is needed when the number of participants per cluster is greater.

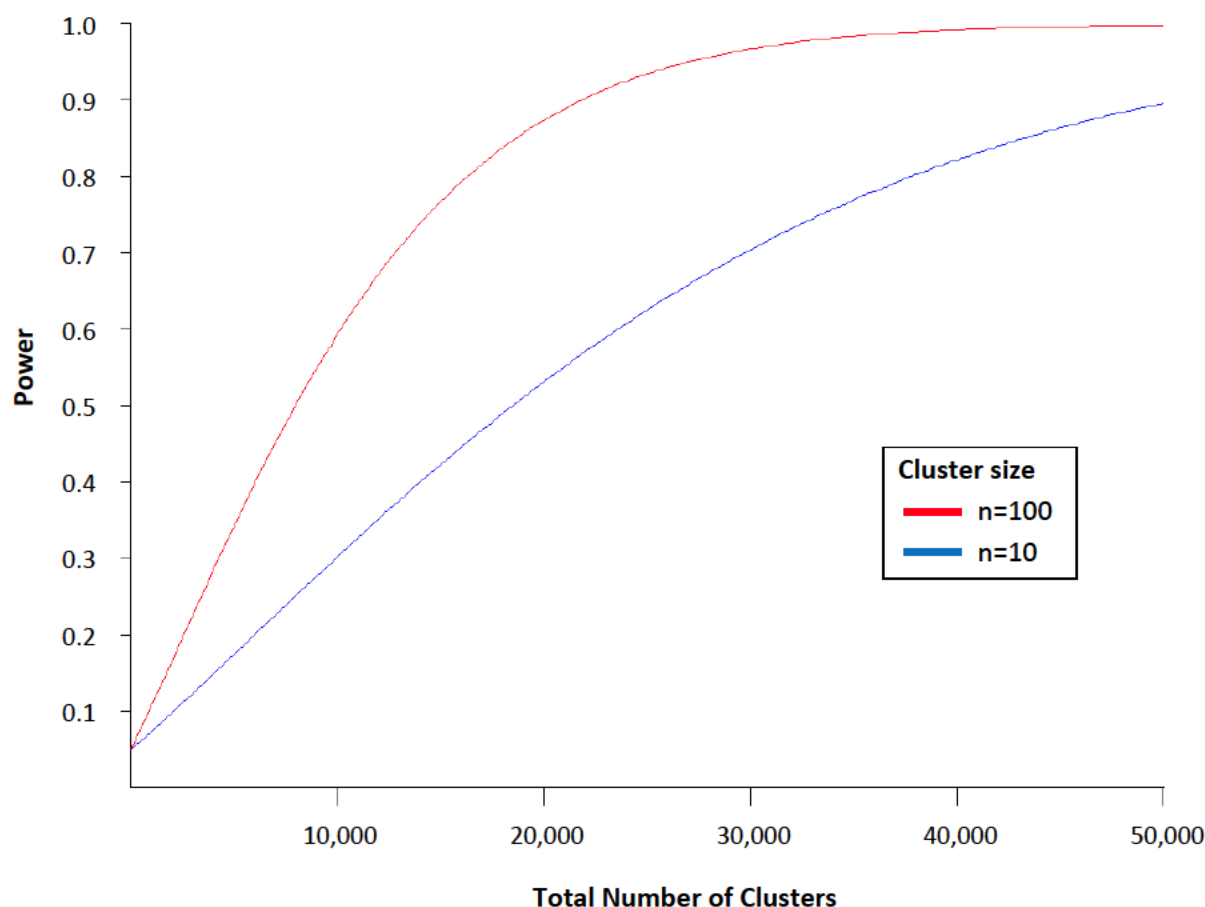
Table 4: Required Sample Size for Scenario 1 CRCT ($\alpha=0.05$, Power=0.80, ICC=0.05)^a

Bacterial Illness or All Foodborne Illness (Scallan et al., 2011)	Restaurant multiplier (CSPI, 2015)	% illness from food handlers (Lipcsei et al., 2019)	Reduction of Illness	Participants per Cluster			
				n=100		n=10	
				No. Clusters	Total Participants	No. Clusters	Total Participants
Bacterial Foodborne Illness (1.22% U.S. pop)	x1	100%	5%	59,040	5,904,000	143,880	1,438,800
		100%	10%	14,386	1,438,600	35,058	350,580
		100%	25%	2,122	212,200	5,172	51,720
		100%	50%	456	45,600	1,110	11,100
	x2	100%	5%	29,166	2,916,600	71,074	710,740
		100%	10%	7,110	711,000	17,324	173,240
		100%	25%	1,050	105,000	2,558	25,580
		100%	50%	226	22,600	550	5,500
All Foodborne Illness (3.14% U.S. pop)	x1	100%	5%	22,494	2,249,400	54,816	548,160
		100%	10%	5,484	548,400	13,364	133,640
		100%	25%	810	81,000	1,974	19,740
		100%	50%	176	17,600	426	4,260
	x2	100%	5%	10,892	1,089,200	26,542	265,420
		100%	10%	2,658	265,800	6,476	64,760
		100%	25%	394	39,400	960	9,600
		100%	50%	86	8,600	208	2,080
Evidence-based Estimate Bacterial Foodborne Illness (1.22%)	x1.608 ^b	58.6%	10%	14,842	1,484,200	36,168	361,680

^a: Sample size calculations made using PASS 2019 software (PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

^b: Multiplier for number of foodborne illnesses from restaurants relative to restaurants and private homes combined is derived using quantities specified in CSPI, 2015 ($1.608 = (21,335 / [21,335 + 12,964])^{-1}$)

Figure 2: Scenario 1 - Evidence-Based Estimate, Total No. of Clusters by Power



6.2.8 Statistical Analysis and Presentation of Results

In this design, it is anticipated that baseline characteristics of participants for all randomized food service facilities would be equally balanced across treatment arms. Validation of successful randomization would be confirmed by performing formal statistical testing by baseline characteristics and presenting said results.

Crude means and 95% confidence intervals for foodborne illness incidence and incidence over time by intervention arm would be presented. The difference in foodborne illness incidence between the food handler antiseptic and control arms would be statistically modeled using generalized estimating equations with an exchangeable working correlations matrix (proposed but dependent upon actual correlation structure) to account for clustering within food service facilities. Adjustment for factors predictive of the outcome (e.g., customer characteristics obtained from the baseline questionnaire) would be considered to improve the precision of the estimated results. Superiority of a given treatment arm would be assessed based upon the standard α -level of 0.05.

6.2.9 Additional Considerations

This trial would be required to be registered in advance with ClinicalTrials.gov. A Data Safety Monitoring Board (blinded to treatment assignment) would need to periodically review study results and determine whether the study needs to be stopped early, for example, due to clear evidence of a difference in efficacy or safety between treatment groups.

6.3 **Study Scenario 2: Broader CRCT Evaluation of Multiple Food Handling Steps**

The following scenario is very similar in approach to the more narrowly defined Scenario 1. However, while Scenario 1 focuses only on the impact of food handlers and foodborne illness at the point-of-service (i.e., restaurants and cafeterias), Scenario 2 would take a broader approach by including additional steps in the food handling and distribution chain. Three stages of the food handling and distribution chain are considered: harvesting, packaging, and preparation. This broader approach results in a substantially more complex study design. Conduct of such a study would be anticipated to require strong control of the food handling and distribution chain to both ensure protocol compliance (see Section 7) and to ensure that the study is conducted in an ethical fashion (see Section 8). Briefly, this broader study would be designed as follows.

6.3.1 Primary Objective

The primary objective of the Scenario 2 CRCT would be to examine whether the provision of a food handler antiseptic, compared with a control, to food handlers at any stage or any combination of stages in the food handling chain reduces the incidence of foodborne illness in food consumers. To test the efficacy (in regard to superiority) of a food handler antiseptic compared to a control treatment in the prevention of foodborne illness in a relatively straightforward manner would require a CRCT with eight treatment permutations evaluating a binary health endpoint, i.e., foodborne illness (yes/no) among food consumers at the end of the food handling chain.

6.3.2 Study Design

This trial is envisioned using essentially the same design as the trial under Scenario 1, i.e., a multi-center, multi-stage, cluster-randomized, open, blinded-endpoint, parallel-group trial conducted at multiple food service facilities in the United States with a minimum follow-up of 1 year (Table 5). The general design of an 8-level CRCT with a binary outcome is that customers (food consumers) are nested (i.e., clustered) within food-service facility (restaurant, cafeteria). Food handling chains are randomized two at each stage (a, b, c) with each permutation in equal proportions (1:1:1:1:1:1:1:1 ratio) to either food handler antiseptic treatment (A – 50%) or control treatment (B – 50%).

Table 5. Key Study Parameters – Multi-stage CRCT

Treatment	Antiseptic (A), Control (B)
Primary health outcome of interest:	Clinical diagnosis of a Foodborne illness (Yes/No)
Unit of randomization:	Food handling chain (combination of stage: harvesting, packaging, preparing)
Unit of analysis:	Individual participant (food consumer)
Study Period:	One year

Table 6 shows the multi-stage CRCT treatment assignment for each combination of stage and treatment for Scenario 2 (8 combinations). Several clusters would be required for each randomized assignment as in Scenario 1.

Table 6. Scenario 2 CRCT Study Design

Stage	Treatment							
	A. Antiseptic wash				B. Soap wash			
	AAA	AAB	ABA	ABB	BBB	BBA	BAB	BBA
a. Harvesting (Farm)	Aa	Aa	Aa	Aa	Ba	Ba	Ba	Ba
b. Packaging (Factory)	Ab	Ab	Bb	Bb	Bb	Bb	Ab	Bb
c. Preparing (restaurant, cafeteria)	Ac	Bc	Ac	Bc	Bc	Ac	Bc	Ac

The additional specifications of this study would correspond closely to those provided in Scenario 1; key differences are (a) the added complexity of coordinating treatment assignment with each stage of the food-handling and distribution chain and (b) the larger sample size required to compare 8 treatment patterns, effectively necessitating 4 times the number of participants as detailed in Table 4 for Scenario 1.

6.3.3 Scenario 2 Sample Size Estimation

An evidence-based sample size estimate for a study of this design this would require between 1.4 and 5.9 million study participants. The statistical analysis and additional considerations for Scenario 2 are essentially equivalent to Scenario 1, and as such are not delineated again here.

6.4 **Alternative Study Designs**

The study designs described for Scenario 1 and Scenario 2 above may be infeasible or inadvisable due to the sample size requirements, non-compliance considerations, and other issues addressed in Section 7 though Section 9 of this document. Therefore, a brief discussion of alternative approaches that could be considered in order to evaluate the clinical efficacy of food handler antiseptics is provided below. These alternative designs focus on (a) self-reported illness (as opposed to clinically confirmed diagnosis) and (b) the use of observational real-world data already generated as part of routine clinical care/state-based surveillance activities.

6.4.1 Self-Reported Illness

While foodborne illness is challenging and costly to diagnose, typical symptoms of foodborne illness are readily identifiable, albeit nonspecific (e.g., diarrhea and vomiting). Self-reporting of these symptoms would result in false positive results due to the non-specificity of these endpoints (i.e., the symptoms can be caused by many exposures other than foodborne pathogens), but would also likely identify the majority of foodborne illness cases. In this approach to outcome measurement, pathogen-specific information would not be obtained from medical records or biospecimens.

For example, self-reported diarrheal illness could in theory be utilized as a primary study outcome measure for the Scenario 1 and Scenario 2 study designs. Diarrhea could be recorded based upon CDC's definition of *persistent diarrhea* (loose, watery stools occurring more frequently than usual with at least 3

episodes within a 24-hour period, and the diarrhea is frequent and severe enough that (a) other people notice the person going to the restroom numerous times, or (b) the ill person or another passenger voices concern about it) (CDC, 2017). Self-report could be done by food consumers on a weekly basis via computer, telephone, or smartphone app-based survey responses.

Use of self-reported diarrhea or vomiting as the primary outcome measure could allow for the reallocation of study resources towards coordination of the very large sample size anticipated to be required for the study at a lower cost. While use of self-reported outcome data in the study design would most likely be substantially more cost-effective and feasible than requiring a clinical diagnosis, the non-specificity of this outcome would create error (i.e., imprecision) in the results. Issues of study implementation at hundreds if not thousands of sites would continue to be an issue as well.

6.4.2 Retrospective Cohort Observational Study

Rather than conducting a randomized clinical trial (RCT), a clinical study can be simulated using observational real-world data already generated as part of routine clinical care/state-based surveillance activities. Propensity score matching (PSM) is a technique used to simulate such a study accounting for both selection bias and confounding. The technique conditions treatment so that observed differences between one intervention arm and the other are the same for all covariates of concern (due to confounding or bias) except the treatment itself.

Using data collected from restaurant managers on their use of antiseptic or non-antiseptics and corresponding foodborne illness outbreak data with follow-up of infected individuals to retrospectively obtain food consumption history (i.e., locations where they ate), PSM could be used to simulate random assignment to consuming food at a food service facility using one food handler antiseptic type or another treatment (e.g. non-antiseptic control). Effects can then be estimated for the probability of foodborne illness. Such a study would require collection of key variables and potential confounding factors from restaurants and their customers, but it would not require randomization of interventions. In order to appropriately capture foodborne illness, it is important that the State or States in which the study is conducted have a thorough and comprehensive capturing of foodborne illness. This approach to a foodborne illness investigation analysis has been taken recently by FDA researchers in its evaluation of handwashing (Ali et al. 2014).

While this study design simulates an RCT, the data obtained would nonetheless be considered inferior to an RCT, which is the gold standard for establishing causality.

Although an observational study would be, in many ways, more feasible than an interventional CRCT, it would still entail numerous logistical challenges. With cases of foodborne illness being captured at the State-level, retrospective exposure assessment would be needed to thoroughly document and examine all locations of food consumption around the time of the suspected pathogenic exposure. Follow-up would also need to be done with all food service facilities visited by the affected food consumers to determine what type(s) of antiseptics were or were not used at each location. This approach would require a larger sample size to differentiate the influences of multiple potential exposures. It may also be challenging to reliably identify food service facilities that exclusively use antiseptic or non-antiseptic products, let alone verify that the product(s) used at a given site are accurately reported.

6.5 Summary

Using prior FDA guidance as a framework for designing a clinical outcomes on this topic, it is estimated that approximately 361,000 to 1.5 million participants would be required to adequately power a clinical outcome study of food handler antiseptics even when the experimental system is narrowly defined to a single step in the food handling and distribution chain. Should the study be underpowered, it would be unlikely to yield definitive outcome measure data for a GRAE evaluation. Alternative study designs, while worth considering, have their own shortcomings and are unlikely to support a definitive evaluation of food handler antiseptic efficacy on their own.

7. Logistical Challenges

As discussed in Section 3 food handler antiseptics are used by a diverse group of workers at multiple steps in the food handling and distribution chain. Each of these use situations is subject to a number of complexities which may be challenging to address and control for (see Section 5) and which would likely necessitate very high number of study participants in order to obtain statistically significant results (see Section 6). Taken together, these factors impose unique logistical challenges that would need to be contended with if clinical outcome studies are employed to evaluate the efficacy of food handler antiseptics. A non-exhaustive list of logistical challenges that may impact the practicability of conducting clinical outcome studies for food handler antiseptics is discussed below.

7.1 Study Bounding

In order to conduct a clinical outcome study, the study's test system must first be defined. As discussed in Section 3, food handlers as a professional category encompass a wide variety of workers conducting a wide variety of tasks within various different regulated environments. Each of these works, tasks, and environments are associated with different complexity factors, which may impact the efficacy of food handler antiseptics. Clinical outcome studies for food handler antiseptics, if conducted, would need to account for this broad diversity while also keeping the test system bounded and well defined.

Broad study design: As discussed in Section 6, one way to address this diversity would be to design and implement large, comprehensive studies incorporating and accounting for as many different workers, tasks, environments, and complexity factors as possible throughout the food handling and distribution chain. Such studies would need to be very large and would also require considerable management with respect to both (a) the scientific components of the clinical study (e.g. medical monitoring, endpoint data collection, monitoring and documenting protocol compliance) and (b) the maintenance and control of the test system itself (e.g. managing food supply and distribution chains). Overall, large, comprehensive clinical studies that encompass broad swaths of the entire food handling and distribution chain are likely to be logistically impracticable for a number of reasons, including the large study size anticipated to be necessary and difficulties in monitoring and ensuring test system integrity (e.g. tracking and controlling "on study" food and keeping it separate from all other inputs into the food handling and distribution chain). These factors are also likely to impact the ability of a large, overarching study to yield interpretable outcome data.

Narrow study design: An alternative means to address the diversity of the food handler test system would be to run one or more smaller studies intended to produce clinical outcome data for subsets of the food handling and distribution chain (for example, studies restricted to food handlers in retail food establishments only). Such studies would be less logistically complicated and would presumably allow for individual studies to be better controlled with respect to the complexity factors believed to be most impactful for the testing scenarios in question. Although smaller and more focused clinical outcome studies may be more feasible on an individual basis, there are a number of downsides with this approach. For example, this approach would require consensus regarding the selection of which food handling workers, tasks, environments, and antiseptic products would be tested. The outcome of consensus-building would likely be a suite of clinical studies covering different use scenarios, which would increase study costs and timeframes. Additionally, this approach would disallow an evaluation of the aggregate impact of food handler antiseptic use when utilized throughout the entire food handling chain. Being unable to evaluate aggregate impacts may make it difficult for such studies to draw accurate and statistically meaningful conclusions since any aggregate effects of antiseptic use, if present, would be masked.

7.2 Anticipated Study Size

As discussed in Section 6, clinical outcome studies for food handler antiseptics are anticipated to require very large numbers of study participants at hundreds of study sites. For example, it is estimated that even a narrow clinical outcome study focused on a single step in the food handling and distribution chain (food retail establishments) would require the participation of $\geq 361,000$ study subjects to yield statistically meaningful results. Large clinical studies such as these are difficult to initiate, coordinate, and manage in a manner that will yield reliable outcome data, and these challenges are more pronounced for studies conducted outside of transitional healthcare settings. Furthermore, obtaining IRB approval for the conduct of such studies may be difficult given that (a) a large number of study participants would need to be assigned to a study's vehicle control arm, and (b) participants within the vehicle control arm may have a higher risk of contracting a serious foodborne illness.

7.3 Establishment Participation

In theory, clinical outcome studies for food handler antiseptics could be conducted in pseudo-healthcare settings (e.g. hospital cafeterias, senior care facilities). However, such study locations are unlikely to be acceptable given that they could serve and otherwise impact sensitive patient populations (80 FR 25166) and also interface with larger institutional infection control programs.

Clinical outcome studies for food handler antiseptics would therefore likely need to be conducted in actual food handling environments such as food processing facilities or food retail establishments. Unless contrived for the purposes of clinical study conduct, these environments are likely to represent actual independent business establishments. The likelihood of such establishments being willing to participate in a clinical study that may adversely impact staff and/or customers, or which would require the provision of informed consent for all establishment customers, is extremely unlikely. This problem is made more complicated by the high number of study sites that would be required as part of a robust clinical outcome study design. Furthermore, some clinical outcome study designs may conflict with federal, state, or local

food handling regulations at some locations (see Section 9.3). This reality will also reduce the likelihood of finding sites that are willing to participate in clinical outcome studies.

7.4 Informed Consent

Because poor food handler hygiene can result in illness to food handlers and/or food consumers, it is important that informed consent be obtained for individuals who may participate in clinical outcome studies of food handler antiseptics. It is anticipated that ensuring the acquisition of informed consent for individuals who may be impacted by the study will be logistically challenging for a number of reasons, including:

Food handling and distribution logistics: Food handling and distribution chains are often large and complex. Unless adequate control is achieved, there is a risk that “on-study” food could be handled or ingested by individuals who have not given informed consent. Such exposures could occur for a variety of reasons such as (a) co-mingling of “on-study” foodstuffs with “non-study” foodstuffs during food preparation or distribution, (b) inadvertent distribution of “on-study” foodstuffs to a “non-study” site, or (c) provision of “on-study” foodstuffs to individuals not formally involved in a study (e.g. sharing of leftovers or home-prepared meals with individuals who have not given informed consent). Such exposures would be unethical and may be challenging to guard against, especially for clinical outcome studies performed outside a controlled healthcare environment and requiring hundreds or thousands of study sites (see Table 4).

Dynamic and non-healthcare environment: Food handling and consumption environments are typically dynamic with respect to both worker and customer base turnover. This dynamism, combined with the relative lack of control for a study conducted outside a traditional healthcare environment, will make it challenging to ensure that informed consent is obtained and maintained for all study participants over the course of the study period.

Potential for third-party transmission: Many foodborne illnesses associated with poor food handler hygiene are communicable. As such, it is possible for a study participant who has given informed consent to pass a study-acquired illness to a third party who has not given consent. Beyond being an issue of study management and oversight, this issue also raises ethical concerns that are further discussed in Section 8.1 and Section 8.2.

7.5 Protocol Compliance and Documentation

As discussed in Section 4.1, documentation of protocol compliance has historically been a key factor in determining whether or not a given clinical outcome study is sufficient to support a GRAE evaluation for topical antiseptic products. Ensuring and documenting protocol compliance for food handlers and consumers participating in a clinical outcome study will be logistically challenging for a number of reasons, including:

Involvement of non-healthcare personnel: Clinical outcome study participants (food handlers and consumers) are unlikely to be well versed in clinical protocol compliance and documentation practices and are also unlikely to be under the direct oversight of a medical professional who could assist in such

compliance over a given study's duration. In the absence of significant oversight, it may be challenging to ensure that study protocols are followed and/or that adequate protocol compliance documentation is collected over the course of a clinical outcome study.

Study conduct in a non-clinical environment. Given the anticipated study size, direct (i.e. observational) monitoring of protocol compliance is likely to be impracticable. This is particularly true for study locations outside of traditional healthcare settings (e.g. multiple food retail establishments) which may be unfamiliar with clinical study protocols and the measures required to ensure that protocol compliance is adequately documented. While study participant documentation practices may assist in determining protocol compliance in such settings, the accuracy of these records will be difficult to confirm in the absence of direct monitoring.

Low baseline compliance: Additionally, it is important to note that food handler compliance with institutional hygiene control programs is typically considered fairly low. As described briefly in the Section 5.4, food handlers at the food service stage demonstrate notoriously low compliance with proper handwashing practices, with only about 17.6 to 34.4% of restaurants being compliant in the most recent FDA survey (FDA, 2018b). Although fewer studies have been conducted at the food processing stage, anecdotal evidence indicates that food manufacturing facilities have better overall compliance, yet, hand washing between breaks and glove usage is also low (Todd et al., 2010). The Environmental Health Specialists Network (EHS-Net) of the Centers for Disease Control and Prevention (CDC) found that hand washing rates differed by work activity in randomly selected restaurants (Green et al., 2006). This study found that food handlers engaged in approximately 8.6 different activities per hour, each of which should prompt a hand washing occasion according to the Food Code. However, only 32% of these activities were observed to prompt handwashing (Green et al., 2006). While glove usage is important in the prevention of the transmission of foodborne disease and is required by the Food Code for numerous activities, there is a negative correlation between activities in which gloves are worn and proper handwashing (Green et al., 2006; Todd et al., 2010). Additionally, handwashing in relation to touching the body or face was also low in comparison to other reasons that should prompt handwashing (Green et al., 2006).

One reason compliance is thought to be low is due to the high frequency and length of hand washing procedures recommended in the Food Code. As described previously, the Food Code recommends washing hands after nine different situations. In addition, the time and procedures described in the ServSafe® program, one of the most common food safety curriculums in the US, could take up to 50 seconds to properly perform (Fraser et al., 2012). If the Food Code procedure is being objectively followed, the average food worker could be washing their hands for 10-30 minutes per hour (Fraser et al 2012). This would explain why proper food-related washing compliance goes down when food handlers are busy.

Handwashing compliance is not just a measure of how often hands should be washed but also how well hands are washed, and poor compliance is often a result of a combination of factors including lack of facilities, worker education, worker training and motivation by managers (Todd et al., 2010). Improvement to these low compliance frequencies is difficult and requires active management and continual monitoring (Todd et al., 2010).

Individual food handler behavior is linked directly to the food safety culture within a business. One study found that supervisors are effective role models in food service settings, however only about 52% of the persons in charge (PICs) could properly describe handwashing procedures in the Food Code and only 42% of workers surveyed demonstrated compliant hand washing (Allwood et al., 2004). Numerous studies have looked into how to improve handwashing compliance and found that for long term compliance, training programs for food handlers should include (a) a hands-on orientation training on hand washing procedures and causes of foodborne illness, (b) management involvement, (c) well stocked and easily accessible hand washing facilities, (d) ongoing refresher training, (e) advice from local health departments and (f) monitoring systems to ensure compliance (Todd et al., 2010).

As has been demonstrated, compliance in the food industry for proper handwashing skills as required by the Food Code is low and correcting that issue can take an overhaul of a business's entire food safety culture, expending time and resources. It can be assumed that the compliance needed to effectively run a food handler clinical outcome study with new and varying food handler antiseptic products and procedures would be very difficult; and these data suggest that even if a clinical outcome study was conducted, low overall protocol compliance rates could very well preclude the support of a robust GRAE evaluation.

7.6 Medical Monitoring

Because poor food handler hygiene has the potential to impact human health, any clinical outcome study conducted for food handler antiseptics would likely need to include a medical monitoring component. Such monitoring, which would in theory encompass ongoing collection and review of potential adverse event (AE) data throughout the experimental time period, is anticipated to be necessary to ensure that adequate protections are in place for study participants.

Adequate medical monitoring for a food handler antiseptic study will be logistically challenging given the high numbers of participants and study locations anticipated to be required (see Section 6). Logistical challenges are anticipated to be especially burdensome if a study protocols requires microbiological or other in-depth clinical evaluation for suspected AEs. If such clinical evaluations are not required then medical monitoring may be based upon non-clinical information (e.g. survey results) which is likely to be retrospective, subjective, and/or encompass general indirect indicators which may or may not be due to foodborne illness (e.g. diarrhea or stomach discomfort). Attribution will be difficult to ascribe to such indicators; and depending upon the study design, it may be challenging to collect and evaluate such data in a sufficiently timely manner to be appropriately protective of study participants' health.

7.7 Analytical Resources

As discussed in Section 4.1, it is anticipated that collection of valid clinical or microbiological endpoint (for example, clinical culture confirmation) would be the preferred indicator of foodborne illness and illness attribution in clinical outcome studies of food handler antiseptics. Given the large number of study participants anticipated to be required for a clinical outcome study as well as the existence of multiple potential illness vectors, it is estimated that sufficient analytical and microbiology laboratory capacity would not be available to support such testing. Likewise, it is unclear if sufficient resources would be available to effectively coordinate and manage such analytical and microbiological testing.

8. Ethical Considerations

As discussed in Section 4.2, ethical considerations impacted FDA's decision to not require clinical outcome studies for healthcare antiseptics. These ethical considerations should also be considered when deciding whether or not to require clinical outcome studies for food handler antiseptics.

8.1 Public Health Implications of Poor Food Handler Hygiene

Food handler hygiene is a serious public health issue. The CDC estimates that foodborne diseases cause approximately 48 million illnesses each year in the United States (Scanlan et al., 2011). In 2016, 61% of the outbreaks reported in the US were associated with restaurants (CDC 2016). A study evaluating restaurant-associated outbreaks between 1998 and 2013 found food handling and preparation practices most often reported as contributing factors for these outbreaks.

When food workers are implicated in foodborne illness outbreaks, the fecal oral route has been associated as the most likely cause (Todd et al., 2007). Unfortunately, worker health status at the time of production is not linked to the risk of contamination due to prolonged asymptomatic carriage of microbiological agents (Todd et al., 2008). The reports of asymptomatic carriage of foodborne pathogens in food workers and the frequent association of restaurants with foodborne outbreaks underscore an FDA study observing 65% and 82% of fast food and full-service restaurants were out of compliance with proper handwashing practices and 13% and 34% respectively, were out of compliance with bare hand contact requirements (FDA, 2018).

Although most of the foodborne illness attributed to food workers is at retail establishments, food workers at the farm and in processing facilities have also been associated with foodborne disease outbreaks (Greig et al., 2007). Based on the scientific literature it is apparent that food workers regularly contaminate food during processing and frequently cause foodborne illness outbreaks in the United States.

The most common symptoms reported from foodborne illness outbreaks are upset stomach, stomach cramps, nausea, vomiting, diarrhea and fever (CDC, 2019). However, some severe infections/intoxications can cause dehydration, muscle weakness, kidney infection, weight loss, paralysis, brain and nerve damage, kidney failure and sometimes death (CDC, 2019), especially in immunocompromised subpopulations. Additionally, the onset of foodborne illness symptoms can range from 30 minutes to up to four weeks, again depending on the causative agent and person (CDC, 2019). CDC estimates that foodborne diseases cause 128,000 hospitalizations and 3,000 annually (Scanlan et al., 2011).

8.2 Ethics of Vehicle Control

As discussed above, poor food handler hygiene has serious implications for public health in the United States. Inadequate food handler hygiene may impact the food handlers themselves. Furthermore, food handlers throughout the food handling and distribution chain interact with food that is later distributed to, and consumed by, numerous individuals. As such, a single instance of poor food handler hygiene has the potential to impact the health of several downstream individuals. This reality is made more impactful by

the fact that many foodborne illnesses are communicable and so a single instance of illness caused by poor food handler hygiene could impact multiple individuals beyond those initially sickened.

Clinical outcome studies of food handler antiseptics involving non-antiseptic vehicle control arms may therefore result in increased risk of illness to food handlers, consumers, and third parties that may be impacted by communicable illnesses. These risks may be exacerbated by the already low compliance rates of food handlers with non-antiseptic hygiene practices as described in FDA's Food Code (for additional discussion, see Section 7.5). **Although the risks of conducting a controlled clinical study of, for example, surgical skin preparations may be different from the case of food handler antiseptics, the public health risks applicable to the clinical outcome study of food handler antiseptics are nevertheless significant.**

As such, there are serious questions regarding whether or not it would be ethical to conduct 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 GRAE evaluation. FDA has previously noted that it is reasonable to assume that reduced bacterial loading may correlate with reduced opportunities for infection (81 FR 42912 at 42919) and has shown a willingness to consider ethical issues and potential public health impacts when evaluating the risk/benefit balance of requiring clinical outcome studies for different antiseptic products (80 FR 25166 at 25176). Therefore, an *in vivo* clinical simulation testing approach would be a reasonable means to better understand the efficacy of food handler antiseptics while not raising the ethical issues associated with conduct of clinical outcome studies.

8.3 IRB Approval

It is likely that clinical outcome studies for food handler antiseptics would require IRB approval(s). In light of the public health and ethical considerations noted above, as well as the anticipated large size required to conduct food handler antiseptic studies (see Section 6), it is not clear that an IRB would approve a controlled study of food handler antiseptic products.

9. Professional Considerations

In the 2015 Proposed Rule for healthcare antiseptics, FDA recognized that one factor complicating the conduct of clinical outcomes studies was the fact that both Centers for Disease Control and Prevention guidelines and hospital accreditation requirements may preclude the conduct of such a study (80 FR 25166 at 25176). Although the food handler use pattern is not subject to these same guidelines and requirements, there are corporate and professional food handler hygiene policies and frameworks that incorporate and allow for the use of antiseptic products in some situations. Conduct of a clinical outcome study that replaces antiseptic products with a placebo may conflict with these professional frameworks and may also conflict with local food handling laws and regulations based upon those frameworks. Replacement of antiseptic products with a placebo may also conflict with existing institutional food handler hygiene guidelines established at a given food handling establishment.

9.1 Food Code

FDA's Food Code is model guidance that is intended to assist local, state, tribal, and federal regulators in the development or maintenance of their own food safety rules. As such, the Food Code plays an important role in establishing acceptable food safety policies and procedures throughout the United States. The 2017 Food Code states that food handlers not serving a "highly susceptible population" may contact exposed, RTE food with their bare hands if a number of conditions are met. One of these conditions is documentation demonstrating that employees contacting RTE food with bare hands employ two or more control measures to provide additional hazard reduction safeguards. Among the allowed safeguards is use of a "*hand antiseptic after handwashing as specified under § 2-301.16*" (2017 Food Code, Section (E)(6)(c)).

Section 2-301.16 of the Food Code acknowledges that the monograph for such products has not been finalized and refers to the 1994 TFM to allow for the determination of if a "specific product" is encompassed by the proposed monograph. The Food Code therefore currently allows for the use of TFM-compliant products to reduce hazards associated with handling some RTE foods.

9.2 Retail Food Protection: Employee Health and Personal Hygiene Handbook

FDA's Employee Health and Personal Hygiene Handbook (the FDA Handbook) was developed to encourage practices and procedures to help prevent the spread of pathogenic microorganisms from food employees to food (FDA, 2018a). Based upon the lengthier Food Code, the FDA Handbook is intended to assist in the design and implementation of food handler hygiene programs in actual retail food handling environments.

The FDA Handbook contains a number of forms that retail food establishments and the public health community can use for training purposes and to assess overall hygiene compliance. One such form is entitled "Form 1D Application for Bare Hands Contact Procedure." This form incorporates guidance from the Food Code regarding under what situations employees may contact RTE food with bare hands. As with the Food Code, the documented use of topical food handler antiseptic products is cited as one hazard reduction method that can be used to allow for the handling of RTE food with bare hands.

9.3 Impacts to Study Feasibility

Food handling hygiene regulations in many state and other local jurisdictions are based largely upon the Food Code. As such, many statutes, for example Colorado (6 CCR 1010-2), Washington (WAC Chapter 246-215), and Arkansas (ADH, 2012), also have regulatory language that allow for the use of antiseptics as a hazard mitigation measure when RTE foods contact bare hands. For many food retail establishments, the FDA Handbook, which also allows antiseptic use when handling RTE food, serves as practical hygiene guidance for both training purposes and on-the-job reference.

For clinical studies involving RTE foods served to populations not considered to be "highly susceptible" the replacement of a food handler antiseptic with a placebo control for this food handling scenario could be in direct conflict with the Food Code and the FDA Handbook, and could also violate the laws and regulations of many states. Such conflicts could potentially be resolved via the addition of additional

hazard control measures when handling RTE foods as specified in the Food Code; however, this approach could (a) require the re-drafting of a given establishment's personnel hygiene program, (b) trigger the need for personnel re-training and potentially impact the likelihood of protocol compliance, and (c) could require a substantial increase in study size, since imposition of the alternative hygiene measure could potentially "mask" clinical outcomes.

It should also be noted that the removal of food handler antiseptic products, either as part of a placebo-controlled trial or following rule making, may result in unique public health risks specific to those establishments that currently use antiseptic products as part of their hygiene program. Presumably, such establishments would be, in many cases, required to select an alternative hazard mitigation method for the handling of RTE food in order to remain compliant with local laws and regulations. It is anticipated that initial compliance with those alternative measures would be low but would improve over time as personnel become more familiar with the alternative procedure(s). As such, there may be a period of time immediately following the implementation of alternative procedures when the infection risks to customers is relatively high because food retail personnel have not yet adjusted to the new hygiene procedures.

10. Alternatives to Clinical Studies and Endpoints

As discussed above, clinical outcome studies for food handler antiseptic products are likely to be impracticably large and logistically difficult to conduct. Furthermore, such studies may be associated with unacceptable public health risks and/or ethical challenges. **Clinical simulation studies provide an alternative means of generating useful efficacy data for food handler antiseptics under conditions that are better controlled and less likely to result in public health risks or raise ethical issues.**

A number of standard *in vivo* methods currently exist to evaluate the efficacy of topical antiseptic products on human hands or other surfaces. For example, ASTM E 1174, ASTM E2755, ASTM E2946, and ASTM E2784-10 are all intended to show the antimicrobial activity of antiseptic products applied to human hands. There are also established and well-regarded methodologies in place to evaluate alternative endpoints relevant to food handler antiseptics, such as the transfer of bacteria from human skin to food products or other surfaces (for example, see ASTM E2784-10). Such methods could theoretically be directly used or adapted to support an evaluate efficacy of food handler antiseptic products under conditions relevant to various food handler use patterns.

FDA reviewed a number of clinical simulation studies based upon these and other methods as part of rule-making for consumer hand washes, consumer hand rubs, and healthcare antiseptics. Although FDA found many of these studies insufficient for use in evaluating efficacy, the various issues identified by FDA during their reviews (e.g. lack of appropriate vehicle or active controls, insufficient demonstration of neutralization) can be addressed as part of the study design for future simulation testing of food handler antiseptics. Furthermore, clinical simulation studies can be designed and controlled to specifically evaluate the impacts of various complexity factors unique to the food handler use pattern (see Section 5).

There is already regulatory precedent for using clinical simulation studies to evaluate the efficacy of topical antiseptic drug products. For example, clinical simulation studies have previously been

considered sufficient to evaluate the efficacy of hand antiseptic drug products approved under New Drug Applications (NDAs) (84 FR 14847). Furthermore, as part of the rule-making process FDA concluded that clinical simulation studies were sufficient to evaluate the GRAE status of consumer hand rubs and healthcare antiseptic products (see Section 4). A similar approach should be sufficient to evaluate the efficacy of food handler antiseptics.

11. Conclusions

Decisions regarding the need for clinical outcome testing for food handler antiseptics should be evaluated with respect to both (a) factors specific to the food handler use pattern (e.g. study complexity and practicability, see Section 5 through Section 9 of this document), and (b) the rationales upon which this same question was resolved for consumer hand wash, consumer hand rub, and healthcare antiseptic products (e.g. availability of alternative products and the public health/ethical implications of conducting or requiring clinical outcome studies).

As discussed throughout this document, the unique complexity of how and where food handler antiseptics are used, as well as the individuals using these products, would make conduct of a clinical outcome study challenging. Such studies would be large (likely requiring several thousand study participants and sites), complex, logistically challenging to conduct and oversee, and may have unacceptable adverse impacts on public health. Furthermore, this complexity may make it challenging to draw meaningful conclusions from clinical outcome studies, if conducted.

With respect to the relationship between food handler antiseptics and similar topical antiseptic products, the decision to not require clinical studies for consumer hand rubs and healthcare antiseptics was based upon a number of factors, including (a) the lack of alternative hygiene products in the case of antiseptic hand rubs, and (b) the public health and ethical challenges associated with conducting placebo-controlled clinical trials for healthcare antiseptics (81 FR 42912, 80 FR 25166). Notably, these factors are also applicable to the case of food handler antiseptics. On the one hand, leave-on hand rubs used by food handlers in occupational settings are presumably utilized only when alternative hygiene measures are not practicable. As such, a clinical outcome study conducted for such products would not be able to incorporate a suitable corresponding non-antiseptic vehicle control, and even if such a control was identified, its use could in some cases violate the Food Code and/or state laws and regulations. On the other hand, food handler hygiene is a legitimate public health issue given that poor hygiene can be associated with instances of serious foodborne diseases or disease outbreaks. As such, the ethical and public health issues associated with conducting a clinical outcome study for healthcare antiseptics are also applicable to the food handling scenario.

Clinical simulation studies offer an alternative means of product testing that can evaluate the efficacy of food handler antiseptics without the need to conduct ethically questionable studies that may represent an unacceptable public health risk. Simulation studies also provide a better opportunity to evaluate the contribution of key complexity factors on product efficacy, which may assist FDA in making regulatory decisions regarding how and where food handler antiseptics should be used.

12. References

6 CCR 1010-2. Colorado Retail Food Establishment Rules and Regulations. Section 3-401.

78 FR 76444. 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 the Administrative Record. Vol. 78, No. 242. December 17, 2013.

80 FR 25166. 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 the Administrative Record. Vol. 80, No. 84. May 1, 2015.

81 FR 42912. 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 the Administrative Record. Vol. 81, No. 126. June 30, 2016.

81 FR 61106. Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use. Vol 81, No. 172. September 6, 2016.

82 FR 60474. Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use. Vol 82, No. 243. December 20, 2017.

83 FR 63168. Food Handler Antiseptic Drug Products for Over-the-Counter Human Use; Request for Data and Information. Vol. 83, No. 235. December 7, 2018.

84 FR 14847. Safety and Effectiveness of Consumer Antiseptic Rubs; Topical Antimicrobial Drug Products for Over-the-Counter Human Use. Vol. 84, No. 71. April 12, 2019.

ADH. 2012. Rules and Regulations Pertaining to Food Establishments. Section 3-301.11.

Ali MM, Verrill L, Zhang Y. 2014. Self-reported hand washing behaviors and foodborne illness: a propensity score matching approach. *J Food Prot.* Mar;77(3):352-8. doi: 10.4315/0362-028X.JFP-13-286.

Allwood, P. B., T. Jenkins, C. Paulus, L. Johnson, and C. W. Hedberg. 2004. Hand washing compliance among retail food establishment workers in Minnesota. *J. Food Prot.* **67**:2825–2828.

CDC. 2016. Surveillance for Foodborne Disease Outbreaks United States, 2016: Annual Report. Available at: https://www.cdc.gov/fdoss/pdf/2016_FoodBorneOutbreaks_508.pdf

CDC. 2019. Food Poisoning Symptoms. Available at: <https://www.cdc.gov/foodsafety/symptoms.html>. Accessed on: 5 June 2019.

CDC. 2017. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Global Migration and Quarantine (DGMQ). Definitions of Symptoms for Reportable Illness. Accessed on: 10 Jun 2019.
<https://www.cdc.gov/quarantine/air/reporting-deaths-illness/definitions-symptoms-reportable-illnesses.html>

CSPI. 2015. Center for Science in the Public Interest. Outbreak Alert! December 1, 2015.

Edmonds, S. L., J. Mann, R. R. McCormack, D. R. Macinga, C. M. Fricker, J. M. Arbogast, and M. J. Dolan. 2010. SaniTwice: a novel approach to hand hygiene for reducing bacterial contamination on hands when soap and water are unavailable. *J. Food Prot.* **73**:2296–2300.

Edmonds, S.L., R.R. McCormack, S.S. Zhou, D.R. Macinga, and C.M. Fricker. 2012. Hand hygiene regimens for the reduction of risk in food service environments. *J. Food Protect.* **75**:1303-1309.

FDA. 2017. Food Code. Available at: <https://www.fda.gov/media/110822/download>. Accessed on 6 June 2019.

FDA. 2018a. Retail food protection: employee health and personal hygiene handbook. Available at: <https://www.fda.gov/food/retail-food-industryregulatory-assistance-training/retail-food-protection-employee-health-and-personal-hygiene-handbook>. Accessed on: 5 June 2019.

FDA. 2018b. FDA Report on the occurrence of foodborne illness risk factors in fast food and full service restaurants, 2013-2014. Available at: <https://www.fda.gov/media/117509/download>. Accessed on: 6 June 2019.

Foddai, A.C.G., I.R. Grant and M. Dean. 2016. Efficacy of instant hand sanitizers against foodborne pathogens compared with hand washing with soap and water in food preparation settings: a systematic review. *J. Food Protect.* **79**:1040-1054.

Fraser, A., J.W. Arbogast, L-A, Jaykus, R. Linton and D. Pittet. 2012. Rethinking hand hygiene in the retail foodservice industries: are recommended procedures based on the best science and practical und real-world conditions? *Food Protect. Trends.* 750-759.

Green, L. R., C. A. Selman, V. Radke, D. Ripley, J. C. Mack, D. W. Reimann, T. Stigger, M. Motsinger, and L. Bushnell. 2006. Food worker hand washing practices: an observational study. *J. Food Prot.* **69**:2417–2423.

Greig, J.D., E.C.D. Todd, C.A. Bartleson, and B.S. Michaels. 2007. Outbreaks where food workers have been implicated in the spread of foodborne disease. Part 1. Description of the problem, methods, and agents involved. *J. Food Protect.* **70**:1752-1761

Hornick, R.B., H.L. DuPont, S.I. Music, M. Snyder, and J.P. Libonati. 1970. Investigations into the pathogenesis of diarrheal diseases. *Trans. Am. Clin. Climatol. Assoc.* **82**:141-147.

Lipcsei LE, Brown LG, Coleman EW, Kramer A, Masters M, Wittry BC, Reed K, Radke VJ. 2019. Foodborne Illness Outbreaks at Retail Establishments - National Environmental Assessment Reporting System, 16 State and Local Health Departments, 2014-2016. *MMWR Surveill Summ.* Feb 22;68(1):1-20. doi: 10.15585/mmwr.ss6801a1.

Montville, T.J., and K.R. Matthews. 2007. Growth, survival, and death of microbes in foods. pp. 3-22. In. Doyle, M.P. and L.R. Beuchat (eds). *Food microbiology: fundamentals and frontiers* (3rd ed.). ASM Press. Washington, DC.

PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Perry, S.M. de la Luz Sanchez, P.K. Hurst, and J. Parsonnet. 2005. Household transmission of gastroenteritis. *Emerg. Infect. Dis.* **11**: 168-171.

Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, Jones JL, Griffin PM. 2011. Foodborne illness acquired in the United States--major pathogens. *Emerg Infect Dis.* Jan;17(1):7-15. doi: 10.3201/eid1701.P11101

ServSafe. 2014. ServSafe Sixth Edition Updated with the 2013 Food Code. Available: <https://www.servsafe.com/ServSafe/media/ServSafe/Documents/6e-food-code-new-content.pdf>. Accessed 7 June 2019.

Sickbert-Bennett, E.E., D.J. Weber, M.F. Gergen-Teague, and W.A. Rutala. 2004. The effects of test variables on the efficacy of hand hygiene agents. *AJIC.* **32**:69-83.

Todd, E.C.D., J.D. Greig, C.A Bartleson, and B.S. Michaels. 2007. Outbreaks where food workers have been implicated in the spread of foodborne disease. Part 2. Description of Outbreaks by Size, Severity, and Settings. *Food Protect.* **70**:1975-1993.

Todd, E.C.D., J.D. Greig, C.A Bartleson, and B.S. Michaels. 2008. Outbreaks where food workers have been implicated in the spread of foodborne disease. Part 4. Infective doses and pathogen carriage. *J. Food Protect.* **71**:2339-2373.

Todd, E.C.D., J.D. Greig, C.A Bartleson, and B.S. Michaels. 2010. Outbreaks where food workers have been implicated in the spread of foodborne disease. Part 11. Use of antiseptics and sanitizers in community settings and issues of hand hygiene compliance in health care and food industries. *J. Food Protect.* **73**:2306-2320.

WAC Chapter 246-215. Washington State Retail Food Code. Subsection C; 03300(4)(f).

Young, I., A. Thaivalappil, D. Reimer, and J. Greig. 2017. Food safety at farmers' markets: a knowledge synthesis of published research. *J. Food Protect.* **80**:2033-2047.

Attachment 5: Studies of the Frequency of Use of Food Handler Products

To address shortcomings in existing data from studies observing topical antiseptic products use by employees in the food service industry, a multi-phase project to research the actual frequency of hand washing in the food service industry is being undertaken.

Background

With respect to potential exposure to food handler antiseptic products during use, none of the limited number of published field studies that have reported observations of employee hand washing practices in the institutional food service, restaurant, and retail grocery store facilities address the frequency of use of antiseptic products. All of them have limitations that impact their ability to provide a combined metadata set which could be assessed to determine actual hand hygiene frequencies as they exist in commercial and regulated environments where food handling occurs. Key limitations include:

- 1) A focus on hand hygiene opportunities and compliance rate rather than 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 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.

Study Summaries

To address these shortcomings for products used by the food service industry, a multi-phase project to research the actual frequency of hand washing in the food service industry is being undertaken. The first 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.

A second phase of the hand hygiene frequency study, utilizing electronic data collection on individual food handlers' hand wash frequency, similar to a study conducted in health care 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.

References

- Albright, J., B. White, D. Pedersen, P. Carlson, L. Yost and C. Littau. 2018. Use patterns and frequency of hand hygiene in health care facilities: Analysis of electronic surveillance data. *Am. J. of Infect. Control* 46: 1104 – 1109
- Allwood, P.B., T. Jenkins, C. Paulus, L. Johnson, C.W. Hedberg. 2004. Hand washing compliance among retail food establishment workers in Minnesota. *J. of Food Prot.* 67: 2825 – 2828.
- Clayton, D. A. and C.J. Griffith. 2004. Observation of food safety practices in catering using notational analysis. *Brit. Food J.* 106:211 - 227.
- do Prado, D.B., A.P. Bettoni, V.A. Correa, B.A. de Abreu Filho, L.B. Garcia, M.C.B. Tognim and C.L. Cardoso. 2015. Practice of hand hygiene in a university dining setting. *Food Control* 57: 35 – 40
- Green, L.R., C.A. Selman, V. Radke, D. Ripley, J.C. Mack, D.W. Reimann, T. Stigger, M. Motsinger, and L. Bushnell. 2006. Food worker hand washing practices: An observation study. *J. Food Protect.* 69: 2417 -2423.
- Strohbehn, C., J. Sneed, P. Paez and J. Meyer. 2008. Hand washing frequencies and procedures used in retail food service. *J. Food Protect.* 71: 1641 - 1650.
- York, V.K., L.A. Brannnon, C.W. Shanklin, K.R. Roberts, B.B. Barrett, and A.D. Howells. 2009. Intervention improves restaurant employees' food safety compliance rates. *Intl J of Contemp Hosp Manag.* 21: 459 – 478