FDA Briefing Document

Nonprescription Drugs Advisory Committee Meeting

March 11, 2020

Current use of OTC antiseptics in the food handler setting and testing criteria to establish the general recognition of safety and effectiveness of these products.

Disclaimer Statement

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FDA Summary Memorandum

Date: February 14, 2020

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To: Members of the Nonprescription Drugs Advisory Committee (NDAC)

Subject: Over-the-counter (OTC) food handler antiseptic drug products regulatory considerations

1. Introduction

Thank you for your participation in the Nonprescription Drugs Advisory Committee meeting to be held on March 11, 2020. As members of the Advisory Committee you provide important expert scientific advice and recommendations to the US Food and Drug Administration (FDA or the Agency) on the scope of efficacy testing to support a determination by FDA that a food handler antiseptic active ingredient is generally recognized as safe and effective (GRASE) for over-the-counter (OTC) drug use.

We are seeking advice on a framework for the evaluation of the rational dosage forms and effectiveness testing of antiseptic active ingredients within a food handler setting. While there are also various issues to be addressed regarding evaluation of safety for food handler antiseptic active ingredients, this topic will not be addressed in this meeting. In this document we provide a description of the data available for the food handler antiseptic products. We will describe how the existing data fit within our current antiseptic framework and would like you to consider the data provided in this document in your discussion regarding the dosage forms and effectiveness testing of these products.

2. Draft Topics for Discussion

Food handler antiseptics may differ from the current categories of antiseptic products given their specific use settings and unique potential exposure of users to food-borne pathogens. The following questions represent draft topics for discussion by the Advisory Committee to help us establish the framework for evaluation of these products to ensure that food handler antiseptics are used safely and effectively in their specific use settings.

1. Discuss: Recognizing that soap and water is the current standard practice in the food handler settings, are there any conditions under which rubs (or wipes, or dips) should be evaluated as food handler antiseptic? If so, what would be those conditions (e.g., specific study design with multiple arms for the different

dosages, challenge (meat/broth) positive and negative controls, surrogate endpoint reduction of organisms)?

2. Discuss: Should the effectiveness of food handler antiseptics against viruses and protozoa, in addition to bacteria, be evaluated? If so, what data and studies would be needed to demonstrate effectiveness?

3. Discuss the adequacy and feasibility of clinical outcome studies vs. clinical simulation studies to support a determination of generally recognized as safe and effective (GRASE) for food handler antiseptics active ingredients.

4. Discuss: Recognizing the diverse environments in which FHAs (e.g., washes, rubs, wipes) are used, is it necessary to demonstrate efficacy in different subgroups within the broader spectrum of farm-to-table settings (e.g., produce harvesters, food preparation workers, food servers)?

3. Background

The CDC estimates that foodborne diseases cause approximately 48 million illnesses, 128,000 hospitalizations, and 3,000 deaths in the United States each year. (Scallan et al. 2011a; Scallan et al. 2011b; CDC 2018b). Data that identify where foodborne disease outbreaks occur point to taking measures during food preparation and handling processes to reduce contamination by pathogens, hand hygiene being an important one of such measures.

For the purposes of this document, we consider food handler antiseptic products to be antiseptic products intended for use by food handlers in commercial or regulated environments where growth, harvest, production, manufacturing, processing, packaging, transportation, storage, preparation, service, or consumption of food occurs.

FDA has tentatively concluded that, based on FDA's current categorization of other antiseptic products, and considering factors that may include exposure to microorganisms commonly encountered in food handling settings as well as the safety of repeated-exposure use patterns, the scope and the role of food handler antiseptics may differ from antiseptic products intended for use in consumer and health care settings.

Over the years we have received requests from industry and interested parties for an over-the-counter food handler antiseptic category, and some information and data have been submitted in support of establishing such a category. In order to obtain additional data and information regarding antiseptic products used in food handler settings, we recently issued a request for data and information (83 FR 63168, Docket No. FDA-2018-N-3458). Some of the key issues addressed in that request are the focus of this meeting. Background information on the current categories of antiseptic products, and literature

summaries pertaining to these questions are included for your consideration in this briefing document.

3.1. Existing Antiseptic Categories and Regulatory Background

In the United States, OTC drugs are regulated through two different processes, the new drug application (NDA) process and the OTC Drug Review process (monograph). In the NDA process, FDA evaluates the safety and effectiveness of individual drug products to determine whether they can be approved for marketing. In contrast, rather than reviewing and approving each individual drug product, FDA can also develop, through the OTC Drug Review, regulations called monographs for different therapeutic drug categories. These monographs establish conditions of use, such as active ingredients, use indications, dosage form, route of administration, and directions under which an OTC drug is generally recognized as safe and effective and not misbranded for its intended use(s). OTC drug products for which there are applicable final monographs, and which conform to the conditions of use in the respective monograph, along with the requirements of 21 CFR. 330.1, are generally recognized as safe and effective and not misbranded, and thus can be marketed without FDA prior approval through a New Drug Application or Abbreviated New Drug Application.

Existing categories of OTC topical antiseptics encompass products indicated to help reduce bacteria on the skin that potentially can cause disease. These products have a broad scope and include products that may contain the same active ingredients, but that are labeled and marketed for different intended uses and settings. Of note, antiviral or disease-specific claims are not permitted for existing categories of antiseptic products marketed under the OTC monograph, since these types of claims are not supported by the data requested for the ingredients. Currently, OTC antiseptic drug products are divided into the following categories:

- First aid antiseptic drug products: these are antiseptic products applied topically by consumers used for the first aid treatment of minor cuts, scrapes, and burns.
- Consumer antiseptic wash products: antiseptic products that are rinsed off with water and used by consumers in daily hand and body cleansing, such as antiseptic soaps and/or liquid soaps as well as antiseptic body wash.
- Consumer antiseptic rub products: antiseptic products that are not rinsed off after use and are also used in consumer settings, such as antiseptic hand rubs (sometimes called hand sanitizers) and antibacterial wipes.
- Health care antiseptic products: antiseptic products intended for use by health care professionals in hospitals or other health care settings. This category includes health care personnel hand washes, health care personnel hand rub products, surgical hand scrubs, surgical hand rub products and patient antiseptic skin preparations (patient preoperative and preinjection skin preparations).

The categories described above are distinct with regard to their use settings, the target population, and the fact that each setting presents a different level of risk for infection for the affected individuals. Notably, disinfectant products used on inanimate surfaces are not drugs and do not fall under FDA jurisdiction.

The first aid antiseptic products and their active ingredients were evaluated in a tentative final monograph (TFM) issued by FDA in 1991 (the 1991 TFM, 56 FR 33644). The remaining OTC topical antiseptic drug products: antiseptic hand wash (i.e., consumer hand wash); health care personnel hand wash; patient preoperative skin preparation; and surgical hand scrub, were addressed in the 1994 Tentative Final Monograph (59 FR 31402). The 1994 TFM did not distinguish between consumer antiseptic washes and rubs and health care antiseptic washes and rubs. In the 2013 consumer antiseptic wash proposed rule, FDA proposed that the evaluation of OTC antiseptic drug products be further subdivided into health care antiseptics and consumer antiseptics (78 FR 76444 at 76446-76447), based on the proposed use setting, target population, and different level of risk for infection. In the 2013 consumer antiseptic wash proposed rule and the 2016 consumer antiseptic rub proposed rule, FDA also proposed that evaluation of OTC consumer antiseptic drug products be further subdivided into consumer washes and consumer rubs (78 FR 76444 at 76446-76447; 81 FR 42912 at 42915-42916). Since then, the Agency has finalized and proposed new regulatory policies for health care antiseptics (82 FR 60474, final rule), consumer antiseptic wash products (81 FR 61106, final rule), and consumer antiseptic rubs (84 FR 14847, final rule).

For the health care antiseptic products, which include health care personnel hand washes and rubs, surgical hand scrubs and rubs, and patient preoperative skin and pre-injection preparations, FDA proposed new safety and effectiveness criteria in 2015 (80 FR 25166). In 2017, following a thorough evaluation of the existing safety and effectiveness data, FDA issued a health care antiseptics final rule (82 FR 60474) and determined that at that time, there were no GRASE active ingredients for this category of antiseptic products. Six active ingredients, ethyl alcohol, isopropyl alcohol, povidone iodine, benzalkonium chloride, benzethonium chloride, and chloroxylenol, for which FDA received commitment from industry to complete all the necessary studies required for their determination of safety and efficacy for use in OTC healthcare antiseptic products, are temporarily deferred from further rulemaking. The determination of safety and efficacy for these six deferred active ingredients will be made at a later date pending the progress, completion, submission, and evaluation of the required safety and efficacy data (FDA 2019a). Subsequently, health care antiseptic products with any of the six active ingredients deferred from final ruling may continue to be marketed as long as they comply with the 1994 TFM testing requirements for health care antiseptics (59 FR 31402), as well as the recent proposed and final rule for health care antiseptics (80 FR 25166 and 82 FR 60474).

New safety and efficacy requirements were also proposed for consumer wash antiseptic products (such as antiseptic bar and liquid soaps used with water) in 2013 (78 FR 76444). In 2016, based on the evaluation of the existing safety and effectiveness data, FDA issued a final rule (81 FR 61106) that determined that there were no active ingredients

considered GRASE for the indication of consumer antiseptic wash products. Three active ingredients; benzethonium chloride, benzalkonium chloride, and chloroxylenol for which FDA received commitment from industry to complete all the necessary studies required for their determination of safety and efficacy for use in OTC consumer wash antiseptics are temporarily deferred from further rulemaking for use in OTC consumer antiseptic wash products (FDA 2019a). Thus, consumer wash products containing any of the three deferred active ingredients may remain on the market pending the review of the required safety and efficacy data, as long as they are in compliance with the requirements determined in the 1994 TFM (59 FR 31402) and the consumer antiseptic wash rules issued in 2013 and 2016 (78 FR 76444 and 81 FR 61106).

Similarly, for the category of consumer antiseptic rubs, a final rule was issued on April 12, 2019 (84 FR 14847). This category comprises antiseptic products used in consumer settings when soap and water are not readily available. Such products left on skin when applied and not rinsed off with water, are also known as leave-on, hand rub, and hand sanitizer products. Three eligible active ingredients were proposed for this category: ethyl alcohol, isopropyl alcohol, and benzalkonium chloride. These active ingredients, in response to requests from industry to conduct all necessary studies required for their determination of safety and efficacy, have also been deferred from further rulemaking to allow time for completion of existing data gaps needed for evaluation of safety and effectiveness for use in OTC consumer antiseptic rub products (FDA 2019a). Although consumer antiseptic rub products were not included in a separate monograph when the 1994 TFM was published, the regulation of antiseptic rubs and wipes used in health care settings and their final product formulation testing requirements is discussed in the 1994 TFM under the category of health care antiseptics. Pending the evaluation of the three active ingredients eligible for this category, consumer antiseptic rub products may also be manufactured and marketed following the testing requirements of 1994 TFM (59 FR 31402) for health care antiseptic products as well as the consumer rub final rule (84 FR 14847).

4. Regulatory History of Food Handler Antiseptics

In the 1994 TFM, FDA identified a category of antiseptic drug products that historically had been marketed for use by food handlers in federally inspected meat and poultry processing plants, and other food handling establishments, and that until then had been regulated by the U.S. Department of Agriculture. Examination of these products' labeling led the Agency to conclude that the intended use of these products (i.e., the reduction of microorganisms on the skin for the purpose of preventing disease caused by transfer of microorganism from hands to foods in contrast to reduction of microorganisms on inanimate surfaces) makes them drugs under the provisions of the Federal, Food, Drug, and Cosmetic Act (FD&C Act). The FD&C Act defines a drug to include an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man (Section 201(g)(1) of the FD&C Act; 21 U.S.C. 321(g)(1)). Therefore, the 1994 TFM proposed that safety and effectiveness of the active ingredients of food handler antiseptic drug products need to be evaluated (59 FR 31402 at 31440).

In addition, FDA received comments pertaining to food handler antiseptics in response to the 2013 OTC Consumer Antiseptic Wash Products proposed rule. One of these comments was submitted by the Personal Care Products Council and the American Cleaning Institute in the form of a citizen petition (Personal Care Products Council (PCPC)/American Cleaning Institute (ACI) Petition, FDA-1975-N-0012-0493), (FDA 2014) requesting that FDA, among other things, define food handler antiseptic hand washes or rubs as antiseptic products for use in commercial establishments and other regulated settings, establish food handler antiseptic hand washes as a separate category, and consider food handler antiseptic products as professional use products similar to health care antiseptics.

Given the FDA's current categorization of OTC antiseptic products, differences in frequency and method of use of food handler antiseptics due to contamination of hands by dirt and grease as well as their potential interference with the products' ability to reduce microorganisms on skin and, most importantly, given the additional concerns raised by the public health consequences of foodborne illness, FDA concluded that a separate evaluation of food handler antiseptics is warranted. The 2016 Consumer Antiseptic Wash Final Rule (81 FR 61106 at 61109) and the 2017 Health Care Antiseptic Final Rule (82 FR 60474 at 60483), state that food handler antiseptics, given their use settings, are separate and distinct from the other OTC topical antiseptic categories.

Food handler antiseptics include antiseptic products labeled for use in commercial or other regulated settings where food is grown, harvested, manufactured, packed, held, transported, prepared, served, or consumed. This broad variety of settings should be taken into consideration when determining the safety and effectiveness criteria of these products. For example, use settings where food is grown and harvested may include conditions where water is not readily available; other settings such as food manufacturing, packaging, and preparation may include specific standard operating procedures set in place by the employer/organization, addressing the frequency, hand wash methodology, use of gloves, hair restraints, or other hygiene measures. Food serving settings (such as restaurants or cafes) may call for a different frequency of hand washing or different hygiene measures.

As mentioned above, in the 1994 TFM FDA proposed that the safety and effectiveness of active ingredients intended for use in food handler antiseptic products need to be demonstrated, and proposed to include an evaluation of the safety and effectiveness of these active ingredients in the rulemaking for OTC topical antimicrobial drug products (59 FR 31402 at 31440). In the 1994 TFM, we requested relevant data and information to assist in characterizing this category of food handler antiseptics (59 FR 31402 at 31440). In response to the 1994 TFM, FDA received public comments pertaining to food handler antiseptic hand washes, including an industry proposal, the Health Care Continuum Model (HCCM), which refers to the effectiveness, effectiveness testing requirements, and labeling of antiseptic products discussed in the 1994 TFM, including the antiseptic hand wash products used by food handlers (FDA 2012). FDA also received a citizen petition regarding testing of antiseptic products including food handler antiseptics, for their inactivation activity against (selected) viruses (FDA 2010a).

The data and comments received in response to these previous rules were discussed in our responses (FDA 2010b) to the citizen petition and were assessed as insufficient to make a determination on food handler antiseptics (83 FR 63168). As a result, on December 7, 2018, FDA issued a request for data asking the public and manufacturers of food handler antiseptics for submission of information and data on the definition, eligibility, active ingredients, current conditions of use, and test methods for demonstration of effectiveness of food handler antiseptics, with the purpose of informing the FDA's review of this category of antiseptic products (83 FR 63168; Appendix A). We received several comments in response to the mentioned request, (FDA 2019b) some of which are the focus of this meeting. At this time, we do not know which active ingredients should be appropriately included in food handler antiseptic drug products; in the future, we will need additional information to evaluate the antiseptic products currently marketed for the food handling industry. A table summarizing the most common active ingredients of these products is provided in Appendix B.

5. Dosage Forms Currently Used in Food Handler Settings

Section 510 of FDA's FD&C Act requires firms that manufacture, prepare, propagate, compound, or process drugs in the U.S. or that are offered for import into the United States to register with the FDA. Review of FDA's electronic Drug Registration and Listing System, labels submitted in response to the 2018 Request for Data and Information, and peer-reviewed literature, revealed that currently marketed food handler antiseptic drug products are available as hand washes (soaps), leave-on rubs (hand sanitizers), hand wipes, and hand dips (Jackson 2005; Edmonds et al. 2010; Edmonds et al. 2012; FDA 2019c). With exception of antiseptic hand washes (soaps), the remaining products are intended for use without water and on hands and potentially arms, they are left on skin and not rinsed off with water. While dips as a dosage form would need to be evaluated separately from rubs, considerations for discussion are likely to be similar. Therefore, for the purposes of this document only, dips are not discussed separately.

It is not clear whether a unique product dosage form could be recommended as the most appropriate for each particular setting, or whether alternative dosage forms may provide valuable benefits that would merit making a different recommendation. For instance, proper hand washing with soap and water has been recognized as one of the most effective hand hygiene intervention used by food handlers to prevent the spread of foodborne illnesses in ready-to-eat foods (Fendler et al. 2002; Montville et al. 2002; Edmonds et al. 2010). We note that the November 26, 2015, *Federal Register*, "Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption; Final Rule," (or Produce Safety Rule), requires all farm workers harvesting produce covered under this rule to wash hands with soap and water to minimize the risk of serious adverse health consequences or death from the use of, or exposure to, contaminated covered produce (80 FR 74354 at 74413) (Kux 2015). FDA's Food Code, a model for safeguarding public health and ensuring that food is unadulterated and honestly presented when offered to the consumer also calls for proper handwashing procedures and a handwashing sink or facility to be readily available in all food establishments (FDA

2019d). Still, some argue that in certain rare occasions where access to soap and water may not be feasible, the use of alcohol-based hand sanitizers could merit further consideration (de Aceituno et al. 2015).

Likewise, gloves are commonly used in food service establishments. However, this intervention may result in less safe hand washing practices (Lynch et al. 2005; Todd et al. 2010b). Given the consistently low hand washing compliance rates, some question whether the use of rubs or wipes may be a feasible effective intervention in preventing foodborne illness (Todd et al. 2010a). The Produce Safety rule suggests that rubs may provide an additional level of protection after handwashing (80 FR 74354). We recognize that, although the use of these dosage forms as an alternative to hand washing may lead to less time away from the food preparation stations, the potential overreliance on the effectiveness of these products is a significant concern. As such, a discussion on the potential benefit, if any, of the use of these products (antiseptic hand washes, rubs, or wipes) in food handler settings where plain soap and water may or may be not readily available is warranted.

FDA's Food Code, which represents FDA's best advice for a uniform system of provisions that address the safety and protection of food offered at retail and in food service (FDA 2019d) provides guidelines to encourage practices and behaviors that help prevent food employees from spreading pathogens to food (FDA 2018). Personal hygiene interventions such as effective hand washing with soap and water can remove soil and reduce microorganisms on the hands that cause foodborne illness and injury. In addition to the Food Code, FDA's Food Safety Modernization Act (FSMA) supports efforts to regulate how produce is grown, packed, processed, shipped, and imported into the United States. This Act allows FDA to strengthen the food safety system by focusing on prevention measures rather than relying on a reactionary approach to food safety related problems after they occur. Consistent with the FDA Food Code, the Produce Safety Rule states that hand sanitizers have not been found to be effective substitutes for washing hands with soap and water because of soiling (80 FR 74354 at 74495) (Kux 2015). FDA concluded that soiling reduces the effectiveness of these products in eliminating bacteria. Furthermore, in the supplement to the 2017 FDA Food Code, the option of using chemically treated towelettes in place of handwashing was removed. The final rule does not, however, prohibit the use of antiseptic hand rubs, since such products may be effective as an additional measure to initial hand washing with soap and water followed by adequate hand drying. This approach is in alignment with our concerns regarding the efficacy of antiseptic hand rubs used alone in food handler settings and warrants further discussion.

As we consider what data and conditions would be needed to support the use of hand sanitizers across the food industry, we expect that any alternative dosage form (rubs or wipes) be as effective as food handler antiseptic hand washes. In addition, to support a GRASE determination, any food handler antiseptic product (regardless of dosage form) would need to be more effective than plain soap and water. Although there are studies indicating that rubs may be as effective as hand washes in reducing microbial populations on the soiled hands of study participants, we are not aware, at this time, of any well-

controlled studies comparing the effectiveness of rubs versus washes (Pickering et al. 2010; de Aceituno et al. 2015; de Aceituno et al. 2016; Morrill et al. 2018). Similarly, we are not aware of any adequate and well controlled studies demonstrating the benefit of antiseptic hand rubs after hand washing with either plain soap and water or antiseptic hand washes in food handler settings (Azor-Martínez et al. 2014; Siddiqui et al. 2017). Moreover, the published data rely on the $\log_{10}$ reduction of a challenge microorganism(s) used in studies that mimic hand contamination and, despite the efforts to evaluate the impact such reductions might have in reducing infections (Schaffner et al. 2014), there are no studies available that correlate the $\log_{10}$ reduction of microorganisms on hands in food handler settings with reduction of infections.

Given the lack of well-controlled studies to evaluate the efficacy of antiseptic hand rubs, we welcome input from the Advisory Committee on whether the antiseptic rubs and wipes could potentially be acceptable dosage forms for food handler antiseptics. If hand rubs or wipes are appropriate dosage forms, we also are looking for input on the specific conditions and settings where these dosage forms could be used, as well as the necessary studies required to support their efficacy.

6. Effectiveness Considerations for Consumer and Health Care Antiseptics

The tests required for demonstration of efficacy of active ingredients used in consumer and health care antiseptics were first proposed in the 1994 TFM. New information and potential risks prompted by the long-term use of certain antiseptic active ingredients led to reconsideration of the criteria and the methods for demonstrating that the active ingredients of consumer and health care antiseptics are GRASE for their intended uses. Based on recommendations from the public meetings held by the Agency, including input from the Nonprescription Drug Advisory Committee meetings in 2005, as well as evaluation of available literature, data and comments received by the Agency in the antiseptic rulemakings, the criteria and test methods required to demonstrate that consumer and health care active ingredients are generally recognized as effective have been reevaluated (78 FR 76444, 81 FR 61106, 81 FR 42912, 84 FR 14847, 80 FR 25166, 82 FR 60474). In brief, for the active ingredients of both consumer and health care antiseptics categories, a combination of in vitro and in vivo tests for demonstration of their bactericidal activity was proposed. The specific efficacy studies and requirements for each of these antiseptic categories is summarized in Table 1.

Table 1: Effectiveness Data Requirements for OTC Consumer and Health Care Antiseptics

Setting	In Vitro	In Vivo	In Vivo - Rationale
Consumer Antiseptic Wash	▪ Time Kill assay* ≥ 3 $\log_{10}$ reduction within 30 seconds	**Clinical Outcome Studies** ▪ Evaluates the effect of antiseptic use in decreasing the incidence of infections ▪ Must show superiority to nonantibacterial soap and water	▪ Lack of sufficient data to clearly demonstrate the benefit from the use of consumer antiseptic wash products compared to nonantibacterial soap and water ▪ Log_{10} reduction of bacteria is insufficient to determine benefit ▪ Studies are considered to be feasible ▪ Recommended by October 2005 NDAC
Consumer Antiseptic Rubs	▪ Minimal Bactericidal Concentration ▪ Time Kill assay ≥ 3 $\log_{10}$ reduction within 30 seconds	**Clinical Simulation Studies***** ▪ Measures the reduction of bacteria on skin due to antiseptic use ▪ 1.5 $\log_{10}$ superiority margin compared to vehicle control within 5 minutes after a single wash	▪ Intended for use where soap and water are not readily available ▪ Demonstration of superiority to soap and water has no meaning if soap and water are not available
Health Care Antiseptics	▪ Minimal Bactericidal Concentration** ▪ Time Kill assay** ≥ 3 $\log_{10}$ reduction within 30 seconds	**Clinical Simulation Studies***** ▪ Measures reduction of bacteria on skin due to antiseptic use ▪ Hand wash: 1.2 $\log_{10}$ superiority margin compared to vehicle control within 5 minutes after a single wash ▪ Hand rub: 1.5 $\log_{10}$ superiority margin compared to vehicle control within 5 minutes after a single wash ▪ Patient preoperative skin preparation: 1.2 $\log_{10}$ superiority margin within 30 seconds or 10 minutes after drying ▪ Patient pre-injection skin preparation: 1.2 $\log_{10}$ superiority margin within 30 seconds after drying	Clinical outcome studies unfeasible due to ethical concerns: ▪ Requires vehicle-control arm (placebo) ▪ Inclusion of a vehicle-control arm could pose unacceptable health risks to study subjects (health care professionals and patients) ▪ Inclusion of a vehicle-control arm could increase risk of infection in a setting where risk of infection is high

Setting	In Vitro	In Vivo	In Vivo - Rationale
		▪ Surgical hand scrub: 0.5 log_{10} superiority margin compared to vehicle control within 5 minutes after a single wash ▪ Surgical hand rub: 1.5 log_{10} superiority margin within 5 minutes after a single rub	
		Persistence**** Patient preoperative skin preparation and surgical hand scrub/rub: bacterial count 6 hours post treatment lower than or equal to baseline	

** Test organisms are representative of bacterial infections occurring in consumer settings.*
*** Test organisms are representative of bacterial infections occurring in health care settings.*
**** The test product should be non-inferior to an FDA-approved active control with a 0.5 margin (log_{10} scale). The upper bound of the 95 percent confidence interval of the average treatment effect (ATE) of the active control compared to the test product to be less than 0.5 (log_{10} scale).*
***** Persistence is a requirement for antiseptic products intended for use in sterile settings, such as health care antiseptic products intended for use as surgical hand scrub/rub or patient preoperative skin preparation where skin is not recontaminated after antiseptic use; however, it is not considered relevant for food handler antiseptics settings.*

6.1. Consumer and Health Care Antiseptics in vitro Studies

The in vitro tests for determination of effectiveness for consumer and health care antiseptics consist of two assays: minimal inhibitory concentration or minimal bactericidal concentration (MIC/MBC) and Time Kill Assay (CLSI 1999). The tests are performed using a panel of microorganisms (bacteria and fungi reference strains and clinical isolates for consumer and health care antiseptics), selected based on their representation of the particular use setting and indication.

a. The MIC/MBC test determines the lowest concentration of the active ingredient that prevents visible growth of a microorganism (MIC) or that is required to kill a microorganism (MBC) for a fixed, extended period of time. The MBC is complementary to the MIC; the MIC test demonstrates the lowest concentration of antimicrobial agent that greatly inhibits growth, the MBC demonstrates the lowest concentration of antimicrobial agent resulting in microbial death. The test is performed against a broad range of organisms; in general, microorganisms known as a source of contamination in settings where the antiseptic product is used are included in the MIC/MBC test. Both reference strains and clinical isolates of these organisms are incubated at the appropriate temperature and media in presence of decreasing concentrations (serial dilutions) of the active ingredient and the lowest concentration able to prevent visible growth or that is lethal to the microorganisms tested is determined.

   Given that the microorganisms included in the test represent organisms most commonly encountered in the specific use settings of the antiseptic product (health care or consumer settings), the MIC/MBC test informs on the in vitro ability of the active ingredient to kill or inhibit organisms commonly encountered in its use settings.

b. The Time Kill assay also consists of testing the antiseptic activity of the active ingredient against a set of microorganisms commonly encountered in the specific settings in which the antiseptic products containing the active ingredient in question will be used, but in this assay, the concentration of active ingredient is within (or near) the concentration range in which the active ingredient is used in the antiseptic product final formulation and the time of contact between the active ingredient and the microorganisms tested is representative of the conditions of use of the antiseptic product. For example, if an antiseptic handwash is expected to be applied in hands for approximately 30 seconds before rinsing, the time of contact between the active ingredient and the test microorganisms in the Time Kill Assay would include at least a 30 seconds time interval at any product formulation tested. Therefore, the Time Kill assay informs on the in vitro ability of the active ingredient to kill or inhibit organisms a time frame consistent with that of product actual use.

We expect that these in vitro tests will also provide useful information regarding the range of antiseptic activity as well as the time of contact needed for an effective product with regard to the active ingredients used in food handler antiseptic products. However, as addressed in section 8 below, when evaluating the effectiveness of food handler active ingredients, it is important to include in such tests microorganisms representative of food handler settings.

6.2. Consumer and Health Care Antiseptics in vivo Studies

The efficacy of active ingredients for antiseptic drug products, as over-the-counter drugs, is required to be demonstrated by controlled clinical investigations, as described in 314.126(b), unless this requirement is waived (21 CFR 314.126(b);(c)). These studies must be well-controlled and able to distinguish the effect of a drug from other influences such as spontaneous change in the course of the disease, placebo effect, or biased observations (314.126(a)).

The in vitro studies described above assess the ability of antiseptic active ingredients to prevent or eliminate the growth of organisms encountered in the specific use settings of the antiseptic product (MIC/MBC) during the time that the product is used (Time Kill assay); however, these in vitro studies do not provide information about the in vivo effectiveness performance of the product in an actual-use setting. To support a GRASE determination for antiseptics, we currently require in vivo clinical outcome studies for consumer antiseptic washes, while we require clinical simulation studies for consumer antiseptic rubs and health care antiseptics.

The Nonprescription Drug Advisory Committee meeting held in October 2005, (NDAC 2005) which prompted a revision of the efficacy standards for consumer antiseptic drug products, concluded that the ability of consumer antiseptic wash products to decrease bacteria on the skin is relevant for a GRASE finding only if it is supported by a direct clinical benefit, and such benefit can only be demonstrated via clinical outcome studies. Consequently, in the 2013 Consumer Wash PR, we proposed a requirement for clinical outcome studies based on the lack of sufficient data to clearly demonstrate the benefit from the use of consumer antiseptic wash products compared to nonantibacterial soap and water. Accordingly, we believe that, for consumer settings where soap and water are readily available, the benefit of using an antiseptic wash product instead of plain soap and water must be supported by clinical outcome studies. Specifically, a clinical outcome study must demonstrate the clinical benefit of consumer antiseptic wash products and their superiority compared to a nonantibacterial wash, such as soap and water.

FDA, after evaluating the studies and comments submitted in response to the proposed rule issued in 2013, determined that the concerns regarding the extended use of antiseptic products and the potential consequences on systemic exposure, as well as consequences on the development of bacterial resistance, could not be ignored (78 FR 76444). Moreover, as previously demonstrated, these studies are considered to be feasible (Larson et al. 2004; Luby et al. 2005). As a result, in 2016, clinical outcome trials, or robust clinical investigation studies, were established as a requirement to support a generally recognized as effective determination for consumer wash active ingredients (81 FR 61106). In brief, the 2016

consumer antiseptic wash products final rule requires demonstration that the effectiveness of a consumer wash active ingredient be significantly better than that of a nonantimicrobial soap (i.e., plain soap) for the reduction of infection in consumer settings.

In contrast, the March 2005 NDAC (NDAC 2005) acknowledged the difficulty in designing clinical outcome trials in health care settings and advised against the requirement of such trials for GRASE determination of health care antiseptic active ingredients. Numerous factors that contribute to hospital-acquired infections would need to be controlled and considered in the design of clinical outcome studies in health care settings. Some of these factors include patient age, nutritional status, health conditions such as obesity, diabetes, smoking, altered immune response, and coexistent infections at a remote body site. Above all, it was concluded that clinical outcome studies in health care settings raise ethical concerns: an adequately controlled study would require the inclusion of a vehicle or negative control arm which could pose health risks to study participants (with increased risk of infection for both patients and healthcare personnel), given the fact that such studies would be conducted in settings with an already elevated risk of infections. It is for these reasons that the requirement of placebo-controlled studies in health care settings was determined unethical (82 FR 60474) and, as advised by the March 2005 NDAC, we continue to assess the effectiveness of health care active ingredients based on the results of clinical simulation studies (FDA 2019a).

Also contrary to consumer antiseptic wash active ingredients, for which clinical outcome studies are required given the available alternative of handwashing with plain soap and water, for active ingredients used in consumer antiseptic rubs a clinical outcome trial has little applicability. First, a negative control, i.e., a waterless non-antimicrobial alternative comparable to handwashing with plain soap and water is not available. Second, consumer antiseptic hand rubs are recommended for use only when soap and water are not readily available and when hands are not visibly soiled, so a comparison of product's efficacy with plain soap and water is meaningless. For these reasons, we continue to determine the efficacy of consumer antiseptic rub active ingredients based on the results of clinical simulation studies (81 FR 42912) (FDA 2019a).

For each of the antiseptic categories, the described studies required for demonstration of efficacy are also summarized in Table 1.

In the in vivo clinical simulation studies described for consumer rubs and health care antiseptics, the effectiveness of the active ingredient against the challenge microorganisms is measured in conditions that simulate conditions of skin contamination with one (or more) of the microorganisms commonly encountered in the specific use settings of the antiseptic product and the ability of the active ingredient to reduce such contamination is evaluated.

Methods for such simulation studies are available and well defined for certain situations. Methods used for measuring the effectiveness of an active ingredient used in health care antiseptic handwash and hand rub products consist of contaminating hands/skin with a challenge organism of known concentration and measuring the reduction of the challenge microorganism on hands after the application of antiseptic active ingredient (ASTM 2013a; ASTM 2015b). This test is intended to mimic the contamination of hands with a transient

microorganism and determine an active ingredient's effectiveness by its ability to reduce transient bacteria on skin. Other simulation methods, used for determination of effectiveness of antiseptic active ingredients for preoperative skin preparation or surgical scrubs, measure the ability of the active ingredient to reduce bacteria and other microorganisms residing on skin, also determined by the $\log_{10}$ reduction of resident bacteria post product/active ingredient application (ASTM 2015a; ASTM 2017a).

7. Demonstration of Effectiveness for Food Handler Antiseptic Active Ingredients

As summarized in Table 1, we believe that a combination of both in vivo and in vitro studies would be informative and necessary for determination of effectiveness of food handler antiseptics active ingredients. However, because determination of efficacy in a food handler setting represents a new paradigm, various challenges exist. Some of the challenges include: 1) what microorganisms should be selected to determine the efficacy of such active ingredients in vitro, 2) what studies would be most informative as well as feasible to demonstrate effectiveness in vivo (e.g., in food handler settings), and 3) what types of claims should be considered for labeling.

7.1. Food Handler Antiseptics in vitro Studies

With regard to the in vitro studies required for consumer and health care antiseptic active ingredients, a group of microorganisms, mainly bacteria representative of consumer and health care settings, are included in the studies (Time Kill assay for consumer wash antiseptics, MIC/MBC and Time Kill assay for health care and consumer rub antiseptics) (see Appendix C). However, when evaluating the effectiveness of active ingredients used in food handler antiseptics, in vitro testing should include microorganisms commonly encountered in food handler settings and known to cause food-borne illness through contamination of food by employee's hands (CDC 2014a) (Appendix D). Data show that each year 31 known pathogens are the main cause of nearly 9.4 million episodes of food-borne illness, including approximately 56,000 hospitalizations and 1,351 deaths (Scallan et al. 2011b). In 2011, 58 percent of illnesses were caused by norovirus, followed by nontyphoidal *Salmonella* spp. (11 percent), *Clostridium perfringens* (10 percent), and *Campylobacter* spp. (9 percent) with the leading causes of hospitalization being nontyphoidal *Salmonella* spp. (35 percent), norovirus (NoV) (26 percent), *Campylobacter* spp. (15 percent), and *Toxoplasma gondii* (8 percent). Also, in 2011 the leading causes of death were nontyphoidal *Salmonella* spp. (28 percent), *T. gondii* (24 percent), *Listeria monocytogenes* (19 percent), and norovirus (11 percent) (Scallan et al. 2011b; CDC 2014a).

In 2013, the Centers for Disease Control and Prevention (CDC) reported that bacterial foodborne illness accounted for 51 percent of food-borne disease outbreaks. Viruses were cited as the second most common cause of disease outbreaks (43 percent). Thus, almost one half of food-borne disease outbreaks included in the CDC report were not caused by bacteria (Gould et al. 2013). Among the foodborne pathogens, norovirus was reported as the most common cause of confirmed, single-etiology outbreaks, accounting for 284 outbreaks (43 percent); its transmission from contaminated hands to food items plays a major role in this foodborne illness. Parasites, including the protozoan species *Giardia lamblia*, *Cryptosporidium* species, and *Cyclospora cayentanensis*, accounted for a much smaller number of outbreaks, but should also be taken into consideration. These considerations raise questions concerning the antimicrobial spectrum of activity that food handler antiseptic active ingredients should demonstrate to be considered effective and the appropriate in vitro studies to assess such activity.

As noted above, the active ingredients of both consumer and health care antiseptics categories are only evaluated for their bactericidal activity via a combination of in vitro and in vivo tests and only general antibacterial claims are allowed for these products. FDA has considered in the past data submitted via a citizen petition (FDA 2010a) requesting inclusion of antiviral claims for OTC topical antiseptics. Such request has been denied due to the deficiencies of the studies submitted, such as lack of proper controls, wide variability in log reductions between studies and failure to demonstrate a significant benefit in comparison to hand washing with soap and water. FDA also concluded at the time that the in vitro results may not predict the antiseptic's effectiveness against viruses on human skin and that an evaluation of effectiveness against viruses on human skin would need to be supported by adequate in vivo studies (FDA 2010b).

We have reviewed the recent literature available and notice that the majority of studies regarding the efficacy of antiseptic active ingredients are conducted using surrogate models of norovirus, primarily feline calicivirus (FCV), and later on murine norovirus (MNV), given the difficulty to routinely propagate the human norovirus in cell culture or animal models or to clearly differentiate its noninfectious versus infectious particles (Richards 2012). The use of surrogates is based on the assumption that they mimic the virus that they represent; however, published data suggest that more than one surrogate may need to be used in combination, depending on the specific conditions or antiseptic products studied (Cannon et al. 2006; Park et al. 2010). In direct comparison, FCV and MNV have been repeatedly shown to behave differently to ethanol inactivation, as ethanol is well known for its ability to destabilize water and hydrophilic amino acids, and while FCV has several hydrophobic domains in its capsid, MNV is mostly hydrophilic. Though there are limited studies directly comparing the inactivation pattern of norovirus and surrogates and while testing conditions are not easily comparable (methods, viral challenge and contact time), they have concluded that there are notable differences between them (as assessed by differences in RNA genomic copies) (Liu et al. 2010; Richards 2012; Tung et al. 2013; Wilson et al. 2019). In a recently published study using a stem cell-derived enteroid culture system for norovirus, the authors studied the inactivation of a norovirus strain from the GII.4 genogroup, responsible for causing 80 percent of norovirus infections worldwide (Costantini et al. 2018). The study reports that although GII.4 replication levels when exposed to 70 percent ethanol for 1 and 5

minutes were significantly lower in comparison to nontreated controls, none of the GII.4 viruses were completely inactivated by ethanol. An earlier study comparing several culturable norovirus surrogates highlighted that Tulane virus, the most recently described surrogate virus from the same family of Caliciviridae, is less susceptible to ethanol treatment, potentially resembling norovirus inactivation profile (Cromeans et al. 2014). Overall, these results, while they demonstrate the differences between noroviruses themselves as well as compared to their surrogate models, also point out the inapplicability of such findings because: i) a 1 to 5 minute time period is much longer than the common duration of a typical hand wash of 30 seconds, and ii) these results were achieved by diluting and incubating the virus in ethanol solutions. An alcohol-based hand antiseptic, once applied on hands evaporates quickly, and as it is well documented, alcohols are rapidly antimicrobial when applied to the skin, but they have no residual activity due to their rapid evaporation (Lowbury et al, 1974).

Studies of other foodborne viruses such as hepatitis A virus, also representative of the food handler environment and notoriously known as environmentally stable, have shown that hepatitis A virus is also resistant and no ethanol concentration tested has been shown to reach a 4 $\log_{10}$ reduction in infectious titer, which otherwise appears to be the standard criterion for some studies (Wolff et al. 2001).

In most studies, the evaluation of efficacy of the antiseptic active ingredient or the antiseptic product formulation is based on the $\log_{10}$ reduction of infectious viral particles, either in vitro or in studies that simulate contamination of skin with known viral titers. EPA recommends for surface (hard, non-porous) sanitizers against norovirus that a test agent is acceptable if there is a minimum of 4 $\log_{10}$ reduction in the cytopathic effect of FCV (EPA 2015) and in most publications a 4 $\log_{10}$ reduction appears to be the desirable result for an inactivating agent to be considered active against viruses (Sattar and Springthorpe 2001; BSIGroup 2013). However, in addition to the challenges posed by the use of surrogate models and different study testing conditions, data that correlate $\log_{10}$ reductions of viral titers in vitro or in simulation studies with the reduction of viral infection in vivo are currently extremely limited (Liu et al. 2010; Steinmann et al. 2012), making determination of a clinically meaningful reduction exceedingly difficult.

We also note that, although both the CDC and World Health Organization recommend the use of alcohol-based hand rubs (in addition, and not as a substitute to hand washing) during outbreaks of noroviral gastroenteritis, their effectiveness in preventing or reducing infections is still to be fully determined, as the broader inactivation activity of alcohols (ethanol, isopropyl alcohol) against the most common non-enveloped viruses in natural food handling settings needs to be re-evaluated.

Protozoa, such as *Cryptosporidium* species, are also known as major causes of foodborne illnesses. In humans, the main causes of disease are *C. parvum* and *C. hominis and Giardia intestinalis* (*lamblia, duodenalis*) (CDC 2014b). The parasite (e.g., cyclospora, cryptosporidium) transmitted by the oocyst, once ingested, results in the release of sporozoites and the infection of intestinal epithelial tissue. In 2015, the Foodborne Diseases Active Surveillance Network (FoodNet) reported infection by *Cryptosporidium* species as the

cause for 16.6 percent of patients hospitalized due to pathogen infections for 15 percent of the United States population surveilled at the time (CDC 2017).

The review of available literature indicates that there is a lack of data regarding the use of antiseptic active ingredients for the prevention of protozoal infection, including *Giardia lamblia*, *Cryptosporidium* species, *Toxoplasma* species, and *Cyclospora cayentanensis*.

According to the CDC, alcohol-based hand sanitizers are not effective against *Cryptosporidium*, and chemicals such as bleach and iodine are unlikely to kill *Cyclospora* (CDC; CDC 2018a; CDC 2018c). A recent study showed that a commercial hand sanitizer containing 70 percent ethanol (Purell) killed *Entamoeba invadens* cysts (a nonpathogenic model for *E. histolyca*) when directly applied to contaminated finger pads (Chatterjee et al. 2015). Promising results were also obtained in vitro by the treatment of *Giardia duodenalis* and *Entamoeba invadens* cysts with 80 percent ethanol, 63 percent isopropanol, and 80 percent of isopropanol, for a contact time of 5 minutes per each active ingredient. The excystation rate after treatment, determined by placement of parasites in an excystation media that mimics the environment in small intestine and causes release of trophozoids, was shown to be ≥80 percent in all treatments. These initial results, however encouraging, will require further validation and analysis. In addition, the significance of reduction of oocysts in vitro with reduction of infections will need to be determined.

7.2. Food Handler Antiseptics in vivo Studies

As described above, the in vivo study requirements to determine effectiveness for antiseptic active ingredients differ for each category of antiseptics. Such requirements are based on careful evaluation of risks versus benefits for each category, on study feasibility depending on each use setting, on simulation models similar to the expected conditions of use, and on ethical concerns for the target population exposed to these studies (see Table 1 above).

Also as mentioned in section 6, for OTC products, demonstration of effectiveness via clinical outcome studies, i.e., clinical investigations, is required by the Code of Federal Regulations (314.126(b)) unless this requirement is waived. With regard to evaluation of effectiveness for food handler antiseptics active ingredients, we would need to determine whether such studies are feasible or, given the specific use settings of food handler antiseptics, whether clinical simulation studies would be adequate and sufficient.

When discussing whether clinical outcome studies need to be required, or not required, for food handler antiseptics, it is important to consider: 1) why clinical outcome studies are required for consumer wash antiseptics and not health care antiseptics; and 2) how are these products different or similar for food handler antiseptics. For health care antiseptics, a potential higher risk to the patient of developing an infection and having a poor clinical outcome if only soap and water were used for hand washing by health care providers and found less effective than an antiseptic, led to the conclusion that requiring a clinical outcome study would be unethical. In contrast, studies of consumer wash antiseptics have already been conducted and did not demonstrate a lower risk to a consumer of developing an

infection and having a poor clinical outcome compared with use of soap and water, leading to a requirement for a clinical outcome study to justify the use of consumer wash antiseptic active ingredients.

In response to our request for data and information (83 FR 63168) we received comments from industry advising against clinical outcome trials given the complexities of the study and the difficulties for controlling all the potential venues that may account for the contamination of the food as it is harvested, processed, packaged, prepared, or served by food handlers to the consumers. Such trials may also require that both professionals (food handlers) and consumers be included in the study design, which may raise ethical concerns regarding the participation of consumers who may be at increased risk of infection, such as consumers who have a compromised immune system or who are elderly. Potential feasibility challenges may also need to be considered in designing these studies.

As part of the potential discussion on the ethical and/or feasibility concerns related to clinical outcome studies for food handler settings, we posit below some of the advantages, disadvantages, and other considerations of clinical outcome studies.

Advantages of Clinical Outcome Studies

Clinical outcome studies are the gold standard for determining efficacy because they measure the endpoint of interest, i.e. the incidence of food borne illness. Thus, it may provide a definitive answer as to whether the use of food handler antiseptics provides a clinical benefit. Clinical outcome studies could also help determine what contribution is made by food handler antiseptics to overall hand hygiene versus that of proper hand washing with plain soap and water, and the benefit of combining food handler antiseptics with hand washing with plain soap and water.

Disadvantages of Clinical Outcome Studies

Clinical benefit and effectiveness that might be shown in a study for a cohort in one segment of the food chain may not be applicable to a cohort in a different segment. If the cohort of study subjects includes food consumers in addition to food handlers, assessing clinical benefit would become more complex as appropriate clinical endpoints might be different for each cohort. Benefit found in one cohort might not be found in the other cohort or benefit that cohort. In addition, clinical outcome studies in food consumers might have feasibility issues due to the need for extended clinical observation and evaluation of a large cohort with unclear endpoints. Furthermore, demonstrating efficacy in clinical outcome studies could be difficult because of the many variables and confounders that would need to be controlled for in food handlers and consumers. Variables and confounders for food handlers would include compliance with applicable food safety regulations, food safety training for food handlers, local work policies regarding food handler's illness, disinfection practices of work spaces, and use of personal protective equipment such as gloves. Variables and confounders for consumers would include exposure to other sources of food borne illness outside of study sites (i.e., consumer homes, other eating establishments) and variability of hand hygiene practices.

Other Considerations for Clinical Outcome Studies

In addition to the advantages and disadvantages of clinical outcome studies described above, other important considerations for performing clinical outcome studies include the following:

Current handwashing practices: One of the more important variables to consider is that of hand washing practices of food handlers. Guidance on current hygiene practices, including products used, when to wash, and how frequently, is imparted by CDC and the Food Code. The CDC has published guidance (CDC 2019) regarding proper hand washing; however, studies of hand washing practices for both the general population (Borchgrevink et al. 2013) and food handlers (Green et al. 2006) indicate that compliance with CDC hand washing guidance is poor, particularly with regards to the recommended duration of hand washing. This raises the question as to whether clinical outcome studies need to measure clinical benefit in the setting of proper hand washing, which appears to be uncommon, or improper hand washing, which appears to be more common place.

Risk to consumers in clinical outcome studies: For food handler antiseptics, most users of the end product, food on the table, are healthy consumers and not patients. However, some may be chronically or acutely ill, or in a higher risk category for a poor outcome if they should acquire an infection (adults aged 65 or older, children younger than age 5, people with weakened immune systems, or pregnant women, per the CDC website). The potential risk and impact associated with the spread of foodborne illness in food handler settings, greatly increases when considering many people can be exposed to the same source. The number of consumers that may fall ill after consuming foods prepared by infected workers can reach in the hundreds or thousands, especially in a ready-to-eat setting. It is noteworthy that there are no approved food handler antiseptics that could be used as an active control for an efficacy study; therefore, some justification and rationale would be needed when defining the best comparator that could be initially used as an active control for performance assessment in addition to a negative control of plain soap and water. The potential impact on consumers and other food handlers when evaluating the feasibility and/or ethical concerns associated with conducting a clinical outcome or clinical simulation study in food handler settings will need to be assessed.

Impact of Food Code recommendations on study design and types of antiseptic products to be studied: We should also consider in the study design the types of products (washes, rubs, hand dips, or wipes) used by food handlers in different settings. Current Food Code recommends only allowing antiseptic hand rubs after proper washing with soap and water followed by drying. Consistent with the Food Code recommendations, the results of of at least one systematic literature review suggest that water and soap appear to be more effective than hand rubs for removal of soil and microorganisms (Foddai et al. 2016). Therefore, it could be argued that, for food handling steps where water is available, plain soap and water would be the standard practice, and a clinical outcome study would therefore be appropriate to prove benefit in reduction of infection, whereas for those rare settings where water is not available, clinical simulation studies, such as those used for consumer antiseptic rubs, would be more applicable to current practice.

Clinical Simulation Studies

Clinical simulation studies, if required for determination of efficacy of food handler antiseptic active ingredients, are not without challenges. Methods for conducting clinical simulation studies currently required for demonstration of efficacy of health care and consumer rub active ingredients are available (ASTM 2013a). Other methods that consider the active ingredients' efficacy in the presence of soil are also available, (ASTM 2013b) and could be modified to appropriately test for the effectiveness of food handler antiseptic active ingredients is such conditions.

If viruses are to be included in testing, most methods used for evaluation of inactivation activity of antiseptics involve contamination of finger pads, (ASTM 2017b) due to inability to propagate large viral titers. This challenge would require validation of the finger pad methods and $\log_{10}$ reduction results would need to be compared to the full-hand contamination methods required for demonstration of effectiveness in health care and consumer rub antiseptic settings. The fact that the finger pad method does not reflect how these products are commonly used would also have to be considered.

Most importantly, if the $\log_{10}$ reduction is used for assessing effectiveness, the required log reduction for viruses and/or protozoa and its significance in reducing food-borne illness would also have to be assessed.

In summary, given the current challenges listed in this section and the lack of data that demonstrate the significance of $\log_{10}$ reduction of viruses and/or protozoa, input from the committee is required to determine whether 1) the activity of food handler active ingredients against viruses and/or parasites should be considered for demonstration of effectiveness of such active ingredients and 2) whether clinical outcome studies should be required for food handler antiseptics, or whether any concerns (such as potential ethical or feasibility difficulties of conducting a well-controlled study, and in which step(s) of the farm to table continuum) may justify that such requirement be waived in lieu of a different approach such as demonstration of effectiveness based on clinical simulation studies.

Appendix E summarizes some of the pros and cons of clinical outcome studies for food handler antiseptics.

8. Summary

Food handler antiseptics are antiseptic products intended for use by food handler professionals in commercial or regulated environments where growth, harvest, production, manufacturing, processing, packaging, transportation, storage, preparation, service, or consumption of food occurs. They play an important role, given the increased risk and the quick spread of food-borne illnesses in settings that affect a significant portion of our population, such as restaurants, food processing, and packaging facilities.

FDA has tentatively concluded that, considering the specific use settings, the potential broad exposure to unique pathogens, and the unique use patterns, the scope and role of OTC food handler antiseptics may differ from that of antiseptic products addressed in other rulemakings.

The safety and effectiveness of food handler antiseptic active ingredients, as for all active ingredients of other topical antiseptic categories, must be determined on the basis of a scientific evidence review. The focus of the upcoming advisory committee meeting is to discuss the appropriate dosage forms of antiseptic products that should be used in food handler settings; to assess and advise on the issues derived from the nature and multiplicity of the pathogens involved in this new setting (e.g., bacteria, virus, protozoa), and to provide input on the framework of the clinical studies that should be conducted to support a determination of generally recognized as safe and effective for food handler antiseptic active ingredients and their products.

FDA believes that establishing a framework that encompasses evolving science is an important step toward the common goal shared by all stakeholders, safe and effective food handler antiseptics that address the serious health consequences of foodborne infections.

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II. Appendices

Appendix A
Food Handler Antiseptic Drug Products for Over-the-Counter Human Use; Request for Data and Information; accessed February 14, 2020:

https://www.govinfo.gov/content/pkg/FR-2018-12-07/pdf/2018-26561.pdf

Appendix B
List of antiseptic products/ingredients used as food handler antiseptics.

- Alcohol 60-90%
- Benzalkonium chloride
- Benzethonium chloride
- Chloroxylenol
- Povidone-iodine 5-10%
- Isopropyl alcohol 70-91.3%
- Triclosan
- Iodine
- Isopropyl alcohol
- Quaternary ammonium chloride
- Phosphoric acid
- Chlorhexidine gluconate
- Benzalkonium chloride
- Dimethyl ethylbenzyl ammonium chloride
- Dodecyl methyl ammonium chloride
- Myristalkonium chloride

Appendix C
List of organisms for consumer and health care-in vitro testing

- **Organisms Proposed for in Vitro Testing of Consumer Antiseptic Wash Active Ingredients**

  Gram positive organisms
  - *Enterococcus faecalis* (ATCC 19433 and 29212)
  - *Listeria monocytogenes* (ATCC 7644 and 19115)
  - *Staphylococcus aureus* (ATCC 6538 and 29213) and methicillin-resistant *S. aureus* (MRSA) (ATCC 33591 and 33592)
  - *Streptococcus pyogenes* (ATCC 14289 and 19615)

Gram positive organisms

- *Campylobacter jejuni* (ATCC 33291 and ATCC 49943)
- *Escherichia coli* (ATCC 11775 and ATCC 25922)
- *Pseudomonas aeruginosa* (ATCC 15442 and ATCC 27853)
- *Salmonella enterica Serovar Enteritidis* (ATCC 13076) and *Serovar Typhimurium* (ATCC 14028)
- *Shigella sonnei* (ATCC 9290 and ATCC 25931)

- **Organisms Proposed for in Vitro Testing of Consumer Antiseptic Rub and Health Care Antiseptic Active Ingredients**

Gram positive organisms

- *Staphylococcus aureus* (ATCC 6538 nd 29213) *Staphylococcus epidermidis* (ATCC 12228) *Staphylococcus hominis*
- *Staphylococcus haemolyticus Staphylococcus saprophyticus Micrococcus luteus* (ATCC 7468) *Streptococcus pyogenes Enterococcus faecalis* (ATCC 29212) *Enterococcus faecium*
- *Streptococcus pneumoniae*

Gram negative organisms

- *Acinetobacter* species
- *Bacteroides fragilis*
- *Haemophilus influenzae*
- *Escherichia coli* (ATCC 11229 and 25922)
- *Klebsiella* species
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa* (ATCC 15442 and 27853)
- *Proteus mirabilis*
- *Serratia marcescens* (ATCC 14756)

Yeast

- *Candida* species
- *Candida albicans*

Appendix D

List of potential organisms for food handler antiseptics in vitro testing

Foodborne Pathogenic Microorganisms		
Bacteria	**Virus**	**Protozoan**
• Salmonella spp. • Salmonella Typhi • Campylobacter jejuni • Yersinia enterocolitica • Vibrio parahaemolyticus	• Norovirus • Hepatitis A virus • Hepatitis E virus • Coronavirus (bovine) • Rotavirus	• Cryptosporidium parvum • **Cyclospora cayetanensis** • Giardia intestinalis (lamblia, duodenalis) • Toxoplasma gondii

• Coxiella burnetii • Brucella spp. • Vibrio cholerae serogroups O1 and O139 including non-O1 and non-O139 • Vibrio vulnificus • Vibrio parahaemolyticus • Cronobacter (Enterobacter sakazakii) spp. • Aeromonas hydrophila and other spp. • Plesiomonas shigelloides • Misc. bacterial enterics (Klebsiella, Enterobacter, Proteus, Citrobacter, Aerobacter, Providencia, Serratia) • Francisella tularensis • Enterotoxigenic E. coli (ETEC) • Enteropathogenic E. coli (EPEC) • Enterohemorrhagic E. coli O157:H7 (EHEC) • Enteroinvasive E. coli (EIEC) • Clostridium perfringens • Staphylococcus aureus • Listeria monocytogenes • Enterococcus • Shigella spp. (causes shigellosis) • Bacillus cereus and other Bacillus spp. • Streptococcus spp. • Streptococcus pyogenes • Mycobacterium bovis • Clostridium botulinum • Clostridium perfringens • Cryptosporidium spp. • Cyclospora cayetanensis • E. coli producing toxin • Shiga toxin-producing E. coli	• Other (astrovirus, sapovirus, enteric adenovirus, parvovirus, aichi virus, v*ibrio cholerae*)	

Appendix E:

Advantages and Disadvantages of a Randomized, Controlled Clinical Outcome Study Comparing Food Handler Antiseptic Use to Handwashing with Plain Soap and Water for Prevention of Infection.

Advantages and Disadvantages of a Randomized, Controlled Clinical Outcome Study Comparing Food Handler Antiseptic Use to Handwashing with Plain Soap and Water for Prevention of Infection		
Advantages of COS*	**Disadvantages of COS***	**Additional Considerations**
Provides a definitive answer to the question: Does use of food handler antiseptics reduce food borne illness?	May be able to answer the question for a segment of the food chain; however, may not answer for all segments from farm to table Unclear if/what endpoint is best and feasible	Studies cost more than simulation studies Not all pathogens that cause foodborne illness may be tested or show benefit
Establishes efficacy with scientific rigor (gold standard) May help determine any contribution to efficacy from the food handler antiseptic versus the hygiene method itself	Many variables and confounders may impact outcome	Examples of variables/confounders may include subjects not confined for duration of study, how to follow-up food handlers who work at a setting or consumers who eat at an establishment, hygiene method of disinfecting hard surfaces, keeping sick employees away from food, use of gloves and masks, variability of consumer hand hygiene practices, exposure to other sources of foodborne illnesses outside of study sites (i.e., consumer homes, other eating establishments) etc.

COS=Clinical Outcome Study