COMMENT SUBMITTED BY

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

June 16, 2014

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

The Personal Care Products Council (the Council) (formerly the Cosmetic, Toiletry, and Fragrance Association) and the American Cleaning Institute (ACI) (collectively, we) are pleased to provide these comments in response to the Food and Drug Administration's (FDA's) proposed amendment (Proposed Rule) to the tentative final monograph for over-the-counter (OTC) antiseptic drug products for human use (Consumer Antiseptics).[1]

Founded in 1894, the Council is the national trade association representing the personal care products industry. Our membership includes approximately 300 active member companies that manufacture or distribute personal care products, including OTC skin antiseptics. We also represent approximately 300 additional associate members who provide goods and services to manufacturers and distributors of personal care products.

The American Cleaning Institute (ACI) is the Home of the U.S. Cleaning Products Industry™, representing producers of household, industrial, and institutional cleaning products, their ingredients and finished packaging; oleochemical producers; and chemical distributors to the cleaning product industry.

We submit these comments to support FDA in its ultimate drafting of a final monograph for Consumer Antiseptics that is based on sound science and policy and that promotes the public health by developing reasonable standards to evaluate the safety and efficacy of these products.

I. Executive Summary

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

[1] 78 Fed. Reg. 76,444 (Dec. 17, 2013).

Consumer Antiseptics is a category of topical antiseptic products that is critical to public health because of the importance hand hygiene plays in the prevention of infection. As discussed below, washing the hands with an antiseptic handwash can help reduce the risk of infection beyond that provided by washing with non-antibacterial soap and water. We calculate that Consumer Antiseptics prevent between 250,000 to 7.5 million instances of foodborne illnesses annually, avoiding $1.3 billion to greater than $38 billion in national costs.

In the Proposed Rule, FDA states that it plans to regulate antiseptic ingredients in Consumer Antiseptics separately from their use in healthcare settings. For Consumer Antiseptics, FDA proposes a new and significant set of testing requirements, including clinical population studies, for establishing generally recognized as safe and effective (GRAS/E) status for active ingredients, but FDA fails to provide surrogate endpoint efficacy test standards for formulated Consumer Antiseptics. This proposal runs counter to FDA's previous position that extensive safety testing should be conducted on the active ingredient and efficacy primarily on a final formulation. FDA also fails to provide a clinical guideline protocol designed to emphasize prevention over treatment. We urge FDA to reconsider the proposed testing requirements for the following reasons.

First, the testing requirements for establishing GRAE, and especially the requirement for clinical population studies, are unprecedented when considered against clinical study data requirements associated with other OTC monograph, New Drug Application (NDA) approvals for antiseptics, international approval standards for similar products and the requirements of other authoritative bodies. In the context of OTC Monographs, active ingredients are GRAS/E on the basis of publicly available data, including scientific literature, rather than prospective clinical studies that are designed to meet (or in this case, go beyond) NDA standards. Given the significance of the change to the testing requirements for Consumer Antiseptics and the lack of precedent for this action, FDA should withdraw the Proposed Rule and reissue it as an Advance Notice of Proposed Rulemaking (ANPR) in order to give us and other stakeholders an opportunity to engage with FDA on the GRAE testing requirements for the active ingredients and surrogate endpoint testing of final formulations.

As we have extensive experience and expertise with respect to Consumer Antiseptics, we can help FDA develop testing requirements that balance practical, real-world limits with the public health need for safe and effective OTC drugs. We request significant technical interaction with FDA prior to any finalization of these requirements. We also recommend that FDA recognize the American Society for Testing and Materials (ASTM) methods E1174 - Standard Method for the Evaluation of Health Care Handwash Formulation, E2783 - Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure, and E2784 - Standard Test Method for Evaluation of the Effectiveness of Handwash Formulations Using the Paper Towel Method (Palmar Method) of Hand Contamination as appropriate to support the surrogate endpoint efficacy testing for finished antiseptic formulations. We submit the ASTM test methods and example protocols for FDA review and consideration.

Second, FDA's definition of Consumer Antiseptics is ambiguous. It does not define consumer use, nor take into account the public and community areas in which these products are used, including schools, airports and other public and commercial facilities.

Consumer Antiseptics play a crucial role in reducing risk of disease and bacteria transmissions in many areas and the failure to account for this role skews FDA's risk/benefit analysis of these products. In the absence of a clear definition of Consumer Antiseptic, it is premature to conduct additional clinical testing to establish GRAS/E.

Third, we ask FDA to formally recognize antiseptic handwashes that are used in the food industry under 21 C.F.R. 333 as a distinct category that should be subject to its own monograph, and pending that development, confirm that Food Handler topical antiseptic products can continue to be marketed under the current regulatory framework. We further recommend FDA's Center for Drug Evaluation and Research (CDER) consult with FDA's Center for Food Safety and Applied Nutrition (CFSAN) regarding these products.

Fourth, we submit new data to support the Melon Ball Disease Transmission Model and validate the Palmar Method and ask FDA to recognize and confirm that the Model has demonstrated the clinical benefit of antiseptics over plain soap and water. FDA proposes new testing to establish efficacy, including clinical population studies, because of asserted design flaws with simulation studies, including an inability to correlate study results with clinical outcome. We contend that there are methods to correlate simulation study results with clinical outcome and submit a study published by Schaffner in 2014. Schaffner used the "Melon Ball Disease Transmission" model coupled with Quantitative Risk Model Analysis (QRMA) to show a definitive benefit of antiseptic handwashes as compared to non-antibacterial liquid soap or "plain soap" in the reduction of *Shigellosis* at multiple levels of bacterial dose. We also submit an expert panel review of the model and additional publications supporting the Palmar Method. For body antiseptics, we also submit an initial protocol outline of a clinical study design to demonstrate the clinical benefit for body wash products.

Fifth, FDA should not require additional safety testing on the basis of increased systemic exposure and its effects on the endocrine system and the potential for development of antibacterial resistance. Biomonitoring studies conducted over a decade for selected active ingredients do not suggest that systemic exposure is increasing, nor that the current levels are approaching a level of potential safety concern. In-situ type studies also continue to show no correlation between topical antiseptic use and antibiotic resistance in the natural setting. Furthermore, results from existing traditional studies currently required by FDA for antiseptic active ingredients designed to provide signals of the potential for hormonal effects have not done so. We request the opportunity to work with FDA to develop scientifically sound and meaningful monitoring programs to address these concerns. Furthermore, we urge FDA to critically review claims of increased exposure in relation to increased risk rather than increased analytic sensitivity, as well as claims of human endocrine effects based on a risk assessment rather than *in vitro* results from high throughput screening and thyroid effects from toxicology evaluations. In addition, FDA should work in collaboration with the intergovernmental task force on antibacterial resistance of which it is a member.

Sixth, in proposing new safety testing, FDA must consider the following factors: actual risks, existing safety assessments and non-animal alternative test methods. We request FDA tp consider the level of human exposure to each of the antimicrobial active ingredients and assess the harm from those exposures to determine the need for additional data. If current product exposures do not present unacceptable risks based on the existing safety data for an

individual ingredient, FDA should refrain from requiring efficacy information that is out of proportion. In instances where further safety evaluation is needed, FDA should recognize and allow the use of alternative toxicity evaluation methods that have been accepted by scientific and regulatory communities. We also suggest that the agency consider other authoritative bodies' safety assessments for active ingredients, such as EPA's reregistration and registration review of active ingredients. Overall, where done, such assessments have not suggested potential human safety concerns. Further, FDA should support safety evaluation approaches that avoid or minimize animal testing.

Seventh, we request an extension of time for the submission of new safety and effectiveness data to the record, consistent with the preamble to the Proposed Rule.[2] We require significant guidance from FDA regarding the studies that the agency deems necessary for the determination of GRAS/E. We request additional time to allow for engagement with, and feedback from, FDA on the appropriate testing protocols and methods. An extension is consistent with past agency practice. FDA has granted extension requests when a Tentative Final Monograph (TFM) is substantially changed from a previous proposed monograph and the required testing guidelines have been extensively modified.[3] This is such a case. The last step in this Rulemaking was a 1978 TFM, which did not address consumer antiseptics. FDA's proposed testing in the Proposed Rule is an extensive modification of the proposal in the 1994 TFM. In particular, FDA requests clinical population studies to support efficacy. Although we believe this requirement is unjustified, especially when compared to prior rulemakings on other OTC monograph drugs, the two studies that FDA is requesting would take several years to design, execute, analyze and report, and additional time to get agency assessment and approval of the protocols. For these reasons, FDA's timeline for new data submission is unreasonable and unrealistic. We request that FDA provide the appropriate extension of time in order to work with FDA to develop the appropriate data requirements and achieve FDA's agreement on detailed protocols.[4] We are submitting with these comments an initial draft protocol that could help start that discussion.

Eighth, should FDA find after performing its usual risk assessment of the antiseptic active ingredients and the Consumer Antiseptic formulations by following established transparent, scientifically acceptable procedures, there is no demonstration of risk under existing use conditions, then FDA should conclude that the active ingredients and formulations are safe for human exposure at the assessed use concentrations. Under these circumstances, FDA should assess efficacy using data from existing procedures that demonstrate bacterial (or other organism) kill without requiring unproven clinical population studies. If the existing data are sufficient to establish efficacy, then FDA should conclude that the active ingredients and

[2] 78 Fed. Reg. at 76447.

[3] *See, e.g.*, 43 Fed. Reg. 4637 (Feb. 3, 1978) (granting extension of time for objections to TFM on antibacterial soaps, surgical scrubs, skin cleaners and first-aid preparations).

[4] As demonstrated by the recent public hearing on the OTC Drug Review, FDA seeks to ensure that the monograph process is responsive to emerging information and evolving science. 79 Fed. Reg. 10168 (Feb. 24, 2014). The proposed monograph for Consumer Antiseptics, with its proposed clinical testing and safety testing for hormonal effects and antimicrobial resistance, is an example of an area of emerging science that requires close FDA and industry engagement.

associated formulations are effective. If the existing data are insufficient to establish efficacy, FDA should require additional efficacy data from existing procedures (and extend the timeframe for submission of additional data) before requiring a clinical population study.

Finally, in connection with our objections to the TFM and in the absence of FDA fulfilling number seven above, we request an oral hearing under 21 C.F.R. § 330.10(a)(7).[5] Under 21 C.F.R. § 330.10(a)(8), the Commissioner shall schedule an oral hearing if she finds that reasonable grounds support objections to a TFM. We request a hearing on each of the reasonable grounds listed below, which are further explained in this document:

- FDA's proposed definition of Consumer Antiseptics is incomplete and indeterminate and overlooks the important role these products play in broader areas such as schools, airports, and other public facilities. Consumer antiseptic products are products that reduce the level of bacteria on skin, which can reduce the risk of disease and bacteria transmission in the home as well as in other areas. Elimination of these products would increase the risk and level of exposure of the general population to bacteria, which could lead to increased infection and disease.

- FDA should allow the "Melon Ball Disease Transmission" model coupled with Quantitative Risk Model Analysis (QRMA) to be used to demonstrate that log reductions in surrogate endpoint testing are correlated with a clinical benefit associated with use of consumer antibacterial handwash product formulations in comparison to non-bacterial handwash product formulations.

- FDA should recognize ASTM methods E1174, E2783 and E2784 as appropriate test methodology to support the surrogate endpoint efficacy testing for finished antibacterial product formulations.

- Before determining that there is a need for additional safety data on Consumer Antiseptics, FDA should consider available data and knowledge on the level of human exposure to each of the active ingredients and assess the risk of human harm that such exposures could pose.

- Biomonitoring studies conducted over a decade for selected active ingredients do not suggest that systemic exposure is increasing, nor that current levels are approaching a level of potential safety concern.

- In-situ type studies continue to show no correlation between antibacterial use and antibiotic resistance in the natural setting.

- FDA should recognize and allow the use of alternative methods—namely those that have been accepted by scientific and regulatory communities—to fill any safety data gaps.

- FDA should support safety evaluation approaches that avoid or minimize animal testing.

[5] 21 C.F.R. § 330.10(a)(7) (permitting an oral hearing request to accompany objections to a TFM).

In summary and for all of the reasons summarized above, we request FDA to:

- Reissue this proposal as an Advance Notice of Proposed Rulemaking (ANPR) consistent with the administrative procedures published at 21 C.F.R. § 330.10(a)(2).

- Grant an extension of the December 2014 data submission deadline to allow for review of the submitted new data for hand antiseptics and proposed protocol for body wash antiseptics, as well as collaboration with FDA to finalize a protocol and allow for data generation and analyses, and

- Schedule an Oral Hearing under 21 C.F.R. § 330.10(a)(7).

II. History of Regulatory and Industry Activities in this Rulemaking

The rulemaking proceedings for the OTC topical antimicrobial monograph have been complex and long-lasting. FDA issued its advance notice of proposed rulemaking in 1974 and its first TFM in 1978, before revising the TFM in 1991 (First Aid antiseptics), 1994 (healthcare antiseptics) and 2013 (consumer antiseptics), as listed below:

- Advance Notice of Proposed Rulemaking, 39 Fed. Reg. 33103 (September 13, 1974)

- Notice of Proposed Rulemaking, 43 Fed. Reg. 1210 (January 6, 1978)

- Notice of Proposed Rulemaking, 56 Fed. Reg. 140 (July 22, 1991) Notice of Proposed Rulemaking (Revised), 59 Fed. Reg. 31402 (June 17, 1994)

- Reopening of the Administrative Record, 68 Fed. Reg. 32003 (May 29, 2003)

- Notice of Proposed Rulemaking (Revised), 78 Fed. Reg. 76443 (December 17, 2013)

We have been responsive to the public health need to assess the safety and effectiveness of OTC antimicrobial products. In particular, since the modern revision of the TFM in 1994, we have actively and repeatedly sought to engage with FDA to discuss the required safety and efficacy data for these products and for Consumer Antiseptics specifically. We have sought every available avenue to submit new safety and efficacy data and to discuss with FDA data requirements, test methods, performance standards, and allowable claims. We have submitted Citizen Petitions, participated in public meetings convened by FDA and the Nonprescription Drugs Advisory Committee (NDAC), convened public symposia, and submitted written responses to FDA's requests for information. Furthermore, even where FDA has not provided guidance, stakeholders, on their own initiative, have moved forward with developing new test methods to advance the science and technology for assessing the safety and efficacy of these products. Below is a sample list of Council and ACI activity since the issuance of the TFM in 1994:

- The Council and ACI on May 30, 2008 requested a meeting with FDA on topical antimicrobial products, and submitted new data and information regarding efficacy on September 23, 2008.

- The Council and ACI participated in an FDA public feedback meeting on November 14, 2008 to discuss the efficacy of topical antimicrobial products.

- The Council and ACI presented testimony at an NDAC meeting convened by FDA on October 20, 2005 to discuss the efficacy and safety features of OTC topical antimicrobial products.

- The Council and ACI presented testimony at an NDAC meeting convened by FDA on March 23, 2005 to discuss the efficacy criteria for professional healthcare topical antimicrobial products.

- The Council and ACI filed three sets of comments and additional data on August 27, 2003 in response to FDA's Reopening of the Administrative Record. The Council and ACI submitted: (1) a supplement to the August 2001 healthcare professional products submission; (2) a submission on the underlying legal and policy considerations; and (3) a submission on the issue of bacterial resistance to antibacterial agents.

- The Council and ACI submitted a Citizen Petition that provided data to support performance criteria for food handler, consumer hand, and consumer body products in May 2003.

- The Council and ACI submitted a Citizen Petition requesting anti-viral claims based on testing and evidence of efficacy on January 17, 2003.

- On November 28, 2001, the Council and ACI submitted a Citizen Petition on surrogate endpoint test methods.

- The Council and ACI submitted a Citizen Petition providing information in support of healthcare professional products on August 6, 2001.

- The Council and ACI filed a Citizen Petition addressing several OTC monograph flexibility issues on June 1, 2001.

- The Council and ACI filed a Citizen Petition for proposed labeling of health care continuum model (HCCM) categories on April 2, 2001.

- On September 29, 1999, the Council and ACI filed an extensive briefing document on the subject of finished product efficacy testing for topical antimicrobial products, which was discussed at a public feedback meeting on November 3, 1999.

- The Council and ACI presented testimony at an NDAC meeting convened by FDA on July 29, 1998 to discuss effectiveness testing for topical antimicrobial products. We provided data to demonstrate that the methods described in the TFM, as well as the proposed performance standards, needed to be re-evaluated.

- The Council and ACI sponsored a public symposium on the HCCM in collaboration with FDA, The American Academy of Dermatology (AAD), International Association of Milk,

Food and Environmental Sanitarians (IAMFES), and Association for Professionals in Infection Control and Epidemiology, Inc. (APIC) on June 2–3, 1998.

- The Council and ACI presented testimony at an NDAC meeting convened by FDA on January 22, 1997. The NDAC panel advised FDA that antiseptic/antibiotic resistance is currently not an issue, but recommended a surveillance plan.

- On July 29, 1996, FDA's Office of Drug Evaluation V held a public "feedback" meeting with the Council and ACI to discuss agenda items for future public workshops on antimicrobial products for 1997.

- The Council and ACI submitted new data on ingredients currently used in antimicrobial soaps for everyday use on December 13, 1995, and March 11, 1996. Data for ingredients such as triclocarban, triclosan, iodine, alcohol, PCMX and quaternary ammonium compounds were submitted.

- On June 15, 1995, the Council and ACI filed written comments on the proposed regulation, calling for adoption of a HCCM for antimicrobial soaps.

The above illustrates our long-term dedication to providing safe and effective products to consumers and professional users. It also demonstrates our desire to respond to and scientifically address the concerns that FDA has raised. We welcome greater collaboration with FDA to work toward finalization of each of the product monographs under the OTC antiseptic category (e.g., Healthcare Antiseptic Drug Products, Consumer Antiseptic Hand Wash Drug Products, First Aid Antiseptic Drug Products, Consumer Antiseptic Hand Sanitizer Drug Products, and Foodhandler Antiseptic Drug Products).

III. FDA Should Issue Any Proposed Rule as an Advance Notice of Proposed Rulemaking.

In the Proposed Rule, FDA requests efficacy data from clinical outcome studies and additional safety data, including data on potential hormonal effects and bacterial resistance, to evaluate ingredients for Consumer Antiseptics as GRAS/E. Because the data requirements described in the Proposed Rule depart significantly from the testing proposed in the 1994 proposed Tentative Final Monograph (TFM), we urge FDA to reissue this proposal as an Advance Notice of Proposed Rulemaking (ANPR) consistent with the administrative procedures published at 21 C.F.R. § 330.10(a)(2).

Under the OTC review process, prior to issuing a TFM, FDA first requests submissions of data and information, including controlled studies on active ingredients, pertinent to a designated category of OTC drugs for review and evaluation by an FDA advisory committee. After such submission of data and committee review, FDA publishes a proposed monograph stating the conditions under which the category of drug active can be GRAS/E. Here, despite issuing the Consumer Antiseptic Proposed Rule as a TFM, FDA is essentially requesting an entirely new set of data, well above what had been required in the previously issued 1978, 1991, and 1994 TFMs. Unlike a TFM, this Proposed Rule does not propose the conditions under which such products can be marketed. For example, the Proposed Rule fails to

address several issues expected in a monograph, such as a definition and labeling indications, that are crucial to ultimate future compliance with the final Monograph. The Proposed Rule only requests testing on the active ingredients to establish GRAE, but fails to confirm whether the agency will impose additional surrogate efficacy requirements for a final formulation. This is in contrast to the 1994 Proposed Rule on Healthcare Antiseptics and previous monographs for other OTC products in which FDA provided direction on the efficacy and safety testing required to establish GRAS/E and the surrogate endpoint efficacy testing to market the products.

The Consumer Topical Antimicrobial Proposed Rule should be reissued as an ANPR. This is especially pressing because, in addition to the absence of guidance on the final conditions under which OTC consumer antiseptics may be marketed, the Proposed Rule imposes data requirements that present novel scientific issues for which standardized valid test methods are not yet available. There is precedent for FDA issuing a request for new data as an ANPR in the OTC drug review process where there is a lack of scientific consensus. For example, due to a lack of consensus on efficacy test requirements for OTC anticaries products, FDA issued an ANPR to request information and data on the use of intraoral appliance models as a substitute for the monograph-required animal caries reduction biological test due to lack of consensus regarding the new model. As with the OTC anticaries rulemaking, the OTC consumer antiseptic rulemaking history highlights the lack of consensus regarding the validity of the "Melon Ball Disease Transmission Model" method to demonstrate clinical benefit, and the need for data relating to the development of antibacterial resistance. The issuance of an ANPR would give FDA an opportunity to clarify and refine the testing requirements with stakeholder input. It could provide sufficient time for stakeholders to work with FDA to develop the appropriate testing requirements for active ingredients and final formulations as well as study design protocols to generate useful data, and for stakeholders to execute, analyze, and report on these studies.

Several independent experts with experience in both safety and clinical trials have reviewed the proposed requirements. According to these experts, FDA's timeline of one year to submit the new data is not possible (Appendix A). Moreover, the TFM does not provide concrete direction on how these studies should be designed and, to date, FDA has consistently rejected novel methods as being "unvalidated" though they may have been published for more than a decade. Therefore, we require interaction with FDA on study design as well as agreement on clinical endpoints. To ensure sufficient time for these steps, reissuance of the Proposed Rule as an ANPR is appropriate.

Even if FDA chooses not to reissue the Proposed Rule as an ANPR, FDA should consider implementing differentiated compliance dates. FDA's regulatory impact analysis proposes a 12-month compliance period as a preferred regulatory option. Compliance dates apply equally to all active ingredients affected by the Proposed Rule. However, some active ingredients may warrant different compliance dates to reflect different, and additional, testing that may be required for certain ingredients. In addition, it may take longer to develop an appropriate alternative for a certain active ingredient, requiring a longer compliance period. Therefore, FDA should allow for different compliance dates for those ingredients for which stakeholders have sufficient safety and efficacy data available than for those active ingredients for which additional data are needed.

IV. FDA Should Clearly Define Consumer Antiseptics.

FDA's proposed definition of Consumer Antiseptics is unclear and fails to recognize the important role these products play in broader areas. The definition also skews the risk/benefit analysis of these drugs by failing to account for the risks of infection outside the home and the potential benefits that Consumer Antiseptics can provide in these settings. In the Proposed Rule, FDA narrows the group of products impacted by this ruling to "rinsed off" hand and body antiseptic wash products used by the general population.[6] These products are described as "used by consumers for personal use in the home on a frequent, even daily, basis."[7] We find this definition to be incomplete and indeterminate because many of these products are also used outside the home in areas other than the healthcare or professional food handling settings that will be, or are recommended to be, covered under separate monograph categories. Additionally, many restaurants and hospitals have shared restrooms for professionals and the public.

FDA should clearly define the intended use and setting for "consumer antiseptics" and separately address handwash products used in healthcare or professional food handling settings under a Food Handler or Healthcare use monograph. As a point of reference, Health Canada in its 2009 Final Guidance Document for Human-Use Antiseptic Drug separated antiseptics into 4 categories based on use, including personal domestic use, personal commercial use, use in professional food premises, and professional healthcare use.[8] Health Canada defined a "Personal Domestic Use" antiseptic as a product "used by an individual in a domestic setting to reduce transient organisms on the skin." A "Personal Commercial Use" product was defined as "[products] made available to the general public for occasional use and are intended to reduce transient organisms on the skin in a commercial or institutional setting." We suggest that FDA consider similar distinctions to better reflect the intended use and setting for "consumer antiseptics," and to account for exposure to different levels of risk of infection and different susceptibility to illness in healthcare or professional food handling settings.

We, therefore, request that FDA provide clear definitions for all of the antiseptic categories that will be encompassed by 21 CFR 333 and direction as to which antiseptic product category specific end-use products fall into (e.g., Consumer Antiseptics used in schools, offices, hotels, etc.). Consumer Antiseptics play an important role in reducing the level of bacteria on skin, which can reduce the risk of disease and bacteria transmission in the home as well as in these other locations. Elimination of these products would put the general population at risk for increased levels of bacteria on the skin, which may lead to increased infection and disease.

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[6] 78 Fed. Reg. at 76447.

[7] *Id.* at 76446.

[8] Health Canada. Guidance Document – Human-Use Antiseptic Drugs (2009) http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/antiseptic_guide_ld-eng.php

V. FDA Should Reconsider the Proposed New Efficacy Requirements.

A. The Efficacy Testing Required in the Proposed Rule Is Unprecedented.

The Proposed Rule would create unprecedented efficacy testing requirements among FDA monographs for antiseptics by establishing NDA-type data standards for establishing GRAS/E. In addition, FDA should not summarily dismiss the utility of data obtained under healthcare conditions as not being applicable to consumers because such a distinction may not be scientifically supportable.

For Consumer Antiseptics, the efficacy testing requirement in the Proposed Rule for establishing Category 1 efficacy cannot be justified on the basis of prior proposed indications of use. Though the Proposed Rule has not stated an indication of use, the preamble for the 1994 monograph for healthcare and consumer antiseptics stated that a permitted indication for such products was "[f]or handwashing to decrease bacteria on the skin."[9] This indication does not state or imply that these products provide a reduction in disease; instead, the only claim is that the products reduce the load of bacteria that is present on the skin. The *in vivo* testing described in the TFM for antiseptics for healthcare use is well matched to prove this indication for Consumer Antiseptics.

The proposed efficacy testing requirements are significantly more burdensome not only in comparison to establishing GRAE for active ingredients in other OTC Monographs, but in comparison to many of the new drugs that have been approved through the NDA approval process. Downing has conducted research into the types of clinical studies used to support NDA approvals from 2005-2012 for antiseptic drugs that do not fall under the Proposed Monograph.[10] Of the NDA approvals that he surveyed, Downing noted that 45% (91/206) of the indications were approved exclusively on the basis of surrogate endpoints and, therefore, were not supported by data from clinical efficacy trials. This record demonstrates that FDA has relied successfully on surrogate endpoints to support drug indications, which stands in striking contrast to the clinical efficacy testing requirements that FDA proposes for the indication of "[f]or handwashing to decrease the number of bacteria on the skin."

Furthermore, the proposed efficacy requirements are far more extensive than what is required for consumer, food industry, or healthcare antiseptics that are used for approval in Canada and Europe. While many of the ingredients that are listed in the TFM are allowed for use as active ingredients in antiseptics that are used globally, we are unaware of any country that requires clinical trials to establish that the active ingredient or formulation is GRAS/E. FDA has a long history of promoting harmonization among international regulatory authorities with respect to testing requirements, and should adhere to this principle as it develops this monograph for consumer antiseptics

[9] 59 Fed. Reg. 31402, 31406-07, 31433 (June 17, 1994) (proposed 21 C.F.R. § 333.455(b)(1)).

[10] Downing N *et al.*, Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012, JAMA 300(4):368-377 (2014).

B. FDA's Efficacy Requirements Are Unjustified by the Risk-Benefit Analysis.

FDA not only proposes unparalleled testing requirements, but attempts to justify them by relying on speculation rather than on sound science. Typically, reassessments of benefits and risks are prompted by a safety signal, such as the appearance of a particular sign, symptom, or symptom-complex. However, there has been no demonstration of a scientifically confirmed risk associated with the usage of Consumer Antiseptic products, but only speculation around potential risks associated with endocrine disruption and antimicrobial resistance. Such speculation cannot be used to justify new testing requirements. FDA also understates the risks of foodborne illness and infection in the home and the increase in risk that would result from consumers not having access to antibacterial product formulations.

In the Proposed Rule, FDA refers to comments received from the public in response to the previous antiseptic TFM that reportedly stated that Consumer Antiseptics have distinct purposes and therefore should require different standards.[11] In general, antiseptics reduce bacteria on the skin and the potential for cross-contamination between people or fomites. While we acknowledge that there are some differences between consumer and healthcare settings based on higher risk patients and the potential of increased morbidity resulting from potential transference of bacteria, FDA's risk assessment overstates the differences between consumer and healthcare settings and ignores published data showing the increased prevalence of foodborne illness in the home, the rising rate of skin infections in the home, increased cases of healthcare conducted in the home by both health care professionals and by family members, and the aging of the population and its consequences for disease prevalence. FDA's proposal to impose a clinical trial standard of efficacy results from this misconception of the risk-to-benefit profile. FDA has failed to show any significant safety risk of these products in the consumer setting that warrants a higher efficacy standard.

FDA understates the risk of foodborne illness and infection in the home. In the Proposed Rule, FDA states that Consumer Antiseptics are used in the "U.S consumer setting, where the target population is composed of generally healthy individuals, [and] the risk of infection is relatively low compared to the healthcare setting."[12] While the risk of infection and illness may be "relatively low," the risk is not low in absolute terms. Typically, most industrial countries report foodborne illnesses associated with the home in the range of 10% to 50%.[13] In fact, the CDC evaluated the contributing factors of the 13,405 foodborne disease outbreaks reported to the CDC in the U.S. from 1998 to 2008, and up to half were associated with food prepared in the home.[14] Cross-contamination from food sources to countertops, cutting boards, and hands of the food preparer have been well documented. For example, Scott found several

[11] 78 Fed. Reg. at 76446.

[12] *Id.*

[13] Redmond E.C. and Griffith CJ. Consumer food handling in the home: a review of food safety studies. J Food Protect 66:130-161, 2003.

[14] CDC. 2014. Outbreak Net: Foodborne Outbreak Database Search Tool. Available at: http://wwwn.cdc.gov/foodborneoutbreaks/. Accessed 3/15/14.

types of bacteria such as *E. coli*, *Staph. aureus*, and *Salmonella* surviving on hands, sponges, clothes, and utensils for hours or days after initial contact with the microorganisms.[15]

Several surveillance studies evaluating the diverse bioburden in the home have reported that the home, and especially the kitchen area, is a common source of pathogenic bacteria. Bacteria are continuously introduced into the home setting by pets, people, food, water, and air. Rusin found higher levels of fecal and total coliforms, including *E. coli*, *Salmonella* and *Camplyobacter*, in the kitchen than in the bathroom.[16] The Food Safety and Inspection Service (FSIS) conducted a testing program in the late 1990's to evaluate the prevalence of pathogens in ready-to-eat meat and poultry products and found that the predominant organisms were *Listeria monocytogenes*, *E. coli*, and *Salmonella*.[17] In addition, *Staphylococcus aureus* is another well-documented microorganism that has been found in the kitchen.[18]

In addition to foodborne illness, skin infections within the home are specifically associated with community acquired-Methicillin-resistant *Staphylococcus aureus* (CA-MRSA). The rates of these CA-MRSA infections have been increasing over the last 20 years. Relevant to the subject of this monograph, outbreaks of CA-MRSA skin infections have significantly increased among healthy members of the community.[19] However, CA-MRSA investigations show that known risk factors such as long-term antibiotic use and underlying health issues found in hospital-acquired MRSA cases of infection are not present.[20] In addition, recent outbreaks have occurred in healthy high school and college students.[21] These MRSA outbreaks have been associated with sports teams where there is frequent skin-to-skin contact. *Staphylococcal* and

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[15] Scott E. *et al.*, The survival and transfer of microbial-contamination via cloths, hands and utensils, Journal of Applied Bacteriology 68, 1990 271 – 278. EPA regulates many of these uses (antimicrobial pesticides) and considers "kill" as sufficient to demonstrate efficacy.

[16] Rusin P.P. et al. Reduction of fecal coliform and heterotrophic plate count bacteria in the household kitchen and bathroom by disinfection with hypochlorite cleaners. Journal of Applied Microbiology 85 (1998) 819 – 828.

[17] Levine P. et al. Pathogen Testing of Ready – to- Eat Meat and Poultry Products Collected at Federally Inspected Establishments in the United States, 1990 – 1999. Journal of Food Protection, Vol 64 no. 8, 2000, 1188 – 1193.

[18] Gorman R. et al. A study of cross-contamination of food-borne pathogens in domestic kitchen in the Republic of Ireland. International Journal of Food Microbiology 76 (2002) 143 – 150.

[19] Herold BC et al. Community acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA 1998; 279: 593 -98.

[20] Naimi TS et al. Comparison of community and health care-associated methicillin resistant Staphylococcus aureus infections. JAMA 2003; 290: 2976 – 84.

[21] Elizabeth M. Begier, Kasia Frenette, Nancy L. Barrett, Pat Mshar, Susan Petit, Dave J. Boxrud, Kellie Watkins-Colwell, Sheila Wheeler, Elizabeth A. Cebelinski, Anita Glennen, Dao Nguyen, James L. Hadler, and The Connecticut Bioterrorism Field Epidemiology Response Team. 2004. A High-Morbidity Outbreak of Methicillin-Resistant *Staphylococcus aureus* among Players on a College Football Team, Facilitated by Cosmetic Body Shaving and Turf Burns, Clin Infec Dis 39:1446-1453. MRSA Outbreak Hits Cheerleader at New Mexico High School. 2012. http://abcnews.go.com/Health/mrsa-outbreak-hits-students-mexicos-belen-high-school/story?id=15338881.

infectious diarrheal illness outbreaks have also been associated with military settings where large numbers of persons are in close contact with each other.[22,23]

FDA ignores the impact of an aging population, which affects infection rates and general health. The number of older adults in today's population is growing, with the number of Americans over 65 years of age expected to reach 71 million by the year 2030 and account for 20 percent of the population.[24] Population aging affects healthcare costs, economic growth, and social support systems.[25] As a result, FDA's assumption that the home consumer is in relatively good health is oversimplified. Chronic diseases such as diabetes, obesity, and high blood pressure can lead to significant complications that may leave individuals with a compromised immune system. The number of immunodeficient persons in the U.S. has been estimated to be 10 million.[26] This figure is based on narrow definition of "immunocompromised" and a more realistic estimate may be even higher. As a result there is an increase in risk of having an infection from what was once assumed to be low-risk activities, such as food preparation in the home, and from minor cuts and abrasions. Also, many individuals undergoing rehabilitation or medical care are being cared for in the home.

FDA also fails to recognize the impact of other aspects of U.S. domestic life that can have an impact the microbial load and transmission in healthy homes. A 2013-2014 report by the American Pet Products Association states that 68% of U.S. households have at least one pet.[27] Based on 2011 statistics, the U.S. Census figures show that approximately 36.7% of U.S. households have children.[28] Both the presence of children and pets in the home may increase the microbial load in the home and the risk of infection and disease.

For all of these reasons, we believe consumers have the right to access safe and effective antiseptic wash products for use in the home and public areas for the purpose of reducing bacteria on the skin that have the same level of antibacterial efficacy as required for the products used in the healthcare setting.

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[22] Ellis MW et al. Natural history of community-acquired methicillin-resistant Staphylococcus aureus colonization and infection in soldiers. Clin Infect Dis. 2004;39(7):971-9.

[23] Lim et al. 2005. History of U.S. Military Contributions to the Study of Diarrheal Diseases. Military Medicine 170: 30-38.

[24] Nat'l Institute on Aging, Nat'l Institutes of Health, U.S. Dep't of Health and Human Servs, U.S. Dep't of State, Why Population Aging Matters, A Global Perspective, Publication, No. 0 7 - 6 1 3 4 March 2007. http://www.nia.nih.gov/research/publication/why-population-aging-matters-global-perspective.

[25] *Id.*

[26] Kemper, A. R., M. M. Davis, and G. L. Freed. 2002. Expected adverse events in a mass smallpox vaccination campaign. Eff. Clin. Pract. 5:84–90.

[27] American Pet Products Association. 2013-2014 APPA National Pet Owners Survey http://www.americanpetproducts.org/pubs_survey.asp.

[28] US Census Bureau. American's Families and Living Arrangements: 2012 (19.6% Married Couples with Children and 17.8% Other Family Households). Issued August 2013.

C. FDA's Proposed Clinical Trial Requirements Are Unrealistic and Infeasible.

1. Testing of Active Ingredients Is Unnecessary.

We disagree with the proposed requirement for clinical testing comparing the benefit of the active ingredient to a vehicle control. FDA generally does not require clinical studies of antimicrobial products such as antibiotic drug products to be performed on the active ingredient itself. We are not aware of any other pharmaceuticals where FDA requires that clinical effectiveness be demonstrated on the unformulated active ingredient. Instead, clinical studies demonstrating antimicrobial activity of a new antibiotic drug product, e.g., the clinical studies required for an antibiotic NDA, are performed on a prototype product formulation. By requiring a showing of direct clinical benefit of the active ingredient alone, FDA ignores relevant formulation considerations that can have an impact on the optimum antibacterial activity, including pH, solubility of the active ingredient, stability, and surfactancy. FDA's proposal is also infeasible. To run a clinical trial of an active ingredient in a specific population, as currently proposed, the active ingredient must be delivered in a system that is safe for daily consumer use and used in a prototype finished product matrix in which the consumer would be able to use the product to ensure compliance. Developing such systems to be placed in a clinical trial may be unattainable. Though FDA asserts that a clinical benefit study is the only definitive way to support Category 1 efficacy of antiseptic active ingredients,[29] these same active ingredients have been on the market for decades, including in drugs approved by FDA through the NDA process.[30] As with these NDA drugs, FDA should limit efficacy testing for the active ingredient to *in vitro* methods, and rely on Time-Kill studies and *in vivo* human simulation studies (e.g., ASTM E1174 or ASTM 2784) for the formulated finished product.[31]

If FDA nevertheless requires the use of clinical testing to demonstrate GRAS/E for active ingredients, it must clarify how this testing will relate to the testing on the final antibacterial product formulation. For example, FDA should clarify whether it will allow final formulations to be tested using surrogate or simulation studies and use a comparative level of efficacy for the "clinical active formula." Such questions need to be addressed before FDA requires active ingredient efficacy testing.

[29] 78 Fed. Reg. at 76,444, 76,450.

[30] These ingredients are benzalkonium chloride, benzethonium chloride, chloroxylenol, cloflucarban, fluorosalan, hexachlorophene, hexylresorcinol, iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate), iodine complex (phosphate ester of alkylaryloxy polyethylene glycol), iodine tincture, methylbenzethonium chloride, nonylphenoxypoly (ethyleneoxy) ethanoliodine, parachlorometaxylenol (chloroxylenol), phenol, poloxamer iodine complex, povidone-iodine, secondary amyltricresols, sodium oxychlorosene, tribromsalan, triclocarban, triclosan, and undecoylium chloride iodine complex. 78 Fed. Reg. at 76,477 (proposed 21 C.F.R. §§ 310.545(a)(27)(iii) & 310.545(a)(27)(iv)). Active FDA-approved NDAs for single ingredient products containing povidone-iodine (N018634, N019522, N019240, and N019476) and a combination product containing triclosan (N020231) exist.

[31] The 1994 TFM allowed for simulation studies, including ASTM methods E1174, ASTM E1115, ASTM E1173. 59 Fed. Reg. at 31432-33, 31445 (proposed 21 C.F.R. § 333.470(a)(2)).

2. Simulation Testing and Surrogate Endpoints Are More Reasonable Than Testing for Reduced Infection Rates.

a) Numerous Precedents Exist for Approving Drugs on the Basis of Simulation Testing and Surrogate Endpoints.

We believe that *in vivo* human simulation studies are a valid and feasible way to determine efficacy for an antibacterial product formulation. Simulation studies have been used in the past to demonstrate the efficacy of antimicrobial 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 products. The 1994 TFM required the use of the surrogate test method ASTM E1174 for hand antiseptics.[32]

Despite this precedent, FDA suggests that the "Health Care Personnel Hand Wash" test is based on an "unvalidated surrogate endpoint" rather than a clinical outcome. However, this method, as well as the required number of bacteria removed from the skin (2 $\log_{10}$ wash 1 and 3 $\log_{10}$ wash 10), have been accepted by FDA when used to support the approval of several NDAs.

A review of the Drugs@FDA database indicates that precedent exists for the use of pivotal Phase 3 challenge model (or direct infection) studies to support new drug approvals.

- NDA-21-074: Avagard™ – Surgical hand scrub and heath care personnel handwash using a combination of chlorhexidine gluconate 1% Solution and Ethyl Alcohol 61% w/w in an emollient-rich lotion base.[33]

- NDA No 21-082: Tavist Allergy/Sinus/Headache - New OTC combination of three active ingredients: acetaminophen; clemastine fumarate; pseudoephedrine hydrochloride for relief of cold symptoms.[34]

- NDA 21-361: XIFAXAN® (rifaximin) Tablets - Rx for Travelers' Diarrhea.[35]

The Avagard™ approval is most comparable to Consumer Antiseptics with regard to proposed surrogate endpoints. FDA approved Avagard™ on the basis of two pivotal Phase 3 challenge studies that supported the immediate and persistent reduction in transient

[32] 59 Fed. Reg. at 31445 (proposed 21 C.F.R. § 333.470(a)(2)(ii)).

[33] US FDA. NDA 21-074. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-074_Avagard_medr.pdf.

[34] US. FDA. NDA No. 21-082. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-082_Tavist_medr_P1.pdf.

[35] US FDA. NDA 21-361. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/gastrointestinaldrugsadvisorycommittee/ucm279646.pdf.

microorganisms on the hands, plus one pivotal Health-Care Personnel Hand Wash Study to support the healthcare personnel handwash indication.[36]

FDA has also approved other drugs on the basis of surrogate markers of disease and disease outcome.[37] For example, antihypertensive agents are generally approved on the basis of clinical trials showing efficacy in lowering of blood pressure rather than reduction in cardiovascular events.[38]

b) Simulation Study Design Could Be Revised to Address FDA's Concerns.

In the Proposed Rule, FDA lists several comments on the deficiencies of simulation type studies to date, including neutralization and lack of adequate controls.[39] These deficiencies can be addressed through revisions in study design, however, and categorically disregarding simulation studies for the above reasons is scientifically unjustified.

Neutralization concerns have been raised in many venues. Stakeholders, in cooperation with the ASTM E35.15 Antimicrobial Committee, modified E1174 to include inactivators in the stripping solution to ensure adequate antibacterial product neutralization and to require controls to confirm product neutralization.[40] Studies submitted to the docket in the last data submission period included neutralization data.[41] We agree that proper product neutralization is a critical aspect in conducting efficacy testing of antibacterial product formulations.

If FDA's concern with respect to simulation studies is lack of a vehicle control, this can be readily incorporated into the study design. FDA has previously suggested including Hibiclens 4% chlorhexidine gluconate as a control product to validate the conduct of such simulation studies.[42] This suggestion, if implemented, would address the second concern that

[36] The 1994 TFM allowed for simulation studies, including ASTM methods E1174, ASTM E1115, ASTM E1173. 59 Fed. Reg. at 31432-33, 31445 (proposed 21 C.F.R. § 333.470(a)(2)).

[37] Downing N *et al.*, Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012, JAMA 300(4):368-377 (2014).

[38] CDER, FDA, Guidance for Industry: Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims (March 2011).

[39] 78 Fed. Reg. at 76451.

[40] ASTM, "Standard Method for the Evaluation of Health Care Handwash Formulation, Designation E1174," in "The Annual Book of ASTM Standards," vol. 11.04, ASTM, Philadelphia, pp. 209-212 (1987).

[41] *See*, *e.g.*, Docket No. FDA-1975-N-0025 (formerly FDA Docket No. 75N-183H), submission #0286, Comment by the Dial Corp. (Aug. 27, 2003).

[42] Paulson, D.S., Handbook of Topical Antimicrobials: Industrial Applications in Consumer Products and Pharmaceuticals CRC Press (2002).

"[s]tudies lack a control."[43] Several studies that include both neutralization and a reference control have been previously submitted to FDA.[44]

Furthermore, during the 2004 NDAC meeting, FDA recommended demonstrating the benefit of antiseptic wash over that of a non-antibacterial soap.[45] FDA should indeed consider the validity of such a comparison between using an antibacterial and non-antibacterial product formulation. We urge FDA to reconsider the use of ASTM method E1174 with inclusion of appropriate controls to substantiate the antibacterial efficacy of final antiseptic formulations.

c) The Melon Ball Disease Transmission Model Addresses FDA's Concerns on Lack of Correlation between Surrogate Endpoints and Reduced Infection.

Stakeholders have developed a Melon Ball Disease Transmission Model that addresses FDA's concerns regarding simulation studies and their lack of correlation between surrogate endpoints and reduced infection rates. FDA and NDAC have previously asked that the benefit of a specific bacterial reduction be correlated to a reduction in infection.[46] In response to NDAC's request, we worked with leading experts throughout the U.S. to develop and validate what is incorrectly referred to by FDA in the Proposed Rule as the "Exposure-Response Study."[47] This model, known as the "Melon Ball Disease Transmission Model," used the "Palmar Method" and quantitative microbial risk assessments (QMRA) to link the transfer of bacteria to food and the subsequent reduction in disease. Dr. Donald Schaffner, who is a leading expert in food safety and Quantitative Risk Model Analysis, has conducted research to demonstrate the validity of the "Melon Ball Disease Transmission Model" in providing data to show the benefit of one antiseptic treatment over another in the reduction of disease.

We strongly disagree with FDA that there has been a failure to link a specific log reduction on the skin with disease reduction. Both FDA and NDAC agreed at the 2005 meeting that data exists showing that antimicrobial washes demonstrate a higher bacterial kill on skin when compared to "plain soap and water" (i.e., a non-antibacterial soap). What was missing at the time of the meeting was quantifying the level of bacterial reduction that is required to provide a clinical benefit. The Melon Ball Disease Transmission Model, coupled with the Palmar Method and QMRA, provides this missing piece.

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[43] 78 Fed. Reg. 76,444 (Dec. 17, 2013).

[44] Dial submission, Docket No. FDA-1975-N-0025.

[45] Transcript, FDA, Joint Session with the Nonprescription and Dermatologic Drugs Advisory Committee, at 105, 367-369 (March 23, 2004) (sic) (Comments of John Powers, MD, Lead Medical Officer for Antimicrobial Drug Development and Resistance Initiatives, Office of Drug Evaluation IV, CDER and Committee consultant Ralph B. D'Agostino, Ph.D., biostatistician, Boston University).

[46] NDAC meeting convened by FDA on October 20, 2005 to discuss the efficacy and safety features of OTC topical antimicrobial products.

[47] Boyce, J.M et al. An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial handwash products. American Journal of Infection Control, 2012; 40: 742-9

Based on the studies executed by our stakeholders and then by independent third-party contract testing laboratories, we have generated data that clearly link the log reduction in bacteria on the skin following the use with an antimicrobial handwash with a predicted reduction in disease compared to the use of two commercially-available non-antibacterial liquid soaps (plain soap) and water. The test data show that the antibacterial products reduce *Shigella* on the hands by > 3 $\log_{10}$ using the Palmar Method, which results in significantly less bacteria on the hands transferred to food when handled compared to non-antibacterial soap, which reduced *Shigella* on the hands by 2 $\log_{10}$. Using these values, Dr. Schaffner, was able to calculate the predicated number of cases of *Shigellosis* using quantitative microbial risk assessment:

> "A simulation that assumed 1 million *Shigella* bacteria on the hands and the use of a nonantibacterial treatment predicted that 50 to 60 cases of shigellosis would result (of 100 exposed). Each of the antibacterial treatments was predicted to result in an appreciable number of simulations for which the number of illness cases would be 0, with the most common number of illness cases being 5 (of 100 exposed). These effects maintained statistical significance from 10^6 *Shigella* per hand down to as low as 100 *Shigella* per hand, with some evidence to support lower levels. This quantitative microbial risk assessment shows that antibacterial hand treatments can significantly reduce *Shigella*." [48]

These surrogate endpoints can be used to correlate a clinical benefit when antibacterial products are compared to the usage of a non-antibacterial soap product and water. The studies demonstrate that antiseptic washes offer a significant benefit in reducing the risk of *Shigella* infections compared to the use of only a non-antibacterial soap (i.e., plain soap) and water for washing the hands.

In the Proposed Rule, FDA makes several scientific misstatements about quantitative microbial risk assessment, the "Melon Ball Disease Transmission Model," and the "Palmar Method." Dr. Schaffner sets forth and responds to these misstatements in Appendix B. However, we note some of the unjustified criticisms that FDA makes here. FDA dismisses the Palmar Method as "novel and unvalidated."[49] We disagree with FDA's conclusion that the method has not been sufficiently validated. In the references to the Proposed Rule, FDA omits citations to several of the peer reviewed journal articles that reference and support the method. The Proposed Rule refers to the Fischler 2007 publication, which describes the use of the method with a product containing triclosan.[50] FDA ignores additional publications and studies that have been performed using this particular method and presented to an expert panel of infectious disease specialists.[51] The expert panel found the model to be valid and that the infectious dose

[48] Schaffner DW, Bowman JP, English DJ, Fischler GE, Fuls JL, Krowka JF, Kruszewski FH. Quantitative Microbial Risk Assessment of Antibacterial Hand Hygiene Products on Risk of Shigellosis. 2014. Journal of Food Protection. 4:528-690.

[49] 78 Fed. Reg. at 76,451.

[50] *Id.*

[51] Boyce published the findings of the expert panel in the *American Journal of Infection Control*. Boyce, J.M et al. An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial handwash

(continued…)

curves clearly show the link between bacterial reduction and subsequent reduction in infection, thus validating the use of a simulation study. Fuls has also published a study that shows that recovery of bacteria from hands after using the Palmar Method is reproducible between hands with several strains tested and at both a high and low inoculum.[52] Additional studies using the contamination method continue to show its robustness.[53]

FDA also criticizes the Palmar Method for its failure to include the fingernails of test subjects. However, as Dr. Schaffner notes in Appendix B, this comment by the agency is scientifically unimportant. Other FDA-accepted methods, including the ASTM method E1174, do not specifically address the presence of microorganisms in the fingernail region.[54] Although bacteria under the fingernails has been identified as a region in which bacteria can accumulate, in most instances, the finger pads and palms of the hands are used to grab and touch objects and, therefore, result in the majority of the bacterial transfer. As long as products are tested under the same conditions, including the method of hand contamination (whole hand, finger pad, or Palmar Method), the measured difference in efficacy is valid and can be used to measure differences between the antiseptic product, reference controls, or vehicles, as well as antibacterial and non-antibacterial soap. The Palmar Method, like the glove juice test E1174, establishes a standardized method for contamination of hands.[55]

Finally, FDA criticizes the "infectious dose studies" because of the small number of test subjects used.[56] FDA's criticism is unjustified. As Dr. Schaffner notes in Appendix B, the small subject size is typical for conducting microbial feeding studies due to the inherent risk in performing such studies to test subjects. Furthermore, the expert panel that reviewed studies using the Palmar Method agreed that the model is a suitable approach that precludes the need for additional live infection studies.[57] As recommended by the panel, Sr. Schaffner and other researchers conducted a larger scale study using several of the active ingredients currently marketed as antiseptics in the consumer market. The findings of these studies were shared with FDA in a feedback meeting in November 2008, submitted to the Docket ID: FDA-1980-N-0006

products. American Journal of Infection Control, 2012; 40: 742-9. The expert panel report was submitted to Docket ID: FDA-1980-N-0006. Docket No. FDA-1980-N-0006, submission #0029, Comment by SDA/Council Topical Antimicrobial Product Coalition, Briefing Package to Support FDA Public Meeting (Sept. 2008).

[52] Fuls et al. 2008. Alternative hand contamination technique to compare the activities of antimicrobial and nonantmicrobial soaps under different test conditions. Appl. Environ. Microbiol. 74:3739-3744.

[53] Schaffner DW, Bowman JP, English DJ, Fischler GE, Fuls JL, Krowka JF, Kruszewski FH. Quantitative Microbial Risk Assessment of Antibacterial Hand Hygiene Products on Risk of Shigellosis. 2014. Journal of Food Protection. 4:528-690.

[54] ASTM, "Standard Method for the Evaluation of Health Care Handwash Formulation, Designation E1174," in "The Annual Book of ASTM Standards," vol. 11.04, ASTM, Philadelphia, pp. 209-212 (1987).

[55] E2784 Standard Test Method for Evaluation of the Effectiveness of Handwash Formulations Using the Paper Towel (Palmar) Method of Hand Contamination.

[56] 78 Fed. Reg. at 76451.

[57] Boyce, J.M et al. An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial handwash products. American Journal of Infection Control, 2012; 40: 742-9.

and recently published in the Journal of Food Protection.[58] Moreover, other branches of FDA also utilize QMRA like the "melon ball method" as valid tools to drive policy to improve food safety.[59] We urge FDA to utilize experts such as Dr. Schaffner and to evaluate other Agency reliance on QMRA and simulation studies to support efficacy.

D. FDA Should Revise Its Proposed *In Vitro* Testing Methods.

1. We Recommend Use of MIC/MLC Test to Document *In Vitro* Antiseptic Potency and Spectrum for Active Ingredients.

FDA states that the usage of Minimum Inhibitory Concentrations for an active ingredient is no longer relevant to demonstrate the effectiveness of an antiseptic active ingredient.[60] FDA proposes instead that a modified Time-Kill assay be used to provide an assessment of how rapidly an antiseptic active ingredient produces a bactericidal effect.[61] FDA does not provide any guidance on how to conduct the study on an active ingredient.

We believe that the use of a modified Time-Kill method should be restricted to testing of final formulated products rather than for evaluation of the active ingredient due to the significant influence that formulation has upon performance outcomes. For demonstrating antibacterial activity of active ingredients, it is more relevant to perform a Minimum Inhibitory Concentration and Minimum Lethal Concentration (MIC/MLC) Test to determine the potency and spectrum of the antibacterial activity of the proposed active ingredient before it is included in an antibacterial product formulation.

We recommend that FDA require MIC/MLC testing of active ingredients on the ATCC reference strains described in the Proposed Rule to determine the spectrum and potency of antibacterial activity by using a modified National Committee for Clinical Laboratory Standards (NCCLS) Microdilution broth method in which all of the proposed ATCC strains are able to grow. As the active ingredient has not yet been formulated, and similar to the 1994 TFM, we recommend that no specific performance criteria be established for MIC/MLC testing of the active ingredients. This information should be provided to FDA as part of the data set required for the ingredient to achieve GRAS/E status. Furthermore, there should be no need to conduct MIC/MLC testing on an active ingredient on a routine basis.

While we are not aware of a currently available standard method that was designed for testing antiseptics, we urge FDA to recommend the use of Clinical and Laboratory

[58] Schaffner DW, Bowman JP, English DJ, Fischler GE, Fuls JL, Krowka JF, Kruszewski FH. Quantitative Microbial Risk Assessment of Antibacterial Hand Hygiene Products on Risk of Shigellosis. 2014. Journal of Food Protection. 4:528-690

[59] *See, e.g.*, FDA, Public Workshop on Measuring Progress in Food Safety: Current Status and Future Directions (March 30, 2010) (Comments of Dr. Kara Morgan, Senior Advisor for Risk Analysis, Office of Regulatory Affairs, FDA)(" I think I would like to see further use of predictive microbiology and QMRA to sort of answer some of these questions."), http://www.fda.gov/downloads/food/newsevents/workshopsmeetingsconferences/ucm214197.pdf.

[60] 78 Fed. Reg. at 76453.

[61] *Id.*

Standards Institute Reference Method M7 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard (current edition) with modifications appropriate for testing of antiseptic formulations.[62] FDA previously recognized this test method in the 1994 TFM for MIC testing. As the method was designed for testing antibiotics, various modifications will be necessary for testing antiseptics (e.g., media selection, FDA-proposed testing strains, and performance criteria).

2. We Support Time-Kill Studies for Formulated Antiseptic Testing With Adequate Revisions to Demonstrate Speed of Antimicrobial Effect.

We urge FDA to adopt ASTM method E2783 Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure as the standard for conducting the Time-Kill testing for speed of antimicrobial effect for evaluation of formulated antiseptics. The use of standardized test methods is critical for regulatory testing and approval to assure consistency. FDA acknowledged this in the 1994 TFM for Healthcare Antiseptic Drug Products when it requested that such a method be developed for antiseptics.[63] In response, ASTM International developed and published E2783.[64] The standard method underwent collaborative testing studies in 2009 and 2010, which resulted in the Precision and Bias statement in the current method.

We support other FDA changes to the *in vitro* testing requirements, including a reduction in the exposure times and number of test strains. We request, however, that FDA reconsider the performance criteria, which are more demanding than the performance abilities of approved healthcare antiseptic products and likely the unformulated active ingredients. The Proposed Rule lists a number of bacterial test strains that must be evaluated by Time-Kill testing and further proposes that 100% of the strains be reduced by 99.9%. Historically, FDA has required an FDA-approved antiseptic be evaluated as a reference control alongside the test substance(s). As FDA has not approved a consumer antibacterial handwash, Mölnlycke's Hibiclens (4% chlorhexidine gluconate healthcare personnel handwash and surgical scrub) could be used for this purpose as it serves this role for Healthcare TFM testing currently.

While Time-Kill data for Hibiclens is not available under the Hibiclens NDA file on the FDA website, we have reviewed its performance in the studies supporting NDA Application No.021074 where it was used as a reference control.[65] These data show that FDA's proposed performance criteria for time kill studies are unrealistic. In Table 2 of the Microbiology Review, there is a list of Hibiclens performance at 60 and 300 seconds for 24

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[62] Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard. Seventh Edition*. M7-A7 Clinical and Laboratory Standards Institute, Wayne, Pennsylvania.

[63] 59 Fed. Reg. at 31,431-432, 31,444-445 (proposed 21 C.F.R. § 333.470((a)(1)(iv)).

[64] E2784 Standard Test Method for Evaluation of the Effectiveness of Handwash Formulations Using the Paper Towel (Palmar) Method of Hand Contamination.

[65] Division of Anti-Infective Drug Products, FDA, Clinical Microbiological Review #1, IND/NDA # 21-074, at 8-9 (May 20, 2000). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-074_Avagard_medr.pdf.

ATCC strains, of which eight strains are proposed for Time-Kill testing in the Proposed Rule.[66] For *S. aureus* (ATCC 6538) and *S. pyogenes* (ATCC 19615), Hibiclens, diluted 1:10, fails to produce a 99.9% reduction after a 60 second contact time, thus 25% (2/8) of the strains listed in the Proposed Rule tested fell below the proposed Time-Kill performance criteria. In Table 3 of the Microbiology Review, Hibiclens is tested full strength at 30 and 60 seconds contact on 15 ATCC strains, of which six strains are also listed in the Proposed Rule. For *S. aureus* and *E. faecalis* (ATCC 29212), Hibiclens fails to produce a 99.9% reduction, thus 33% (2/6) of tested strains fell short of the proposed performance criteria. Hibiclens is labeled for a 15 second hand wash so we expect that if FDA requires the use of a 15 second Time-Kill evaluation of this reference material, additional proposed microbial test strains would fall below the 99.9% performance criteria.[67]

Though FDA has not posted the Hibiclens Microbiology Review, we also reviewed the Time-Kill data provided at www.hibiclens.com against the proposed performance standard. Of the 22 strains shown in the Hibiclens Clinical Compendium, seven were proposed by FDA for *in vitro* testing for Consumer Antiseptics.[68] The data provided by Hibiclens do not afford an evaluation at 99.9% as the data was reported as the time required to achieve a 99.999% reduction. As shown above, however, the time kill test data do show that three strains (ATCC 29212, 6538, and 29213) required a 10 minute exposure to achieve the 5 $\log_{10}$ reduction, which is far beyond the 15-second wash time utilized for the product.

We recommend evaluation of the TFM-proposed ATCC strains be conducted with Hibiclens prior to the adoption of the proposed performance criteria for *in vitro* testing. FDA should use the resulting data to inform its selection of the appropriate performance criteria for formulated antiseptics, including the percentage of strains that must meet these criteria (e.g., require a 99.9% reduction for 75% of test strains listed). The performance criteria should not be established at a level higher than the level at which Hibiclens (a well-respected, FDA-recommended reference material for antiseptic testing) currently performs.

VI. Proposed Efficacy Testing Scheme for Antiseptics

A. For Consumer Handwash Products

As described in Section V above, the clinical benefit of hand antiseptics over two non-antibacterial plain soaps has been described for three formulations (0.46% triclosan, 4% chlorhexidine gluconate, and 62% ethyl alcohol) in the pivotal Melon Ball Disease Transmission

[66] Division of Anti-Infective Drug Products, FDA, Clinical Microbiological Review #1, IND/NDA # 21-074, at 9 (May 20, 2000). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-074_Avagard_medr.pdf

[67] Three additional strains only narrowly achieved the 3 log reduction (LR) requirement (ATCC 25922=3.02LR, ATCC27853=3.05LR, ATCC 33592=3.07LR), which results in 83% (5/6) of strains failing to meet the proposed criteria.

[68] *See* Mölnlycke Healthcare. Hibiclens Clinical Compendium. Accessed from www.hibiclens.com on April 22, 2014. The Compendium also describes testing on ten *S. aureus* MRSA strains (five strains were community-acquired), but none were those strains were identified by FDA in the Proposed Rule. The data show that Hibiclens requires between 3-5 minutes to achieve a 99.9% reduction for these strains.

Model.[69] An expert panel reviewed this surrogate infection study design and agreed that the model was sound and represented a realistic evaluation to confirm the efficacy of consumer hand antiseptics.[70] As the triclosan and chlorhexidine gluconate formulations in the Schaffner study met the current 1994 TFM performance criteria proposed for Healthcare Personnel Handwash, we propose that FDA permit the ASTM E1174 test method to be used to confirm *in vivo* efficacy of consumer antiseptic formulations.

Based on these publications and prior submissions, we recommend the following efficacy testing scheme or equivalent for consumer hand antiseptics:

Test Method	Proposed Consumer Monograph Hand Antiseptic Efficacy Testing
In vitro **Time-Kill**	**Test Method:** ASTM E2783 **Test organisms** (ATCC): 20 strains[71] **Exposure**: Labeled wash time (e.g., 30 seconds) **Test Materials**: Vehicle, Product **Concentration**: neat **Controls**: Neutralization Confirmation, per ASTM E1054 **Performance Criteria**: To Be Determined – See above discussion
In vivo: ***Select 1 method***	**Option 1: Palmar Method** **Test Method:** ASTM E2784 **Test organism:** *Shigella flexneri* (ATCC 700930 **Exposure**: Labeled wash time (e.g., 30 seconds) **Test Materials**: Product, Reference Product (e.g., Hibiclens), Commercially Available Non-antibacterial liquid **Concentration**: neat **Controls**: Neutralization Confirmation, per ASTM E1054 **Performance Criteria**: A demonstration of a reduction with statistical significance over non-antibacterial soap

[69] Schaffner DW, Bowman JP, English DJ, Fischler GE, Fuls JL, Krowka JF, Kruszewski FH. Quantitative Microbial Risk Assessment of Antibacterial Hand Hygiene Products on Risk of Shigellosis. 2014. Journal of Food Protection. 4:528-690.

[70] Boyce, J.M et al. An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial handwash products. American Journal of Infection Control, 2012; 40: 742-9.

[71] 78 Fed. Reg. at 76453.

	Option 2: Healthcare Personnel Handwash Method **Test Method:** ASTM E1174 **Test organism:** *Serratia marcescens* (ATCC 14756) or *E. coli* ATCC11229 **Exposure**: Labeled wash time (e.g., 30 seconds) **Test Materials**: Product, Reference Product (e.g., Hibiclens) **Concentration**: neat **Controls**: Neutralization Confirmation, per ASTM E1054 **No. of Washes:** Single wash or an optional 10 washes (for cumulative microbial reduction) **Performance Criteria**: 2 Log_{10} Reduction after Wash 1, and 3 Log Reduction after Wash 10

For healthcare, food handler, or other monographs, different test organisms and application concentrations may need to be considered.

B. For Consumer Body Wash Products

In contrast to the above recommendation for handwash antiseptics, the consumer body wash category requires establishing an appropriate surrogate model based on clinical testing. While we anticipate a similar *in vitro* testing construct as above, additional research is required before we can propose an appropriate protocol or surrogate disease model for *in vivo* efficacy testing. In Appendix A, Dr. Ronald Turner provides a University of Virginia (UVA) protocol to begin the process of identifying a study design for these purposes. Additionally, we propose ASTM E1874 as an appropriate method for sampling and recovering bacterial flora from the skin.[72]

VII. FDA Should Reconsider the Proposed New Safety Testing Requirements.

A. FDA's Premises for Requesting Additional Safety Data Are Flawed.

1. FDA Should Consider Exposure-Driven Risk Assessments Before Requiring More Data.

FDA should base its decision to require additional data on more robust analysis of current knowledge about human exposure and risk and this should precede any proposal requiring additional testing. In other words, FDA should consider the extent of human or environmental exposure as part of the process for deciding the nature and extent of hazard data required to understand potential safety concerns. Before declaring that a dataset is inadequate to assess the risks associated with an antiseptic active ingredient, FDA should understand the margins of safety using the available data to the extent possible. Data generation based on an understanding of human exposures prevents the irresponsible use of laboratory animals and

[72] ASTM E1874 – 14 Standard Test Method for Recovery of Microorganisms From Skin using the Cup Scrub Technique.

waste of resources to generate toxicology data that will not further inform potential safety decisions. All available data should be analyzed before FDA requires any additional studies.

Therefore, while we agree that it is necessary to perform a safety assessment for all the endpoints cited in the Proposed Rule, this does not necessarily mean that animal toxicity data need to be generated. It is unclear from the Proposed Rule whether FDA envisions a more information-driven and flexible approach to data generation. For example, physiologically-based pharmacokinetic (PBPK) modeling has become more established for understanding the potential for systemic exposure in animals compared to humans. These models have been applied not only in the pharmaceutical sector, but also for general chemicals, an example that is particularly relevant because FDA's proposal deals exclusively with chemicals that are applied and rinsed off the body after application, resulting in a very low systemic exposure potential.

Furthermore, numerous scientific and regulatory bodies have performed exposure-driven risk assessments on at least two of these ingredients and have not requested the types of animal study data mentioned in FDA's proposal.[73] This is especially noteworthy since those evaluations considered cumulative human exposure from common use products as listed in the European Commission's Scientific Committee on Consumer Safety opinion rather than focusing on just individual product types.

a) Animal and Human Pharmacokinetic Data Can Provide a Margin of Exposure.

In the Proposed Rule, FDA comments that the lack of pharmacokinetic data prevents FDA from calculating a margin of exposure for the risk assessment.[74] Although the safety evaluation of drugs may rely on correlating findings from animal toxicity studies to humans based on kinetic information in both species, safety evaluations for antiseptic ingredients in consumer products are not based on kinetic information under standard international practice. Instead, safety evaluations are based on conservative assumptions of exposure and potential differences between species.[75] Kinetic information is only required when use of these conservative assumptions fails to provide a sufficient margin of exposure. Using these conservative and internationally accepted approaches, other scientific bodies and regulatory authorities have been able to complete the risk assessment for these types of ingredients in formulations with much greater levels of human exposure than rinse-off products.[76]

Therefore, FDA should not require additional animal testing unless the following conditions are met:

a. Use of conservative approaches to calculate the margin of exposure is inadequate.

[73] *See, e.g.*, http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_054.pdf.

[74] 78 Fed. Reg. at 76453.

[75] *E.g.* http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf.

[76] http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_054.pdf.

b. The margin of exposure justifies the need for more data, but it is not possible to generate the data by non-animal approaches, such as using physiologically-based pharmacokinetic modeling, or through animal alternative test methods.

c. There is perceived need for all active ingredients to have the same type of information.

2. FDA Should Consider the Long Record of Safety and Relative Low Risk of Consumer Antiseptics.

In considering additional safety data requirements, FDA should weigh the long record of safety of Consumer Antiseptics. FDA closely monitors safety of drug products through MedWatch, which is an adverse event reporting program that allows stakeholders, students, health professionals (FDA Form 3500), and consumers (FDA Form 3500B) to report safety-related problems to FDA. FDA keeps a comprehensive online database initiated in 2000 of these complaints.[77] A search of this database fails to find any safety-related complaints related to antibacterial hand soaps and/or body washes.

In the event that safety issues are detected through the monitoring program, FDA releases "safety alerts," which address the safety concern and make recommendations to minimize risk. The safety alert may include a recommendation to recall the product. To date, no safety alerts have been released in response to concerns related to antibacterial hand soaps and/or body washes.

In addition to FDA's MedWatch adverse effects monitoring program, stakeholders also have product surveillance programs that monitor consumer use and reported adverse effects associated with their products.

3. There Is No Evidence of Higher Systemic Exposure.

FDA calls for additional safety data in the Proposed Rule because of "new information regarding the potential risks from systemic absorption and long-term exposure to antiseptic active ingredients" and notes that exposure may be "higher than previously thought."[78] FDA offers no definitive evidence to support the statement that a "higher than previously thought" consumer exposure is associated with the use of these ingredients. To substantiate this statement, FDA must document the level of systemic exposure from rinse-off products that was used in its prior safety assessment and how this differs from any new information the agency has received. Further, any such data do not appear in the public docket for the healthcare antiseptic rulemaking and are not available to stakeholders. FDA should also clarify that the new information provides either *in vitro* or dose dependent data, not "risk," as we are unaware of FDA's current thinking on specifics regarding risk assessment.

[77] MedWatch: The FDA Safety Information and Adverse Event Reporting Program. http://www.fda.gov/Safety/MedWatch/default.htm.

[78] 78 Fed. Reg. at 76445, 76454.

In addition, FDA may be overstating what the "new information" actually demonstrates. The authors producing the data cited by FDA describe extrapolation of their observations with conditional statements of "may", "might", or "could." FDA should establish more definitive conditions before declaring a situation of higher risk, imminent or otherwise. For example, FDA cites studies for triclosan to support its statement that systemic exposure to topical antiseptic active ingredients may be greater than previously thought.[79] However, the data in these studies do not suggest an increase in systemic exposure over time. Rather, data from these studies reveal an increase in detection, which is not equivalent to, nor should it be interpreted as, either an increase of exposure or an increase in risk. Absorption of triclosan following oral exposure is relatively rapid and complete, with the predominant route of elimination from the body being urine. Approximately 90% of triclosan and its metabolites in the human body would be expected to be eliminated in urine.[80] If individual use and daily intake of triclosan products is assumed to be constant, the samples taken as part of the National Health and Nutrition Examination Survey (NHANES) represent a steady-state concentration of triclosan in urine.[81] These data do not, however, indicate there is greater systemic exposure. Furthermore, the estimated oral exposures that would be associated with these urine concentrations are calculated to have large margins of safety (>1000), suggesting that systemic exposure from ingestion or dermal penetration would have to increase significantly to increase safety concerns.[82] Given the absence of risk, and the very large margins of exposure in this risk assessment, further animal testing to demonstrate a purported risk from increased systemic exposure to antiseptic active ingredients is simply not justified.

4. Animal Studies Suggesting Hormonal Effects Are Not Directly Applicable to Human Exposure.

In determining the need for additional data or understanding the significance of existing data, it is important for FDA to consider that the endocrine system is very complex with significant differences among organisms. Many of the studies cited by FDA as raising concern for hormonal effects from antiseptic washes are rat thyroid studies.

The thyroid system has been studied for differences among species and genders. For example, there are species differences in the plasma half-lives of thyroid hormones.[83] In most mammalian species, the thyroid hormones T3 and T4 are bound to plasma proteins and are, therefore, unavailable for metabolism, serving as a buffer for changes in peripheral T3 and T4

[79] Calafat et al. 2007; Dayan 2007; CDC 2013.

[80] Rodricks, JV., Swenberg, JA., Borzelleca, JF., Maronpot, R.R. and Shipp, A.M. (2010). Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology, 2010; 40(5): 422–484.

[81] Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES). Atlanta, GA. http://www.cdc.gov/nchs/nhanes.htm.

[82] Rodricks et al. 2010. Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology, 2010; 40(5): 422–484.

[83] USEPA 1998. Assessment of thyroid follicular cell tumors. US EPA, Risk Assessment Forum, Washington, DC. EPA/630/R-97/002, March 1998. Online: http://www.epa.gov/raf/publications/thyroid-follicular-cell-tumor.htm.

levels. In addition, humans have high affinity T3 and T4 binding globulins and a large percentage of T3 and T4 are bound to these proteins.[84] In contrast, rats and mice lack these binding proteins and only a small fraction of T3 and T4 is bound to proteins. This results in high free (unbound) T3 and T4 available for metabolism, which in turn results in a faster hormone turnover in rodents when compared to humans.[85]

The reported plasma half-lives for T4 are 12-24 hours, and 5-9 days in rats and humans, respectively.[86] Therefore, due to the rapid hormonal turnover, the rat thyroid gland would work harder (TSH levels are 6-60 times higher in rats) to maintain T3 and T4 within physiological levels.[87] This will make the thyroid gland in rats more susceptible to chemical perturbation of thyroid hormone homeostasis. Also, the levels of TSH are higher in male rats than in female rats, resulting in higher demand on the thyroid gland.[88] Therefore, chemicals that interfere with thyroid hormone homeostasis would likely have more impact in male rats than female rats.[89] Therefore, known differences between human and selected animal models should be considered before relying on animal results for concluding that there are potential human safety concerns.

B. FDA Should Reconsider the Requirement for Carcinogenicity Studies.

We agree that a carcinogenicity assessment of Consumer Antiseptics is critical. For the majority of the active ingredients listed in FDA's proposal, a good quality oral carcinogenicity data set exists, along with *in vitro* genetic toxicology studies. It is unclear why FDA is concerned enough to propose dermal carcinogenicity studies on these ingredients, particularly for triclosan, in light of the ongoing National Toxicology Program (NTP) dermal carcinogenicity study with triclosan which is scheduled for completion in 2015. While there are ADME differences between oral and dermal exposure, in the absence of tumors in an oral study, and provided that good quality *in vitro* genetic toxicity data are available, it is difficult to envisage which modes of action would cause concern for these ingredients when applied by the dermal route. Under international standards, "[s]ince carcinogenicity studies are time consuming and resource intensive they should only be performed when human exposure warrants the need for information from life-time studies in animals in order to assess carcinogenic potential."[90]

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[84] Personal Care Products Council (PCPC) – Cosmetic Ingredient Review (CIR). Final Report on Triclosan. December 14, 2010.

[85] *Id*.

[86] USEPA 1998. Assessment of thyroid follicular cell tumors. US EPA, Risk Assessment Forum, Washington, DC. EPA/630/R-97/002, March 1998. Online: http://www.epa.gov/raf/publications/thyroid-follicular-cell-tumor.htm.

[87] *Id.*

[88] Chen, HJ. (1984) Age and sex difference in serum and pituitary thyrotropin concentrations in the rat: influence by pituitary adenoma. Exper Gerontol 19:1-6.

[89] USEPA 1998. Assessment of thyroid follicular cell tumors. US EPA, Risk Assessment Forum, Washington, DC. EPA/630/R-97/002, March 1998. Online: http://www.epa.gov/raf/publications/thyroid-follicular-cell-tumor.htm.

[90] International Conference on Harmonization - Safety, Guideline for Industry: The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals, at 1 (March 1996). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074911.pdf.

Furthermore, "[p]harmaceuticals showing poor systemic exposure from topical routes in humans may not need studies by the oral route to assess the carcinogenic potential to internal organs."[91]

We are not aware of any chemical that provides negative *in vitro* genetic toxicity data and negative oral carcinogenicity data, but is positive by the dermal route. In addition, it is highly unlikely that intermittent dermal exposure would result in systemic exposures higher than those obtained following oral exposure. We therefore strongly advocate that, rather than establishing "studies to be performed," FDA rephrases the proposal to focus on "health effects to be addressed in the safety assessment." This will allow the use of a more integrated and data-based approach to risk assessment rather than the 'check-the-box' approach currently presented.

The potential requirement of additional studies by the dermal route exposure should be justified because it is highly unlikely that systemic exposure would be higher than that resulting from oral exposure. For example, the existence of factors which could be considered "of concern" may include: (1) previous demonstration of carcinogenic potential in the product class that is considered relevant to humans; (2) structure-activity relationship suggesting carcinogenic risk; (3) evidence of pre-neoplastic lesions in repeated dose toxicity studies; and (4) long-term tissue retention of parent compound or metabolite(s) resulting in local tissue reactions or other pathophysiological responses.

C. FDA Should Take a Flexible Approach on Measuring Hormonal Effects.

Any potential for hormonal effects has been, and can be, addressed by the interpretation of repeat-dose or developmental and reproductive toxicity testing (DART) data. FDA defines a "hormonally active compound" as a "substance that interferes with the production, release, transport, metabolism, binding, activity, or elimination of natural hormones, which results in a deviation from normal homeostasis, development, or reproduction."[92] Results from *in vitro* high throughput screening fail to satisfy this definition. Despite varying modes of action, actual adverse effects from endocrine disrupting chemicals are typically manifested as: (1) alterations in development; (2) reproductive impairment; and/or (3) reduction in growth. These types of effects can be noted in traditional DART studies of antiseptic active ingredients.

Section 2 of the Proposed Rule states that "data are also needed to assess whether antiseptic active ingredients have hormonal effects that could produce developmental or reproductive toxicity."[93] We agree that any toxicological risk assessment should consider whether, under conditions of use, an ingredient could cause adverse effects as a result of its ability to interfere with endocrine homeostasis. The Proposed Rule also correctly states that general and reproductive toxicology studies are generally adequate to identify potential hormonal effects. We welcome the apparently flexible approach to determining risks to endocrine-sensitive tissues on a case-by-case basis. However, FDA should emphasize that a repeat-dose or reproductive and developmental toxicity study will provide the point of departure for an

[91] *Id.* at 4.

[92] 78 Fed. Reg. at 76455.

[93] 78 Fed. Reg. at 76455.

ingredient that acts by an endocrine mode of action.[94] These animal studies form the highest tier of endocrine testing strategies.[95] Therefore, where data from these studies exist, there is rarely a need to go back and generate *in-vitro* data to inform the risk assessment. As a general principle, therefore, FDA should not require further testing for endocrine modulation, where the adverse outcomes associated with endocrine modes of action have already been adequately addressed in existing *in vivo* tests.

DART studies for Consumer Antiseptics should not be required to resemble studies for NDA approval because OTC products must follow acceptable ingredients, doses, formulations, and labeling set forth in an OTC monograph. FDA also should remain cognizant that, in other countries these types of ingredients have other intended uses (e.g., industrial uses) and will have study designs more appropriate for those uses.[96]

D. FDA Should Work With Stakeholders in its Approach on Measuring Antimicrobial Resistance.

1. There Is No Evidence of Real-World Antibacterial Resistance from Use of Consumer Antiseptics.

The impact of widespread antiseptic use on the development of bacterial resistance is a topic that has been discussed for many years. Antibacterial resistance is an issue demonstrated to occur due to the indiscriminate use of antibiotics, but not to use of antibacterial hand soaps and/or body washes. More recently, a group of experts participated in a workshop to evaluate the interconnection between microbial resistance and antibiotics.[97] They found that even though mutant strains resistant to antibiotics have been identified to have transient resistance, the observed level of resistance was lower than predicted because the concentration required for the expression of resistance was toxic to bacteria. When molecular mechanisms were evaluated in three different scenarios, the conclusion was that biocides show very low correlation coefficients with antibiotic resistance.

In addition, while antimicrobial resistance has been demonstrated in laboratory settings, it has not been demonstrated in real world scenarios, as reflected by data from current monitoring programs. Dr. Eugene Cole reviews the current studies on bacterial resistance in Appendix C and concludes that "the fact remains that the relationship between the public's use of such products and the current antibiotic resistance crisis remains very weak." For example, laboratory studies to evaluate antimicrobial resistance have typically been conducted under unrealistic conditions (i.e., evaluating the active ingredient on its own at sub-lethal

[94] (*e.g.*, NOAEL, BMDL10)

[95] *See*, *e.g.*, EPA, Endocrine Disruptor Screening Program, *available at* http://www.epa.gov/endo/.

[96] *See*, *e.g.*, OECD, Guidelines for Testing of Chemicals Section 4: Health Effects, Test Nos. 414 (Prenatal Development Toxicity Study), 416 (Two-Generation Reproduction Toxicity Study), 443 (Extended One-Generation Reproductive Toxicity Study).

[97] Oggioni MR, Furi L, Coelho JR, Maillard J-Y, Martinez JL (2013) Recent advances in the potential interconnection between antimicrobial resistance to biocides and antibiotics. *Expert Rev. Anti Infect. Ther.* 11(4), 363-366

concentrations). In contrast, a realism-based laboratory study would take into account in-use scenarios (e.g., foreseen in-use concentrations and contact times). Recent studies have reinforced the evidence that resistance and cross-resistance associated with biocides and antiseptics is a laboratory phenomenon, observed only when tests are conducted under unrealistic conditions.[98]

We disagree with the proposed testing requirement set forth in the Proposed Rule. As FDA recognizes, there are currently no standard laboratory methods for evaluating the development of antimicrobial reistance.[105] FDA, nevertheless, requests extensive laboratory studies that would evaluate the active ingredient as opposed to the final formulation. Testing the antiseptic active on its own will not represent consumer use in final formulations.

Studies about the mechanism of antiseptic action are important as a research tool, but would be an unrealistic requirement for a GRAS determination. Identifying cellular targets of antimicrobial activity is not a simple or straightforward undertaking. It can take several years, and the results can be inconclusive. In fact, for many of the antiseptic active ingredients used today, the mechanism of action has not been fully elucidated. In the context of safety assessment, we accept that a general understanding of the mechanism of action can provide useful information for establishing relative risks of resistance amongst a group of antiseptic active ingredients. However, it must be recognized that it is unlikely this information can be elucidated for all active ingredients, particularly given that the mechanism(s) of action may be concentration dependent and combination/formulation effects may be highly relevant.

Data characterizing the potential for transferring a resistance determinant to other bacteria is also an unrealistic requirement for GRAS determination. Currently, it is unclear which methods could be used to determine the transfer of resistance. Furthermore, transfer of resistance by exposure to an antiseptic active is a theoretical risk.

While some urge FDA to curb the consumer use of antimicrobial consumer wash products to lower the risk for development of antibiotic resistance, the fact remains that the relationship between the public's use of such products and the evidence for the current antibiotic resistance crisis remains very weak. While some *in vitro* lab studies have been successful in forcing the expression of resistance in some bacteria to wash product actives, real world data from community studies using actual product formulations, although also few in number, show no correlation between the use of such products and antibiotic resistance.[99, 100, 101, 102, 103 104, 105, 106, 107] Further evidence of real world data showing no

[98] Condell, O., Iversen, C., Cooney, S., Power, K.A., Walsh, C., Burgess, C. and Fanning, S. (2012) Efficacy of Biocides Used in the Modern Food Industry To Control *Salmonella enterica*, and Links between Biocide Tolerance and Resistance to Clinically Relevant Antimicrobial Compounds. *Applied and Environmental Microbiology* 78, 3087-3097.

[99] Rutala, W.A., Weber, D.J., Barbee, S.L., Gergen, M.F. and Sobsey, M.D. (2000) Evaluation of antibiotic resistance bacteria in home kitchens and bathrooms. *Infection Control and Hospital Epidemiology,* 21, 132.

[100] Aiello, A.E., Marshall, B., Levy, S.B., la-Latta, P. and Larson, E. (2004) Relationship between triclosan and susceptibilities of bacteria isolated from hands in the community. *Antimicrob. Agents Chemother.* 48, 2973-2979.

antimicrobial resistance development after continued use of consumer products containing antimicrobial active compounds can be extracted from oral care clinical studies. These provide *in vivo* data, under well controlled conditions, on exposure to antimicrobial-containing formulations over prolonged periods of time (e.g., 6 months to 5 years). A considerable number of studies are available in the scientific literature; these have been reviewed by Gilbert et al. (2007) and Sreenivasan (2002).[108,109] A recent 5-year study with triclosan-containing products has been reported.[110]

As Dr. Cole points out in his comments, the majority of studies investigating antiseptic modes of action at the cellular level have predominantly focused on the activity of triclosan and whether induced resistance to triclosan should even be considered a precursor to antibiotic resistance. Researchers know that mechanisms of resistance can vary from one microbial species to another, and they typically involve one or more pathways, such as alteration of the drug target in the bacterial cell, enzymatic modification or destruction of the drug itself, limitation of drug accumulation as a result of drug exclusion or active drug reflux, or mutation frequency.[111, 112, 113, 114] And while triclosan resistance from laboratory studies may be

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[101] Marshall BM, Robleto E, Dumont T, Levy SB (2012) The frequency of antibiotic-resistant bacteria in homes differing in their use of surface antibacterial agents *Current Microbiology*, 65, pp. 407-415. Aiello A.E., Marshall B., Levy S.B., Della-Latta P., Lin S.X. and Larson E. (2005) Antibacterial cleaning products and drug resistance. *Emerg Infect Dis*, 11(10): 1565-1570.

[102] Aiello AE, Marshall B, Levy SB, Della-Latta P, Lin SX, Larson E (2005) Antibacterial cleaning products and drug resistance. *Emerg Infect Dis,* 11(10): 1565-1570.

[103] Cole, E.C., Addison, R.M., Rubino, J.R., Leese, K.E., Dulaney, P.D., Newell, M.S., Wilkins, J., Gaber, D.J., Wineinger, T. and Criger, D.A. (2003) Investigation of antibiotic and antibacterial agent cross-resistance in target bacteria from homes of antibacterial product users and nonusers. *J. Appl. Microbiol.* 95, 664-676

[104] Cole, E.C., Addison, R.M., Dulaney, P.D., Leese, K.E., Madanat, H.M. and Guffey, A.M. (2011) Investigation of antibiotic and antibacterial susceptibility and resistance in *Staphylococcus* form the skin of users and non-users of antibacterial wash products in home environments. *Int. J. Microbiol. Res.* 3, 90-96.

[105] Marshall B.M., Robleto E., Dumont T. and Levy S.B. (2012) The frequency of antibiotic-resistant bacteria in homes differing in their use of surface antibacterial agents *Current Microbiology*, 65, pp. 407-415.

[106] Rutala, W.A., Weber, D.J., Barbee, S.L., Gergen, M.F. and Sobsey, M.D. (2000) Evaluation of antibiotic resistance bacteria in home kitchens and bathrooms. *Infection Control and Hospital Epidemiology* 21, 132.

[107] Weber, D.J. and Rutala, W.A. (2006) Use of germicides in the home and the healthcare setting: is there a relationship between germicide use and antibiotic resistance? *Infection Control and Hospital Epidemiology* 27, 1107-1119.

[108] Gilbert, P., McBain, A. and Sreenivasan, P. (2007) Common therapeutic approaches for the control of oral biofilms: microbiological safety and efficacy. *Clin Microbiol Infect*; 13 (Suppl. 4): 17–24.

[109] Sreenivasan, P. and Gaffar, A. (2002) Antiplaque biocides and bacterial resistance: a review. *J Clin Periodontol*, 29(11): 965-974.

[110] Cullinan, M.P., Bird, P.S., Heng, N, West, MJM.J. and Seymour, GJG.J. (2014) No evidence of triclosan-resistant bacteria following long-term use of triclosan-containing toothpaste. *J Periodont Res*; 49: 220-225.

[111] Poole, K. (2002). Mechanisms of bacterial biocide and antibiotic resistance. *Journal of Applied Microbiology* 92 Suppl:55S-64S.

[112] Randall, L.P., Cooles, S.W., Piddock, L.J., Woodward, M.J. (2004). Effect of triclosan or a phenolic farm disinfectant on the selection of antibiotic-resistant *Salmonella enterica*.

associated with changes in antibiotic susceptibility, comprehensive environmental surveys have not demonstrated any association between triclosan usage and antibiotic resistance.[135] This again speaks to the fact that while triclosan "could" potentially in the future be directly linked with resistance to an antibiotic in the natural environment, the most rational approach toward detection of such an occurrence, should it occur, is by community monitoring of households that use products containing triclosan (or other actives) compared to those households that do not.

For the purposes of human health safety assessment, the relevance of generating data to characterize concentrations and activity of the antiseptic active in biological and environmental compartments is unclear. The scope of the Proposed Rule is consumer topical antiseptics, therefore exposure of organisms to the antiseptic active will occur mainly (if not solely) on the skin, and in a domestic setting. As such, the value of generating data on concentration and antimicrobial activity in the gut or in environmental matrices is not relevant.

In-situ type studies continue to show no correlation between antibacterial use and antibiotic resistance in the natural setting. We request to work with FDA to develop scientifically sound and meaningful monitoring programs to address these concerns. Since FDA is part of an intragovernmental agency task force working on the issue of antimicrobial resistance, we would greatly appreciate being kept informed of, or perhaps help with, its deliberations and decisions. It would be helpful to have access to FDA's critical review of the data supporting the presence of antimicrobial resistance.

E. More Time Is Needed to Develop and Perform Clinical Population Studies.

Although we believe that the requirement for clinical population studies is unjustified, we note that the studies referenced by FDA took several years to design, execute, analyze, and report. FDA's timelines for new data submission therefore are unreasonable and unrealistic. If FDA decides to adopt these proposed testing requirements, we request that FDA provide an appropriate extension of time for fulfillment of these requirements, so that we can work with FDA to confirm the appropriate data requirements and study protocols.

The two studies cited by FDA concerning the clinical outcome for antimicrobial and non-antimicrobial product formulations show that population studies are complex and take several years to execute.[115] The number of subjects required is large and identifying the correct clinical endpoint is critical to demonstrating the desired benefit of the drug formula. The studies also show how flaws in the study designs can lead to the overly-broad conclusion that antimicrobial handwashes are not effective. Neither of these studies showed a reduction in symptoms of infectious disease or disease transmission as a result of using an antimicrobial product compared to a non-antimicrobial one, but this failure can be attributed, at least in part, to confounding issues of viral etiologies and proper statistical powering.

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[113] Birosova, L., Mikulasova, M. (2014). Development of triclosan and antibiotic resistance in *Salmonella enterica* Serovar Typhimurium. *Journal of Medical Microbiology* 58, 436-441.

[114] Russell, A.D. (2004). Whither Triclosan? *Journal of Antimicrobial Chemotherapy* 53, 693-695.

[115] 78 Fed. Reg. at 76,452.

The first study FDA references is Luby's 2005 study, which compares a consumer antiseptic bar soap containing 1.2% Triclocarban (TCC) to a non-antimicrobial bar soap product.[116] The study compared their usage for the reduction in the incidences of diarrhea, impetigo, and acute respiratory infections in at least 900 households that had been separated into 3 groups of at least 300 households.[117] The study authors concluded that there was no difference in infection rate between the use of a non-antibacterial soap and a TCC-containing soap.[118]

The problem with using the Luby study to draw efficacy conclusions lies in the types of infections that Luby examined. The study examined diarrhea and acute respiratory tract infections, but there was no attempt made to examine the etiology of these infections, a large number of which could be caused by viruses.[119] As the study did not differentiate between viral and bacterial disease, it is impossible to ascribe a proportion of the cases to either bacterial or viral causes. TCC, the active ingredient in bar soap, is an antibacterial agent and thus was not developed for antiviral activity and is not labeled with antiviral claims. Because a TCC-containing product formulation was used, it is not surprising that the study did not demonstrate a reduction in the rate of diarrhea or acute respiratory infections as the contribution from viral causes would have been the same for both products, which may have masked any reductions experienced in bacterial-based disease. Furthermore, this study has never been repeated, nor has a similar study comparing the effects of antibacterial soap to plain soap been reported in the literature; thus, it is possible that this result would not be replicated if the same study were run again. It is also possible that there is a more appropriate study design to look for the impact of an antibacterial soap on disease specifically caused by bacterial infections, and it is for this reason that further discussions with FDA are required.

The second study that FDA references is Larson's 2004 study, which randomly assigned 224 inner city households to use hand soap and household cleaning products with and without antimicrobial ingredients.[120] Larson measured the incidence of diarrhea in the home over a 48-week period.[121] There are two issues with this study design that may have confounded the outcome. First, the number of participants in the study was low. A statistical study by Schaffner concluded that an "N" of 1,000 to 10,000 may be necessary to show the effectiveness of an antibacterial product formulation in reducing the rate of infection for a bacterial disease.[122] Second, the study design measured the change in the rate of viral infections instead of a change in the rate of bacterial infections. While quaternary ammonium surface cleaner and oxygenated

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[116] *Id.*

[117] *Id.*

[118] *Id.*

[119] For example, most cases of viral gastroenteritis in which diarrhea is one of the symptoms are caused by a virus such as a Rotavirus, Calicivirus, Adenovirus or Astrovirus. Most acute upper respiratory infections are caused by virus such as Adenovirus or Rhinovirus. Impetigo infections, which are caused by bacterial species such as Staphylococcus or Streptococcus, would have been a more appropriate infection rate study marker.

[120] 78 Fed. Reg. at 76,452.

[121] *Id.*

[122] Schaffner et al. Quantitative Microbial Risk Assessment of Antibacterial Hand Hygiene Products on Risk of Shigellosis. 2014. Journal of Food Protection. 4:528-690.

bleach laundry detergent are effective against viruses, the specific Triclosan-containing liquid handwash was not effective against viruses that cause diarrhea.

The Larson study cited by FDA required the following timing, which did not include FDA review and acceptance of the study design.[123]

Nov 99-Mar 00	Completion of pilot work on revised instruments Mar-May 00 Development of job descriptions and training manuals and procedures for project staff
May-Jul 00	Finalization of household recruitment plans, randomization strategy and orientation scripts and materials for households
Jul 00-Sept 00	Staff hiring, household recruitment
Sept 00-Dec 01	Intervention phase (entry of households into study will be staggered over several months)
Jan 02-Jun 02	Data cleaning, analysis, and manuscript preparation

In Appendix A, we provide a proposed protocol designed to look at the reduction in recurring skin infections following use of a body wash antiseptic. This protocol is based off a recently published trial looking at the reduction in recurrent skin infections using "Bleach Baths" compared to routine hygienic measures, which took 4 years to complete.[124] This proposed protocol could be used to demonstrate clinical efficacy of antiseptic body washes. However, before beginning any trials, we request interaction with FDA and agreement on design, clinical endpoints, and timing, as well as an extension of the monograph deadlines to conduct and analyze the study.

F. More Time Is Needed for Submission of New Safety Data.

In the Proposed Rule, FDA states that new data or information may be submitted to the docket within 12 months of publication, and comments on any new data or information may then be submitted for an additional 60 days.[125] In addition, FDA states that it will also consider requests for an extension of the time to submit new safety and/or effectiveness data to the record if such requests are submitted to the docket within the initial 180-day comment period.[126]

[123] Larson, E. L. et al., ''Effect of Antibacterial Home Cleaning and Handwashing Products on Infectious Disease Symptoms: A Randomized, Double-Blind Trial,'' *Annals of Internal Medicine,* 140:321–329, 2004.

[124] Kaplan S.L. et al. Randomized Trial of "Bleach Baths" Plus Routine Hygienic Measures vs Routine Hygienic Measures Alone for Prevention of Recurrent Infections. Clinical Infectious Diseases, Dec, 11, 2013.

[125] 78 Fed. Reg. at 76447.

[126] *Id.*

It would be impossible to complete the studies proposed by FDA by the proposed deadline for safety data submission. It could take up to four years to identify and complete the proposed tests, including the time needed for designing and reviewing protocols, designing testing schemes, reviewing and interpreting the data, and finalizing the study report. FDA should set a more realistic schedule to complete all of the safety and efficacy tests and should provide recommendations on prioritizing testing based on risk-based assessments of the different active ingredients.

VIII. FDA's Regulatory Impact Analysis Fails to Address Key Considerations.

FDA's regulatory impact analysis (RIA) does not account for all costs associated with the proposed regulatory alternative and it overestimates the benefits of the Proposed Rule. A detailed evaluation of the deficiencies of the RIA may be found in Appendix D.

FDA fails to meet the requirement under Executive Orders 12866 and 13563 to assess *all* costs and benefits of available regulatory alternatives.[127] Two of the major regulatory costs that FDA has failed to account for are: (1) costs to institutional suppliers of antibacterial soap products or their customers; and (2) cost associated with additional illnesses due to the lack of availability or diminished use of antibacterial hand soap products. A detailed estimate of the costs and benefits that were omitted from FDA's analysis may be found in Appendix D.

A. Costs Associated with Institutional Markets

FDA did not assess the regulatory costs to institutional suppliers of antibacterial soap products or to their customers, namely schools, airports, restaurants, cruise ships, hotels, and office buildings where antiseptic hand soaps are used.

We provide an alternative estimate of the total sales of antibacterial soap in the U.S. using the Census data from 2011. Our assessment of FDA's estimate for total sales shows that those estimates did not account for, or consider, a relatively large component of total sales that is attributable to institutional sales. Institutional sales represent other than household use of retail products and include sales to commercial, industrial, and institutional organizations, such as restaurants, fast-food chains, hotels, and other establishments.

Below we estimate the total sales of anti-bacterial soap, including the amount of institutional sales. Table 1 presents the total sales data by product category using Census 2011.

Table 1. Total retail and institutional hand soap sales

Product Category	Total Sales ($ Billion)
Soaps and detergents—commercial, industrial, and institutional	11.9
Household detergents	8.8
Soaps, excluding specialty cleaners, household	4.2

[127] Exec. Order No. 12,866, 58 Fed. Reg. 51,735 (Oct. 4, 1993); Exec. Order No. 13,563, 76 Fed. Reg. 3,821 (Jan. 21, 2011).

Soap and other detergent manufacturing, not elsewhere classified, total	2.4
Glycerin, natural	0.4
Toothpaste, including gels and tooth powder	1.1
TOTAL	28.8

Source: Census, 2011

Using the Census data and information from two member companies, we estimate the range for institutional sales of antibacterial soap to be at $0.21–$0.72 billion per year.[128] Additionally, we estimate that total annual *retail* sales of antibacterial soap are $1 billion. Institutional antibacterial soaps represent 21%–72% of retail antibacterial soaps in sales ($0.21–$0.72 billion of $1 billion). Therefore, FDA omitted a large fraction of total sales from its analysis. FDA should fully account for these associated costs in their analysis.

B. Costs to Other Affected Industries

As noted above, the institutional hand soap market includes a number of customers who may be indirectly impacted by the regulation, including institutional customers outside of the food industry, such as schools, airports, and government buildings, and commercial customers, such as military, airlines, hotels, and office buildings. The Proposed Rule would eliminate access to antiseptic hand soaps for these customers. The Regulatory Impact Analysis should quantify the costs to institutional and commercial customers to adapt to the loss of antiseptic hand soaps in the market.

C. Costs Associated with Additional Illnesses Due to Lack Antiseptic Hand Soaps

We estimated the costs of the Proposed Rule associated with preventable gastrointestinal illnesses that would occur if antiseptic handwash products were not available.[129] Dr. Schaffner helped us estimate the annual range (low, medium, high) of the number of cases of gastrointestinal disease associated with hand hygiene in the United States by pathogen. His methods and full results appear at the end of Appendix D. He considered four foodborne pathogens: shiga-toxigenic *E. coli* (STEC O157 and non-O157), *Salmonella* spp., nontyphoidal, *Shigella*, and *Campylobacter*. A summary of the key output appears in Table 2.

Table 2. Number of cases and projected additional cases

	Number of Hand-Hygiene-Related Cases			Additional Cases: Plain vs. Antibacterial Soap (based on mean number of cases)	
Pathogen	Low	*Mean*	High	1000 CFU dose	Worst case
STEC O157				15,942	360,293
STEC non-O157				28,342	640,521
All STEC	7,314	*44,284*	110,002	44,284	1,000,813

[128] See Appendix D, Section 2.3.3.

[129] See Appendix D, Section 3.1.3

Salmonella, nontyphoidal	29,759	*47,426*	77,523	33,198	905,835
Shigella	24,511	*131,254*	374,789	55,502	1,771,929
Campylobacter	78,880	*197,772*	377,062	118,663	3,836,769

Additionally, we estimated the range (low, medium high) of cost associated per case for each of the four pathogens examined. A summary of key output appears in Table 3.

Table 3. Cost per case of illness by pathogen

Pathogen	Low	Mean	High
STEC O157	$5,350	$10,805	$3,014,355
STEC non-O157	$995	$9,048	$1,516
***Salmonella*, nontyphoidal**	$1,956	$5,948	$14,146
Shigella	$1,168	$3,989	$16,273
Campylobacter	$1,066	$4,196	$13,925

Using the data in the two above tables, we multiplied the costs per case by the most conservative value for possible cases averted (i.e., assuming a 1000 CFU dose response relationship). We also multiplied the costs per case by the least conservative value (i.e., using a 1 CFU dose-response relationship). The results are provided in Table 4 below.

Table 4. Estimate of additional annual national cost burden

	Mean Cost (based on mean number of cases and mean cost per case)	
Pathogen	1000 CFU dose	Worst case
STEC O157	$172,248,337	$3,892,812,417
STEC non-O157	$256,431,548	$5,795,352,977
All STEC	$428,679,885	$9,688,165,394
Salmonella, nontyphoidal	$197,471,741	$5,388,157,496
Shigella	$209,423,107	$7,068,029,869
Campylobacter	$497,853,944	$16,097,277,532
Total	$1,333,428,677	$38,241,630,291

Based on the findings presented here, a conservative estimate of the additional burden of gastrointestinal illness caused by the selected pathogens is more than $1.3 billion *annually* in the United States. Under a high-end, but not absolutely maximum, scenario (i.e., by using mean costs but a low dose-response ratio), the additional cost burden would exceed $40 billion annually.

Other scenarios not detailed in this table include a low cost estimate (assuming that patients are not hospitalized and/or that they have public insurance coverage, and with the highest dose-response relationship) of $336 million annually and a high cost estimate (assuming

that patients require hospital admission and have long-term sequelae, that they have commercial insurance coverage, and the lowest dose-response ratio) exceeds $1.182 trillion annually.

Additionally, it is important to note that this estimate is based solely on bacterial gastrointestinal diseases associated with these four pathogens and does not consider the costs associated with other gastrointestinal pathogens or dermal (e.g., MRSA) or respiratory pathogens. Moreover, this estimate does not include costs associated with lost productivity on the part of the patient or caregiver, or public health cost of managing a disease outbreak, including testing of food and water sources, associated communication and reporting, and ongoing surveillance.

D. Costs Underestimated by FDA

1. Relabeling Costs

Using unit cost information from member companies, we estimated costs associated with relabeling retail handwash products.[130]

Table 5. Estimated total relabeling costs

Product	Number Products	% Unique formulations	Number of Affected Products	Unit Relabeling Costs	Total Relabeling Costs
Bar Soap	472	70%	330	$147,518*	$48,740,057
Liquid Body Wash	726	91%	661	$142,652	$94,244,470
Liquid Hand Soap	285	91%	259	$149,952**	$38,889,922
TOTAL	1,483	AVG=84%	1,250	-	$181,874,449

*Represents an average of relabeling costs for liquid handwash, liquid hand soap, and liquid body wash.

**Represents an average of relabeling costs for liquid handwash and liquid hand soap.

As presented in the above table, the estimated total cost of relabeling is $182 million. The estimate reported in the RIA ranges from $42.1 to $88.1 million, with an average of $60.7 million. The estimated total cost of relabeling calculated using member company unit cost information resulted in the estimate that is three times higher than the average estimate in the RIA ($182 million / $60.7 million = 3 times).

2. Reformulation Costs

We estimated costs associated with reformulating retail handwash products.[131] The total reformulation costs we estimated at $52 million to $1 billion, depending on the percentage of companies that would need to reformulate their product, and the unit cost for

[130] See Appendix D, Section 2.6

[131] See Appendix D, Section 2.7

reformulation. This was slightly lower than the estimate on the low end from the RIA ($70 million) and nearly four times greater than the RIA on the high end ($281 million).

3. Costs of Conducting Safety and Efficacy Studies

An estimate of the range of costs associated with conducting clinical and non-clinical safety studies for each active ingredient was reported in the RIA as $12.9-35.3 million. The range of costs estimated for conducting clinical outcome effectiveness studies for each active ingredient was reported in the RIA as $3.9-28.7 million. For non-clinical effectiveness studies, the RIA estimated costs associated with each test in the range of $0.9-4.0 million; we believe these tests would have to be conducted on final finished product formulations rather than individual active ingredients.

We estimated the initial one-time costs associated with conducting safety and efficacy studies under scenarios where 1 (low), 3 (medium) or 5 (high) active ingredients are supported for use in a future final monograph and where 6 (low), 9 (medium) and 12 (high) finished products tested for non-clinical effectiveness. Using these assumptions, we estimate total initial one-time costs associated with conducting safety and efficacy tests $22.3 million to $368 million. Complete details regarding our estimation are provided in the table below.

Table 6. Costs Associated with Safety and Effectiveness Studies (one-time costs)

Test	Testing Costs		
	Low	**Medium**	**High**
Tests Performed on Active Ingredients			
Per Ingredient Cost			
Total Non-clinical Testing Costs (w/o resistance testing)	$12,129,989	$12,129,989	$12,129,989
Clinical Safety Studies	$725,734	$2,542,114	$23,202,190
Clinical Outcome Effectiveness Studies	$3,918,581	$14,308,034	$28,656,974
Subtotal Per Ingredient Cost	$16,774,304	$28,980,137	$63,989,153
Total Cost (Ingredient Testing)			
1 active ingredient	$16,774,304	$28,980,137	$63,989,153
3 active ingredients	$50,322,912	$86,940,411	$191,967,459
5 active ingredients	$83,871,520	$144,900,685	$319,945,765
Tests Performed on Final Products			
Per Ingredient Cost			
Non-Clinical Effectiveness Studies	$916,257		$3,983,724
Subtotal Per Product Cost	$916,257		$3,983,724
Total Cost (Product Testing)			
6 products	$5,497,542		$23,902,344
9 products	$8,246,313		$35,853,516
12 products	$10,995,084		$47,804,688

	Total Testing Cost		
Low (1 active ingredient and 6 products)	**$22,271,846**	**$28,980,137**	**$87,891,497**
Medium (3 active ingredients and 9 products)	**$58,569,225**	**$86,940,411**	**$227,820,975**
High (5 active ingredients and 12 products)	**$94,866,604**	**$144,900,685**	**$367,750,453**

E. Comparison of Total Costs Associated with the Proposed Rule

We compared the total costs of the Proposed Rule as estimated in the RIA against the costs we estimated including those components not considered. A summary is provided in the table below.

Table 7. Summary of Costs of the Proposed Regulation

Cost/ Benefit Component	**FDA Analysis**		**ACI/ PCPC Analysis**	
	Low Estimate	**High Estimate**	**Low Estimate**	**High Estimate**
		Costs		
Relabeling (Retail)	$42 million	$88 million	$182 million	$182 million
Reformulation (Retail)	$70 million	$280 million	$52 million	$1,041 million
Relabeling (Institutional)	N/A	N/A	$53 million	$167 million
Reformulation (Institutional)	N/A	N/A	$15 million	$958 million
Safety/ Efficacy Testing*	$17.7 million	$68 million	$22 million	$368 million
Costs of Preventable Illnesses (GI only)	N/A	N/A	$1,333 million	$38,242 million
TOTAL COSTS	**$129.7 million**	**$436 million**	**$1,657 million**	**$40,958 million**

*Notes: safety and efficacy testing costs estimated by FDA are reported per ingredient. Therefore, the total cost estimate would be higher if more than one ingredient would need to be tested.

** Benefits resulting from reduced exposure are reported in pounds of active ingredients in the RIA.

We found that our estimated range of costs associated with the Proposed Rule ($1,657-$40,958 million) were 13-94 times greater than those costs estimated in the RIA ($130-436 million).

F. Benefits of the Proposed Rule

FDA has also incorrectly calculated and overestimated the benefits associated with the Proposed Rule. Benefits reported in the RIA are not substantiated, because data are lacking that would show the relationship between active ingredients and adverse health effects, invalidating parts of the net benefits calculation. FDA's conclusions rely on an assumption that the active ingredients in Consumer Antiseptics have adverse health effects, but there is no scientific basis for this assumption. No scientific studies are available that demonstrate a statistically significant relationship between the active ingredients considered in the Proposed

Rule and adverse health effects on consumers. As a result, there are no measureable benefits of the Proposed Rule.

IX. FDA Should Formally Recognize the Food Handler Category as a Distinct Monograph Category.

A. FDA Should Formally Recognize the Food Handler Category as Distinct Monograph Category.

We ask FDA to recognize the category of antiseptics for use by the food industry (Food Handler Category) and clarify how it intends to address this in formal rulemaking. FDA first distinguished products for food industry use as a potential separate category in the 1994 TFM and requested relevant data and information on the category.[132] As a result, food handler topical antiseptic products (Food Handler Products) were tacitly included within the subcategory of "antiseptic handwash" products in Subpart E.

FDA has never formally defined the category of Food Handler Products. We propose the following definition:

> Antiseptic handwash products for use in commercial establishments or regulated settings (at the federal, state, or local level) where food production, packaging, transportation, storage, preparation, service, or consumption occurs.
>
> This definition is intended to include the full continuum of environments with potential hand contact with food, where such food is then made available for consumption, from farm to food processing plants to foodservice and food retail. This definition is intended to exclude food handling that occurs in the home. This definition would include use of antiseptic hand rubs or hand sanitizers. Antiseptic hand rubs or hand sanitizers are used in food industry settings such as federally inspected meat and poultry plants and may be used after washing with a non-antimicrobial handwash. In other instances they may be used to reduce the number of bacteria on hands when hands are not visibly soiled.

The Proposed Rule mentions Food Handler Products but does not address how those products will be regulated.[133] On one hand, it is clear that FDA recognizes that Food Handler Products do not fit within the definition of Consumer Antiseptics. On the other hand, it is not evident that Food Handler Products are included in the category of "healthcare personnel handwash products." Therefore, unless Food Handler Products are explicitly recognized in a further amendment to the TFM, they could be effectively removed from the market without ever being given a fair hearing on their GRAS/E status and their importance in maintaining public

[132] 59 Fed. Reg. at 31440.

[133] 78 Fed. Reg. at 76446 ("Antiseptics for use by the food industry are not discussed further in this document.").

health. We attach as Appendix E a copy of a Citizen Petition that will be separately filed by ACI.

As such, we ask FDA to publish a formal notice clarifying the status of Food Handler Products. Until FDA publishes a Food Handler monograph, we recommend that FDA confirm that Food Handler topical antiseptic products can continue to be marketed under the current regulatory framework.

B. Food Handler Use of Antiseptic Handwash Products Is Distinct.

1. Food Handler Products Have a Distinct Disease Transmission Intervention Objective.

A food handler is effectively an agent in the transmission of bacteria from a source of contamination to food. The objective of food safety programs is to reduce the transfer of bacteria to food below those levels which will result in foodborne illness when food is consumed. Hence, the focus of handwashing in this context is the reduction of bacteria levels on the hands to accomplish the food safety program objective.[134]

2. Contamination in Food Handler Products Presents a Significant Public Health Concern.

The food industry is caught between a high concentration of sources of contamination (*e.g.*, food source, bodily fluids, or surfaces) and food. Further, the food industry environment fosters a multiplier effect with a single food handler contamination having the potential to infect dozens or hundreds of meals per day.[135] Hand-to-food bacterial transfer is a recognized public health issue and the food industry aggressively deploys food safety programs to manage this risk through the continuous, on-going reduction of bacterial levels on hands via handwashing.[136]

[134] Fischler, G. E., Fuls, J. L., Dail, E. W., Duran, M. H., Rodgers, N. D. and Waggoner, A. L. 2007. Effect of hand wash agents on controlling the transmission of pathogenic bacteria from hands to food. J Food Prot. 70(12): 2873-2877. Fuls, J. L., Rodgers, N. D., Fischler, G. E., Howard, J. M., Patel, M., Weidner, P. L., & Duran, M. H. 2008. Alternative hand contamination technique to compare the activities of antimicrobial and nonantimicrobial soaps under different test conditions. Appl Environ Micro. 74(12):3739-3744. Schaffner, D.W., Bowman, J.P., English, D.J., Fischler, G.E., Fuls, J.L., Krowka, J.F., and Jruszewski, F.H. 2014. Quantitative microbial risk assessment of antibacterial, hygiene products on risk of Shigellosis .J .Food Prot. Doi10.4315/0362-28-JFP-13-366. DeWit, J.C. 1985. The importance of hand hygiene in contamination of foods. Antonie van Leeuwenhoek J. Micro. 51:523-527. Luber, P., S. Brynestad, D. Topsch, K. Scherer, and E. Bartelt. 2006. Quantification of Campylobacter species cross-contamination during handling of contaminated fresh chicken parts in kitchens. Appl.Environ. Microbiol. 72:66–70.

[135] NRA. 2013. http://www.restaurant.org/News-Research/Research/Facts-at-a-Glance Accessed 3/15/14. Restaurant News. 2011. Despite Recession, Americans Eat Whopping 250 Restaurant Meals Per Year.

[136] *See* FDA, Food Code (2013); 21 C.F.R. § 110.10(b)(3)("and sanitizing if necessary to protect against contamination with undesirable microorganisms").

3. Food Handler Handwash Protocols Realize a Cumulative Antiseptic Benefit.

Food industry handwash protocols call for repeat hand washes and on-going compliance. The nature of an on-going repeat wash protocol is consistent with the potential to realize an on-going benefit from the antiseptic active ingredient.

4. Food Handler Setting Is a Professional Use Setting.

The use of antiseptic handwash products by food handlers is a defined, prescribed use by a trained, professional work force who use these products during their work day at a food operations facility. Decades ago, the USDA established a regulatory program governing the antiseptic handwash products used by professional workers in food preparation facilities. In the late 1990's, the USDA's program transferred to a private certification program currently operated by NSF International. NSF continues to certify antibacterial hand care products for use in food handling operations.

FDA CFSAN's Food Code provides a uniform system of provisions that address the safety and protection of food. Building on the foundation of the former USDA program, the Food Code establishes hand hygiene standards for professional workers in food preparation establishments. There are currently 13.5 million restaurant industry and 1.5 million food & beverage manufacturing professional workers in the U.S. today. These professional uses warrant a distinct food handler category.

C. Regulators Recognize the Integral Role of Food Handler Products.

Food Handler Products are an integral part of a complex set of regulatory and industry standards for ensuring food safety and require a unique evaluation in the OTC monograph process.

- The FDA Food Code establishes practical, science-based guidance and enforceable provisions for mitigating risk factors known to cause foodborne illness at food service and food retail establishments. It includes detailed information on how, where, and when food handlers should wash their hands. Since 2001, this document has recognized that antiseptic handwashes are used.[137]

- Food facilities subject to Food Safety Modernization Act FSMA employ an arsenal of intervention strategies, including antiseptic handwash products, to combat known and emerging foodborne pathogens in their pursuit to reduce foodborne illness. Rules proposed for Preventive Controls and Produce Safety require food processors to implement food safety plans to reduce the risk of transmission of food pathogens.[138]

[137] *See, e.g.,* FDA, Food Code 48-49 (2013); FDA, Food Code, at § 2-301.16 (2001).

[138] FSMA, http://www.fda.gov/food/guidanceregulation/fsma/ucm242500.htmhttp://www.fda.gov/food/guidanceregulation/fsma/ucm242500.htm. Accessed 5/25/14.

Antiseptic handwash products are a critical intervention step to reduce the risk of transmitting pathogens.

- The current Good Manufacturing Practices, which focuses on food manufacturing, also states that hands must be washed thoroughly.[139]

- NSF International provides public health standard guidelines and certification programs to help protect consumer products. It was founded in 1999 and continues the work of the USDAs Non-Food Compounds program. USDA originally established the guidelines for handwash compounds within food production facilities. That jurisdiction has, however, transferred to FDA CDER in 1999.

- ASTM standard test methods E1174, E2946 and E2755 are used by the industry to evaluate the efficacy of antibacterial handwash and sanitizer products such as those used in the food industry.[140]

We recommend that FDA consult on the Proposed Rule with non-governmental organizations, such as NSF International, that provide certification, registration, and other food safety compliance services to the commercial foodservice industry. These organizations play an important role in delivering food safety outcomes for society. If Food Handler Products are not addressed in a manner that incorporates these food safety compliance programs and processes, there is potential for significant disruption to food delivery processes. FDA should carefully consider and coordinate these standards for Food Handler Products.

D. Efficacy of Handwashing by Food Handlers is Best Measured with a Surrogate Endpoint Test.

Efficacy testing for antiseptic handwash products intended for food handler use should reflect the characteristics and intended use of the product. The critical considerations in the food industry are: (1) the presence of elevated levels of transient bacteria on food handler hands and the transient bacteria as the primary focus of cause of foodborne illness; and (2) the role of handwash activities in a food safety program as an intervention point to reduce bacteria levels on hands and subsequent transfer of bacteria. Efficacy testing should also focus on the true efficacy potential of the antiseptic handwash product as handwash protocols and food safety education programs can be employed to drive proper use of the product toward achieving the full efficacy potential of the handwash product. These considerations support the application of the 1994 TFM surrogate endpoint efficacy test standards to antiseptic products for food industry use.

[139] 21 C.F.R. § 110.10.

[140] ASTM, "Standard Method for the Evaluation of Health Care Handwash Formulation, Designation E1174," in "The Annual Book of ASTM Standards," vol. 11.04, ASTM, Philadelphia, pp. 209-212 (1987); ASTM , "Standard Test Method for Determining the Bacteria-Reducing Effectiveness of Food-Handler Handwash Formulations Using Hands of Adults Designation E2946" in "the Annual Book of ASTM Standards," vol. 11.05, ASTM, Philadelphia (2013).

The 1994 TFM efficacy test standard is generally aligned with the food handler use application for the following reasons. First, the inoculation of the hands with 6 $\log_{10}$ of a marker organism is appropriate to test the efficacy of the product against the higher levels of transient bacteria of concern versus the resident bacteria flora. Second, the express intent and claimed indication of handwash use as part of a food safety program *is* the reduction of bacteria on the hands. Third, the use of a consistent test procedure ensures comparability and reliability of test results. Further, the test results capture the efficacy of each product under the prescribed test procedure conditions as a basis of demonstrated performance potential.

As noted, FDA has previously recognized the simple reduction of bacteria as an endpoint objective in the 1994 TFM and in the approval of historic and subsequent New Drug Applications. Recent studies have taken the next step and further confirmed the link between reduction of bacteria count on the hands and subsequent reduction of bacteria transferred from the hands to ready-to-eat food.[141] These same studies went on to translate the levels of bacteria present on ready-to-eat food into expected illness if consumed. The cumulative effect of these three steps shows that reduction of bacteria on the hands does affect the clinical outcome of expected illness and hence, that the use of bacterial log reduction as a surrogate measure of clinical outcome efficacy is appropriate.

ASTM method E1174 has been utilized since 1987 to evaluate the effectiveness of handwash formulations by using reduction of bacteria as the endpoint. More recent methods have re-affirmed this concept and are currently being used and were developed for evaluating the efficacy of products for use in the Food Handler industry. In 2013, ASTM developed E2946 (Standard Test Method for Determining Bacteria-Reducing Effectiveness of Food Handler Handwash Formulations Using Hands of Adults). This method determines the effectiveness of handwashes against common foodborne bacteria *E. coli*. incorporated into organic soils of broth and ground beef. Test material effectiveness is measured by comparing the number of challenge bacteria recovered from contaminated hands after a single application of the test material to the number recovered from contaminated hands not exposed to the test material.

Other regulatory organizations and authorities also utilize surrogate endpoints to evaluate efficacy of Food Handler Products.

- NSF International has established requirements for both handwashing and hand sanitizing products for use in federally inspected meat and poultry plants. Antibacterial handwashing and hand sanitizing products are required to be found equivalent to 50 ppm chlorine including effectiveness against *Salmonella typhi* ATCC 6539.[142]

[141] Fischler et al 2007 and Schaffner et al 2014.

[142] 59 Fed. Reg. at 31,431 (FDA "is proposing that in vitro antiseptic antimicrobial activity of the antiseptic ingredient, the vehicle, and the formulated product be characterized by the determination of their antimicrobial spectrum and by minimal inhibitory concentration determinations performed against selected organisms.").

- Health Canada provides for testing the reduction of various bacteria, fungi, and viruses in their *in vivo* and *in vitro* testing methodology.[143] Health Canada uses the data from these test methods to conduct an evaluation of the efficacy of products for food handler use.

E. Clinical Trials Are Not Suited to the Food Handler Environment.

The nature of the role and use of antiseptic handwash products in the food industry creates even more significant challenges to the feasibility and appropriateness of a clinical outcome trial. The study execution itself is impractical. Further, the study introduces a risk without offering any offsetting benefit. And finally, the results are difficult to measure. Because such trials would focus not on the therapeutic benefit to food handlers, but the prophylactic benefit to food consumers, the results of the drug itself are difficult to isolate. Without adequately designed controls, such trial results will likely measure the behavior and practice of food handlers more than the actual efficacy of the product.

The logistics and practicality of both recruiting food handler establishments to participate and then securing the participation of the patrons is daunting. The food industry uses every tool at their disposal to ensure food safety because of the irreparable brand and significant economic and public health costs of a foodborne illness. These institutions will not want to publicize that they are participating in a study that may put their customers' health at risk, even with informed consent of the individual participants. Furthermore, the tracking and synthesis of potential foodborne illness conditions of the patrons or ultimate food consumers is fraught with feasibility concerns such as follow-up and reporting participation levels.

Because antibacterial soap is used in the food industry today, this reflects the base level experience. The very nature of the clinical trial in this situation would be to demonstrate that more people get sick if the product is not used. Eliminating a disease prevention tool that is currently part of the industry standard creates an ethical and business dilemma. A number of deaths each year can be attributed to complications from foodborne illness.[144] Introducing the risk of more foodborne illness, with the potential of significant public harm, is unjustified.

Finally, the results of a clinical trial may suffer from confounding factors that bias toward reducing the demonstrated efficacy of the antibacterial soap without a mirror negative bias to the performance of a non-antibacterial soap and water under the same conditions. For instance, research has demonstrated that wash times and soap volumes may impact the efficacy results of antibacterial soap, but without a similar impact on non-antibacterial soap and water.[145] The resulting effect of these factors could be a systemic depression and dilution of the measured efficacy of antibacterial soap performance versus non-antibacterial soap and water irrespective of the active's efficacy potential.

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[143] Health Products and Food Branch, Health Canada, Guidance Document: Human-Use Antiseptic Drugs 27 (Oct. 2009).

[144] Scallan E, Griffin PM, Angulo FJ, Tauxe RV, Hoekstra RM. Foodborne illness acquired in the United States—unspecified agents. *Emerging Infectious Diseases.* 2011; 17(1):16–22.

[145] Fuls et al . 2008. Alternative hand contamination technique to compare the activities of antimicrobial and nonantimicrobial soaps under different test conditions. Appl Environ Micro. 74(12):3739-3744

X. Conclusion

We respectfully request that FDA consider the recommendations outlined in these comments, which address the scientific weaknesses and practical implications of the Proposed Rule. In summary, our recommendations are:

- FDA should re-issue the Proposed Rule as an ANPR.
- FDA should clarify the definition of Consumer Antiseptics.
- FDA should set an alternative timeline for the finalization of the monograph and engage with stakeholders to develop appropriate efficacy and safety data requirements and detailed protocols to generate these data.
- FDA should recognize the ASTM methods E1174, E2783, and E2784 as appropriate to support the efficacy testing for finished antiseptic formulations.
- FDA should confirm that the Melon Ball Disease Transmission Model, Palmar Method, and QRMA may be used to demonstrate the clinical benefit of consumer antibacterial handwash formulations.
- FDA should work with stakeholders to develop scientifically sound and meaningful monitoring programs to address safety concerns.
- FDA should formally recognize and acknowledge a separate subcategory for Food Handler Products before the Consumer Rule is finalized. FDA should define Food Handler Products as antiseptic handwash products for use in commercial establishments or regulated settings (at the federal, state or local level) where food production, packaging, transportation, storage, preparation, service, or consumption occurs. The definition should include antiseptic hand rubs or hand sanitizers.
- FDA should confirm that Food Handler Products can continue to be marketed under the existing regulatory framework until FDA publishes a Food Handler monograph. FDA should solicit comments and any new data and information specifically addressing the safety and effectiveness of active ingredients for use in Food Handler Antiseptic Handwash Products in an ANPR. FDA should consult with relevant food safety authority, such as CFSAN.

We welcome an opportunity to discuss these issues with FDA as they are of critical importance to our members. If you have any questions, please contact Farah K. Ahmed, Associate General Counsel, Personal Care Products Council at (202) 331-1770.

Respectfully submitted,

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Appendix A

Dr. Ronald Turner (University of Virginia) - Research Study Design

A. Specific Aims.

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has become the predominant cause of skin and soft tissue infections (SSTI) in the US. The emergence of this organism has been associated with a dramatic increase in recurrent infections in patients and their household contacts. Efforts to prevent these recurrent infections by decolonization or decontamination of the index patient have had limited success. Decolonization of all household contacts was more successful but protection was incomplete and this method raises concern about development of resistance to the antibiotics used for the decolonization.

The purpose of this proposed study is to evaluate the effect of antibacterial soaps for prevention of recurrent staphylococcal infections; either MRSA or methicillin-sensitive *Staphylococcus aureus* (MSSA), by addressing the following specific aims:

1) Evaluate the effect of daily bathing with antibacterial soap by all members of affected households on frequency of recurrent SSTI by assessing:
    a. incidence of recurrent infection in the index patient
    b. incidence of infection in household contacts of the index patient
2) Determine the effect of daily bathing with antibacterial soap on the severity of recurrent and household SSTIs by assessing the incidence of medically attended infections in the index patient and household contacts.

<u>The primary outcome variable for the study will be the incidence of recurrent SSTI in the index patient.</u>

B. Background and Significance.

Staphylococcus aureus has long been recognized as an important cause of skin and soft tissue infections. While most of these infections are sporadic, there is a subset of patients and their household contacts that develops recurrent skin infections (1, 2). These infections are typically localized and are not associated with dissemination or systemic illness. Some of these patients

have a definable underlying immunodeficiency; however, the majority of these recurrent infections occur in apparently healthy individuals.

The emergence of community-associated methicillin-resistant *Staphylococcus aureus* in the first decade of the 21st century has been associated with a dramatic increase in the incidence of skin and soft tissue infections (3). This epidemic has also been associated with an increase in recurrent infection and infection in household contacts.(4). This seems to be related to a greater propensity for CA-MRSA to cause skin infection relative to methicillin sensitive Staphylococcus aureus (MSSA) (5). In contrast to sensitive staphylococcal organisms, CA-MRSA is less likely to colonize the nose and more likely to colonize healthy skin in the axilla or groin regions of the body (6).

The recurrent staphylococcal skin infections are associated with substantial morbidity. Patients frequently require drainage procedures and/or systemic antibiotics for treatment. A number of approaches have been tried to prevent these infections. Prolonged treatment with oral antibiotics (7) and decolonization with a combination of chlorhexidine and mupirocin (8) both have been shown to have a beneficial effect on recurrence. These approaches; however, result in repeated and prolonged exposure of patients to clinically useful antibiotics and raise concern about development of resistance. A recent attempt to decolonize the skin of patients with a history of CA-MRSA skin infections was not successful (9). The use of anti-microbial soaps that have the potential to decolonize the skin without exposure to antibiotics presents an attractive option for prevention of recurrent staphylococcal infections.

C. Research Design and Methods.

C.1. Study design. This will be a randomized, placebo-controlled double-blinded study of the effect of antibacterial soap on the occurrence of recurrent SSTI. The unit of randomization will be the household with all members of each household using either antibacterial or non-antibacterial soap. After randomization, households will be contacted weekly to assess the occurrence of skin infections and whether the infection required medical attention. All households will be followed for six months after randomization. The effectiveness of the

antibacterial soap will be assessed by comparing the rate of recurrent infection in the treated and control households.

C.2. Volunteers. Patients with documented staphylococcal skin or soft tissue infections (either methicillin-sensitive or methicillin-resistant *Staphylococcus aureus*) within the last 6 months will be identified by medical record review. These patients will be contacted and invited to participate in the study. Patients and households that meet the following inclusion/exclusion criteria will be randomized to study treatment:

Inclusion Criteria:

- At least two individuals in the household
- At least one individual in the household with documented staphylococcal skin or soft tissue infections (either methicillin-sensitive or methicillin-resistant *Staphylococcus aureus*) within the last 6 months
- Written informed consent by all participating adults with consent by the parent or guardian for children and assent for participation from all children older than 7 years old.

Exclusion criteria:

- Families in which at least two household members are unable or unwilling to provide informed consent.
- Presence in the household of individuals with medical conditions requiring frequent (>1/year in the last 3 years) or recent (within last 6 months) hospitalizations.
- Presence in the household of individuals with chronic underlying skin conditions (i.e., eczema) or chronic breaks in normally intact skin (i.e. tracheostomy).
- Presence in the household of individuals with known congenital or acquired immunodeficiency.
- Presence in the household of individuals who are receiving systemic antibiotic treatment for any reason.

C.3. Methods.

C.3.1. Definitions.

Skin or soft tissue infection will be defined as any boil, furuncle, abscess, cellulitis or impetigo.

Household contact will be defined as any individual living in the home of the index subject at least 5 days out of each week during the study period.

C.3.2. Study intervention. The study intervention will be the exclusive use of antibacterial soap in the household during the observation period. The control group will use standard commercially available soap without antibacterial additives. Subjects will be asked to refrain from using other antibacterial products such as antimicrobial laundry detergent or household cleaners or hand sanitizers in the home for the duration of the observation period.

C.3.3. Surveillance for Skin or Soft Tissue Infection. A responsible adult in each family will be taught to keep a study diary on all participating family members. The diary will note any Skin or Soft Tissue Infections (SSTI) in participating family members and participants will be instructed to contact study staff if these infections occur. In addition, households will be contacted once each week by either telephone or email (with an acknowledgement of receipt) to assess the occurrence of SSTI. If an SSTI occurs in the household, information will be collected by the study staff about whether medical attention was sought and any treatment provided.

C.4. Statistics and Data Analysis.

C.4.1. Sample size. The baseline incidence of recurrent SSTI in patients with documented staphylococcal skin or soft tissue infections is not well defined. Published incidence during a 12 month observation period varies from 21% for medically attended recurrences to 72% for self-reported recurrences in individuals with demonstrated CA-MRSA colonization. The sample size for this study was calculated based on an assumption that 40% of index patients with a documented staphylococcal SSTI in the control group would have a recurrent infection during the 6 month observation period. Based on this assumption, 300 households will need to be enrolled in each arm of the study and monitored for 6 months to detect a 20% reduction in recurrent infection in the treatment group with $p_{\alpha}=0.05$ (two-sided) and $p_{\beta}=0.2$ (one-sided).

C.4.2. Data analysis. The proportion of index patients who have recurrent infection, the proportion of index patients who require medical attention for their infection, and the proportion of households with any SSTI will be compared between the anti-bacterial and control groups by chi-square test. Differences with $p_{\alpha} \leq 0.05$ (two-sided) will be considered statistically significant.

D. Estimated Timeline for the Study.

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

- Initiation to 9 months: Hiring of CRO, identification of study sites, site initiation at each site. Estimated 15-20 sites.
- 9 months to 36 months: Enrollment and completion of 600 families (300/arm)
- 36 months to 48 months: Data checking and analysis, preparation of manuscript.

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Appendix B

Comments on
Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record

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Scientific Misstatements In The Proposed Rule

The Proposed Rule makes a number of statements that are not consistent with current scientific understanding in the fields of quantitative microbial risk assessment, and cross-contamination and handwash science.

- **Misunderstanding Microbial Dose Response**

> *FDA CDER states "Here, exposure-response data refers to the correlation between the amount of* S. flexneri *ingested and the severity of clinical disease (e.g., diarrhea) that results from that ingestion."*

In fact the terminology that is used in microbial risk assessment "dose response", not "exposure-response" and it is not the correlation between the amount of a pathogen ingested and the severity of disease, but rather the correlation between the number of pathogen cells ingested and the probability that an illness develops (*17*).

> *FDA CDER states that "[T]he bacterial exposure-response data for* S. flexneri *are based on a small number of control subjects in human feeding studies (Refs. 29 through 33)."*

We will refer to these data as a dose response data, as this is how they are referred to in the published literature. Essentially all published dose response data are based on a small number of subjects in human feeding studies. Quantitative microbial risk assessment, which includes dose response modeling is a well-established scientific field. FDA CFSAN (*6*), FDA CVM, FDA CBER (*5*), USDA FSIS (*15*), US EPA (*16*), Codex Alimentarius (*3*), the World Health Organization and the Food and Agriculture Organization of the United Nations (*8*, *9*), and the World Trade Organization (*18*) all either specifically endorse and use QMRA for food safety decision-making or endorse the risk assessment framework generally for decision making. Despite the limitation of such feeding studies, all these organizations have founds ways of overcoming these limitations, and using dose-response modeling in quantitative microbial risk assessment.

> *FDA CDER writes that "[T]he bacterial exposure-response data from feeding studies are not linear, which means that an increase in the bacterial dose does not necessarily correlate with an increase in the number of subjects who become ill."*

This shows a significant lack of understanding of the science of dose-response modeling. It's well known that dose response data from feeding studies are not linear (*17*). In the case of many pathogens, the preferred dose-response model (called a Beta Poisson model) is sigmoidal, with the probability of illness rising slowly at first with the increase in the dose as measured in the logarithm of the number of cells, typically expressed as colony forming units (CFU). After an inflection point the probability of illness rises faster with the change in log (CFU). After another inflection point, the probability of illness rises slowly again with increasing dose, as the probability of illness approaches 100%. Some dose-response relationships for some pathogens (e.g. *Listeria monocytogenes*) are best fit by an exponential model, where the probability of illness rises linearly with pathogen dose expressed in log (CFU). In either case, as dose rises probability of illness also rises. Because dose response models are not linear, the increase in risk does not change linearly with dose. It is true that at very high and very low doses, the risk changes less with changing log(CFU) dose, but the assumption in all cases is lowering dose lowers the probability of illness.

- **The Importance or Lack Thereof of Fingernails**

  FDA CDER also states "In addition, we believe this novel hand contamination method [talking about Fischler et al.] does not accurately reflect an antiseptic handwash's intended use because it ignores an important reservoir of bacteria on the hands (i.e., the area around and under the fingernails), which is evaluated when the whole hand contamination method is used."

While it might be true that this method ignores the area under the fingernails, essentially all major published hand contamination and recovery methods (fingerpad, glove juice or European Standard EN 1500 based methods) do the same. While the area under the fingernails might be a reservoir for bacteria, it's not clear that reservoir is relevant in the cross-contamination of food.

- **Melon ball model**

  FDA CDER states "Further, although the study authors report that the transfer of bacteria to melon balls decreased with use of a consumer antiseptic handwash, it is not clear what factors other than the antiseptic may influence bacterial transfer from skin to ready-to-eat foods such as melon. Therefore, the results of this study do not demonstrate the effectiveness of the consumer antiseptic handwash used in this study because of the novel and unvalidated methodology."

Although the science of bacterial transfer from skin to food or between surfaces is relatively young, quantitative experiments of this nature have been going on for almost 15 years (*2*). Numerous examples can be found in the peer-reviewed literature where researchers quantified from skin to ready-to-eat foods, or vice versa, or from not ready-to-eat foods like meat to skin and other surfaces. The data reported by Fischler et al. (*7*) and others (*10*) using the melon ball protocol, are consistent with many other published reports found in the literature.

Introduction to Quantitative Microbial Risk Assessment

Quantitative microbial risk assessment can be used in complex problem solving and decision-making. It is being used increasingly to help solve microbial safety problems and better understand the complex interactions of pathogens, transmission vehicles, and human hosts.

The Strengths of Quantitative Microbial Risk Assessment

Risk assessment is an important tool to inform risk managers about hazards, health risks, and technical control options. Microbial risk assessment links the presence of pathogens to public health outcomes, which facilitates regulatory and business decision making with regard to disease control. The mathematical models associated with a microbial risk assessment can be used to determine the equivalence of different systems. A risk model could, for example be used to demonstrate that two different processes or technologies, yield the same level of disease control and public health protection when applied in a given circumstance. Whereas sporadic and epidemic diseases can be described epidemiologically, microbial risk assessment combines epidemiological data and inferences with data and assumptions from other information sources in a rigorous, clear manner to describe more fully the microbial hazard and the possible impact of risk control measures

The presence of identifiable, diagnosable ill persons whose illnesses can be attributed epidemiologically to given exposures creates information that can be used to characterize and quantify microbial disease risks. The exact nature of human microbial hazard exposures, however, is uncontrolled and difficult or impossible to quantify and characterize because of poor or incomplete information. At a basic level, microbial risk assessment models integrate exposure data with dose-response data for specific pathogens to characterize risk by predicting numbers of illnesses. This can be done even in the absence of human health statistics.

Risk models are more useful and credible if derived from real world data, but when such data are not available, risk assessment can still be used to estimate the impact of various public health interventions in a transparent manner. Once a risk model is developed, risk assessors and risk managers can modify assumptions and determine the effect on risk. Because quantitative microbial risk assessment lays out existing data and assumptions in a structured and clear manner, data gaps can be identified and surrogate data, default assumptions, and expert estimates can all be questioned and explored.

Although the microbial risk assessments conducted to date have focused on single pathogens, risk assessment techniques also can be applied to the comparison and ranking of risks associated with multiple microbial hazards for the purpose of setting research or intervention priorities (*11*).

Quantitative Microbial Risk Assessment as Used for Policy

The nucleus of modern thinking about risk assessment in the US can be traced to the 1983 publication by the National Academy of Science's National Research Council (NAS–NRC) entitled “Risk Assessment in the Federal Government: Managing the Process” (*12*). The recommendations contained in this document have generally been adopted by many agencies and

organizations around the world. The United Nations (UN) Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Consultation on the Application of Risk Analysis to Food Standards Issues (*4*) recommended adapting this process for food safety issues.

Risk assessment has been used to assist the development of food safety policy. It was prominently featured in the Uruguay Round of talks to develop policies for what was to become the World Trade Organization (WTO) in 1995. In particular, the Agreement on Sanitary and Phytosanitary Measures (SPS Agreement) establishes the rules under which WTO members will operate with respect to food safety (*18*). This means risk assessment is used to evaluate the effectiveness of control measures used in food hygiene standards. The use of risk assessment is required by international trade agreements.

The first quantitative microbial risk assessment in support of a US regulatory initiative was the *Salmonella enteritidis* risk assessment for shell eggs and egg products completed in 1998 (*1*) and updated in 2005 (*14*). Dozens of others quantitative microbial risk assessments addressing different hazards and commodities have been completed by national governments, international intergovernmental organizations, and professional and/or trade associations.

QMRA for Antibacterial Hand Hygiene Products on Risk of Shigellosis

In light of the importance of QMRA in setting food safety policy the American Cleaning Institute and the Personal Care Products Council commissioned research to assess the effect of such products on the risk of shigellosis. That research was published in 2014 in the Journal of Food Protection (*13*).

In brief, this research used new laboratory data, together with simulation techniques, to compare the ability of nonantibacterial and antibacterial products to reduce shigellosis risk. The laboratory portion of the study used 163 subjects and compared five different hand treatments: two nonantibacterial products and three antibacterial products, i.e., 0.46% triclosan, 4% chlorhexidine gluconate, or 62% ethyl alcohol. Data were collected on the effectiveness of the five treatments on reducing *Shigella* concentration on hands, as well as subsequent transfer from hands to melon balls. All three antibacterial treatments resulted in statistically significantly lower concentration on the melon balls relative to the nonantibacterial treatments. These data were used as inputs to a QMRA simulating an event in which 100 people would be exposed to *Shigella* from melon balls that had been handled by food workers with *Shigella* on their hands. A simulation that assumed 1 million *Shigella* bacteria on the hands and the use of a nonantibacterial treatment predicted that 50 to 60 cases of shigellosis would result (of 100 exposed). Each of the antibacterial treatments was predicted to result in an appreciable number of simulations for which the number of illness cases would be 0, with the most common number of illness cases being 5 (of 100 exposed). These effects maintained statistical significance from 1 million *Shigella* per hand down to as low as 100 *Shigella* per hand, with some evidence to support lower levels. This quantitative microbial risk assessment shows that antibacterial hand treatments can significantly reduce *Shigella* risk.

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Appendix C

ANTISEPTIC PRODUCTS AND ANTIBIOTIC RESISTANCE

Comments relative to Proposed Rule, Federal Register/Vol. 78, No. 242, December 17, 2013, DHHS, FDA, 21 CFR Parts 310 and 333, Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use.

Eugene C. Cole, PhD

The Proposed Rule is looking to "…establish conditions under which OTC consumer antiseptic products intended for use with water (referred to throughout as consumer antiseptic washes) are generally recognized as safe and effective. The agency is also "…proposing that all consumer antiseptic wash active ingredients have data that demonstrate a clinical benefit from the use of these consumer antiseptic wash products compared to non-antibacterial soap and water". The FDA has also expressed "…concerns about the impact of widespread antiseptic use on the development of antimicrobial resistance".

From a public health perspective, the need for effective topical OTC antimicrobial drug products in the U.S., as part of an overall public health risk reduction/hygiene promotion approach, makes sense amidst an increasing population at risk from burgeoning foodborne disease outbreaks, emerging infectious disease agents, infection transmission among susceptible risk groups (children, elderly, the immunosuppressed), and the realization that the home remains the largest health care environment, as well as the primary location where disease transmission is most likely to occur.

While some urge the FDA to curb the consumer use of antimicrobial consumer wash products to lower the risk for development of antibiotic resistance, the fact remains that the relationship between the public's use of such products and the current antibiotic resistance crisis remains very weak. While some in-vitro lab studies have been successful in forcing the expression of resistance in some bacteria to wash product actives, real world data from community studies using actual product formulations, although also few in number, show no correlation between the use of such products and antibiotic resistance (Aiello et al, 2004; Cole et al, 2003; Cole et al, 2011; Weber and Rutala, 2006). The fact remains that there is no conclusive evidence that the use of antimicrobial antiseptic products such as hand soaps and body washes for example, is in any way related to the antibiotic resistance crisis currently facing the U.S. Here is where a cooperative effort between stakeholders and FDA to develop a consensus protocol for continued community monitoring is an essential and key approach to addressing the issue. This would be a very prudent approach, as opposed to one that advocates eliminating antiseptic products based on their detection in the environment and their laboratory-generated "potential" to contribute to antimicrobial resistance. The latter approach could be tantamount to discarding the baby with the bathwater, relative to seeking credible, multi-faceted public health approaches to curbing infectious disease transmission, as well as limiting the recognized increase in antibiotic resistance.

Laboratory Data and Mechanisms of Action

In the Proposed Rule, the FDA cites 12 published studies as "ample evidence" of bacterial resistance mechanisms that "could" select for antiseptic or antibiotic resistance in the natural

setting. This position is based upon the Agency's view, as also stated in the Rule, that those studies "demonstrate the development of reduced susceptibility to antiseptic active ingredients and some antibiotics after growth in nonlethal amounts of the antiseptic." An emphasis however on educating the public on how to properly use antiseptic products to effect proper inactivation of bacterial agents at optimum lethal concentrations must also be considered.

The majority of studies investigating antiseptic modes of action at the cellular level have predominantly focused on the activity of triclosan and whether induced resistance to triclosan should be considered a precursor to antibiotic resistance. We know that mechanisms of resistance vary from organism to organism, and they typically involve one or more, such as alteration of the drug target in the bacterial cell, enzymatic modification or destruction of the drug itself, limitation of drug accumulation as a result of drug exclusion or active drug reflux, or mutation frequency (Poole, 2002; Randall et al, 2004; Birosova and Mikulasova, 2009; Russell, 2004). And while triclosan resistance from laboratory studies may be associated with changes in antibiotic susceptibility, comprehensive environmental surveys have not demonstrated any association between triclosan usage and antibiotic resistance (Russell, 2004). This again speaks to the fact that while triclosan "could" potentially in the future be directly linked with resistance to an antibiotic in the natural environment, the most rational approach toward detection of such an occurrence, should it occur, is by community monitoring of households that use products containing triclosan (or other actives) compared to those households that do not.

In consideration of laboratory study data showing a potential for antibacterial agents to induce organism resistance to those agents in association with changes in antibiotic susceptibility, is the publication of a definitive review of the literature to determine whether or not a link exists between the use of germicides (antiseptics and disinfectants) and bacterial resistance to antibiotics (Weber and Rutala, 2006). Of particular note, the authors addressed laboratory studies that showed development of bacterial mutants with reduced susceptibility to antiseptics and disinfectants. The authors raised key points, such as the antibiotic resistance described was not clinically relevant because the test organism was rarely a human pathogen, the altered level of antimicrobial susceptibility was within achievable serum levels for the antibiotic, or the antibiotic tested was not clinically used to treat the study pathogen. In consideration of the need for appropriate hygiene practices in the home or healthcare environment, and recognizing that biocides such as antiseptics and disinfectants can be effectively used at optimum kill concentrations to reduce human infections, the authors address the essence of the antibiotic resistance issue as they state: "By reducing infection in these settings, we will reduce the need for antibiotic therapy and hence, the main selective pressure for the development of antibiotic-resistant pathogens."

Clinical Dental Studies

Multiple clinical studies of antibacterial consumer dental products have shown a lack of evidence of developed resistance to actives such as triclosan, while showing tremendous clinical benefit. In a study investigating whether long-term continuous exposure to triclosan in toothpaste selects for triclosan-resistant bacteria within oral biofilm, dental plaque samples were collected from 40 cardiovascular and periodontal participants during year 5 of a randomized controlled trial involving 438 persons (Cullinan et al., 2014). Results showed that the triclosan MICs of bacterial isolates from both intervention and control groups were similar, indicating "that long-term use of triclosan toothpaste over the 5-year period did not lead to an increase in the MIC of bacterial isolates from dental plaque." Such findings are reflective of a comprehensive review of

previous clinical studies of oral microflora that demonstrate "the clinical benefits of hygiene adjuncts such as triclosan and triclosan/copolymer in oral care products where these compensate for deficiencies in mechanical hygiene (brushing and flossing)" (Gilbert et al, 2007). Based upon their intensive review of the clinical dental literature, the authors definitively conclude that "the clinical effectiveness of oral hygiene formulations containing triclosan, including their role in the prophylaxis and treatment of common oral maladies, is unquestionable, and the risk of resistance development following from triclosan use is overstated and does not justify its removal from oral hygiene products."

Comprehensive Home Environment Studies

While the proposed Rule categorizes 12 papers providing laboratory data on the development of reduced susceptibility to antiseptic actives and some antibiotics as "ample evidence," it goes on to say that data generated from studies of potential resistance in the "natural setting" are "very limited in scope." While there are almost as many papers studying antibiotic resistance related to antibacterial product use in the natural setting, as opposed to those studies conducted in the laboratory, the bulk of those home studies were designed and conducted to be very comprehensive. One of the first of those – and one not referenced in the Proposed Rule - took the bulk of an entire year to conduct across two locations in the US and one in the UK, as target environmental and clinical bacteria were isolated from the homes of antibacterial product users and nonusers and tested for antibiotic and antibacterial agent susceptibility (Cole et al, 2003). A total of 180 homes were utilized, having been randomly selected from those households that met inclusion criteria as either antibacterial product users or non-antibacterial product users. Target bacteria included *Staphylococcus* sp., *Staphylococcus aureus*, *Enterococcus* sp., *Pseudomonas* sp., *Acinetobacter* sp., and *E. coli* and other *Enterobacteriaeceae*. Isolates (n = 1238) were tested for antibiotic susceptibility and also for susceptibility to four commonly used antibacterial agents (triclosan, PCMX, Pine oil, and a quaternary ammonium product). Data analysis focused particularly on cross-resistance – i.e., whether the most antibiotic resistant isolates were also highly resistant to the biocidal agents and vice-versa. Results showed no evidence of cross-resistance and that susceptibility/resistance patterns were comparable between user and nonuser homes across the spectrum of gram-positive and gram-negative organisms.

Another comprehensive and long-term study was carried out for one year in 224 households, half of which were randomly assigned non-bacterial household products, including liquid soap for hand washing, while the other households used a similar soap product containing 0.2% triclosan (Aiello et al. 2004). Hand cultures were obtained from the primary caregiver in each household at the start of the study and after one year. A total of 628 bacterial isolates were examined for triclosan MICs and susceptibilities to selected antibiotics. Data analysis showed no statistically significant association between elevated triclosan MICs and reduced antibiotic susceptibility. Certainly this study can't be categorized as "very limited", since 224 households were followed for an entire year, and in many ways this is analogous to an actual clinical trial of a pharmaceutical drug wherein 200 to 400 patients are enrolled and followed for a year.

A more recent study investigating antibiotic and antibacterial susceptibility in staphylococci from the skin of users and nonusers of antibacterial wash products used 210 participants comprising three groups of 70: 1) those that frequently used wash products containing triclosan, 2) those that frequently used products containing triclocarban, and 3) a control group that used no antibacterial wash products (Cole et al, 2011). Results showed no statistically significant difference in antibiotic resistance in *Staphylococcus* isolates from regular antibacterial wash

product users compared with nonusers for both triclosan and triclocarban. Supporting those results are data from a snapshot study of 38 households in Boston and Cincinnati where a variety of antibacterial household and personal care products were used, and 13 kitchen and bathroom sites were sampled for total aerobic bacteria and screened for susceptibility to six antibiotic drug families. The study concluded that "no significant differences were noted between biocide users and non-users" (Marshall et al, 2012).

Assessment of Natural Microbial Populations

Of tremendous importance in assessing the relationship between commonly used antibacterial agents and the development of subsequent resistance to them across a variety of bacterial organisms, is a very recently published study looking at natural populations of human pathogenic bacteria and resistance to triclosan, chlorhexidine, and benzalkonium chloride (Morissey et al, 2014). This study, supported by the European Community FP7 Project aimed at evaluation of the impact of biocide use on the generation of antibiotic resistance, looked at minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) distributions across 3,319 clinical isolates from "different geographical origins (world-wide), representing both hospital and community acquired infections." Pathogens included *Salmonella* species, *Escherichia coli, Klebsiella pneumonia, Enterococcus faecium, Enterococcus faecalis, Enterobacter* species, and *Candida albicans*. Study results showed that "resistance to biocides and, hence any potential association with antibiotic resistance, is uncommon in natural populations of clinically relevant microorganisms."

Conclusion

In summary, while the FDA Proposed Rule claims "ample evidence" of bacterial resistance mechanisms that "could" select for antiseptic or antibiotic resistance in the natural setting, a preponderance of evidence from a variety of both clinical and home studies reflective of the global microcosm, concludes that the development of antiseptic and antibiotic resistance, and the relationship between the two, relative to the use of antiseptic agents and consumer products, is not occurring in the natural setting.

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Appendix D

Development of Comments on the Regulatory Impact Analysis for the FDA Proposed Rule—*Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph* (Draft)

Executive Summary

The Food and Drug Administration failed to meet the requirements of Executive Orders (EO) and statutes in preparing a regulatory impact analysis and regulatory alternatives to the propose rule for Topical Antimicrobial Drug Products for Over-the-Counter Human Use.

- FDA failed to assess *all* costs and benefits of available regulatory alternatives associated with the Proposed Rule as required by EO 12866 and EO 13563.
    - FDA did not assess the regulatory costs to institutional suppliers of antibacterial soap products or their customers
    - FDA failed to assess the cost of the regulation associated with additional illnesses due to the lack of availability or diminished use of antibacterial hand soap products
- FDA incorrectly calculated and overestimated the benefits associated with the Proposed Rule.
    - No scientific studies have been found to show a statistically significant relationship between the active ingredients considered in the Proposed Rule and potential adverse health effects on consumers
- FDA failed to protect or improve the health and safety of the public, and to maximize net benefits associated with the Proposed Rule as required by EO 12866 and EO 13563.

FDA should take the following actions in revising the Proposed Rule:

- Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE) determinations should be made for an individual active ingredient based on availability of data, not on the arbitrary timeline of the Consent Order for triclosan.
- In order to maximize net benefits of the Proposed Rule, an alternative timeline for the finalization of the monograph should be developed to allow for the development of safety and efficacy data so that the public can continue to enjoy the benefits of reduced infections conferred by antibacterial handwash products.
- Given the lack of benefit quantified for the Proposed Rule, alternative regulatory options should be developed and adopted. In particular, the rule should have an

extended period of compliance in order to mitigate impacts to small businesses including institutional suppliers and to their customers.

1 Extent to which the Agency's Preliminary Regulatory Impact Analysis Meets the Requirements of the Relevant Executive Orders and Statutes

Executive Order (EO) 12866,[146] "Regulatory Planning and Review," issued in 1993, marked the beginning of the government program to reform and streamline the regulatory process. The EO provided the following main requirements related to the RIA:

1. Federal agencies should promulgate regulations that are required by law or are made necessary by public needs such as material failure of private markets to protect or improve the health and safety of the public and the environment.
2. Agencies should assess all costs and benefits of available regulatory alternatives, including the alternative of not regulating.
3. Costs and benefits should include both quantifiable and qualitative measures.
4. When choosing among regulatory alternatives, agencies should select those approaches that maximize net benefits.

The preliminary regulatory impact analysis (RIA) prepared by FDA for the OTC Consumer Antiseptic Proposed Rule estimates and reports costs and benefits associated with the proposed changes either quantitatively or qualitatively, as defined in (3) above, depending on the data availability. However, we found a certain category of benefits to be omitted from the analysis of all costs and benefits (see Task 4 for the detailed discussion), as defined in (2) above. Also, benefits reported in the RIA are not substantiated, because data are lacking that would show the relationship between active ingredients and adverse health effects, invalidating parts of the net benefits calculation required in (4).

Additionally, an alternative of not regulating (i.e., No Action), is required by the EO but is not discussed or analyzed in the RIA. This issue is discussed in more detail in the following section in which guidelines from OMB's Circular A-4 are analyzed. Also, when choosing among regulatory alternatives presented in the RIA, it was not possible to evaluate different alternatives based on net benefits, because the benefits presented in the RIA are presented in pounds of active ingredient and not dollars. By contrast, a properly-conducted RIA would estimate both benefits and costs in dollars, as defined in the EO, which allows the estimation of net benefits as a difference of total costs and total benefits resulting from the rule.

1.1 Executive Order 13563

Executive Order 13563,[147] "Improving Regulation and Regulatory Review," was issued in 2011 to improve regulation and regulatory review. The EO emphasizes the use of the best available

[146] Available at: http://www.archives.gov/federal-register/executive-orders/pdf/12866.pdf

techniques to quantify anticipated present and future benefits and costs as accurately as possible. The EO also stresses the need to assess all costs and benefits (both quantitative and qualitative) of available regulatory alternatives. The regulatory impacts may include and discuss qualitatively, where appropriate and permitted by law, values that are difficult to quantify, including equity, human dignity, fairness, and distributional impacts. The EO also promotes flexibility of regulatory approaches that could include warnings, appropriate default rules, and disclosure requirements. Because the general requirements of EO 13563 closely follow the requirements of EO 12866, this RIA for the Proposed Rule meets the requirements of EO13563 to the extent that it meets the requirements of EO 12866 as described above.

1.2 Regulatory Flexibility Act of 1980

Requirements of the Regulatory Flexibility Act of 1980 (Title 5 of the United States Code, sections 601–612),[148] as amended in 1996 and 2010, requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities consistent with statutory objectives.

The Regulatory Flexibility Analysis of the RIA assessed the potential impact on small entities and concluded that the Proposed Rule, if finalized, would have a significant economic impact on a substantial number of small entities. Therefore, the RIA follows the requirements of the Regulatory Flexibility Act.

1.3 Unfunded Mandates Reform Act of 1995

Section 202(a) of the Unfunded Mandates Reform Act of 1995[149] requires a written statement assessing anticipated costs and benefits that may result in the expenditure of $100,000,000 annually (adjusted annually for inflation). The current threshold after adjustment for inflation is $156 million, using the appropriate (2013) Producer Price Index, given the date of the Proposed Rule (December 2013). This numeric threshold ($156 million for 2013) defines whether a rule is considered to have a significant impact on affected entities. In this RIA, FDA has determined that this Proposed Rule is significant under the Unfunded Mandates Reform Act and presented the cost-benefit analysis in corresponding sections.

1.4 Comments and Recommendations

1.4.1 Consider Additional Regulatory Alternatives (in Addition to Compliance Extension for all Companies)

Only one regulatory action is considered in the Proposed Rule, and no alternative regulatory options are presented. Regulatory Impact Analyses for FDA regulatory actions are subject to

[147] Available at: http://www.gpo.gov/fdsys/pkg/FR-2011-01-21/pdf/2011-1385.pdf

[148] Available at: http://www.sba.gov/content/rfa-overview-0

[149] Available at: http://www.gpo.gov/fdsys/pkg/PLAW-104publ4/pdf/PLAW-104publ4.pdf

requirements of EO 12866. Circular A-4, Office of Management and Budget's (OMB's) guidance to federal agencies on the development of regulatory analysis as required under Section 6(a)(3)(c) of Executive Order 12866,[150] presents guidelines for regulatory agencies by defining good regulatory analysis and standardizing the way benefits and costs of federal regulatory actions are measured and reported. A number of regulatory alternatives are typically considered for proposed federal rules, to examine a range of potential impacts on the affected facilities and the public. Circular A-4 guidelines provide the following regarding alternative regulatory actions:

> *"A good regulatory analysis is designed to inform the public and other parts of the Government (as well as the agency conducting the analysis) of the effects of alternative actions."*
>
> *"A good regulatory analysis should include the following three basic elements: (1) a statement of the need for the proposed action, (2) an examination of alternative approaches, and (3) an evaluation of the benefits and costs—quantitative and qualitative—of the proposed action and the main alternatives identified by the analysis."*
>
> *"Benefits and costs are defined in comparison with a clearly stated alternative. This normally will be a "no action" baseline: what the world will be like if the proposed rule is not adopted. Comparisons to a "next best" alternative are also especially useful.*
>
> *"With this information, you should be able to assess quantitatively the benefits and costs of the proposed rule and its alternatives."*
>
> *"You should present a summary of the benefit and cost estimates for each alternative."* (emphasis added).

1.4.2 Recommended Alternative Regulatory Options

A number of alternative regulatory actions could be developed for this Proposed Rule. The purpose of alternative regulatory actions is to provide different levels of stringency and/or timelines for various types of affected facilities. While the list of alternative actions varies across federal regulations, several alternative actions are commonly considered for proposed federal regulations according to OMB's Circular A-4. The following is a list of alternative regulatory actions recommended by Circular A-4 for consideration in the RIA.

Recommended alternative regulatory actions that are commonly considered and analyzed in the RIA include:

- No Action
- Differentiated Requirements.

[150] OMB, 2003. Available at: http://www.whitehouse.gov/sites/default/files/omb/assets/regulatory_matters_pdf/a-4.pdf

Under *No Action*, for every proposed regulation, a no-action scenario is usually considered to compare the alternative regulatory options and their associated costs and benefits.

Under *Differentiated Requirements*, two types of regulatory approaches could be developed:

- Different regulatory requirements for different active ingredients: this regulatory option would provide an exemption from the proposed regulatory requirements for certain active ingredients because of the severity of the economic impact related to regulating such ingredients. Because FDA has the ability to make Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE) determinations on an individual basis, the Proposed Rule could provide different requirements for different active ingredients. These differentiated requirements would reflect data availability for different ingredients and allow additional time to develop studies for those ingredients for which data are not readily available.

- Different compliance dates for different active ingredients: the RIA proposes a 12-month compliance period as a preferred regulatory option. In addition to the preferred option, it considers two additional regulatory options, one with a 6-month compliance period and one with an 18-month compliance period. Compliance dates apply equally to all active ingredients affected by the rule. However, some active ingredients may warrant different compliance dates. The basis for different compliance dates may be driven by different timelines that would reflect when the Agency receives commitment from stakeholders to conduct the required studies to show safety and effectiveness. It might take longer to develop an appropriate alternative for a certain active ingredient, requiring a longer compliance period. Therefore, ingredients for which stakeholders have data available to show safety and effectiveness may be given compliance dates that are different from those active ingredients for which additional data need to be developed. A total of two years from the time the rule goes into effect may be a reasonable amount of time to develop necessary studies for the active ingredients affected by the rule. Therefore, a two year compliance extension may be considered as an alternative to the proposed one-year extension.

- Another reason for requesting additional time to comply with the regulatory requirements is a potential effect of the rule on the "downstream" sectors, such as restaurants, hotels, and other establishments that handle food. A potential impact of this rule would be the additional time necessary to educate employees regarding the change in availability of hand washing products and potentially replacing the products. To estimate additional time for the compliance period, we recommend that the Agency conduct research to assess the appropriate amount of time necessary to educate employees regarding new hand hygiene practices.

1.4.3 Missing Cost Category

A certain category of costs was found to be omitted from the analysis of all costs and benefits, as defined in applicable EOs. Those potential costs would stem from treating additional illnesses currently prevented due to use of antibacterial products affected by the Proposed Rule. These potential costs need to be considered and quantified in the RIA for the Proposed Rule.

A description of potential costs avoided as a result of the use of anti-bacterial hand-washing products and a preliminary quantitative analysis is presented in Section 3 of these comments.

2 Costs and Benefits Presumed to Result from the Proposed Rule, and Assumptions Used to by FDA to Calculate the Costs and Benefits

The evaluation of costs and benefits, as well as the assumptions used to develop cost and benefit estimates, are closely related. Therefore, we present our evaluation of both components in one section.

We reviewed the analysis of costs and benefits conducted by the FDA for this Proposed Rule. Our analysis focused on evaluating the economic approach and assumptions used and verifying the estimates presented in the RIA. During our review, we also looked at references and related materials for this economic analysis. As a result of our review, we identified several items in relation to estimated costs and benefits that were not addressed in the RIA. We also developed alternative estimates for key components of the analysis. Alternative estimates are based on the data that were obtained from other sources, or a combination of estimates provided in the RIA and independently obtained figures.

Key assumptions and estimates are evaluated and commented on. Table 1 presents a summary of the key assumptions and estimates reviewed.

Table 1. Summary of the key assumptions and estimates reviewed

Assumption/ Estimate	Finding
Potential Additional Costs Omitted	Costs associated with avoided illnesses as a result of using anti-bacterial hand-washing products are not accounted for.
Adjustment Factor to Account for Non-representation in the Nielsen data	The FDA's use of the adjustment factor for dietary supplements, instead of the factor for OTC products, results in over-estimation of the key cost and benefit components by a factor of 2.2.
Estimate for Total Sales	The adjustment factor for OTC products is more appropriate than that for dietary supplements. The FDA approach results in over-estimation of total sales. Institutional sales omitted: Institutional sales are estimated to account for 29%–92% of anti-bacterial retail soap sales. The FDA approach results in under-estimation of the total anti-bacterial soap market by 29%–92%. The use of the adjustment factor for dietary supplements, instead of the factor for OTC products, results in over-estimation of the total number of affected products by a factor of 2.2.
Estimate for the Number of Affected Products or Universal	Alternative industry estimates show the total number of products at 1,483. The estimate for the number of UPCs reported in the RIA is 2,247 (1.5 times higher).

Product Codes (UPCs)	
	Using the adjustments factor of 1.4 (OTCs-specific), the total benefits are estimated at 447,062-1,538,259 pounds (average is 992,660 pounds). The adjustment factor used in the RIA results in an over-estimation of benefits by a factor of 2.2.
FDA Estimate for Total Pounds of Active Ingredient—Claimed Benefits	The estimated total pounds using the reported market data is approximately 682,352 pounds per year (2011). The average estimate for the total pounds reported in the RIA is 3.2 times higher than the industry estimate. However, accounting for institutional sales would increase the total volume of active ingredients affected by the rule. The net effect of potential changes on the estimated pounds of active ingredients would be two-fold: 1) decreasing the total volume by using alternative estimates for retail sales, and 2) increasing the total volume by accounting for institutional sales.
Estimate for Relabeling Costs	The estimated total cost of relabeling calculated using a unit cost provided by a member is three times higher than the average estimate in the RIA ($182 million/ $60.7 million = 3 times).
Estimate for Reformulation Costs	The total reformulation costs are estimated at $52 million to $1 billion using the FDA range for the percentage of companies that would need to reformulate their product (25%–100%) and the full range of unit reformulation costs from the RIA. The resulting upper bound is significantly higher than FDA's estimate ($70.2 to $280.6 million).

2.1 Potential Additional Costs Omitted

Potential additional costs associated with the Proposed Rule are the costs that may arise from currently avoided illnesses as a result of using anti-bacterial hand-washing products. These potential increased costs resulting from treating those illnesses if the antibacterial products considered in this rule were not available are not acknowledged or quantified in the RIA. A description of potential costs avoided as a result of use of anti-bacterial hand washing products, and a preliminary quantitative analysis, are presented in Section 4 of this report.

2.2 FDA Estimated Adjustment Factor to Account for Non-Representation in the Nielsen Data

The RIA states that affected products likely exist that we were unable to identify as antibacterial, and affected products not captured in the A.C. Nielsen data, such as sales from warehouses, the Internet, and other specialty outlets. "To account for underrepresentation as recommended and adopted in the RTI Labeling Cost Model Report for this product category, we apply an adjustment factor of 3.1 to the raw UPC counts, formulas, annual unit sales, and annual dollar sales to obtain estimates representing the entire market of affected products (Ref. R3). The adjustment factor is based on the assumption that consumer antibacterial soaps are sold in a similar range of outlets and retailers as dietary supplements, for which sales represented by A.C. Nielsen was estimated as 32.5 percent of total sales from all sources. The dietary supplement adjustment factor provides a reasonable approximation because our adjusted estimates of sales are similar in order of magnitude to industry estimates (Refs. R25 and R26). Given that there is uncertainty in estimating the size of the consumer antibacterial soap market, we invite comment supported by data on this assumption."

2.2.1 Comment

The adjustment factor of 3.1 was used to adjust the number of products from the Nielsen database, to estimate the total number of affected products. The adjustment factor is based on the report, "Model to Estimate Costs of Using Labeling as a Risk Reduction Strategy for Consumer Products Regulated by the Food and Drug Administration" by RTI (2002). The adjustment factor of 3.1 used in the RIA is for dietary supplements. The adjustment factor for over-the-counter products (OTCs) is 1.4, as reported in the same table of adjustment factors (Table 4-4 of the RTI document). According to the definition, hand and body washes that are analyzed in the RIA report fall into the OTC category, "had cleaners and hand sanitizers" (Table 4-12, Table C-1). The table reporting the adjustment factor is developed specifically for using Nielsen data (Table 4-4 "Adjustments to UPCs, Formulas, and Sales Units to Account for Nonrepresentation in the Nielsen ScanTrack Data"); therefore, the same product category (OTCs) should be used when obtaining data on both the number of products and the adjustment factor. The factor developed specifically for OTC products is the more appropriate factor for this analysis. Therefore, the result of using the higher factor (3.1 instead of 1.4) is an overestimation of the total number of affected products by a factor of 2.2 (3.1/1.4).

2.3 Estimate for Total Sales

The total sales reported in the RIA are $566 million for liquid soap and $320 million for bar soap, totaling $886 million annually (2009).

2.3.1 Comment 1: Adjustment Factor

A reference used in the RIA (R26) refers to an article citing the sales data for liquid and bar soap for 2001—$960 million for liquid soap sales, and $1.3 billion for bar soaps—that combined total to $2.26 billion. This estimate, adjusted for growth between 2001 and 2014, would result in a larger number. The RIA reports that the adjustment factor for dietary supplements is chosen because it provides the adjusted sales estimates comparable to industry estimates (Refs. R25 and 26) and not because the dietary supplements category is more appropriate for any particular reason. The total sales reported in the RIA are $566 million for liquid soap and $320 million for bar soap, totaling to $886 million (using the adjustments factor for dietary supplements—see a detailed discussion above). Using the adjustment factor for OTCs (1.4), the total sales would be estimated at $400 million total, less than half of that estimated in the RIA.

2.3.2 Comment 2: Referenced Data

We checked the data references in the RIA. Reference 25 refers to the comment by Dial Corporation from 1995 in response to the 1994 TFM (Comment No. C14 in Docket No. 1975N-0183H)[151] that reports the total sales of approximately $1 billion. On page 59, it provides the following:

> *"It is estimated that the total size of the antimicrobial handwash and bodywash category is approximately $1 billion. Further, it is estimated that this segment has attained an average growth rate of approximately 8 percent in the last five years. This growth is*

[151] Available at: http://www.regulations.gov/#!searchResults;rpp=25;po=0;s=1975N-0183H;dct=PS%252BN

attributed to actual market expansion (i.e., increased frequency of hand washing), and not merely replacement of non-antimicrobial product sales. This expansion demonstrates a significant change in hand-washing practices, as consumers have come to value the specific and important benefit these products provide.

Based on consumer use patterns, it has been conservatively estimated that a loss of the antimicrobial wash category would result in a 10 to 15 percent decline in the consumption of all soap products (i.e., these sales would not be redistributed among non-antimicrobial soaps). This represents a permanent $300-$450 million loss per year in sales to manufacturers of antimicrobial products. The Dial Corp's share of that loss could easily amount to $100 to $165 million."

2.3.3 Comment 3: Omitted Institutional Sales

We provide an alternative estimate of the total sales of antibacterial soap in the U.S. using the Census data from 2011. Our assessment of the FDA's estimate for total sales shows that those estimates did not account for or consider a relatively large component of total sales that is attributed to institutional sales. Institutional sales represent other than household use and include sales to commercial, industrial, and institutional organizations such as restaurants, fast-food chains, hotels, and other establishments.

Below we estimate the total sales of anti-bacterial soap, including the amount of institutional sales. Table 2 presents the sales data by product category using Census 2011.

Table 2. Retail and institutional sales

Product Category	Total Sales ($ Billion)
Soaps and detergents—commercial, industrial, and institutional	11.9
Household detergents	8.8
Soaps, excluding specialty cleaners, household	4.2
Soap and other detergent manufacturing, not elsewhere classified, total	2.4
Glycerin, natural	0.4
Toothpaste, including gels and tooth powder	1.1
TOTAL	28.8

Source: Census, 2011

Using the Census data, institutional sales (commercial, industrial, and institutional) accounted for $11.9 billion, while household sales accounted for $13.0 billion in 2011. Assuming the same proportion of soap to detergent for institutional sales as that for household sales (4.2 to 8.8), the total sales of institutional soap is $3.84 billion. Using the ratio of bar to liquid soap (3 to 2) and the corresponding percentages of antibacterial product within each category (14.5% for bar soap and 38% for liquid hand soap), the total antibacterial institutional sales are estimated at $0.9 billion in 2011. Of that total, 20% is for the healthcare market which is not the subject of the Proposed Rule. Therefore, total antibacterial institutional sales which are the subject of this Proposed Rule are estimated at $0.72 billion in 2011. The resulting fraction of antibacterial soap is estimated at 17% ($0.9/$4.2 billion = 17%). In addition, we received estimates from two

member companies indicating a total institutional market for hand soap of $1.2 billion per year. Applying the same percentage (17%) to that estimate, we estimate the lower bound for total *antibacterial* institutional hand soap sales at $0.21 billion.

Therefore, the range for antibacterial institutional sales which are the subject of this Proposed Rule is estimated at $0.21–$0.72 billion. The range for total institutional sales is estimated at $1.2–$3.8 billion.

Total sales of retail antibacterial soap are estimated at $1 billion using the Census data and the assumptions presented above. Therefore, institutional antibacterial soaps represent 21%–72% of anti-bacterial retail soaps in sales ($0.21–$0.72 billion of $1 billion). The lower-bound estimate is based on the input from the member company, and the upper bound is based on Census data.

Therefore, a large fraction of total sales (up to 50% of the total) is omitted from the FDA analysis. Accounting for institutional sales, the total sales are estimated at $1.21–$1.72 billion per year (2011) instead of $886 million (2009) annually.

2.4 Estimate for the Number of Affected Products or Universal Product Codes (UPCs)

To determine the number of affected products in the current market for OTC consumer antiseptic hand and body washes, data from A.C. Nielsen were used in the RIA, which provides nationally representative sales information from drugstores, supermarkets, and mass merchandisers (excluding Walmart). The RIA estimated the total number of affected UPCs at 2,200.

2.4.1 Comment 1: Verification of FDA Estimate

The estimates for the number of UPCs and total sales of those products come from a proprietary database by the global marketing research firm, Nielsen (http://www.nielsen.com/us/en/reports.html). The estimates developed in the RIA were not verified due to the proprietary nature of the data source.

2.4.2 Comment 2: The Adjustment Factor

The number of UPCs is critical to estimating the cost and benefits of the Proposed Rule. It drives the following key estimates: 1) presumed benefits of reduced exposure, and 2) costs of compliance with the rule that are calculated as a sum of relabeling and reformulation costs (calculated as the number of UPCs adjusted for the percentage of unique formulations multiplied by unit costs of relabeling and reformulating).

This adjustment factor has a significant impact on the estimate for the number of UPCs affected by the rule. The number of UPCs reported by the Nielsen data is 725, which was adjusted by a factor of 3.1 (factor for dietary supplement), which resulted in the total estimate of 2,200 reported in the RIA (725*3.1=2,247). The estimated number of UPCs drives the estimated relabeling and reformulation costs. Therefore, the relabeling and reformulation costs are over-estimated by a factor of 2.2 as a result of using this adjustment factor.

2.4.3 Comment 3: Alternative Estimate

The estimated number of products using the IRI data is 1,483 (Table 3). This alternative estimate is 34% lower than the estimate for the number of UPCs reported in the RIA (2,247), and 46% higher than the estimate using the OTC-specific adjustment factor of 1.4 (1,015).

Table 3. Total number of products and total pounds of active ingredient based on IRI data

Product Category	Number of Products	Market Volume (pounds)	Fraction Antibacterial	Active Ingredient	Split for Active Ingredients	Concentration	Total Pounds of Active Ingredient
Bar Soap	472	507,101,557	14.5%	Triclocarban	-	0.30%	220,589
Liquid Body Wash	726	524,488,063	2.5%	Triclosan	-	0.15%	19,668
Liquid Hand Soap	285	337,219,232	38.0%	Triclosan	75%	0.46%	442,094
				Benzalkonium chloride	25%	0.13%	41,647
TOTAL	1,483	1,368,808,852	-	-	-	-	682,352

Note: Institutional sales are not included.

2.4.4 Comment 4: Institutional Sales Not Included

The main discrepancy in the Agency's estimate for the number of UPCs comes from the omission of institutional sales. Based on our calculations above, total institutional antibacterial soaps represent 21%–72% of anti-bacterial retail soaps in sales ($0.21–$0.72 billion of $1 billion). Therefore, the total number of affected products might be up to 21%–72% higher than reported in the RIA.[152]

2.5 FDA Estimate for Total Pounds of Active Ingredient—Claimed Benefits

The estimate for the adjustment factor has a significant influence on the estimated benefits of the rule, as presented in the RIA. The benefits of the rule are expressed in pounds of active ingredient that would have been taken off the market and, arguably, would result in reduced exposure to the public. The adjustment factor is used to estimate the total benefits in pounds of active ingredient presented in the summary table (page 5) and tables E2, E4, E5, and E7. The total pounds of active ingredients estimated in the RIA range from 989,922 to 3,406,145 pounds per year (with an average of 2,198,033 pounds). Almost all of the estimated total pounds are attributed to triclosan and triclocarban (99.99%).

[152] This estimate is independent of the potential adjustment that would correct for the use of the more appropriate adjustment factors (OTC-specific).

2.5.1 Comment 1: Adjustment Factor

Using the more appropriate adjustments factor of 1.4 (OTCs-specific), the total benefits would be 447,062 to 1,538,259 pounds (average is 992,660 pounds). Therefore, the adjustment factor used in the RIA results in an over-estimation of benefits by a factor of 2.2.

2.5.2 Comment 2: Alternative Estimates

Market data on sales volume of hand and body soap in the United States, including antibacterial products, was provided by the ACI (2011 data). The source of data is a market research firm IRI.[153] The table below presents the number of products and volume (in pounds) by category: bar soap, liquid body wash, and liquid hand soap. Additional information on the fraction of antibacterial soap within each category and the concentration of active ingredients allows for the estimation of the total pounds of active ingredients for each category. The estimated total pounds using the reported market data is approximately 682,352 pounds per year (2011). This estimate is substantially lower than that estimated in the RIA. Using the 2011 estimate based on market data from IRI, the potential benefits as claimed in the RIA would be significantly lower. The average estimate for the total pounds reported in the RIA is 3.2 times higher than the industry estimate presented in Table 4 (2,198,033/682,352=3.2). Using the adjustment factor of 1.4 (OTCs-specific), the total pounds of active ingredients in the RIA would be 1.5 times higher than the industry estimate.

2.5.3 Comment 3: Institutional Sales

As discussed above, the FDA analysis does not include institutional sales. The analysis of total pounds of active ingredient attributed to retail sales discussed in Comments 1 and 2 above shows that FDA over-estimated the potential volume of active ingredients affected by the Proposed Rule. However, accounting for institutional sales would increase the total volume of active ingredients affected by the rule. As described above, a large fraction of total sales (up to 72%) of retail sales is omitted from the FDA analysis. Therefore, the net effect of potential changes on the estimated pounds of active ingredients would be in opposite directions: (1) decreasing the total volume estimate by using alternative estimates for retail sales, and (2) increasing the total volume estimate by accounting for institutional sales.

2.6 Estimate for Relabeling Costs

FDA assumptions regarding relabeling costs are as follows:

- The RIA estimates 1,954 unique formulations: implies that 89% of all UPCs (liquid and bar soaps) are unique formulations (1,954/2,200=89%).

- 91% of UPCs of liquid soaps and 70% of UPCs of bar soaps are unique formulations (source: TRI model). RTI report, "Model to Estimate Costs of Using Labeling as a Risk Reduction Strategy for Consumer Products Regulated by the Food and Drug Administration," from 2002 reports estimates for the number of products and number of UPCs for liquid and bar soap for 2008 (Table 4-3).

[153] http://www.iriworldwide.com/SolutionsandServices.aspx

- The RIA assumes that 100% of UPCs with unique formulations would have to re-label their product.
- Under a regulatory scenario with the compliance period of 12 months, the RIA assumes that label changes for approximately 6% of branded UPCs and 4% of private-label UPCs can be coordinated with planned changes. The remainder of UPCs (94% of branded UPCs and 96% of private-label UPCs) would have to incur additional costs associated with labeling as a result of this rule.

To estimate the costs of relabeling, the Agency used a model developed by its contractor, RTI International (RTI). For the majority of affected UPCs, the estimated uncoordinated relabeling costs per UPC were estimated between $18,695 and $39,738 for branded labels and between $22,030 and $44,875 for private labels. These per-UPC costs are then multiplied by the number of UPCs (over-estimation of these estimates is described above). Therefore, the unit estimates for the re-labeling costs have a direct impact on the total costs estimated for the rule.

2.6.1 Comment

One member company provided information regarding re-labeling of their products. Cost components and corresponding estimates are summarized in Table 4by product category. The total costs associated with relabeling are estimated between $137,600 and $142,700 depending on product category.

Table 4. Relabeling unit costs provided by a member company

Product	Label Artwork	Corrugate Artwork	Corrugate Tooling	Total
Hand wash	$34,572	$33,561	$69,495	$137,628
Hand soap	$59,219	$33,561	$69,495	$162,275
Body wash	$39,596	$33,561	$69,495	$142,652

The total cost associated with relabeling was calculated using the unit costs for relabeling provided by a member company, as presented in Table 4. It is important to note that the unit cost estimate represents one company's costs, and a result, may over-estimate or under- estimate the average cost for the industry, to the extent that this company is not representative of the average expense incurred in association with relabeling. The calculation steps include the following.

1. Calculate the total number of affected products by adjusting the total number of products (provided by the ACI based on IRI data) for the percentage of unique formulations (provided in the RIA based on the TRI model, p. 19).
2. Use the unit cost of relabeling provided by a member company as an average cost across all products. This may result in over-estimation or under-estimation of the average cost for the industry.
3. Calculate total relabeling costs by multiplying unit costs associated with relabeling with the total number of affected products.

Table 5. Estimated total relabeling costs using unit costs provided by a member company

Product	Number Products	% Unique formulations	Number of Affected Products	Unit Relabeling Costs	Total Relabeling Costs
Bar Soap	472	70%	330	$147,518*	$48,740,057
Liquid Body Wash	726	91%	661	$142,652	$94,244,470
Liquid Hand Soap	285	91%	259	$149,952**	$38,889,922
TOTAL	1,483	AVG=84%	1,250	-	$181,874,449

*Represents an average of relabeling costs for liquid handwash, liquid hand soap, and liquid body wash.

**Represents an average of relabeling costs for liquid handwash and liquid hand soap.

As presented in Table 5, the estimated total cost of relabeling is $182 million. The estimate reported in the RIA ranges from $42.1 to $88.1 million, with an average of $60.7 million. The estimated total cost of relabeling calculated using a unit cost provided by a member company resulted in the estimate that is three times higher than the average estimate in the RIA ($182 million / $60.7 million = 3 times).

2.7 Estimate for Reformulation Costs

FDA assumptions regarding reformulation costs included:

- Because many manufacturers already have non-antibacterial soap in their product lines, the Agency expects that the cost of removing the antiseptic active ingredient in hand and body washes to become antibacterial soap would be closer to the lower bound of the per-product reformulation range. However, reformulation would require resources to re-evaluate product lines, formula development, and process validation.
- The RIA assumes that 25%–100% of all unique formulations would need to be reformulated. The RIA states that estimates of the cost of reformulating may be overstated if manufacturers produce data consistent with the monograph changes in this Proposed Rule and do not need to reformulate. In such a scenario, the costs of producing the data would be incurred instead. The RIA requested comments and data specifically on these estimates.

The RIA used an estimate of $143,618 cost per product, resulting in the total costs of reformulation from $70.2 to $280.6 million, corresponding to the assumed proportion of products undergoing reformulation.

2.7.1 Comment 1: Alternative Reformulation Costs

The cost estimate of $143,618 per product used in the RIA reflects the lower bound of the range of $143,618 to $718,090 published in 67 FR 78158, inflated by 44% from 2002 to 2009. The underlying rule, "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for

Over-The-Counter Human Use; Final Monograph for Combination Drug Products," estimated the reformulation costs from $100,000 to $500,000 (with an average of $250,000) per product. The estimated cost in that rule is associated with reformulations that involve the substitution of one cough-cold ingredient for another, or the reformulation of a product containing a cough-cold ingredient and an oral healthcare ingredient, where such a combination has not been established as safe and effective. The required level of effort associated with reformulation for cold, cough, allergy, bronchodilator, and antiasthmatic drug products is comparable to the level of effort that would result from reformulation required by this Proposed Rule.

The estimate of $143,618 cost per product is then multiplied by the number of UPCs (over-estimation of these estimates by a factor of 2.2 is described above). Therefore, the unit estimates for the reformulation costs have a direct impact on the total costs estimated for the rule. A range from 25% to 100% of total UPCs with unique formulations is considered in the RIA, because this cost item would apply only to the fraction of facilities that would need to reformulate. Those that produce data consistent with the monograph changes proposed in this rule would not need to reformulate.

The required level of effort associated with reformulation of products in the OTC drug rule (67 FR 78158) is comparable to the level of effort that would result from reformulation required by this Proposed Rule; therefore, a full range of costs is appropriate to use. We used the same range for the fraction of companies that would need to reformulate their product as that presented in the RIA. The total reformulation costs estimated using the full range of unit costs reported in the RIA and the number of uniquely formulated products provided (based on IRI data) is presented in Table 6. The total reformulation costs are estimated at $52 million to $1 billion, depending on the percentage of companies that would need to reformulate their product, and the unit cost for reformulation.

Table 6. Total reformulation costs

Reformulation Cost Components	Unit Reformulation Cost		
Range of Reformulation Costs	MIN	AVG	MAX
Unit Reformulation Costs (2009)	$143,618	$359,045	$718,090
Unit Reformulation Costs (2013) using PPI	$166,597	$416,492	$832,984
Total Number of Products		1,483	
Percentage of Unique Formulations*		84%	
Number of Uniquely Formulated Products**		1,250	
Number of Affected Products (25% Need Reformulation)		313	
Number of Affected Products (50% Need Reformulation)		625	
Number of Affected Products (100% Need Reformulation)		1,250	
Total Reformulation Costs (25% Need Reformulation)	$52,078,601	$130,196,503	$260,393,006
Total Reformulation Costs (50% Need Reformulation)	$104,157,202	$260,393,006	$520,786,012
Total Reformulation Costs (100% Need Reformulation)	$208,314,405	$520,786,012	$1,041,572,024

*The overall percentage of unique formulations across all products is calculated using 91% for liquid products and 70% for bar soaps reported in the RIA.

**The number of uniquely formulated products is calculated in Table 5.

Note: Producer Price Index is used to adjust costs from 2009 to 2013.

The table above does not include institutional sales of anti-bacterial products hand washing. Based on our calculations, total institutional anti-bacterial soaps represent 29%–92% of anti-bacterial retail soaps in sales ($0.3–$0.9 billion of $1 billion). Therefore, the reformulating costs associated with institutional sales are estimated at between $15 million and $958 million. As a result, the total relabeling cost is estimated at $67–$1,999 million ($52 million * 1.29 as the low-end estimate, and $1,042 million * 1.92 as the high-end estimate).

2.7.2 Comment 2: Additional Unit Cost Estimate Provided by a Member Company

A rough estimate for reformulation cost provided by a member company was in the range of $1 million. This estimate is close to the upper bound of the re-formulation costs provided in the RIA ($143,618 to $718,090). In addition, there may be some additional costs or savings associated with manufacturing changes. For example, the same company estimated $2.5 million savings as a result of reformulation for one product, in addition to the additional cost of $4 million for reformulation of a second product. As a result, the net additional cost for the company was estimated at $1.5 million, on top of the development costs. Note that the total reformulation costs in the RIA are estimated by product and not by company; therefore, the net cost presented here is not comparable to the unit reformulation costs in the RIA.

2.8 FDA Assumption on Industry Behavior as a Result of the Rule

In recognition of the potential reaction by affected manufacturers, the RIA includes a discussion of the effects resulting from the possibility of relabeling products for other uses without removal of the antiseptic active ingredient. The RIA also states that it is unclear whether such a strategy would be profitable for manufacturers.

2.8.1 Comment

Relabeling a product without reformulating is a potential outcome resulting from this Proposed Rule. Some manufacturers may continue producing products that contain active ingredients while relabeling those products (e.g., adding a “cosmetic” or other permitted claim to the label that would not require demonstrating the safety of the ingredients).

2.9 FDA Assumption on Industry Behavior as a Result of the Rule

One of the potential reactions to the Proposed Rule by affected companies considered in the RIA is discontinuation of product.

2.9.1 Comment

This potential outcome for industry behavior is very unlikely and should not be considered as a potential reaction. This outcome would result in significant losses to the manufacturers.

2.10 FDA Assumption Regarding Regulatory Alternatives for Small Businesses

The RIA considers an alternative compliance option that would provide an exemption for small businesses. As a result of this consideration, FDA concluded that "exempting small businesses would not be desirable." The reason is that 99.2% of the consumer antiseptic wash industry is estimated to be small businesses, as defined by the Small Business Administration (SBA); thus, an exemption for small businesses would prevent realization of the majority of potential benefits resulting from the rule.

2.10.1 Comment

This conclusion seems reasonable. Most economically significant proposed rules issued by federal agencies such as FDA and EPA are estimated to affect a large number of small businesses, according to the SBA definition. Also, a large fraction of facilities affected by federal regulations represent small businesses because of the nature of the "small business" definition by the SBA. Exempting small businesses is not a common regulatory alternative, due primarily to the fact that most regulated entities are classified as small businesses. A rule exempting small businesses would not achieve its goals in terms of additional requirements intended by the rule and estimated benefits resulting from those regulatory changes.

2.11 FDA Cost Estimates for Conducting Safety and Efficacy Studies

The RIA reported that other studies have reported the estimated cost of safety and efficacy to range from $1-$7.5 million, while the pharmaceutical industry has estimated the cost to range from $5 million to over $35 million (Ref. R19). The RIA also provides a number of estimates for various tests that would be required in order to show safety and efficacy of the active ingredients and the final products. Since the Agency does not have information on the number of active ingredients and products that would be tested, these estimates reflect per-ingredient costs.

2.11.1 Comment 1

The GAO report, "Substantial Increase in Studies of Drugs for Children, but Some Challenges Remain," from 2001 (R19) emphasizes that precise data on study costs are not publicly available, and the estimates vary considerably. They provide the following cost information based on estimates by National Institute of Child Health and Human Development: "A safety and efficacy study may cost between $1 million and $7.5 million. Limited data provided by the Pharmaceutical Researchers and Manufacturers of America suggested higher study costs, ranging from under $5 million to more than $35 million." It is unclear how the referenced costs for studies associated with drug development compare to the study costs for antiseptic soaps and washes.

2.11.2 Comment 2

The RIA presents estimated costs associated with testing of active ingredients for safety and efficacy per ingredient. We used the per-ingredient costs associated with safety and efficacy testing to calculate a total cost for conducting the studies. While the exact number of active ingredients to be tested is unknown, we developed a range that reflects the variation in the number of active ingredients per company. A range of one to five (with an average of three) active ingredients per company is considered for this analysis, given the total number of active

ingredients with highest production volume. We also developed a range for the number of final products that would need initial testing. The range of six to twelve (with an average of nine) products for testing is assumed in the first year. Non-clinical effectiveness studies would need to be conducted on the final finished product. Other studies would need to be conducted for each active ingredient. Costs are presented for initial testing only (one-time costs); costs associated with subsequent testing are not estimated in this analysis. As a result, the total costs associated with safety and efficacy testing are estimated at $22.3 million to $368 million. The lower bound of the range represents a combination of the low-end assumption on the number of active ingredients and the low-end assumption on the number of final products for testing. Similarly, the upper bound of the range represents a combination of the high-end assumption on the number of active ingredients and the high-end assumption on the number of final products for testing. The table below presents estimates for the cost associated with safety and effectiveness studies.

Table 7. Costs Associated with Safety and Effectiveness Studies (one-time costs)

Test	Testing Costs		
	Low	**Medium**	**High**
Tests Performed on Active Ingredients			
Per Ingredient Cost			
Total Non-clinical Testing Costs (w/o resistance testing)	$12,129,989	$12,129,989	$12,129,989
Clinical Safety Studies	$725,734	$2,542,114	$23,202,190
Clinical Outcome Effectiveness Studies	$3,918,581	$14,308,034	$28,656,974
Subtotal Per Ingredient Cost	$16,774,304	$28,980,137	$63,989,153
Total Cost (Ingredient Testing)			
1 active ingredient	$16,774,304	$28,980,137	$63,989,153
3 active ingredients	$50,322,912	$86,940,411	$191,967,459
5 active ingredients	$83,871,520	$144,900,685	$319,945,765
Tests Performed on Final Products			
Per Ingredient Cost			
Non-Clinical Effectiveness Studies	$916,257		$3,983,724
Subtotal Per Product Cost	$916,257		$3,983,724
Total Cost (Product Testing)			
6 products	$5,497,542		$23,902,344
9 products	$8,246,313		$35,853,516
12 products	$10,995,084		$47,804,688
Total Testing Cost			
Low (1 active ingredient and 6 products)	**$22,271,846**	**$28,980,137**	**$87,891,497**
Medium (3 active ingredients and 9 products)	**$58,569,225**	**$86,940,411**	**$227,820,975**
High (5 active ingredients and 12 products)	**$94,866,604**	**$144,900,685**	**$367,750,453**

2.12 FDA Cost Estimates for Conducting Clinical Studies to Establish GRAS

The RIA estimates the cost of a human pharmacokinetic study from $250,000 to $750,000 per age group (Reference R19).

2.12.1 Comment

We confirmed the estimates referenced in the GAO report, "Substantial Increase in Studies of Drugs for Children, but Some Challenges Remain," from 2001 (R19), which reports the following costs: "the cost of a pharmacokinetic study can range from $250,000 to $750,000 per age group."

2.13 FDA Cost Estimates for Conducting Time-Kill Studies

The RIA reports that, based on estimates submitted by industry in response to the 1994 TFM, the costs to conduct the necessary Time-Kill studies would range from $916,257 to $3.98 million, updating to 2010 dollars (Refs. R23, R24).

2.13.1 Comment

We obtained the cited documents to verify the estimates used in the RIA. References 23 and 24 provide cost information from the comments submitted by industry in response to the 1994 proposed rule (1994 TFM) (59 FR 31402). Reference 23 is a comment submitted by Ciba Corporation in 1995 that provides a range of costs associated with Time-Kill studies (presented in Table 1) from $828,000 to $3,600,000 depending on a laboratory. Adjusting the 1995 estimates for inflation to 2010 dollars using the Producer Price Index (PPI), a range of costs is estimated at $1,203,241 to $5,231,484. The calculated PPI to adjust dollar values from 1995 to 2010 is 1.453. Reference 24 is a comment submitted by ConvaTec in 1995 that provides the following cost information related to Time-Kill studies: "The cost for conducting time-kill studies as identified in the TFM is $10,000 to $30,000 or $200,000 to $500,000 depending on the interpretation of the wording of the monograph. Further clarification of the micro-organisms required for time-kill testing is necessary as it will obviously have a significant economic impact on development of products regulated under the monograph." The total cost of Time-Kill studies would depend on the number of organisms to be tested. It is not clear from the RIA how the cost estimates provided by ConvaTec were used in estimating the cost range of $916,257 to $3.98 million.

2.14 Other Potentially Affected Industries

This Proposed Rule has the potential to affect a number of additional facilities from the "downstream" sectors. Those industries would include restaurants, hotels, cruise ships, other food services, cafeterias, grocery stores (those that handle meats), airlines, schools, universities, office buildings that handle food, and other establishments. A potential impact of this rule would be the additional time necessary to educate their employees regarding the change in hand hygiene practices related to availability of products and potentially replacing the existing products.

3 Estimation of Costs of the Proposed Rule Associated with Preventable Illnesses that would Occur if Antibacterial Hand-Wash Products Were Not Available

The RIA neglected to identify the costs associated with preventable illnesses that may no longer be prevented, as it were, if the regulation is enacted as proposed. Based on national estimates of cases of illnesses (gastrointestinal only), assumptions about the proportion that are associated with hand hygiene, and published literature on the cost of these illnesses (specific to each pathogen), a total national estimate of the potential lost benefits of the proposed regulation is presented. To account for the various sources of uncertainty in each input to the model, a conservative base case and sensitivity analyses are presented.

3.1 Methods

3.1.1 Literature Search

A literature search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was conducted for publications through April 10, 2014. The search looked for publications with estimates for the cost of gastrointestinal illness associated with selected pathogens (*Campylobacter,* Shiga toxin-producing *Escherichia coli* [STEC] O157 and non-O157, nontyphoidal *Salmonella, and Shigella*) in the United States in the past 25 years. These studies were considered eligible for the data abstraction process if they presented cost per case, rather than cost per household or total cost for an outbreak or total cost nationally. This exclusion criterion was introduced to limit the need to introduce assumptions for the cost estimate. For example, a cost analysis was conducted around a *Salmonella typhimurium* outbreak in Colorado in 2008, but the study reports on the cost per household (Ailes et al. 2013); thus, converting to the cost per case is unclear. Further, publications that provided only reviews of cost estimates presented in other papers (e.g., Batz et al. 2012), but not primary analyses, were retained for review, but the estimates were not included in the data abstraction to avoid double-counting and overweighting individual estimates.

On full-text review, a subset of these publications was found to contain cost-per-case estimates for one or more pathogens of interest. The references listed in the identified articles were also reviewed, which resulted in identifying several government reports and bulletins of interest. A final set of six studies were used for cost inputs (Buzby et al. 1996, Frenzen 2007, Scharff et al. 2009, Collier et al. 2012, Scharff 2012). Estimates from the more recent papers include output from the USDA's Economic Research Service Foodborne Illness Cost Calculator. The tool is currently offline while updates are being made.

3.1.2 Data Abstraction

Two key elements of information were abstracted from each publication. First, the cost estimate per case was identified, along with details about the derivation of the estimate. For example, some of the analyses present a single value that is already weighted based on the distribution of severity of illnesses, while others present a range. Second, the fiscal year in which costs are presented was recorded. These data points allow for the selection of the appropriate base case and extreme (minimum and maximum) costs for each pathogen-induced GI condition, as well as the ability to inflate each to 2014 U.S. costs.

3.1.3 Number of Cases Avoided

The number of cases of gastrointestinal disease associated with hand hygiene by pathogen was estimated by Dr. Donald Schaffner. His methods and full results appear in Appendix A. The Appendix explains the method used to derive estimates of the number of foodborne disease cases prevented by the use of antibacterial hand-wash products. The four foodborne pathogens considered were shiga-toxigenic *E. coli* (O157 and non-O157), *Salmonella* spp., nontyphoidal, *Shigella*, and *Campylobacter*. For reference, a summary of key output from Dr. Schaffner's calculations that are used in this analysis appears in Table 8.

Table 8. Number of cases and projected additional cases

	Hand-Hygiene-Related Cases			Additional Cases: Plain vs. Antibacterial Soap (based on mean number of cases)	
Pathogen	Low	*Mean*	High	1000 CFU dose	Worst case
STEC O157				15,942	360,293
STEC non-O157				28,342	640,521
All STEC	7,314	*44,284*	110,002	44,284	1,000,813
Salmonella, nontyphoidal	29,759	*47,426*	77,523	33,198	905,835
Shigella	24,511	*131,254*	374,789	55,502	1,771,929
Campylobacter	78,880	*197,772*	377,062	118,663	3,836,769

3.1.4 Cost per Case (in 2014 dollars)

Costs presented in the publications vary in terms of the year in which they were presented. Costs were inflated to 2014 dollars using the Consumer Price Index for medical care, published by the Bureau of Labor Statistics (series ID CUUR0000SAM).

After inflating costs to 2014 dollars, estimates were aggregated within each pathogen by taking the average of available estimates in each category. For example, the means were averaged, the low estimates were averaged with other low estimates, and the high estimates were averaged with other high estimates. The meanings of "low" and "high" varied by study. To simplify, they were aggregated for this table. For example, "low" in estimates from Buzby et al. (1996) meant illness that did not require a physician visit, while "high" referred to costs for a patient who did require hospitalization. For Collier, "low" meant costs for a patient covered by Medicaid treated as an outpatient, and "high" meant costs for a patient covered by commercial insurance who was admitted as an inpatient. The "low" estimate from Scharff et al. is based on the basic cost of illness model, while "high" refers to an estimate from the enhanced cost of illness model.

While the "low" and "high" values could be used to calculate cost estimates, given the variation across estimation methods, they are presented here primarily to provide context. With one exception, the mean estimate falls between the low and high values. This was the only condition (STEC non-O157) for which there was a single study that provided a mean estimate and a

(different) single study that provided the low/high estimates. As a result, this may have an effect on the robustness of the estimates.

Table 9 demonstrates the range of cost per case from the literature, while also providing a sense of the uncertainty and assumptions surrounding each estimate. Mean costs typically included direct medical costs (physician visits, hospital charges, prescriptions, etc.) and were developed considering the expected range of severity of illness (that is, if it was assumed that 5% of patients would not need medical care, $0 was assigned to them, whereas if 50% of patients required two outpatient visits and one prescription, the appropriate cost was assigned to that proportion of the cases). They did not include lost productivity on the part of the patient or caregiver, nor did they consider long-term sequelae from severe illnesses. It is important to note that the high cost presented for STEC O157 is partly driven by the proportion of patients who develop hemolytic uremic syndrome, a complication that can include kidney and heart problems and require substantial medical care to treat.

Table 9. Cost per case of illness by pathogen

Pathogen	Low	Mean	High
STEC O157	$5,350	$10,805	$3,014,355
Sources: Mean: Frenzen 2007, Scharff 2009 Low/High: Buzby et al. 1996 ERS, Frenzen 2007, Scharff et al. 2012			
STEC non-O157	$995	$9,048	$1,516
Sources: Mean: Scharff 2009. Low/High: Scharff et al. 2012			
***Salmonella*, nontyphoidal**	$1,956	$5,948	$14,146
Sources: Mean: Scarff 2009. Low/High: Buzby et al. 1996 ERS, Collier et al. 2012, Scharff et al. 2012			
Shigella	$1,168	$3,989	$16,273
Sources: Mean: Scharff 2009. Low/High: Collier et al. 2012, Scharff et al. 2012			
Campylobacter	$1,066	$4,196	$13,925
Sources: Mean: Scharff 2009. Low/High: Buzby et al. 1996, Collier et al. 2012, Scharff et al. 2012			

3.2 Results

Using data in Table 8 and Table 9, the costs per case were multiplied by the most conservative value for possible cases averted (i.e., assuming a 1000 CFU dose response relationship), as shown in Table 10. Also provided is the least conservative value (i.e., using a 1 CFU dose-response relationship).

Table 10. Estimate of additional national cost burden

	Mean Cost (based on mean number of cases)	
Pathogen	1000 CFU dose	Worst case
STEC O157	$172,248,337	$3,892,812,417
STEC non-O157	$256,431,548	$5,795,352,977
All STEC	$428,679,885	$9,688,165,394
Salmonella, nontyphoidal	$197,471,741	$5,388,157,496

Shigella	$209,423,107	$7,068,029,869
Campylobacter	$497,853,944	$16,097,277,532
Total	$1,333,428,677	$38,241,630,291

Based on the findings presented above, a conservative estimate of the additional burden of gastrointestinal illness caused by the selected pathogens is more than $1.3 billion annually in the United States. A high-end, but not absolutely maximum, scenario (using mean costs but a low dose-response ratio) found that the additional cost burden would exceed $38 billion annually.

Other scenarios not detailed in this table include a low cost estimate (assuming that patients are not hospitalized and/or that they have public insurance coverage, and with the highest dose-response relationship) of $336 million annually and a high cost estimate (assuming that patients require hospital admission and have long-term sequelae, that they have commercial insurance coverage, and the lowest dose-response ratio) exceeds $1.182 trillion annually.

3.3 Limitations

There is a limited amount of literature on the cost of foodborne illness, with a variety of methods used to derive estimates. Thus, sensitivity analyses have been conducted to provide the most conservative and least conservative estimates ($336 million and exceeding $1 trillion). These estimates all assume that the distribution of severity for these pathogens for hand-hygiene-related cases would be identical to the severity across all cases. There are no published data to substantiate or refute this assumption.

The estimates here do not, as a rule, include the cost of managing the outbreak from a public health perspective. Testing of food and water sources, communication, and reporting are additional costs associated with outbreaks that are not reflected in these estimates. Other tasks, such as ongoing surveillance, are also excluded from these estimates.

4 Summary of Total Costs of the Proposed Regulation

A summary table below (Table 10) presents costs and benefits estimated in the RIA, and the alternative estimates developed in this document. The estimates present one-time costs associated with the rule and do not include subsequent costs.

Table 711. Summary of Costs of the Proposed Regulation

Cost/ Benefit Component	**FDA Analysis**		**ACI/ PCPC Analysis**	
	Low Estimate	**High Estimate**	**Low Estimate**	**High Estimate**
		Costs		
Relabeling (Retail)	$42 million	$88 million	$182 million	$182 million
Reformulation (Retail)	$70 million	$280 million	$52 million	$1,041 million
Relabeling (Institutional)	N/A	N/A	$53 million	$167 million

Reformulation (Institutional)	N/A	N/A	$15 million	$958 million
Safety/ Efficacy Testing*	$17.7 million	$68 million	$22 million	$368 million
Costs of Preventable Illnesses (GI only)	N/A	N/A	$1,333 million	$38,242 million
TOTAL COSTS	**$129.7 million**	**$436 million**	**$1,657 million**	**$40,958 million**

*Notes: safety and efficacy testing costs estimated by FDA are reported per ingredient. Therefore, the total cost estimate would be higher if more than one ingredient would need to be tested.

** Benefits resulting from reduced exposure are reported in pounds of active ingredients in the RIA.

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Appendix D-1. Estimates of the Number of Foodborne Disease Cases Prevented by the Use of Antibacterial Hand-Wash Products: Methods and Results

Prepared by Donald Schaffner, Ph.D.

This document explains the logic used to derive estimates of the number of foodborne disease cases prevented by the use of antibacterial hand-wash products. CDC annual case estimate ranges for four different foodborne pathogens were obtained from a CDC published report (Scallan et al. 2011). The four foodborne pathogens considered were shiga-toxigenic *E. coli* (O157 and non-O157), *Salmonella* spp., nontyphoidal, *Shigella* and *Campylobacter*. STEC O157 and STEC non-O157 cases were combined, because the contributing factor data (see below) do not differentiate between the two STEC types.

The data extracted from Scallan et al. (2011) are shown below:

Microorganism	Low Case Estimate	Mean Case Estimate	High Case Estimate
STEC O157	17,587	63,153	149,631
STEC non–O157	11,467	112,752	287,321
All STEC (sum of above)	29,054	175,905	436,952
Salmonella spp., nontyphoidal	644,786	1,027,561	1,679,667
Shigella	24,511	131,254	374,789
Campylobacter	337,031	845,024	1,611,083

CDC contributing factors for three different factors related to hand hygiene were used to estimate the percent of cases where hygiene played a role (Gould et al. 2013). The three contributing factors used in our calculations were:

- C10—Bare-handed contact by handler/worker/preparer (e.g., with ready-to-eat food)
- C11—Glove-handed contact by handler/worker/preparer (e.g., with ready-to-eat food)
- C12—Handling by an infected person or carrier of pathogen (e.g., *Staphylococcus*, *Salmonella*, etc.)

We summed the number of outbreaks where hand-hygiene-related factors contributed to the outbreak and divided that by the number of outbreaks where any factor was reported. These estimates ranged from a low of 4.6% for *Salmonella* to a high of 100% for *Shigella*. The details of the calculations are shown below.

Microorganism	Outbreaks with Hand-Hygiene-Related Contributing Factors	Outbreaks with Any Contributing Factor	Percent Hand-Hygiene-Related
All STEC	36	143	25.2%

Salmonella spp.	36	780	4.6%
Shigella	54	54	100.0%
Campylobacter	33	141	23.4%

We assumed that outbreaks where hand hygiene was a contributor was a surrogate for the number of outbreaks where antibacterial handwash played a role in the outbreak.
Dose-response curves for the four different pathogens were collected from the peer-reviewed literature. The *E. coli* dose-response curve was taken from Cassin et al. (1998). The *Salmonella* dose response curve was taken from the FAO/WHO (year) *Salmonella* in broilers risk assessment. The Shigella dose-response curve was taken from Crockett et al. (1996). The *Campylobacter* dose-response curve was taken from the FAO/WHO (2009) risk assessment of *Campylobacter* in broiler chickens.

We assumed that 100% of all soap being used at present contained an antibacterial agent and estimated the effect of switching to 100% of all soap being non-antibacterial. Dose-response curves were used at the lowest possible dose (one cell) and at a proportionally higher level (1.4 log CFU higher doses for bland soap), representing the average difference between the effectiveness of bland soap and antibacterial soap (Schaffner et al. 2014). This represented the worst-case situation. Higher doses (10, 100, and 1000 cells) were also used. The results of these calculations are shown below.

Assumed baseline dose:	1 CFU	10 CFU	100 CFU	1000 CFU
Microorganism	Times greater cases with non AB soap			
All STEC	23.6	15.8	5.3	2
Salmonella	20.1	9	3	1.7
Shigella	14.5	4.8	2	1.4
Campylobacter	20.4	9.2	2.9	1.6

The assumed baseline dose is shown across the top. This represents the dose when antibacterial soap is used. The assumed dose for non-antibacterial dose is ~25 times higher (i.e., 1.4 log CFU higher doses for non-antibacterial soap). Because of the shape of the dose-response curve when the low dose is assumed, the effect of substituting bland soap for antibacterial soap is greater, from about 15 times more cases to about 24 times more cases for bland soap when 1 CFU is the dose when antibacterial soap is used. As the assumed dose rises, the differential between antibacterial and bland soap becomes less, such that when the assumed dose is 1000 cells, substituting bland soap results in from 1.4 times more cases to two times more cases, depending on the pathogen.

Appendix E

CITIZEN PETITION: DOCKET NO. FDA-1975-N-0012

June 16, 2014

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION: DOCKET NO. FDA-1975-N-0012

The undersigned submits this petition pursuant to 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to reopen the administrative record and amend the 1994 tentative final monograph (TFM) for Over-the-Counter (OTC) Health-Care Antiseptic Drug Products, Proposed 21 C.F.R Part 333, Subpart E, to include a specific category for Food Handler Antiseptic Handwash Products.

A. Action Requested

Petitioner requests that the Commissioner reopen the administrative record and amend the TFM for OTC Health-Care Antiseptic Drug Products to create the food handler category as the threshold step to address the safety and efficacy of active ingredients for use in this category of products. Specifically, Petitioner requests the Commissioner to:

- Formally recognize and acknowledge a separate category for Food Handler Antiseptic Handwash Products, either within Subpart E [included with §333.410 or New § 333.416] or in a new Subpart before the Consumer Rule is finalized.

- Define Food Handler Antiseptic Handwash Products as antiseptic handwash products for use in commercial establishments or regulated settings (at the federal, state or local level) where food production, packaging, transportation, storage, preparation, service or consumption occurs. [Amend § 333.403] The recommended definition intentionally speaks to the establishment or setting as the defining element of scope. Beside commercial, institutional, and industrial activities that are confined to food handling, food handlers can very often share a common bathroom and wash sinks with patrons and/or administrative workers in these settings. Therefore, the food handler handwash product should be defined as the handwash product used in the food handler facility. Further, the definition should include all antiseptic hand wash products used in these settings, including the use of antiseptic hand rubs or hand sanitizers. Including antiseptic hand

rubs within the Food Handler category is consistent with the FDA approach to the Healthcare monograph.

- Solicit comments and any new data and information specifically addressing the safety and effectiveness of active ingredients for use in Food Handler Antiseptic Handwash Products.

- Until FDA publishes a Food Handler monograph, FDA should confirm that Food Handler topical antiseptic products can continue to be marketed under the current regulatory framework.

B. Statement of Grounds

In the June 17, 1994 TFM for Health-Care Antiseptic Drug Products, FDA first recognized the category of topical antiseptics in use by the food industry, noting that "the intended use of the products, i.e., the reduction of micro-organisms on human skin for the purpose of the prevention of disease caused by contaminated food, makes them drugs." 59 Fed. Reg. 31402, 31440. Since then, FDA has included a Food Handler category in references to the TFM in rulemaking agenda notices (see e.g. 75 Fed. Reg. 79772), and in communications and discussions with industry representatives. As recently as August 2013, the Deputy Director of the FDA's Division of Nonprescription Regulation Development stated in a declaration submitted to a federal court that: "FDA previously announced plans to reissue the 1994 TFM in multiple parts to separately address antiseptic drug products for use by health care workers and consumers, and to add a new category for topical antiseptic drug products marketed for use by food handlers." Declaration of Debbie L. Lumpkins, Nat. Resources Def. Council v. FDA, 10-CV-5690 (AKH) (S.D.N.Y. Aug. 2, 2013) (emphasis added). We agree with and support the FDA's position that Food Handler products should be recognized as a new category.

On December 17, 2013, FDA published a proposal to reopen the administrative record and amend the TFM, which addressed only "consumer antiseptic washes." (78 Fed. Reg. 76444). In the preamble, FDA referred to "four remaining categories of topical antimicrobials" in the 1994 TFM, but added that the TFM "also identified a new category of antiseptics for use by the food industry and requested relevant data and information." Id. at 76446. However, FDA did not take steps formally to define or provide for a category of food handler antiseptic products in the TFM and the preamble continued: "Antiseptics for use by the food industry are not discussed further in this document." Id.

As a practical matter, food handler antiseptic products were tacitly included within the category of "antiseptic handwash" products in Subpart E. However, the proposed amendments to separate Consumer handwash into Subpart F from Healthcare handwash retained in Subpart E appears to create a void in the TFM process for addressing antiseptic handwash products in the food industry. Further, the November 21, 2013 Consent Decree provides a TFM timeline for the

monographs for Consumer Antiseptic Hand Wash Products, Healthcare Antiseptic Products, and Consumer Antiseptic Hand Rub Products, but not for Food Handler Products.

We agree with the FDA that food handler antiseptic handwash products should be a separate category. FDA has recognized that distinction since 1994 and reconfirmed it in the 2013 proposal. However, it is not evident, nor potentially appropriate, that revised Subpart E "healthcare personnel handwash products" is meant to include food handler antiseptic handwashes. Therefore, unless food handler products are explicitly recognized in the TFM, they could be effectively removed from the market without an assessment regarding their safety and efficacy and important public health use to promote food safety.

Antiseptic handwashes for food handlers do share several common traits with antiseptic handwashes for health care settings. These similarities create a logical pairing of the two categories for purposes of approval of actives. Further, process efficiencies and the short amount of time available under the Consent Decree timeline are conducive to addressing these two categories either simultaneously, or to addressing food handler as a separate monograph category.

The notable common traits include:

- Disease transmission intervention objective: As in healthcare settings, topical antimicrobial products are used in food handling operations to decrease micro-organisms on human skin to reduce the risk of disease caused by contaminated hands.

- Significant public health concern: Bacterial transfer to food at food handling operations can potentially affect large numbers of people through their exposure to or consumption of contaminated food.

- Repeat handwash/handwash protocols: Industry and state, local and federal regulatory protocols recommend or require continuous, on-going compliance with identified handwash intervention points for food handlers.

- Professional use: The use of antiseptic washes is limited to a trained, professional workforce employed in the food industry and governed by food safety standards.

1. Disease Transmission Intervention

Handwashing in the food industry has a purposeful use as an effective disease intervention tool just as it does in the healthcare setting. While some of the more prevalent transient pathogens in the food industry differ from those in a healthcare setting, the nature of both environments involves a concentration of sources of potential contamination.

Handwashing is employed to reduce the spread of food-related diseases, specifically the transfer of pathogenic organisms by a food handler from a source of contamination (e.g., a food source or surface) to other foods, individuals, and surfaces. Analysis from several studies indicates that substantial numbers of microorganisms can be transferred to the hands from contaminated food products, surfaces, or bodily excretions, creating the potential for a transient level of bacteria significantly above resident bacterial levels. [1, 2, 3] Research has demonstrated that total bacterial populations on food handlers' hands are substantially higher than in non-food handlers.[4,5] Subsequently, the hands can transfer microbial populations to food products at levels sufficient to produce illness and infection when these food products are eaten. Risks and incidences of microbial transfer and cross contamination of food are elevated in the food industry where hand contact with potential contaminants and hand contact with food is a continuous cycle. The use of antiseptic handwash products plays an important role in reducing these transfer rates and providing an effective intervention in the prevention of foodborne disease.[3]

2. <u>Public Health</u>

The food and healthcare industries both pose a significant risk of disease transmission related to the public health. In both environments, there is a high concentration of vulnerable end points, be it food or patients, to which the pathogenic organisms can be transferred. Hand to food bacterial transfer from food handlers is a recognized public health issue. Foodborne illness is believed to affect 1 in 6 Americans.[6] The estimated 48 million episodes of foodborne illness in the United States each year result in 120,000 hospitalizations and 3,000 deaths. [6] The CDC evaluated the contributing factors of the 13,405 foodborne disease outbreaks reported to the CDC in the US from 1998 to 2008, more than half of which were associated with food prepared in a restaurant or deli.[7] It found 11% of the outbreaks to be attributed to bare hand contact with food.[8] These same data suggest that as many as 35% of these bare hand contact issues involved bacterial contamination.[8] If these statistics are applied to the total number of foodborne illness episodes in the US annually, the number of people experiencing illness associated with bare hand contact with food prepared at a restaurant would be about 2.6 million. If the food industry no longer had access to antiseptic handwash products, these figures could quickly grow to be substantially higher.

Further, the food industry environment creates a significant multiplier effect where bacteria present on the hands of one individual can then infect a large number of other individuals. For instance, on a typical day, 130 million Americans will be foodservice patrons at approximately 1,000,000 foodservice establishments.[9,10] Consequently, a single food handler with excessive bacteria on his or her hands has the potential to infect a significant number of meals per day at any given establishment, assuming an average number of meals per establishment and a single food handler working one shift of two to three shifts staffed at the establishment. This same multiplier effect is true in food production and other dimensions of the food industry. Whether or not a meal is eaten out, all people are continuously exposed to the potential for a foodborne illness resulting from bacterial transfer from a food handler in the food industry every time they consume food.

3. Repeat Hand Wash Protocols

Handwashing by food handlers is a broadly recognized cornerstone of any food safety program and the FDA Food Code, alongside companion activities related to surface sanitization and proper food handling. Further, as a foundational food safety element, handwashing is a repeated, continuous activity. Industry or regulatory defined handwash protocols recommend and even require when individuals are to wash their hands (e.g. part of standard good manufacturing and retail practices). The FDA Food Code[11] establishes practical, science-based guidance for mitigating risk factors known to cause foodborne illness at foodservice and food retail establishments. The Food Code includes detailed information on how, where, and when food handlers should wash their hands. § 2.301. A failure to conduct proper hand washing is regarded as a violation in jurisdictions that have formally adopted the Code. The FDA's current Good Manufacturing Practice regulations also state that hands must be washed thoroughly, and should be sanitized if necessary.[12]

4. Professional Use

The use of antiseptic handwash products by food handlers is a defined, prescribed use by a trained, professional work force who use these products during their work day at a food operations facility. Decades ago, the USDA established a regulatory program governing the antiseptic hand wash products used by professional workers in food preparation facilities. In the late 1990's, the USDA's program transferred to a private certification program currently operated by NSF International. NSF continues to certify antibacterial hand care products for use in food handling operations.

FDA CFSAN's Food Code provides a uniform system of provisions that address the safety and protection of food. Building on the foundation of the former USDA program, the Food Code establishes hand hygiene standards for professional workers in food preparation establishments. There are currently 13.5 million restaurant industry[9] and 1.5 million food & beverage manufacturing[13] professional workers in the U.S. today. These professional uses warrant a distinct food handler category.

Conclusion

The Food Code recognizes the use of antiseptic handwashes to meet handwash protocols. § 2.301.16. In practice, antiseptic handwashes in the food industry are a critical component of any food safety program to reduce the risk of food-borne disease transmission. The TFM is the proper venue for the FDA to identify those products which it believes meet the OTC monograph requirements for antiseptic handwash use in the food industry.

At present, however, food handler antiseptic washes are not addressed in the TFM. This raises a serious risk that they will be omitted from the ultimate monograph, without any

opportunity afforded to the industry and user communities to demonstrate the safety and efficacy of these products. Given their importance to public health, petitioner requests that FDA:

- Confirm that Food Handler Antiseptic Handwash products can continue to be marketed under the current regulatory framework until FDA publishes a Food Handler monograph.

- Formally recognize and acknowledge a separate category for Food Handler Antiseptic Handwash Products, either within Subpart E [included with §333.410 or New § 333.416] or in a new Subpart before the Consumer Rule is finalized.

- Define Food Handler Antiseptic Handwash Products as antiseptic handwash products for use in commercial establishments or regulated settings (at the federal, state or local level) where food production, packaging, transportation, storage, preparation, service or consumption occurs. The definition should include antiseptic hand rubs or hand sanitizers. [Amend § 333.403]

- Solicit comments and any new data and information specifically addressing the safety and effectiveness of active ingredients for use in Food Handler Antiseptic Handwash Products.

C. Environmental Impact

Petitioners claim a categorical exclusion under 21 C.F.R. § 25.31(a) from the requirement for an environmental assessment.

D. Economic Impact

In accordance with 21 C.F.R. § 1030(b), information on economic impact will be provided if requested by the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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