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# Consumer Antiseptic Wash Final Rule Questions and Answers

## Guidance for Industry

*(Small Entity Compliance Guide)*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**July 2017**

**OTC**

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**Consumer Antiseptic Wash Final Rule  
Questions and Answers  
Guidance for Industry<sup>1</sup>**

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**I. INTRODUCTION**

This guidance is intended to help small businesses better understand and comply with the final rule establishing that certain active ingredients used in over-the-counter (OTC) consumer antiseptic wash products are not generally recognized as safe and effective (GRASE), and thus, are ineligible for inclusion in the OTC topical antiseptic monograph. On September 6, 2016, FDA published a final rule that finalizes the nonmonograph status of 19 active ingredients, including triclosan and triclocarban, which are intended for use in OTC consumer antiseptic wash products (81 FR 61106) (Consumer Antiseptic Wash Final Rule). Three active ingredients— benzalkonium chloride, benzethonium chloride, and chloroxylenol — were deferred from the final rule to allow more time for sponsors who proposed to complete the studies necessary to fill the safety and effectiveness data gaps identified for these ingredients. These deferrals are for one year, subject to renewal if adequate progress is made in filling the data gaps.

The final rule applies to consumer antiseptic wash products that are intended for use with water and are rinsed off after use, including consumer hand washes and consumer body washes. No additional safety or effectiveness data were submitted to support monograph conditions for the 19 consumer antiseptic wash active ingredients. Therefore, with the exception of the three deferred active ingredients, this rule finalizes the nonmonograph status of the remaining 19 active ingredients which are found to be not GRASE for use in consumer antiseptic wash products. Consumer antiseptic wash drug products containing one or more of these non-GRASE active ingredients will be considered new drugs for which approved new drug applications (NDAs) are required for marketing (21 USC 355(a)). The Consumer Antiseptic Wash Final Rule is effective September 6, 2017.

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<sup>1</sup> This guidance has been prepared by the Office of Regulatory Policy and Division of Nonprescription Drug Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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FDA has prepared this guidance in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121, as amended by Public Law 110-28)<sup>2</sup> to assist small businesses in complying with the Consumer Antiseptic Wash Final Rule.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

The final rule finalizes the Consumer Antiseptic Wash Proposed Rule published in the *Federal Register* of December 17, 2013 (78 FR 76444) (2013 Consumer Antiseptic Wash PR) and amends the 1994 tentative final monograph (TFM) for OTC antiseptic drug products that published in the *Federal Register* of June 17, 1994 (59 FR 31402) (the 1994 TFM). The final rule is part of FDA's ongoing rulemaking to evaluate the safety and effectiveness of OTC drug products marketed in the United States on or before May 1972 (OTC Drug Review). The Consumer Antiseptic Wash Final Rule is one of three OTC topical antiseptic rules involving triclosan required to be published pursuant to a Consent Decree entered by the United States District Court for the Southern District of New York on November 21, 2013, in *Natural Resources Defense Council, Inc. V. United States Food and Drug Administration, et al.*, 10 Civ. 569 (S.D.N.Y.).

As explained in the 2013 Consumer Antiseptic Wash PR, new information on potential risks posed by the use of certain consumer antiseptic washes prompted us to reevaluate the data needed for classifying consumer antiseptic wash active ingredients as generally recognized as effective (GRAE). As a result, we proposed that the risk from the use of a consumer antiseptic wash drug product must be balanced by a demonstration — through studies that demonstrate a direct clinical benefit (i.e., a reduction of infection) — that the product is superior to washing with nonantibacterial soap and water in reducing infection. In the final rule, we determined that the data and information submitted for 19 consumer antiseptic wash active ingredients were insufficient to demonstrate that there is any additional benefit from the use of these active ingredients in consumer antiseptic wash products compared to nonantibacterial soap and water. Consequently, we found that the available data do not support a GRAE determination for the 19 consumer antiseptic wash active ingredients.

As also explained in the 2013 Consumer Antiseptic Wash PR, several important scientific developments that affect the safety evaluation of consumer antiseptic wash active ingredients have occurred since FDA's 1994 evaluation of the safety of consumer antiseptic wash active ingredients under the OTC Drug Review. New data suggest that the systemic exposure to some of these active ingredients is higher than previously thought, and new information about the potential risks from systemic absorption and long-term exposure is now available. New safety information also suggests that widespread antiseptic use could have an impact on the

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<sup>2</sup> 5 U.S.C. 601 (note).

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development of bacterial resistance. Accordingly, to support a classification of generally recognized as safe (GRAS) for consumer antiseptic wash active ingredients, we proposed that additional safety data are needed to demonstrate that these ingredients meet current safety standards. We determined in the final rule that the available information and published data for 19 active ingredients were insufficient to establish the safety of long-term, daily repeated exposure to these active ingredients for use in consumer antiseptic wash products. Consequently, we found that the available data do not support a GRAS determination for the 19 consumer antiseptic wash active ingredients.

The final rule finalizes the nonmonograph status of 19 active ingredients, including triclosan and triclocarban, which are intended for use in consumer antiseptic wash products. As explained, either no additional data were submitted or the data and information that were submitted were not sufficient to support monograph conditions for these 19 consumer antiseptic wash ingredients. Therefore, in the final rule, we found that these 19 consumer antiseptic wash active ingredients are not GRASE. Accordingly, consumer antiseptic wash drug products that contain one or more of these 19 active ingredients are misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 352) and are considered new drugs under section 201(p) of the FD&C Act (21 U.S.C. 321(p)) for which approved applications under section 505 of the FD&C Act (21 U.S.C. 355) and part 314 (21 CFR part 314) of the Code of Federal Regulations are required for marketing.

In response to several comments submitted to the 2013 Consumer Antiseptic Wash PR, FDA has deferred further rulemaking on three specific active ingredients used in OTC consumer antiseptic wash products to allow for the development and submission of new safety and effectiveness data to the record for these ingredients. The deferred active ingredients are benzalkonium chloride, benzethonium chloride, and chloroxylenol. Accordingly, FDA does not make a GRASE determination for these three active ingredients in the Consumer Antiseptic Wash Final Rule. The monograph or new drug status of these three ingredients will be addressed either after completion and analysis of ongoing studies to address the safety and effectiveness data gaps of these ingredients or at a future date if these studies are not completed.

### **III. QUESTIONS AND ANSWERS**

#### **Q1. What active ingredients are subject to this final rule?**

In the final rule, we found that there are 22 active ingredients eligible for the OTC Drug Review for use as a consumer antiseptic wash. An OTC drug is covered by the OTC Drug Review if its conditions of use existed in the OTC drug marketplace on or before May 11, 1972 (37 FR 9464).<sup>3</sup> As noted above, three of these active ingredients have been deferred from this

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<sup>3</sup> Conditions of use include, among other things, active ingredient, dosage form and strength, route of administration, and specific OTC use or indication of the product (see 21 CFR 330.14(a)). Also, note that drugs initially marketed in the United States after the OTC Drug Review began in 1972 and drugs without any U.S. marketing experience can be considered in the OTC monograph system based on submission of a time and extent application (see § 330.14).

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rulemaking. The 19 remaining ingredients found eligible for the OTC Drug Review for use in consumer antiseptic wash products and subject to this final rule are:

- Cloflucarban
- Fluorosalan
- Hexachlorophene
- Hexylresorcinol
- Iodophors (Iodine-containing ingredients)
  - Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
  - Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
  - Nonylphenoxypoly (ethyleneoxy) ethanoliiodine
  - Poloxamer–iodine complex
  - Povidone-iodine
  - Undecoylium chloride iodine complex
- Methylbenzethonium chloride
- Phenol<sup>4</sup>
- Secondary amyltr cresols
- Sodium oxychlorosene
- Tribromsalan
- Triclocarban
- Triclosan
- Triple dye

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<sup>4</sup> Although phenol is listed twice in the final rule as “greater than 1.5 percent” and “less than 1.5 percent”, phenol—regardless of concentration—is eligible for the OTC Drug Review but was found to be not GRASE for use in consumer antiseptic wash products.

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In the final rule, we also found certain other active ingredients ineligible for evaluation under the OTC Drug Review as a consumer antiseptic wash because insufficient information was submitted to show that their conditions of use existed in the OTC drug marketplace on or before May 11, 1972. FDA considers a drug that is ineligible for inclusion in the OTC monograph system to be a new drug that will require FDA approval through the NDA process (21 CFR Part 314). The ineligible active ingredients are:

- Alcohol (ethyl alcohol)
- Benzalkonium cetyl phosphate
- Cetylpyridinium chloride
- Chlorhexidine gluconate
- Isopropyl alcohol
- Polyhexamethylene biguanide
- Salicylic acid
- Sodium hypochlorite
- Tea tree oil
- Combination of potassium vegetable oil solution, phosphate sequestering agent, and triethanolamine

### **Q2. What antiseptic products are covered by the final rule?**

The Consumer Antiseptic Wash Final Rule covers the group of products referred to as “consumer antiseptic washes.” Consumer antiseptic washes include a variety of personal care products that are intended for use with water and are rinsed off after use, such as antibacterial soaps, antibacterial hand washes, and antibacterial body washes. These products may be used by the general population for personal use in the home and public settings on a frequent, daily basis.

This final rule does not cover or have an impact on the monograph status of other OTC antiseptic products, including: (1) consumer antiseptic rubs, which are products that are not rinsed off after use such as hand rubs (i.e., “hand sanitizers”) and antibacterial wipes; (2) health care antiseptics, which are antiseptic products that are intended for use by health care professionals in a hospital setting or other health care situations outside the hospital; (3) first aid antiseptics; and (4) antiseptics used by the food industry. The monograph status of the active ingredients intended for use in these other OTC antiseptic products will be addressed separately.

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### **Q3. What is the significance of triclosan and triclocarban under this final rule?**

Based on available data, triclosan and triclocarban have been two of the most widely used OTC consumer antiseptic wash active ingredients on the market — with triclosan being used primarily in liquid antiseptic soaps and triclocarban being used primarily in bar antiseptic soaps. Emerging research shows that some antibacterial ingredients could pose health risks. For example, some data suggest that triclosan and triclocarban can cause alterations in thyroid, reproductive growth, and developmental systems of neonatal and adolescent animals. Because consumer antiseptic washes are chronic use products, evaluation of the potential for chronic toxicity and the effects on reproduction and development are essential to the safety assessment of these active ingredients.

As explained in the final rule, insufficient data were submitted to demonstrate the safety and effectiveness of triclosan and triclocarban for use as a consumer antiseptic wash product, and thus, we found that triclosan and triclocarban are not GRASE for use in consumer antiseptic wash products. Accordingly, to continue marketing as of the effective date of the final rule, OTC consumer antiseptic wash products containing triclosan or triclocarban will require (1) reformulation to remove triclosan or triclocarban and relabeling of the reformulated products; or (2) approval of a new drug application.

### **Q4. When and how do manufacturers have to comply with this final rule?**

The Consumer Antiseptic Wash Final Rule is effective September 6, 2017. In the final rule we found active ingredients to be either ineligible for inclusion in the OTC monograph system or not to be GRASE. On or after September 6, 2017, any OTC consumer antiseptic wash drug products containing such ingredients are misbranded and cannot be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved NDA. This means that manufacturers will need to obtain an NDA to market consumer antiseptic wash drug products containing any of these 19 active ingredients. Alternatively, manufacturers of consumer antiseptic washes containing nonmonograph antiseptic active ingredients can comply with this final rule by removing the products from the market or reformulating those products to remove the nonmonograph antiseptic active ingredient and marketing the products as soaps or washes without antibacterial claims.

### **Q5. What are the effectiveness criteria for consumer antiseptic wash active ingredients?**

FDA's OTC regulations (21 CFR 330.10(a)(4)(ii)) define the standards for establishing an OTC active ingredient as GRAE. These regulations require the effectiveness of active ingredients for OTC drug products be demonstrated by controlled clinical trials (§§ 330.10(a)(4)(ii) and 314.126(b)), unless this requirement is waived as provided in § 330.10(a)(4)(ii). These studies must be well controlled and able to distinguish the effect of a drug from other influences, such as a spontaneous change in the course of the disease, placebo effect, or biased observation (§ 314.126(a)).

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The controlled clinical trials required by FDA's regulations are intended to demonstrate that the pharmacological effect of the drug when used under adequate directions for use will provide clinically significant relief of the type claimed, i.e., efficacy for the stated indication.

Accordingly, to demonstrate the GRAE status of consumer antiseptic wash active ingredients, the effectiveness criteria include conducting adequate clinical outcome studies that identify the conditions of use on which an antiseptic active ingredient can demonstrate a reduction in the number of infections. Specifically, the risk from the use of a consumer antiseptic wash drug product must be balanced by a demonstration — through studies that demonstrate a direct clinical benefit (i.e., a reduction of infection) — that the product is superior to washing with nonantibacterial soap and water in reducing infection. To determine that the active ingredient is GRAE, the clinical outcome studies should include at least two arms: the final formulation of the product and the vehicle. The effectiveness of the active ingredient, and hence its contribution in the reduction of infection, is determined by comparing the infection rate in a consumer population washing with the antiseptic product that contains the active ingredient in question to the infection rate in a consumer population washing with the vehicle alone.

The requirement for clinical outcome studies is based on the fact that there are insufficient data to demonstrate a direct benefit from the use of consumer antiseptic washes compared to nonantibacterial soap and water. The log reduction standard (a clinical simulation standard) proposed in the 1994 TFM, which was based on a non-validated surrogate endpoint (i.e., number of bacteria removed from the skin), is insufficient for establishing the effectiveness of consumer antiseptic washes. In addition, existing data cannot demonstrate a correlation between log reductions of bacteria achieved by antiseptic hand washing in surrogate testing and the reduction of infection. Thus, in consumer settings where soap and water are readily available, the benefit of using an antiseptic wash product must be supported by these clinical outcome studies.

In addition to the clinical outcome studies, the effectiveness criteria for consumer antiseptic wash active ingredients include an *in vitro* study consisting of a modified time-kill assay that must be conducted with selected reference organisms and their respective clinical isolates, which are representative of bacterial strains most commonly encountered in general consumer settings. The purpose of the *in vitro* study is to characterize the antimicrobial activity of the active ingredients used in consumer antiseptic wash products.

### **Q6. What are the safety criteria for consumer antiseptic wash active ingredients?**

As explained in the rulemaking, the safety data needed to make a GRAS determination for active ingredients used in consumer antiseptic washes are based on several important scientific developments that affect the safety evaluation of these active ingredients. New data suggest that the systemic exposure to these active ingredients is higher than previously thought, and new information about the potential risks from systemic absorption and long-term exposure has become available. Moreover, new safety information also suggests that widespread antiseptic use can have an impact on the development of bacterial resistance. Accordingly, the safety data needed to demonstrate safety for consumer antiseptic wash active ingredients fall into three broad categories: (1) safety data studies in current FDA guidance (e.g., preclinical and human

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pharmacokinetic studies (including maximal use trials, developmental and reproductive toxicity studies, and carcinogenicity studies); (2) data to characterize potential hormonal effects; and (3) data to evaluate the development of resistance. These data requirements are the minimum data necessary to establish the safety of long-term, daily, repeated exposure to antiseptic active ingredients used in consumer wash products (81 FR 61106 at 61107).

### **Q7. Why did FDA find the 19 active ingredients to be not GRASE?**

With respect to effectiveness, in the final rule we found that the data and information submitted for the 19 active ingredients were insufficient to demonstrate that there was any additional benefit from the use of these active ingredients in consumer antiseptic wash products compared to nonantibacterial soap and water in reducing infection. Consequently, we found that the available data did not support a GRAE determination for these 19 consumer antiseptic wash active ingredients.

With respect to safety, in the final rule we found that the available information and published data for the 19 active ingredients were insufficient to establish the safety of long-term, daily repeated exposure to these active ingredients used in consumer antiseptic wash products. Consequently, we found that the available data did not support a GRAS determination for these 19 consumer antiseptic wash active ingredients.

### **Q8. What information did FDA rely on to make its GRASE Determinations?**

FDA issued this final rule based on its evaluation of the available information, including the published literature, the received comments, and all the data that were submitted to the rulemaking on the safety and effectiveness of the 19 consumer antiseptic wash active ingredients. The decisions in the final rule are also based on the recommendations of the Nonprescription Drugs Advisory Committee,<sup>5</sup> as well as recommendations from other public meetings held by the Agency on antiseptics.

### **Q9. Why did FDA not address final formulation testing or labeling in this final rule?**

We did not address final product formulation testing or labeling requirements in this final rule because none of the 19 consumer antiseptic wash active ingredients that are the subject of this final rule were found to be GRASE for use in consumer antiseptic wash products. Final formulation testing and labeling for the deferred ingredients may be addressed in the future once their GRASE determination is concluded.

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<sup>5</sup> See transcript of the January 22, 1997, Meeting of the Joint Nonprescription Drugs and Anti-Infective Drugs Advisory Committees, OTC. Available at <https://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4098T1.htm>; also, see transcript of the October 20, 2005, Meeting of the Nonprescription Drugs Advisory Committee, 2005. Available at <https://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf>.

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### **Q10. Why were three consumer antiseptic wash active ingredients deferred from this final rule?**

As explained in the final rule, we understood that, in certain circumstances, planning, implementing, and analyzing the data generated from the safety and effectiveness studies can be a time-consuming process that may not be completed within the period granted for submission of additional data in response to the 2013 Consumer Antiseptic Wash PR (78 FR 76444). Accordingly, in the 2013 Consumer Antiseptic Wash PR, we provided a process for seeking an extension of time to submit the required safety and effectiveness data if needed. We stated that we would consider all the data and information submitted to the record in conjunction with all timely and completed requests to extend the timeline to finalize the monograph status for a given ingredient. Consideration for deferral for an ingredient was given to requests with clear statements of intent to conduct the necessary studies required to fill all the data gaps identified in the proposed rule for that ingredient.

After analyzing the data and information submitted related to the requests for extensions, we determined that deferral was warranted for three consumer antiseptic wash active ingredients — benzalkonium chloride, benzethonium chloride, and chloroxylenol — to allow more time for interested parties to complete the studies necessary to fill the safety and effectiveness data gaps identified for these ingredients. Thus, these three active ingredients are not included in the final rule and will be addressed either after completion and analysis of ongoing studies to address the safety and effectiveness data gaps of these ingredients or at a later date if these studies are not completed.

### **Q11. What is the deferral time period for these three ingredients?**

FDA deferred rulemaking on benzalkonium chloride, benzethonium chloride, and chloroxylenol for 1 year. These deferrals are subject to renewal to permit sponsors to conduct the necessary studies to address the data gaps. On March 24, 2017, we renewed these deferrals for another 1-year period, subject to renewal. If the studies in progress do not appear, in FDA's judgment, to be productive, the Agency expects that it will proceed to rulemaking for these ingredients after this deferral stage.

To facilitate this process, as laid out in the deferral letters, sponsors submitted clear statements of intent to conduct all necessary studies and submitted full study outcomes reports to the public docket. Further detail on the necessary studies, including FDA's guidance on study objectives and design for certain studies, can be found on the Agency's Antiseptic FDA Letters website available at <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm538131.htm>.

### **Q12. Where can I get more information, if needed?**

Questions regarding compliance with the Consumer Antiseptic Wash Final Rule should be directed to [CDERCompliance@fda.hhs.gov](mailto:CDERCompliance@fda.hhs.gov). Questions regarding other OTC issues should be directed to [OTCDrugs@fda.hhs.gov](mailto:OTCDrugs@fda.hhs.gov).