Consumer Antiseptic Rub 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)

December 2020
OTC

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance is intended to help small businesses understand and comply with the Consumer Antiseptic Rub Final Rule; Finding of Ineligibility for Inclusion in Final Monograph (Consumer Antiseptic Rub FR) (84 FR 14847, April 12, 2019), which applies to active ingredients used in over-the-counter (OTC) consumer antiseptic rub products that are sometimes referred to as *rubs*, *leave-on products*, or *hand sanitizers*. The Consumer Antiseptic Rub FR also applies to active ingredients used in OTC consumer antiseptic wipes.

The Consumer Antiseptic Rub FR established that 28 active ingredients used in nonprescription consumer antiseptic rub products are not eligible for evaluation under FDA's ongoing rulemaking to evaluate the safety and effectiveness of OTC drug products marketed in the United States on or before May 1972, which is known as the *OTC Drug Review*. Drug products containing these active ingredients will require approval under a new drug application (NDA) or an abbreviated new drug application (ANDA) before they can be marketed.

The Consumer Antiseptic Rub FR also established that three active ingredients used in consumer antiseptic rub products—benzalkonium chloride, ethyl alcohol, and isopropyl alcohol—are eligible for evaluation under the OTC Drug Review.[2] In response to several requests submitted to the 2016 Consumer Antiseptic Rub Proposed Rule (Consumer Antiseptic Rub PR) (81 FR 42912, June 30, 2016), FDA temporarily deferred further rulemaking on making a generally recognized as safe and effective (GRAS/GRAE) determination for these three eligible active

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

[2] On March 27, 2020, the Over-the-Counter Monograph Safety, Innovation, and Reform Act (OMSIRA) was signed into law as part of the newly enacted Coronavirus Aid, Relief, and Economic Security Act (CARES Act) (Public Law No. 116-136, 134 Stat. 281 (March 27, 2020)). OMSIRA is intended to modernize the process by which FDA regulates over-the-counter monograph drugs. FDA is in the process of implementing the changes set forth in OMSIRA, however, OMSIRA does not revise the findings in the Consumer Antiseptic Rub FR.

ingredients. Rulemaking was temporarily deferred to allow time for interested parties to complete the studies necessary to fill the safety and effectiveness data gaps FDA has identified for these three ingredients.[3]

The Consumer Antiseptic Rub FR was published on April 12, 2019, with an effective date of April 13, 2020.

On March 27, 2020, the President signed into law H.R. 748, "the Coronavirus Aid, Relief, and Economic Security Act" or the "CARES Act". The law includes statutory provisions, which FDA refers to as OTC Monograph Reform, that reforms and modernizes the OTC monograph drug development and review process. The law replaces the rulemaking process with an administrative order process to add, remove, or change an OTC monograph. The administrative order process is expected to improve efficiency, timeliness and predictability in the OTC Drug Review process. FDA is in the process of implementing the changes set forth in the CARES Act, however, this legislation does not affect the Agency's findings in the Consumer Antiseptic Rub FR.[4]

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)[5] to assist small businesses in complying with the Consumer Antiseptic Rub FR.

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 Consumer Antiseptic Rub FR finalizes the 2016 Consumer Antiseptic Rub PR published in the *Federal Register* of June 30, 2016 (81 FR 42912) 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 Consumer Antiseptic Rub FR is one of three final rules involving the active ingredient triclosan required to be published pursuant to a

[3] More information on the antiseptic rulemaking deferral letters is available here: https://www.fda.gov/drugs/information-drug-class/antiseptic-fda-letters.

[4] We note that under 505G(a)(3) of the FD&C Act, which was enacted as part of the CARES Act as described above, drugs that were classified as category III in a tentative final monograph (TFM), including the 1994 TFM for over-the-counter topical antiseptics (59 FR 31402) as further amended by the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912), are not required to have an approved application under section 505 in order to be marketed, as long as they are in conformity with the relevant conditions of use outlined in the applicable TFM and comply with all other applicable requirements for nonprescription drugs.

[5] 5 U.S.C. 601 (note).

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. 5690 (S.D.N.Y.).

The Consumer Antiseptic Rub FR confirmed the ineligibility status of 28 active ingredients, including triclosan, as proposed in the 2016 Consumer Antiseptic Rub PR. Prior to the enactment of the CARES Act, an OTC drug was eligible for evaluation under the OTC Drug Review if its conditions of use existed in the OTC drug marketplace on or before May 11, 1972 (37 FR 9464). 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 (§ 330.14(a) (21 CFR 330.14(a))). After the publication of the 2016 Consumer Antiseptic Rub PR, no additional information was submitted demonstrating that any of the 28 active ingredients was marketed as a consumer antiseptic rub on or before May 11, 1972. OTC consumer antiseptic rub products containing these ineligible ingredients are new drugs for which approved NDAs or ANDAs are required before marketing.

In response to several requests submitted to the 2016 Consumer Antiseptic Rub PR, FDA temporarily deferred a GRAS/GRAE determination for three active ingredients—benzalkonium chloride, ethyl alcohol, and isopropyl alcohol--to allow time for interested parties to complete the studies necessary to fill the safety and effectiveness data gaps identified for these ingredients.

As a result of the deferrals, the Consumer Antiseptic Rub FR does not include a determination on the GRAS/GRAE status of benzalkonium chloride, ethyl alcohol, or isopropyl alcohol for use in consumer antiseptic rubs. FDA intends to address the GRAS/GRAE status of these three active ingredients either after completion and analysis of studies to fill the identified safety and effectiveness data gaps for these ingredients or at another time if these studies are not completed.[6]

The Consumer Antiseptic Rub FR also describes the studies that are necessary, as a scientific matter, for FDA to determine whether an active ingredient is GRAS/GRAE for use in consumer antiseptic rubs.

III. QUESTIONS AND ANSWERS

Q1. What types of antiseptic products are covered by the Consumer Antiseptic Rub FR?

The Consumer Antiseptic Rub FR covers OTC consumer antiseptic rub products that are sometimes referred to as rubs, leave-on products, or hand sanitizers. The Consumer Antiseptic

[6] The CARES Act added section 505G to the Federal Food, Drug, and Cosmetic (FD&C Act). Under 505G(a)(3) of the FD&C Act, drugs that were classified as category III in a tentative final monograph (TFM), including the 1994 TFM for over-the-counter topical antiseptics (59 FR 31402) as further amended by the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912) are not required to have an approved application under section 505 in order to be marketed, as long as they are in conformity with the relevant conditions of use outlined in the applicable TFM and comply with all other applicable requirements for nonprescription drugs.

Rub FR also covers OTC consumer antiseptic wipes. These products are intended to be used when soap and water are not available and are left on and not rinsed off with water.

The Consumer Antiseptic Rub FR does not address the monograph status of other OTC antiseptic products, including: (1) consumer antiseptic washes, which are 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; (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 of the hospital; (3) first aid antiseptics, which are skin antiseptics, skin-wound cleansers, and skin-wound protectants used primarily by consumers for first aid use; and (4) antiseptics used by the food industry. The monograph status of the active ingredients intended for use in these other OTC antiseptic products has been and/or will be addressed separately.

Q2. What active ingredients are subject to the Consumer Antiseptic Rub FR?

In the Consumer Antiseptic Rub FR, we found that three active ingredients were eligible for evaluation under the OTC Drug Review for use in a consumer antiseptic rub. The three ingredients are:

- Benzalkonium chloride
- Ethyl alcohol
- Isopropyl alcohol

As noted above, FDA temporarily deferred a final determination regarding the GRAS/GRAE status of these three active ingredients to allow time for interested parties to complete the studies necessary to fill the safety and effectiveness data gaps identified for these ingredients.

In the Consumer Antiseptic Rub FR, we also found 28 active ingredients ineligible for evaluation under the OTC Drug Review as a consumer antiseptic rub. The 28 ingredients are:

- Benzalkonium cetyl phosphate
- Benzethonium chloride
- Cetylpyridinium chloride
- Chloroxylenol
- Chlorhexidine gluconate
- Cloflucarban
- Combination of potassium vegetable oil solution, phosphate sequestering agent, and triethanolamine

- Fluorosalan
- Hexachlorophene
- Hexylresorcinol
- Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
- Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
- Methylbenzethonium chloride
- Nonylphenoxypoly (ethyleneoxy) ethanoliodine
- Phenol (equal to or less than 1.5 percent or greater than 1.5 percent)
- Poloxamer iodine complex
- Polyhexamethylene biguanide
- Povidone-iodine (5 to 10 percent)
- Salicylic acid
- Secondary amyltricresols
- Sodium hypochlorite
- Sodium oxychlorosene
- Tea Tree Oil
- Tribromsalan
- Triclocarban
- Triclosan
- Triple dye
- Undecoylium chloride iodine complex

Q3. When and how do manufacturers have to comply with this final rule?

In the Consumer Antiseptic Rub FR, FDA found 28 active ingredients ineligible for evaluation under the OTC Drug Review as a consumer antiseptic rub. On or after the April 13, 2020, effective date of the Consumer Antiseptic Rub FR, any OTC consumer antiseptic rub drug product containing one or more of the 28 ingredients that FDA has found ineligible cannot be introduced or delivered for introduction into interstate commerce unless the drug product is the subject of an approved NDA or ANDA. This means that manufacturers will need to obtain an NDA or ANDA to market consumer antiseptic rub drug products containing any of these 28 active ingredients. Alternatively, manufacturers of consumer antiseptic rubs containing ineligible antiseptic active ingredients can comply with the Consumer Antiseptic Rub FR by removing their products from the market, or reformulating them to remove the ineligible active ingredients, and then marketing them appropriately (e.g., by substituting one of the three active ingredients described above or by marketing the products as antiseptic-free rubs or wipes without drug claims).

Q4. What if my OTC antiseptic product uses an active ingredient not mentioned in the Consumer Antiseptic Rub final rule?

OTC consumer antiseptic rub or wipe products containing active ingredients not mentioned in the Consumer Antiseptic Rub FR are considered new drugs, for which an approved NDA or ANDA is required before marketing such products. Manufacturers of such products can also pursue one of the alternatives explained in Q3 to comply with this final rule.

Q5. Why did FDA not address final formulation testing or labeling in the Consumer Antiseptic Rub FR?

We did not address final product formulation testing or labeling requirements in the Consumer Antiseptic Rub FR because none of the consumer antiseptic rub active ingredients that are the subject of the Consumer Antiseptic Rub FR were found to be GRAS/GRAE for use in consumer antiseptic rub products. Final formulation testing and labeling for the three deferred active ingredients may be addressed in the future once their GRAS/GRAE determination has been concluded.

Q6. Why were three consumer antiseptic rub active ingredients deferred from further rulemaking?

FDA temporarily deferred a final determination on the GRAS/GRAE status of three active ingredients used in consumer antiseptic rubs—benzalkonium chloride, ethyl alcohol, and isopropyl alcohol—to allow time for interested parties to complete the studies necessary to fill the safety and effectiveness data gaps identified for these ingredients. FDA made the decision to defer that determination in response to several requests submitted to the 2016 Consumer Antiseptic Rub PR.

Q7. Where can I get more information, if needed?

Questions regarding compliance with the Consumer Antiseptic Rub FR should be directed to CDERCompliance@fda.hhs.gov. Questions regarding other OTC issues should be directed to OTCDrugs@fda.hhs.gov.