U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration

Final Administrative Order (OTC000030):

Over-the-Counter Monograph M003: First Aid Antiseptic Drug Products for Over-the-Counter Human Use (Posted May 2, 2023)

I. Summary

Over-the-Counter Monograph M003: First Aid Antiseptic Drug Products for Over-the-Counter Human Use, as set forth in this document, is a final administrative order (final order) deemed by section 505G(b)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h(b)(8)), and effective upon enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Public Law 116-136, on March 27, 2020.

II. Background

The CARES Act added section 505G of the FD&C Act, which revised the framework for the regulation of over-the-counter (OTC) monograph drug products. Among other things, section 505G of the FD&C Act provides as a baseline status that, as of the date of enactment of the CARES Act, drugs that satisfy certain requirements described in section 505G(a)(1) or (2) are deemed to be generally recognized as safe and effective under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)), not a new drug under section 201(p), and not subject to section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)). To obtain this status, among other things, a drug either must be one that is in conformity with the requirements for nonprescription use of a final monograph issued under part 330 (21 CFR part 330) (except as provided in section 505G(a)(2)),[1] as well as other requirements;[2] or must be one that is (i) classified in category I for safety and effectiveness under a tentative final monograph that is the most recently applicable proposal or determination issued under part 330, and (ii) in conformity with the proposed requirements for nonprescription use of such tentative final monograph and any applicable subsequent determination by the Secretary, as well as other requirements.[3] Other applicable requirements in section 505G(a)(1) of the FD&C Act include conditions or requirements under section 505G(b) of the FD&C Act.

Complementary to the requirements for conformity to tentative final or final monographs described in section 505G(a)(1) and (2) of the FD&C Act, Congress provided that, under section

[1] Section 505G(a)(2) of the FD&C Act is inapplicable here. It establishes the applicable requirements in terms of conformity with a final monograph, for purposes of section 505G(a)(1)(A)(i) of the FD&C Act, for sunscreen drugs subject to section 505G of the FD&C Act.
[2] Section 505G(a)(1)(A) of the FD&C Act.
[3] Section 505G(a)(1)(B) of the FD&C Act.

505G(b)(8) of the FD&C Act, a final monograph or tentative final monograph that establishes conditions of use for a drug described in section 505G(a)(1) or (2) and that represents the most recently promulgated version of the conditions of use, including as modified, in whole or in part, by any proposed or final rule, is deemed to be a final order. The final order may be amended, revoked, or otherwise modified in accordance with the procedures under section 505G of the FD&C Act. Under section 505G(b)(8)(C) of the FD&C Act, the deemed establishment of a final order is construed to include technical amendments necessary to ensure that the order is appropriately harmonized, in terms of terminology or cross-references, with the applicable provisions of the FD&C Act (and regulations) and any other final orders issued under section 505G of the FD&C Act.

In the *Federal Register* of July 22, 1991 (56 FR 33644), FDA issued a tentative final monograph under the procedure in part 330, that would establish conditions under which OTC first aid antiseptic drug products are generally recognized as safe and effective (GRASE). In the *Federal Register* of January 9, 1992 (57 FR 858), FDA issued corrections to the tentative final monograph for OTC first aid antiseptic drug products.

Accordingly, this final order for OTC first aid antiseptic drug products incorporates the requirements of the tentative final monograph for OTC first aid antiseptic drug products issued under part 330, as proposed in the *Federal Register* of July 22, 1991 (56 FR 33644) and in the *Federal Register* of January 9, 1992 (57 FR 858), with technical amendments.

III. Final Administrative Order

Over-the-Counter Monograph M003:

First Aid Antiseptic Drug Products for Over-the-Counter Human Use

Part A—General Provisions

Sec.
M003.1 Scope
M003.3 Definitions

Part B—Active Ingredients

M003.10 First aid antiseptic active ingredients
M003.20 Permitted combinations of active ingredients

Part C—Labeling

M003.50 Labeling of first aid antiseptic drug products
M003.60 Labeling of permitted combinations of active ingredients

Part D—Testing Procedures

M003.70 Testing of first aid antiseptic drug products

SOURCE: 56 FR 33644, Jul. 22, 1991, unless otherwise noted.

Part A—General Provisions

§ M003.1 Scope

An over-the-counter (OTC) first aid antiseptic drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this OTC monograph and each general condition established in 21 CFR 330.1.

§ M003.3 Definitions

As used in this OTC monograph:

(a) Antiseptic drug. In accordance with section 201(o) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(o)), "The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body."

(b) First aid antiseptic. An antiseptic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns.

Part B—Active Ingredients

§ M003.10 First aid antiseptic active ingredients

The active ingredient of the product consists of any of the following within the specified concentration established for each ingredient, and the product is labeled according to §§ M003.50 or M003.60:

(a) Alcohol 48 to 95% by volume in an aqueous solution denatured according to Bureau of Alcohol, Tobacco, and Firearms regulations in 27 CFR part 20.

(b) Alcohol 26.9% when combined in accordance with § M003.20(c).

(c) Benzalkonium chloride 0.1 to 0.13%.

(d) Benzethonium chloride 0.1 to 0.2%.

(e) Camphorated metacresol (camphor 3 to 10.8% and metacresol 1 to 3.6% in a ratio of 3 parts camphor to 1 part metacresol).

(f) Camphorated phenol (camphor 10.8% and phenol 4.7%) in a light mineral oil, USP vehicle.

(g) Eucalyptol 0.091% when combined in accordance with § M003.20(c).

(h) Hexylresorcinol 0.1%.

(i) Hydrogen peroxide topical solution USP.

(j) Iodine tincture USP.

(k) Iodine topical solution USP.

(l) Isopropyl alcohol 50 to 91.3% by volume in an aqueous solution.

(m) Menthol 0.042% when combined in accordance with § M003.20(c).

(n) Methylbenzethonium chloride 0.13 to 0.5%.

(o) Methyl salicylate 0.055% when combined in accordance with § M003.20(c).

(p) Phenol 0.5 to 1.5%.

(q) Povidone-iodine 5 to 10%.

(r) Thymol 0.063% when combined in accordance with § M003.20(c).

§ M003.20 Permitted combinations of active ingredients

(a) Any single first aid antiseptic active ingredient identified in § M003.10 may be combined with any single external analgesic active ingredient identified in § M017.10(a) of OTC Monograph M017 provided the product is labeled according to § M003.60.

(b) Any single first aid antiseptic active ingredient identified in § M003.10 may be combined with any single skin protectant active ingredient identified in § M016.10 of OTC Monograph M016 provided the product is labeled according to § M003.60.

(c) The ingredients identified in §§ M003.10 (b), (g), (m), (o), and (r) may be combined provided the product is labeled according to § M003.60.

Part C—Labeling

§ M003.50 Labeling of first aid antiseptic drug products

(a) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the product as a “first aid antiseptic.”

(b) Indications. The labeling of the product states, under the heading "Uses"," the following: "First aid to help" (select one of the following: "prevent," ("decrease" ("the risk of" or "the chance of")), ("reduce" ("the risk of" or "the chance of")), "guard against," or "protect against") (select one of the following: "infection," "bacterial contamination," or "skin infection") "in minor cuts, scrapes, and burns." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in § M003.50(b), may also be used, as provided in 21 CFR 330.1(c)(2), subject to the provisions of section 502 of the FD&C Act (21 U.S.C 352) relating to misbranding and the prohibition in section 301(d) of the FD&C Act (21 U.S.C. 331(d)) against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act (21 U.S.C. 355(a)).

(c) Warnings. The labeling of the product contains the following warnings under the heading "Warnings":

(1) For products containing any ingredient identified in § M003.10.

(i) "For external use only. Do not use in the eyes or apply over large areas of the body. In case of deep or puncture wounds, animal bites, or serious burns, consult a doctor."

(ii) "Stop use and ask a doctor if the condition persists or gets worse. Do not use longer than 1 week unless directed by a doctor."

(2) For products containing any ingredient identified in §§ M003.10(a) and (l). "Flammable, keep away from fire or flame."

(3) For products containing any ingredient identified in §§ M003.10(e), (f), and (p). "Do not bandage."

(d) Directions. The labeling of the product contains the following statements under the heading "Directions":

(1) "Clean the affected area."

(2) For products that are ointments, creams, and liquids. "Apply a small amount of this product on the area 1 to 3 times daily."

(3) For products labeled for use as a wet compress. "Bandage lightly. Keep bandage wet with solution."

(4) For products packaged as sprays. "Spray a small amount of this product on the area 1 to 3 times daily."

(5) For products containing any ingredient identified in §§ M003.10(a), (b), (c), (d), (g), (h), (i), (j), (k), (l), (m), (n), (o), (q), and (r). "May be covered with a sterile bandage."

(6) For products packaged as liquids or sprays. “If bandaged, let dry first.”

(e) The word “physician” may be substituted for the word “doctor” in any of the labeling statements in § M003.50.

§ M003.60 Labeling of permitted combinations of active ingredients

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) Statement of identity. For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC monograph. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC monographs.

(b) Indications. The labeling of the product states, under the heading “Uses” the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC monographs, unless otherwise stated in § M003.60(b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in § M003.60(b), may also be used, as provided in 21 CFR 330.1(c)(2), subject to the provisions of section 502 of the FD&C Act relating to misbranding and the prohibition in section 301(d) of the FD&C Act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act.

(1) For permitted combinations identified in § M003.20(a). In addition to the required indication identified in § M003.50, the labeling of the product may state, under the heading “Uses,” the following additional indication: “First aid for the temporary relief of” (select one of the following: “pain,” “discomfort,” “pain or discomfort,” or “pain and itching”) “in minor cuts, scrapes, and burns.”

(2) For permitted combinations identified in § M003.20(b). In addition to the required indication identified in § M003.50, the labeling of the product may state, under the heading “Uses,” the following additional indication: “First aid for the temporary protection of minor cuts, scrapes, and burns.”

(3) For permitted combinations identified in § M003.20(c). The indications in § M003.50 should be used.

(c) Warnings. The labeling of the product states, under the heading “Warnings,” the warning(s) for each ingredient in the combination, as established in the warnings section of the applicable OTC monographs.

(d) Directions. The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC monographs, unless otherwise stated below. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product:

(1) May not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC monograph(s), and

(2) May not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient.

Part D—Testing Procedures

§ M003.70 Testing of first aid antiseptic drug products

A first aid antiseptic drug product in a form suitable for topical application will be recognized as effective if it contains an active ingredient included in § M003.10 and if at its lowest recommended use concentration it decreases the number of bacteria per milliliter in *Staphylococcus aureus* (ATCC No. 6538), *Escherichia coli* (ATCC No. 8739), and *Pseudomonas aeruginosa* (ATCC No. 9027) cultures (available from American Type Culture Collection (ATCC)) by 3 $\log_{10}$ within 10 minutes at 32 °C in the presence of 10% serum in vitro. Drugs identified in §§ M003.10 (j), (k), and (l) are exempt from this testing procedure. Furthermore, an antiseptic drug product for inhibitory use as a wet dressing, ointment, dusting powder, or such other use involving prolonged contact with the body, will be recognized as effective if its active ingredient is included in § M003.10 and if a 1:120 dilution of the formulated drug product in growth medium without neutralizers prevents an increase in the number of organisms from an inoculum of 10^8 organisms of the above cultures when incubated at 32 °C for 48 hours. First aid antiseptic drug products that are not exempt from this provision must meet the specified requirements when tested in accordance with the following procedures unless a modification is approved as specified in § M003.70(e).

(a) Laboratory facilities, equipment, and reagents.

(1) Laboratory facilities. To prevent the contamination of test microorganism cultures with extraneous microorganisms, perform the test using aseptic techniques in an area as free from contamination as possible. Because test cultures of microorganisms may be adversely affected by exposure to ultraviolet light or chemicals in aerosols, do not test under direct exposure to ultraviolet light or in areas under aerosol treatment. Do environmental tests to assess the suitability of the testing environment frequently enough to assure the validity of test results.

(2) Equipment. Use laboratory equipment that is adequate for its intended use. Thoroughly cleanse the equipment after each use to remove any antiseptic residues. Keep the equipment covered when not in use. Sterilize clean glassware intended for holding

and transferring the test organisms in a hot air oven at 200 to 220 °C for 2 hours. Use volumetric flasks, pipets, or accurately calibrated diluting devices when diluting standard and sample solutions. Use plastic or glass Petri dishes having dimensions of 20x100 millimeters. Use covers of suitable material.

(3) Reagents.

(i) Phenol stock solution. Prepare a 5% weight to volume solution of phenol by the method described in the "Official Methods of Analysis of the Association of Official Analytical Chemists," Kenneth Helrich (ed.), 15th Ed., 1990, pp. 133-134, which is incorporated by reference.[4]

(ii) Serum. Use inactivated fetal bovine serum without added preservatives and/or anti-infective products.

(b) Culture media and diluting fluids.

(1) Ingredients. Use Soybean-Casein Digest Medium for culture media and diluting fluids that conform to the standards prescribed by the USP XXII/The National Formulary (NF) XVII.[5] In lieu of preparing the media from the individual ingredients, the media may be made from dehydrated mixtures which, when reconstituted with distilled water, have the same or equivalent composition as media prepared from individual ingredients. Media prepared from dehydrated mixtures is to have growth-promoting, buffering, and oxygen tension-controlling properties equal to or better than media prepared from individual ingredients. Adjust the pH of each medium with 1 Normal hydrochloric acid or sodium hydroxide before sterilization, if necessary, so that after sterilization the pH will fall within the specified range prescribed by the USP XXII/NF XVII.[6] Steam sterilize the media in an autoclave at 121 °C for 20 minutes.

(2) Neutralizers. When neutralizers are added to culture media and diluting fluid, perform the following tests.

(i) Neutralizer inactivation of antiseptic test. Assay the neutralizer efficacy for the test antiseptic as follows: Prewarm the test antiseptic, culture medium, test culture, and serum to 32 °C by incubating appropriate volumes of all solutions in a water bath at 32 °C for 5 minutes. Mix 0.8 milliliter of antiseptic (for controls use 0.8 milliliter of sterile water) with 9.0 milliliters of culture medium containing an appropriate antiseptic neutralizer followed by the addition of 0.2 milliliter of

[4] K Helrich (1990) Official Methods of Analysis of the Association of Official Analytical Chemists, 15th edition, pp. 133-134, is incorporated by reference and is available for inspection at FDA. For further information about inspecting incorporated material, contact druginfo@fda.hhs.gov. Copies may also be available from the publisher, Association of Official Analytical Chemists.
[5] United States Pharmacopeia (USP) XXII/ National Formulary (NF) XVII (January 1990), is incorporated by reference and is available for inspection at FDA. For further information about inspecting incorporated material, contact druginfo@fda.hhs.gov. Copies may also be available from the publisher, United States Pharmacopeia.
[6] See footnote 5.

the test culture in 50% serum. Incubate the mixture of cells, serum, antiseptic, and neutralizer at 32 °C for 10 minutes. Remove aliquots, dilute, and assay for surviving bacteria by the plate-count assay method using diluting and plating media containing appropriate neutralizers, if required. Results obtained showing differences greater than 20% between test and control cultures indicate that the neutralizer used to inactivate the test antiseptic is ineffective. Reject results obtained from tests employing ineffective neutralization procedures.

(ii) Neutralizer effect on bacteria viability test. Test the effect of neutralizers used to inactivate antiseptic active ingredients on cell viability by diluting aliquots of each test organism culture in Medium A (without neutralizer), specified in § M003.70(b)(3)(i), and in the appropriate diluting fluid (neutralizing medium), specified in § M003.70(b)(4). Determine the number of bacteria in aliquots of appropriate dilutions by the plate-count assay method utilizing growth agar medium containing the same neutralizer concentration as the diluting medium. Determine neutralizer effects on cell viability by comparing the relative number of microorganisms growing on Medium B, specified in § M003.70(b)(3)(ii), with and without added neutralizers. Results obtained showing differences greater than 20% between cultures diluted in medium with and without neutralizers indicate that, at the concentration utilized, the antiseptic neutralizer alters the determination of viable cells in the test cultures. Reject results obtained from tests in which the neutralizer employed alters the determination of viable cell numbers.

(3) Culture media.

(i) Medium A (without neutralizers). Use soybean-casein digest fluid medium corresponding to that described in § M003.70(b).

(ii) Medium B. Soybean-casein digest agar medium. Same as Medium A, except for the addition of 15 grams of agar per liter.

(iii) Medium C. Same as diluting fluid 1, except for the addition of 15 grams of agar per liter.

(iv) Medium D. Same as diluting fluid 2, except for the addition of 15 grams of agar per liter

(v) Medium E. Same as diluting fluid 3, except for the addition of 15 grams of agar per liter.

(4) Diluting fluids.

(i) Diluting fluid 1. Diluting medium for neutralizing quaternary ammonium and phenolic antiseptic ingredients. Same as Medium A, except for the addition of 5 grams of lecithin and 40 milliliters of polysorbate 20 per liter.

(ii) Diluting fluid 2. Diluting medium for neutralizing iodophor antiseptic ingredients. Same as Medium A, except for the addition of 5 grams of sodium thiosulfate per liter.

(iii) Diluting fluid 3. Diluting medium for neutralizing mercurial antiseptic ingredients. Same as Medium A, except for the addition of 1 gram of sodium thioglycolate and 2.5 grams of sodium bisulfite per liter.

(c) Test organisms.

(1) Use cultures of the following microorganisms:

(i) *Staphylococcus aureus* (ATCC No. 6538).

(ii) *Pseudomonas aeruginosa* (ATCC No. 9027).

(iii) *Escherichia coli* (ATCC No. 8739).

(2) Preparation of suspension. Maintain stock cultures on Medium B agar slants by monthly transfers. Alternatively, cultures may be lyophilized and stored at -70 °C. Incubate new stock transfers 2 days at 32 °C; then store at 2 to 5 °C. From stock culture, inoculate tubes of Medium A and make at least 4 but less than 30 consecutive daily transfers in Medium A, incubating at 32 °C, before using the culture for testing. Use a 22- to 26-hour culture of organisms grown in Medium A at 32 °C for the test.

(3) Determination of cell number in broth cultures. Prepare serial 1:10 dilutions of each culture in Medium A and determine the number of cells per milliliter of culture by the plate-count assay method. Do not use cultures stored at 4 °C for more than 48 hours for assay. Do not use cultures containing less than 10^9 cells per milliliter.

(4) Plate-count assay. For each culture to be assayed, pipet 1 milliliter of each prepared dilution into each of two sterile Petri plates. To each plate, add 20 milliliters of sterile Medium B that has been melted and cooled to 45 °C (if neutralizers are required, use the corresponding agar growth medium with the appropriate neutralizer). Mix the sample with the agar by tilting and rotating the plate and allow the contents to solidify at room temperature. Invert the Petri plates and incubate at 32 °C for 48 hours. Following incubation, count the number of developing colonies. Use Petri plates containing between 30 and 300 colonies in calculating the number of bacteria per milliliter of original culture.

(5) Test organism antiseptic resistance test. To ensure that antiseptic resistance properties of each organism have not altered substantially, determine the resistance to phenol at 20 °C for each organism as described in “Phenol Coefficient Methods” referenced in § M003.70(a)(3).

(i) *Escherichia coli*. A culture of *Escherichia coli* (ATCC No. 8739) is satisfactory for test purposes if it has resistance to phenol at 20 °C at least as follows:

Phenol	5 min	10 min	15 min
1:90 dilution	+ or 0	+ or 0	0
1:100 dilution	+	+	+ or 0

(ii) *Pseudomonas aeruginosa*. A culture of *Pseudomonas aeruginosa* (ATCC No. 9027) is satisfactory for test purposes if it has resistance to phenol at 20 °C at least as follows:

Phenol	5 min	10 min	15 min
1:80 dilution	+ or 0	+ or 0	0
1:90 dilution	+	+	+

(iii) *Staphylococcus aureus*. A culture of *Staphylococcus aureus* (ATCC No. 6538) is satisfactory for test purposes if it has resistance to phenol at 20 °C at least as follows:

Phenol	5 min	10 min	15 min
1:60 dilution	+ or 0	+ or 0	0
1:70 dilution	+ or 0	+	+

(d) Test procedures.

(1) Method 1.

(i) Method validation. This test is valid only for those antiseptics that are water soluble and/or miscible and that can be neutralized by one of the subculture media specified in §§ M003.70(b)(3) and (b)(4) or that can be overcome by dilution.

(ii) Bactericidal assay procedure. Prewarm all test solutions by incubating appropriate volumes at 32 °C in a water bath for 5 minutes. Pipet 1.0 milliliter of serum, 1.0 milliliter of appropriate bacterial test culture, and 8.0 milliliters of test antiseptic at its recommended use concentration into a medication tube and mix well. Incubate at 32 °C for 10 minutes. Remove triplicate 1-milliliter sample aliquots and dilute in Medium A containing appropriate neutralizers. Determine the number of surviving organisms per milliliter of test culture by the plate-count method using plating media containing appropriate neutralizers, if required.

(iii) Bacteriostatic assay procedure. Prewarm all test solutions by incubating appropriate volumes at 32 °C in a water bath for 5 minutes. Pipet 1.0 milliliter of serum, 1.0 milliliter of appropriate bacterial test culture and 8.0 milliliters of test antiseptic at its recommended use concentration into a medication tube and mix well. Pipet 1.0 milliliter aliquots of this test mixture into triplicate medication tubes containing 100 milliliters of Medium A without neutralizers and mix well. Incubate at 32 °C for 48 hours and determine the number of organisms per milliliter of culture by the plate-count method.

(e) Test modifications. The formulation or mode of administration of certain products may require modification of the testing procedures in § M003.70. In addition, alternative assay methods (including automated procedures) employing the same basic chemistry or microbiology as the methods described in § M003.70 may be used. Any proposed modification or alternative assay method shall be submitted as a petition in accord with 21 CFR 10.30 or in accord with section 505G(b)(5) of the FD&C Act, as applicable. The submission should contain data to support the modification or data demonstrating that an alternative assay method provides results of equivalent accuracy.