U.S. Food and Drug Administration

Proposed Administrative Order (OTC000036):

Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use

(Issued November 8, 2024)

Pursuant to section 505G(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h(b)), the U.S. Food and Drug Administration (FDA) is issuing a proposed administrative order as described herein and set forth in Section IX below.

I. Introduction

FDA is issuing this proposed administrative order (proposed order) to amend the requirements for cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter (OTC) human use, as currently described in Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (OTC Monograph M012).[1]

This proposed order, if finalized, will amend OTC Monograph M012 to remove oral phenylephrine hydrochloride and oral phenylephrine bitartrate as nasal decongestant active ingredients because they are not effective.

II. Public Comments

A. Dates

Submit electronic comments on the proposed order by 11:59 p.m. Eastern Time at the end of May 7, 2025. Comments submitted after this time will not be considered.

B. Instructions

Comments must be submitted electronically. The Federal eRulemaking Portal https://www.regulations.gov will accept comments at any time until 11:59 p.m. Eastern Time at the end of May 7, 2025.

[1] OTC Monograph M012 is set forth in Final Administrative Order OTC000026 Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use, available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf.

Submit electronic comments to Proposed Order ID [OTC000036] as follows:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. All comments received must include the Proposed Order ID Number [OTC000036] and the Docket No. FDA-2024-N-4734 for "Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use."

- Comments submitted electronically, including attachments, to https://www.regulations.gov will generally be posted to the docket unchanged, subject to any FDA redactions of confidential information as discussed below and subject to FDA's review of content that may have copyright protections.

- Confidential information will be identified and redacted by FDA: Submissions should not contain any redactions for claimed confidential information. FDA will review submissions to determine whether they contain information that, pursuant to section 505G(d) of the FD&C Act (21 U.S.C. 366h(d)) and any other applicable disclosure law, will not be made public. FDA will redact any such information prior to the comment being publicly viewable.

- Under section 505G(d) of the FD&C Act, FDA must make any information submitted by any person with respect to this order available to the public upon submission, with limited exceptions. FDA will not make public any information pertaining to pharmaceutical quality information unless such information is necessary to establish standards under which a drug is generally recognized as safe and effective under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)) (see section 505G(d)(2)(B)(i) of the FD&C Act). FDA will also not make public information that is of the type contained in raw datasets (see section 505G(d)(2)(B)(iv) of the FD&C Act).

- Additionally, for information not subject to any FDA redactions of confidential information and not subject to FDA's review of content that may have copyright protections, your comment should not include any information that you or a third party may not wish to be publicly posted, such as medical information or your or anyone else's Social Security number. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- Comments that are submitted in a timely manner (see Dates and Addresses) will be placed in the docket and will be publicly viewable on https://www.regulations.gov after FDA's review and redaction for confidential information.

C. Contact Information

For further information, contact: Dan Brum, Center for Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-0578.

III. Background

OTC Monograph M012 describes the conditions under which OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products are generally recognized as safe and effective under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)).[2] OTC Monograph M012 is set forth in Final Administrative Order OTC000026, which was deemed established by section 505G(b)(8) of the FD&C Act (21 U.S.C. 355h(b)(8)), and was effective upon enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Public Law 116-136, on March 27, 2020. The conditions described in OTC Monograph M012, as set forth in final order(s), may be amended, revoked, or otherwise modified in accordance with the procedures of section 505G(b) of the FD&C Act (21 U.S.C. 355h(b)).[3] Under OTC Monograph M012, orally administered phenylephrine hydrochloride and phenylephrine bitartrate in an effervescent dosage form[4] are generally recognized as safe and effective as nasal decongestant active ingredients under the conditions of use described in the monograph (see §§ M012.20(a)(1) and (4) of OTC Monograph M012).

FDA is issuing this proposed order pursuant to section 505G(b) of the FD&C Act. This proposed order, if finalized, will remove orally administered phenylephrine hydrochloride and phenylephrine bitartrate in an effervescent dosage from OTC Monograph M012 as nasal decongestant active ingredients because they are not effective.[5,6]

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[2] See section 505G(a)(1) of the FD&C Act.

[3] See section 505G(b)(8)(A) of the FD&C Act.

[4] An effervescent dosage form is intended to be dissolved in water before taking by mouth. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.

[5] When not otherwise specified, all doses and dosages are for phenylephrine hydrochloride. However, the implication for effectiveness applies to both oral phenylephrine hydrochloride and oral phenylephrine bitartrate because the inclusion of phenylephrine bitartrate in OTC Monograph M012 was based solely on the bioavailability data that phenylephrine bitartrate was comparable to phenylephrine hydrochloride (see 71 FR 83358). Therefore, in general, "oral phenylephrine" is used throughout the document to refer to both orally administered phenylephrine hydrochloride and orally administered phenylephrine bitartrate in an effervescent dosage form.

[6] This proposed administrative order applies to oral phenylephrine as a nasal decongestant and therefore does not apply to the following: (1) intravenous phenylephrine approved under an NDA; (2) generally recognized as safe and effective status of topically administered phenylephrine under OTC Monograph M015: Anorectal Drug Products for Over-the-Counter Human Use; (3) generally recognized as safe and effective status of ophthalmic administered phenylephrine under OTC Monograph M018: Ophthalmic Drug Products for Over-the-Counter Human Use; and (4) generally recognized as safe and effective status of intranasally administered phenylephrine for nasal congestion under OTC Monograph M012.

A. Regulatory History for Oral Phenylephrine

1. Relevant Historical Rulemaking

In the *Federal Register* of September 9, 1976 (41 FR 38312), FDA issued an advanced notice of proposed rulemaking proposing to establish the conditions under which OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products are generally recognized as safe and effective, based on the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products (Panel). Among other things, the Panel reviewed safety and efficacy data for oral phenylephrine and concluded that oral phenylephrine was safe and effective as a nasal decongestant.

In the *Federal Register* of January 15, 1985 (50 FR 2220), FDA issued a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which OTC nasal decongestant drug products used for relieving the symptoms of nasal congestion caused by acute or chronic rhinitis are generally recognized as safe and effective and not misbranded. Among other things, FDA proposed finding oral phenylephrine generally recognized as safe and effective as a nasal decongestant.

In the *Federal Register* of October 2, 1986 (51 FR 35339), FDA issued a final OTC monograph under the procedure in part 330, establishing conditions under which OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products are generally recognized as safe and effective. This final OTC monograph was codified under 21 CFR 341 and subsequently amended by numerous final rules. Relevant to this proposed order, in the *Federal Register* of August 23, 1994 (59 FR 43409), FDA issued a final rule in the form of a final OTC monograph establishing conditions under which OTC nasal decongestant drug products, including oral phenylephrine, are generally recognized as safe and effective (1994 final rule).

In the *Federal Register* of August 1, 2006 (71 FR 83358), FDA issued a final rule to amend the final OTC monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products to add phenylephrine bitartrate in an effervescent dosage form—both individually and in combination with other active ingredients—as generally recognized as safe and effective as an oral nasal decongestant.

2. Citizen Petitions

A citizen petition was submitted to FDA on February 1, 2007 (2007 citizen petition) (Hendeles L 2007), which asserted that the available data do not support the adult and pediatric doses of phenylephrine that are generally recognized as safe and effective in the OTC monograph for cold, cough, allergy, bronchodilator, and antiasthmatic drug products.[7] The petitioners proposed that the maximum dose of oral phenylephrine be increased for those 12 years of age and older and that "approval" for use of oral phenylephrine in children less than 12 years old be withdrawn. The petitioners explained that additional studies should be required to validate the dosage of oral phenylephrine for efficacy and safety. The citizen petition was based on the

[7] See 72 FR 60377 (Oct. 24, 2007) Nonprescription Drugs Advisory Committee; Notice of Meeting.

petitioners' systematic review and meta-analysis of the studies considered by FDA when including oral phenylephrine in the 1994 final rule and the lack of data on the safety of oral phenylephrine in children.

On November 4, 2015, some of the individuals that submitted the 2007 citizen petition submitted a second citizen petition (2015 citizen petition) (Hendeles L 2015) requesting FDA remove oral phenylephrine as a nasal decongestant from the OTC monograph. The 2015 citizen petition was based on the results of four studies,[8,9] published after the Meeting of the Nonprescription Drug Advisory Committee in 2007 (see section III.A.3. 2007 Meeting of the Nonprescription Drugs Advisory Committee), which the petition contends clearly demonstrated that oral phenylephrine is no more effective than placebo in decreasing nasal congestion and increasing the dose of oral phenylephrine fourfold did not provide additional benefit.

On June 19, 2023, the petitioners withdrew the 2007 citizen petition (Hendeles L 2023), asserting that subsequent studies have been performed and show that a dose of oral phenylephrine 4 times the maximum nonprescription dose is not more effective than placebo at relieving nasal congestion and that there has been no evidence demonstrating that oral phenylephrine is safe and effective in children under 12 years old.

3. 2007 Meeting of the Nonprescription Drugs Advisory Committee

In the *Federal Register* of October 24, 2007 (72 FR 60377), FDA announced the meeting of a public advisory committee to discuss the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as an OTC oral nasal decongestant and to address the 2007 citizen petition.[10]

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[8] The four studies cited by the 2015 citizen petition include: Horak, F, P Zieglmayer, R Zieglmayer, P Lemell, R Yao, H Staudinger, and M Danzig, 2009, A placebo-controlled study of the nasal decongestant effect of phenylephrine and pseudoephedrine in the Vienna Challenge Chamber, Ann Allergy Asthma Immunol, 102(2):116-120 (Horak et al. 2009); Gelotte, CK and BA Zimmerman, 2015, Pharmacokinetics, safety, and cardiovascular tolerability of phenylephrine HCl 10, 20, and 30 mg after a single oral administration in healthy volunteers, Clin Drug Investig, 35(9):547-558 (Gelotte and Zimmerman 2015); Day, JH, MP Briscoe, JD Ratz, M Danzig, and R Yao, 2009, Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit, Ann Allergy Asthma Immunol, 102(4):328-338 (Day et al. 2009); Meltzer, EO, PH Ratner, and T McGraw, 2016, Phenylephrine hydrochloride modified-release tablets for nasal congestion: a randomized, placebo-controlled trial in allergic rhinitis patients, Ann Allergy Asthma Immunol, 116(1):66-7 (Meltzer et al. 2016).

[9] FDA's Scientific Review Supporting Proposed Administrative Order is available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf, under the supporting documents for this Proposed Administrative Order OTC000036. For FDA's comprehensive review of these four studies, see the Scientific Review Supporting Proposed Administrative Order, section II.B. Review of Efficacy Data Available After the Publication of the 1994 Final Rule.

[10] In particular, the advisory committee planned to address the petitioner's 2007 request that the cold, cough, allergy, bronchodilator, and antiasthmatic monograph be amended to increase the adult dose of phenylephrine hydrochloride from 10 to 25 milligrams (mg) and that of phenylephrine bitartrate from 15.6 to 40 mg.

On December 14, 2007, FDA convened a meeting of the Nonprescription Drugs Advisory Committee (Committee) (2007 meeting).[11] There were many presentations at the 2007 meeting, including from the petitioners of the 2007 citizen petition, a group from industry represented by the Consumer Healthcare Products Association (CHPA),[12] FDA, and several industry speakers, notably Schering-Plough and Schering-Plough Merck. Many of the presentations, including those by the petitioners of the 2007 citizen petition, CHPA, and FDA, included meta-analysis or analysis of the studies reviewed by the Panel.[13]

The results of two meta-analyses were presented—one conducted by industry and one conducted by the petitioners. The meta-analysis conducted by the petitioners did not confirm the findings from the original efficacy studies evaluated by the Panel, while the industry meta-analysis did. FDA reviewed the statistical results from both sets of meta-analyses and concluded that the two meta-analyses (1) included different studies, (2) utilized different endpoints than the original studies themselves, and (3) found indications of heterogeneity and limited poolability, all of which led to an assessment by FDA that neither meta-analysis was conclusive.[14]

Schering-Plough Merck presented the results for two environmental exposure unit studies, which were the only new data on oral phenylephrine presented at the meeting (see section IV.A. Scientific Review of Efficacy Data).[15,16]

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[11] The FDA uses committees and panels to obtain independent expert advice on scientific, technical, and policy matters. The Nonprescription Drugs Advisory Committee reviews and evaluates available data concerning the safety and effectiveness of nonprescription human drug products, or any other FDA-regulated product, for use in the treatment of a broad spectrum of human symptoms and diseases and advises the Commissioner either on the promulgation of OTC monographs establishing conditions under which these drugs are generally recognized as safe and effective and not misbranded or on the approval of new drug applications for such drugs. For more information on Nonprescription Drugs Advisory Committee, see https://www.fda.gov/advisory-committees/human-drug-advisory-committees/nonprescription-drugs-advisory-committee.

[12] CHPA is a national trade association representing manufacturers and marketers of consumer health care products, including OTC medicines, dietary supplements, and consumer medical devices (www.chpa.org).

[13] See 41 FR 38312 for information about the studies reviewed by the Panel. See also FDA's comprehensive review of the studies evaluated by the Panel in FDA's Scientific Review Supporting Proposed Administrative Order, section II.A. Review of Historical Data Regarding Efficacy, available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf, under the supporting documents for this Proposed Administrative Order OTC000036.

[14] Meeting materials, including presentation slides and briefing documents for the 2007 meeting, December 14, 2007, are available at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs.

[15] See Schering-Plough Merck Briefing Document for 2007 meeting, December 14, 2007. The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis. 2007-4335b1-02-Schering-Plough-Merck.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm. Slides available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm. Based on the two environmental exposure unit studies, Schering-Plough Merck concluded that a single 10 mg or 12 mg dose of oral phenylephrine failed to provide benefit over placebo. However, a single 60 mg oral dose of pseudoephedrine provided relief of congestion symptoms.

[16] Meeting materials, including presentation slides and briefing documents for the 2007 meeting, December 14, 2007, are available at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs.

FDA explained that many studies discussed at the meeting, in which the efficacy of oral phenylephrine as a nasal decongestant was assessed, differed in many ways, including the following:

- Patient inclusion criteria (healthy subjects or subjects with common cold, upper respiratory tract infection, acute rhinitis, or seasonal allergic rhinitis)
- Congestion model (naturally occurring, induced by exposure to pollen in an environmental exposure unit)
- Endpoints (reduction in nasal airway resistance, improvement in symptoms scores)
- Dose (10 mg, 25 mg), dosing interval, and endpoint assessment interval

Therefore, FDA asked the Committee to discuss which aspects of the data, if any, are supportive of the effectiveness of phenylephrine for the symptomatic treatment of nasal congestion due to the common cold or upper respiratory allergies. The Committee noted that in the studies discussed during the 2007 meeting, the standard to support effectiveness was not clearly defined and that, while individual studies showed some benefit of oral phenylephrine 10 mg, results were not consistent across studies for nasal airway resistance or symptom measures. The Committee explained that while half of the studies were positive (i.e., studies reporting positive findings demonstrating efficacy for phenylephrine) and half were negative (i.e., studies not reporting positive findings demonstrating efficacy for phenylephrine) and in no studies was placebo superior to phenylephrine, the Committee felt that efficacy may not be generalizable to a wide population based on small studies. The available evidence was conducted 40 years prior to the 2007 meeting and included fewer than 200 people across all studies.[17]

The Committee recommended that additional trials be conducted to evaluate the safety and effectiveness of oral phenylephrine as a nasal decongestant and provided recommendations as to how the trials should be conducted.[18] These included the following:

- Multicenter, parallel, randomized, double-blind, placebo-controlled trials, preferably with an active control (e.g., pseudoephedrine) to evaluate nasal congestion scores and symptom relief with a sufficient sample size to evaluate efficacy and safety
- Studies to characterize the phenylephrine dose response; and the effect of dosing interval, formulation, administration, and potentially genetic factors on safety and efficacy endpoints

[17] Summary minutes of the 2007 meeting, December 14, 2007, are available at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4335m1-Final.pdf.

[18] Summary minutes of the 2007 meeting, December 14, 2007, are available at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4335m1-Final.pdf.

- Studies to compare the pharmacokinetics of single-ingredient products versus multiple-ingredient products

- Studies to evaluate the safety of phenylephrine on blood pressure, on the cardiovascular system, and in patients with comorbidities

4. 2023 Meeting of the Nonprescription Drugs Advisory Committee

In the *Federal Register* of July 12, 2023 (88 FR 44370), FDA announced the meeting of a public advisory committee to discuss new data regarding the generally recognized as safe and effective status of oral phenylephrine as a nasal decongestant that have become available since FDA last examined the issue.

On September 11–12, 2023, FDA convened a meeting of the Nonprescription Drugs Advisory Committee (2023 meeting)[19] to discuss and review data developed in follow up to the 2007 meeting. There were many presentations, including from industry representatives, speakers on behalf of the public, and FDA.[20] The Committee discussed the current scientific efficacy, safety, and pharmacokinetic data for oral phenylephrine and noted that, while the results from older studies were questionable, the multiple, newer studies are credible, compelling, and fail to demonstrate that oral phenylephrine is effective to relieve nasal congestion in the study populations. In discussing the pharmacokinetic data, the Committee acknowledged the low bioavailability of oral phenylephrine explains its lack of efficacy.[21]

The Committee was asked to vote on the following question: "Do the current scientific data that were presented support that the monograph dosage of orally administered phenylephrine is effective as a nasal decongestant? If yes, discuss what data you consider supportive. If no, discuss what additional data, if any, are needed to assess phenylephrine pharmacokinetics or efficacy." The Committee unanimously voted "No" (16 to 0) that the current scientific data do not support that the dosage of oral phenylephrine allowed under OTC Monograph M012 (see § M012.80(d)(1) of OTC Monograph M012) is effective as a nasal decongestant. While some Committee members were in favor of additional studies to assess the pharmacokinetics or efficacy of oral phenylephrine, most dismissed any need for further research due to the compelling existing evidence.[22]

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[19] Meeting materials, including presentation slides and briefing documents for the 2023 meeting, September 11-12, 2023, are available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-september-11-12-2023-meeting-nonprescription-drugs-advisory-committee-meeting-announcement.

[20] Ibid.

[21] See final summary of minutes of the 2023 NDAC and the transcript for details of the Committee's discussion, available at available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-september-11-12-2023-meeting-nonprescription-drugs-advisory-committee-meeting-announcement.

[22] See final summary of minutes of the 2023 NDAC and the transcript for details of the Committee's discussion, available at available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-september-11-12-2023-meeting-nonprescription-drugs-advisory-committee-meeting-announcement.

The Committee also reached unanimous consensus that the scientific data presented do not support higher doses of oral phenylephrine to treat nasal congestion, citing reasons such as pharmacokinetic data, potential cardiovascular safety risks, resource allocation, and the availability of effective alternative treatments.[23]

IV. Statement of Reasons for Issuance of Proposed Order

FDA conducted a comprehensive scientific review[24] of available data on the efficacy, pharmacology, and safety of oral phenylephrine as a nasal decongestant for adult and pediatric populations.[25] Based on this scientific review, FDA proposes that oral phenylephrine is not effective[26] as a nasal decongestant under the conditions described in OTC Monograph M012. FDA proposes to amend OTC Monograph M012 to remove oral phenylephrine as an active ingredient within the dosage limits and dosage forms allowed under OTC Monograph M012 because it is not generally recognized as safe and effective under sections 505G(b)(1)(C) and 201(p)(1) of the FD&C Act and therefore subject to the requirement for an approved application under section 505 of the FD&C Act (21 U.S.C. 355).

A. Scientific Review of Efficacy Data

FDA conducted a comprehensive review of data regarding the effectiveness of oral phenylephrine as a nasal decongestant.[27] FDA reviewed the historical data used to support FDA's generally recognized as safe and effective determination for oral phenylephrine as a nasal decongestant in the 1994 final rule. FDA also reviewed the data on phenylephrine that have become available since the publication of the 1994 final rule. FDA evaluated this newer data within the context of the long history of oral phenylephrine use and the data used to support the 1994 final rule. FDA evaluated this newer data on the effectiveness of oral phenylephrine as well as the historical data that previously supported the generally recognized as safe and effective determination.

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[23] Ibid.

[24] FDA's Scientific Review Supporting Proposed Administrative Order is available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf, under the supporting documents for this Proposed Administrative Order OTC000036.

[25] In OTC Monograph M012, FDA's generally recognized as safe and effective determination on the doses of oral phenylephrine for ages less than 12 years old was based entirely on historical use and not clinical data in those age groups (see 41 FR 38312 at 38333). Since all of the generally recognized as safe and effective determinations for drug products under OTC Monograph M012, including oral phenylephrine, were made based on extrapolation of efficacy and dosing from adult data, FDA evaluates these pediatric issues by addressing the adult data under the pediatric extrapolation principles set forth in the draft guidance for industry (CDER 2022b) and in the draft guidance (CDER 2022a). Guidances are updated periodically. For the most recent version of a guidance, see https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[26] Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed (see 21 CFR 330.10(a)(4)(ii)).

[27] For FDA's comprehensive review of data regarding the effectiveness of oral phenylephrine as a nasal decongestant, see the Scientific Review Supporting Proposed Administrative Order, section II. Scientific Review of Efficacy Data.

As part of FDA's review of the historical data, FDA reviewed each of the 14 study reports and publications reviewed by the Panel to support the effectiveness of oral phenylephrine as a nasal decongestant.[28] FDA proposes that due to significant issues with study design, methodology, disease context, conduct, and statistical analysis, the studies should not be relied upon to support general recognition of the effectiveness of oral phenylephrine as a nasal decongestant.

As part of FDA's review of data on oral phenylephrine that have become available since the publication of the 1994 final rule, FDA reviewed the results for two environmental exposure unit studies conducted by Schering-Plough Merck.[29] The data from these two studies fail to demonstrate efficacy of oral phenylephrine as a nasal decongestant. The two studies compared oral phenylephrine with placebo and either oral pseudoephedrine or a combination of oral loratadine and montelukast. FDA determines that the studies' design and methodology, study population, and endpoints were appropriate. FDA agrees with Schering-Plough Merck's conclusion that a single 10 mg or 12 mg dose of oral phenylephrine failed to provide any benefit over placebo.

FDA reviewed three additional clinical trials: two clinical trials completed by Merck to support the efficacy of doses of oral phenylephrine, other than doses of 10 mg, and one clinical trial completed by Johnson & Johnson Consumer, Inc. (J&J). While FDA acknowledges several limitations with the clinical trials, the clinical trials provided high quality evidence demonstrating that oral phenylephrine is not effective as a nasal decongestant.[30] The data from the clinical trials do not demonstrate the efficacy of oral phenylephrine doses including 10 mg, 20 mg, 30 mg, and 40 mg immediate-release formulations, nor for a 30 mg extended-release formulation.

Based on FDA's review of the efficacy data, FDA proposes that the data demonstrate that oral phenylephrine is not effective as a nasal decongestant within the dosage limits and in the dosage forms allowed under OTC Monograph M012.

B. Scientific Review of Pharmacology Data

FDA conducted a comprehensive review of pharmacology data for oral phenylephrine and its metabolites.[31] FDA reviewed clinical trials with pharmacokinetic and pharmacodynamic data. Additionally, FDA also reviewed publicly available pharmacokinetic data in one new drug application (NDA) for a phenylephrine drug product.

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[28] For FDA's comprehensive review of the 14 study reports and publications reviewed by the Panel, see the Scientific Review Supporting Proposed Administrative Order, section II.A. Review of Historical Data Regarding Efficacy

[29] For FDA's comprehensive review of the two environmental exposure unit studies, see the Scientific Review Supporting Proposed Administrative Order, section II.B.1. Review of Environmental Exposure Unit Studies.

[30] For FDA's comprehensive review of these clinical trials on the efficacy of oral phenylephrine, see the Scientific Review Supporting Proposed Administrative Order, section II.B.2. Review of Clinical Trials on Efficacy of Oral PE.

[31] For FDA's comprehensive review of the pharmacology of oral phenylephrine as a nasal decongestant including the oral bioavailability and the pharmacokinetic/pharmacodynamic relationship, see the Scientific Review Supporting Proposed Administrative Order, section III. Scientific Review of Pharmacology Data.

Phenylephrine is an alpha-1 adrenergic receptor agonist.[32] The actual oral bioavailability of phenylephrine is less than 1 percent, which explains the lack of efficacy of oral phenylephrine.[33] The low oral bioavailability of phenylephrine is due to a high first-pass metabolism effect. The major metabolites of phenylephrine are not pharmacologically active. In comparison, when administered via intravenous infusion, a relatively higher systemic exposure is achieved with a much lower dose of phenylephrine due to the lack of first-pass metabolism.

FDA conducted a review of the relationship between phenylephrine pharmacokinetic and systemic alpha-1 adrenergic pharmacodynamic response (systolic blood pressure change from baseline) and compared those relationships between orally administered phenylephrine and intravenously administered phenylephrine.[34] FDA concludes that an oral dose of approximately 50 mg phenylephrine is needed to achieve a noticeable systemic pharmacodynamic change, such as an increase in systolic blood pressure of 5 mmHg. Although there are insufficient data to directly translate the systemic pharmacodynamic changes (such as change of systolic blood pressure) to local nasal decongestant effect, these data suggest that a dose higher than 40 mg of phenylephrine is likely needed.

Based on FDA's review of the pharmacology data, FDA concludes that oral phenylephrine has very low systemic exposure with little systemic pharmacologic effect within the dosage limits and dosage forms allowed under OTC Monograph M012, which further explains the lack of efficacy data.

C. Scientific Review of Safety Data

FDA conducted a comprehensive review of data regarding the safety of oral phenylephrine as a nasal decongestant.[35] FDA reviewed safety data on oral phenylephrine that have become available since the publication of the 1994 final rule. FDA identified one clinical trial that was specifically a safety study comparing extended release oral phenylephrine 30 mg tablets and placebo; this trial found no meaningful difference in blood pressure between oral phenylephrine and placebo.[36] To evaluate whether there is a safety signal (i.e., potential safety issue) for oral phenylephrine, FDA evaluated safety reports for single-ingredient oral phenylephrine products in

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[32] For FDA comprehensive review of the pharmacologic activity of oral phenylephrine, see Scientific Review Supporting Proposed Administrative Order, sections III.A. Background and III.B.1. Pharmacologic Activity of PE and Its Metabolites.

[33] For FDA's comprehensive review of studies on the oral bioavailability of phenylephrine and the pharmacokinetic and pharmacodynamic relationship, see Scientific Review Supporting Proposed Administrative Order, sections III.B.2. Oral Bioavailability and III.B.3. Pharmacokinetic/Pharmacodynamic Relationships.

[34] For FDA's comprehensive review of studies on the pharmacokinetic and pharmacodynamic relationship, see Scientific Review Supporting Proposed Administrative Order, section III.B.3. Pharmacokinetic/Pharmacodynamic Relationships.

[35] For FDA's comprehensive review of safety data regarding oral phenylephrine as a nasal decongestant, see Scientific Review Supporting Proposed Administrative Order, section IV. Scientific Review of Safety Data.

[36] For FDA's review of the clinical trial on the safety of oral phenylephrine, see Scientific Review Supporting Proposed Administrative Order, section IV.B.1. Study P07529 (NCT0874120).

the FDA Adverse Event Reporting System (FAERS),[37] America's Poison Centers - National Poison Data System (APC-NPDS), and medical literature. Despite widespread use of phenylephrine, FDA identified very few cases reporting serious adverse events for oral phenylephrine.[38] Analysis of FAERS data also indicated that consumers who reported adverse events used oral phenylephrine products at higher doses, or at more frequent dosing intervals or for longer duration of therapy than specified on the label, which might reflect oral phenylephrine's poor bioavailability and lack of effectiveness.

Based on FDA's review of available data specifically focused on the safety of oral phenylephrine, in addition to the efficacy and pharmacology studies that provided additional information on safety, FDA concludes that no safety signal was identified for oral phenylephrine within the dosage limits and in the dosage forms allowed under OTC Monograph M012.

D. FDA Proposal to Remove Oral Phenylephrine from the Conditions of Use under OTC Monograph M012

Based on our comprehensive scientific review of available data, FDA is proposing that oral phenylephrine—both phenylephrine hydrochloride and phenylephrine bitartrate—is not generally recognized as safe and effective under section 201(p)(1) of the FD&C Act because it is not effective as a nasal decongestant within the dosage limits and in the dosage forms allowed under OTC Monograph M012. Furthermore, there are no data that demonstrate that oral phenylephrine is effective as a nasal decongestant at any dosage. Rather, data demonstrates that oral phenylephrine is not effective within the dosage limits and in the dosage forms allowed under in OTC Monograph M012.

FDA conducted a careful and thorough review of all available efficacy, pharmacology, and safety data for oral phenylephrine. FDA reviewed significant data on oral phenylephrine which was not available at the time of the FDA's initial generally recognized as safe and effective determination for oral phenylephrine in the 1994 final rule, specifically new efficacy and pharmacology data. The data on phenylephrine that have become available since the 1994 final rule demonstrates that oral phenylephrine is not effective as a nasal decongestant. In addition, due to significant issues with study design, methodology, disease context, conduct, and statistical analysis, the historical studies cannot be relied upon as evidence of efficacy of oral phenylephrine as a nasal decongestant. The lack of efficacy for oral phenylephrine can be explained with clinical pharmacology data demonstrating that oral phenylephrine has no meaningful systemic exposure within the dosage limits and in the dosage forms set forth in OTC Monograph M012. While FDA did not identify a safety signal for oral phenylephrine within the dosage limits and in the dosage forms under OTC Monograph M012, available data

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[37] FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. For more information, see Questions and Answers on FAERS available at https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers.

[38] For FDA's comprehensive review of the safety reports on the safety of oral phenylephrine, see Scientific Review Supporting Proposed Administrative Order, section IV.B.2. Safety Reports.

suggests that a much higher dose of phenylephrine would be needed to achieve a clinically meaningful outcome which would raise significant questions about safety.

Therefore, FDA is proposing to amend OTC Monograph M012 to remove oral phenylephrine hydrochloride and phenylephrine bitartrate as nasal decongestant active ingredients. If finalized, OTC nasal decongestant drug products containing oral phenylephrine hydrochloride and phenylephrine bitartrate will be deemed new drugs under section 201(p) of the FD&C Act and subject to the requirements for an approved new drug application under section 505 of the FD&C Act. This proposed order also includes minor stylistic and formatting changes to improve the readability and presentation of OTC Monograph M012, including removing references to historical *Federal Register* notices because OTC monographs are no longer modified through notice and comment rulemaking.

V. Exclusivity

This proposed order, if finalized, will not have the effect of authorizing marketing exclusivity under section 505G(b)(5)(C) of the FD&C Act for any entity or with respect to any drug.

VI. Effective Date

This proposed order, if finalized, shall take effect one year (365 calendar days) from the date the final order based on this proposed order is published.

VII. Analysis of Environmental Impact

FDA has carefully considered the potential environmental effects of this proposed order. FDA has concluded, under 21 CFR 25.31(a), that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. References

For references that support this proposed order, see the Federal eRulemaking Portal: https:/www.regulations.gov.

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IX. Proposed Administrative Order (OTC000036)

A. Proposed OTC Monograph Determinations

FDA proposes to remove oral phenylephrine hydrochloride and oral phenylephrine bitartrate as nasal decongestant active ingredients because they are not effective and therefore not generally recognized as safe and effective under section 201(p)(1) of the FD&C Act.

Thus, FDA is issuing Proposed Administrative Order (OTC000036), which if finalized would amend OTC Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (OTC Monograph M012) as follows:

1. Amend § M012.20(a) of OTC Monograph M012 to remove paragraphs (1) and (4).

2. Amend § M012.20(a) of OTC Monograph M012 to redesignate paragraphs (2) and (3) as (1) and (2), respectively.

3. Amend § M012.80(c)(1)(i) of OTC Monograph M012 to read as follows:

   (i) For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in §§ M012.20(a)(1) and (a)(2) when labeled for adults.

4. Amend § M012.80(c)(1)(ii) of OTC Monograph M012 to read as follows:

   (ii) For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in §§ M012.20(a)(1) and (a)(2) when labeled for children under 12 years of age.

5. Amend § M012.80(d)(1) of OTC Monograph M012 to remove paragraphs (i) and (iii).

6. Amend § M012.80(d)(1) of OTC Monograph M012 to redesignate paragraph (ii) as paragraph (i) and read as follows:

   (i) For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in §§ M012.20(a)(1) and (a)(2). Adults and children 12 years of age and over: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours. Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

B. Proposed Revision: OTC Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use

Upon the effective date of this order, if finalized, as a reflection of the cumulative product of all relevant final orders previously established and in effect, OTC Monograph M012 would read, in its entirety, as follows:

U.S. Food and Drug Administration

Over-the-Counter (OTC) Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use

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Sec.

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M012.80 Labeling of nasal decongestant drug products

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Part D—Professional Use

M012.90 Professional labeling

Part E—Exemption From Prescription Requirements

M012.100 Exemption from prescription requirements

Part A—General Provisions

§ M012.1 Scope

An over-the-counter (OTC) cold, cough, allergy, bronchodilator, or antiasthmatic drug product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this OTC monograph and each of the general conditions established in 21 CFR 330.1.

§ M012.3 Definitions

As used in this OTC monograph:

(a) Bronchodilator drug. A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the symptomatic treatment of the wheezing and shortness of breath of asthma.

(b) Oral antitussive drug. A drug that either is taken by mouth or is dissolved in the mouth in the form of a lozenge and acts systemically to relieve cough.

(c) Topical antitussive drug. A drug that relieves cough when inhaled after being applied topically to the throat or chest in the form of an ointment or from a steam vaporizer, or when dissolved in the mouth in the form of a lozenge for a local effect.

(d) Expectorant drug. A drug taken orally to promote or facilitate the removal of secretions from the respiratory airways.

(e) Antihistamine drug. A drug used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis).

(f) Oral nasal decongestant drug. A drug that is taken by mouth and acts systemically to reduce nasal congestion caused by acute or chronic rhinitis.

(g) Topical nasal decongestant drug. A drug that when applied topically inside the nose, in the form of drops, jellies, or sprays, or when inhaled intranasally reduces nasal congestion caused by acute or chronic rhinitis.

(h) Calibrated dropper. A dropper calibrated such that the volume error incurred in measuring any liquid does not exceed 15 percent under normal use conditions.

(i) Effervescent dosage form. A dosage form intended to be dissolved in water before administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.

Part B—Active Ingredients

§ M012.12 Antihistamine active ingredients

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient:

(a) Brompheniramine maleate

(b) Chlorcyclizine hydrochloride

(c) Chlorpheniramine maleate

(d) Dexbrompheniramine maleate

(e) Dexchlorpheniramine maleate

(f) Diphenhydramine citrate

(g) Diphenhydramine hydrochloride

(h) Doxylamine succinate

(i) Phenindamine tartrate

(j) Pheniramine maleate

(k) Pyrilamine maleate

(l) Thonzylamine hydrochloride

(m) Triprolidine hydrochloride

§ M012.14 Antitussive active ingredients

The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient in § M012.74(d):

(a) Oral antitussives.

(1) Chlophedianol hydrochloride

(2) Codeine ingredients. The following ingredients may be used only in combination in accordance with § M012.100 and 21 CFR 1308.15(c)

(i) Codeine

(ii) Codeine phosphate

(iii) Codeine sulfate

(3) Dextromethorphan

(4) Dextromethorphan hydrobromide

(5) Diphenhydramine citrate

(6) Diphenhydramine hydrochloride

(b) Topical antitussives

(1) Camphor

(2) Menthol

§ M012.16 Bronchodilator active ingredients

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient:

(a) Ephedrine

(b) Ephedrine hydrochloride

(c) Ephedrine sulfate

(d) Epinephrine

(e) Epinephrine bitartrate

(f) Racephedrine hydrochloride

(g) Racepinephrine hydrochloride

§ M012.18 Expectorant active ingredient

The active ingredient of the product is guaifenesin when used within the dosage limits established in § M012.78(d).

§ M012.20 Nasal decongestant active ingredients

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage forms established for each ingredient:

(a) Oral nasal decongestants

(1) Pseudoephedrine hydrochloride

(2) Pseudoephedrine sulfate

(b) Topical nasal decongestants

(1) Levmetamfetamine

(2) Ephedrine

(3) Ephedrine hydrochloride

(4) Ephedrine sulfate

(5) Naphazoline hydrochloride

(6) Oxymetazoline hydrochloride

(7) Phenylephrine hydrochloride

(8) Propylhexedrine

(9) Xylometazoline hydrochloride

§ M012.40 Permitted combinations of active ingredients

The following combinations are permitted provided each active ingredient is present within the dosage limits established in OTC Monographs M012, M013, and M022 and the product is labeled in accordance § M012.70 or § M012.85:

(a) Any single antihistamine active ingredient identified in § M012.12 may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(b) Any single antihistamine active ingredient identified in § M012.12 may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) provided that the product is labeled according to § M012.85.

(c) Any single antihistamine active ingredient identified in § M012.12 may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(d) Any single antihistamine active ingredient identified in §§ M012.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in §§ M012.14(a)(1) through (a)(4) provided that the product is labeled according to § M012.85(c)(4). Diphenhydramine citrate in § M012.12(f) and § M012.14(a)(5) or diphenhydramine hydrochloride in § M012.12(g) and § M012.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § M012.70(a).

(e) Any single antihistamine active ingredient identified in §§ M012.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in §§ M012.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § M012.20(a) provided that the product is labeled according to § M012.85(c)(4). Diphenhydramine citrate in § M012.12(f) and § M012.14(a)(5) or diphenhydramine hydrochloride in § M012.12(g) and § M012.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § M012.70(a).

(f) Any single antihistamine active ingredient identified in §§ M012.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in §§ M012.14(a)(1) through (a)(4) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85(c)(4). Diphenhydramine citrate in § M012.12(f) and § M012.14(a)(5) or diphenhydramine hydrochloride in § M012.12(g) and § M012.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § M012.70(a).

(g) Any single antihistamine active ingredient identified in §§ M012.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in §§ M012.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § M012.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85(c)(4). Diphenhydramine citrate in § M012.12(f) and § M012.14(a)(5) or diphenhydramine hydrochloride in § M012.12(g) and § M012.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § M012.70(a).

(h) Any single oral antitussive active ingredient identified in §§ M012.14(a)(1) through (a)(4) may be combined with any single expectorant active ingredient identified in § M012.18 provided that the product is labeled according to § M012.85.

(i) Any single oral antitussive active ingredient identified in § M012.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) provided that the product is labeled according to § M012.85.

(j) Any single oral antitussive active ingredient identified in §§ M012.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) and any single expectorant active ingredient identified in § M012.18 provided that the product is labeled according to § M012.85.

(k) Any single antitussive active ingredient identified in §§ M012.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth. Menthol in § M012.14(b)(2) and OTC Monograph M022 may be both the antitussive and the anesthetic/analgesic active ingredient provided that the product is labeled according to § M012.70(b).

(l) Any single oral antitussive active ingredient identified in § M012.14(a) may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(m) Any single oral antitussive active ingredient identified in § M012.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(n) Any single oral antitussive active ingredient identified in §§ M012.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) and any single expectorant active ingredient identified in § M012.18 and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(o) Any single expectorant active ingredient identified in § M012.18 may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(p) Any single expectorant active ingredient identified in § M012.18 may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) provided that the product is labeled according to § M012.85.

(q) Any single expectorant active ingredient identified in § M012.18 may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(r) Any single oral nasal decongestant active ingredient identified in § M012.20(a) may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § M012.85.

(s) Any single oral nasal decongestant active ingredient identified in § M012.20(a) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient identified, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85.

(t) Any single oral nasal decongestant active ingredient identified in § M012.20(a) may be combined with any single antitussive active ingredient identified in §§ M012.14(a) or (b)(2) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(u) Camphor identified in § M012.14(b)(1) may be combined with menthol identified in § M012.14(b)(2) and eucalyptus oil (1.2 to 1.3 percent) provided that the product is available only in a suitable ointment vehicle and provided that the product is labeled according to § M012.85.

(v) Levmetamfetamine identified in § M012.20(b)(1) may be combined with aromatics (camphor (54 milligrams (mg)), menthol (80 mg), methyl salicylate (11 mg), and lavender oil (4 mg)) provided that the product is available only as a nasal inhaler and provided that the product is labeled according to § M012.85.

(w) Any single antitussive active ingredient identified in §§ M012.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(x) Any single oral nasal decongestant active ingredient identified in § M012.20(a) may be combined with any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85.

(y) Any single antitussive active ingredient identified in §§ M012.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(z) Any single antitussive active ingredient identified in §§ M012.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient or any combination of anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(aa) Any single oral nasal decongestant active ingredient identified in § M012.20(a) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient or any combination of oral anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85.

(bb) Any single antitussive active ingredient identified in §§ M012.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § M012.20(a) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient identified or any combination of anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § M012.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

Part C—Labeling

§ M012.70 Labeling of OTC drug products containing ingredients that are used for treating concurrent symptoms (in either a single-ingredient or combination drug product)

The statements of identity, indications, warnings, and directions for use 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) For products containing diphenhydramine citrate and diphenhydramine hydrochloride identified in §§ M012.14(a)(5) and (a)(6). The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antihistamine/cough suppressant" or "antihistamine/antitussive (cough suppressant)." The indications shall be combined from § M012.72(b) and § M012.74(b). The warnings shall be combined from §§ M012.72(c)(1), (c)(2), (c)(4), and (c)(6) and §§ M012.74(c)(1), (c)(2), (c)(3), and (c)(4). Alternatively, all of the warnings in § M012.74(c) shall be used. The directions for OTC labeling shall follow §§ M012.74(d)(1)(iv) or (d)(1)(v), as applicable.

(b) For products containing menthol identified in § M012.14(b)(2) and § M022.12(f) of OTC Monograph M022. The product contains 5 to 10 milligrams menthol. The labeling of the product contains the established name of the drug, if any, and identifies the product as a "cough suppressant/oral anesthetic" or "antitussive (cough suppressant)/oral anesthetic." The indications shall be combined from § M012.74(b) and OTC Monograph M022. The warnings shall be combined from §§ M012.74(c)(1), (c)(2), and (c)(3) and OTC Monograph M022. The directions shall be: "Directions [in bold type] [bullet][39] adults and children 2 years and over: dissolve lozenge slowly in the mouth. Repeat every 2 hours as needed or as directed by a doctor. [bullet] children under 2 years of age: ask a doctor."

§ M012.72 Labeling of antihistamine 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 an "antihistamine."

[39] See 21 CFR 201.66(b)(4) for definition of bullet symbol.

(b) Indications. The labeling of the product states, under the heading "Uses," any of the phrases listed in § M012.72(b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in § M012.72(b), may also be used, as provided in 21 CFR 330.1(c)(2), subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (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)).

(1) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

(2) "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

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

(1) "May cause excitability especially in children."

(2) "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland."

(3) For products containing brompheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in §§ M012.12(a), (b), (c), (d), (e), (i), (j), (k), (l), and (m). "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(4) For products containing diphenhydramine citrate, diphenhydramine hydrochloride, or doxylamine succinate identified in §§ M012.12(f), (g), and (h). "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(5) For products containing phenindamine tartrate identified in § M012.12(i). "May cause nervousness and insomnia in some individuals."

(6) For products that are labeled only for use by children under 12 years of age. The labeling of the product contains only the warnings identified in §§ M012.72(c)(1) and (c)(5) as well as the following:

(i) "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

(ii) For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in §§ M012.12(a), (c), (d), (e), (i), (j), (k), (l), and (m). "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(iii) For products containing diphenhydramine citrate, diphenhydramine hydrochloride, or doxylamine succinate identified in §§ M012.12(f), (g), and (h). "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(iv) For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in §§ M012.12(f) and (g). "Do not use [bullet] with any other product containing diphenhydramine, even one used on skin."

(7) For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in §§ M012.12(f) and (g). "Do not use [bullet] with any other product containing diphenhydramine, even one used on skin."

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

(1) For products containing brompheniramine maleate identified in § M012.12(a). Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(2) For products containing chlorcyclizine hydrochloride identified in § M012.12(b). Adults and children 12 years of age and over: oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 12 years of age: consult a doctor.

(3) For products containing chlorpheniramine maleate identified in § M012.12(c). Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(4) For products containing dexbrompheniramine maleate identified in § M012.12(d). Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(5) For products containing dexchlorpheniramine maleate identified in § M012.12(e). Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(6) For products containing diphenhydramine citrate identified in § M012.12(f). Adults and children 12 years of age and over: oral dosage is 38 to 76 milligrams every 4 to 6 hours, not to exceed 456 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 to 38 milligrams every 4 to 6 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(7) For products containing diphenhydramine hydrochloride identified in § M012.12(g). Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(8) For products containing doxylamine succinate identified in § M012.12(h). Adults and children 12 years of age and over: oral dosage is 7.5 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 3.75 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(9) For products containing phenindamine tartrate identified in § M012.12(i). Adults and children 12 years of age and over: oral dosage is 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(10) For products containing pheniramine maleate identified in § M012.12(j). Adults and children 12 years of age and over: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(11) For products containing pyrilamine maleate identified in § M012.12(k). Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 200 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(12) For products containing thonzylamine hydrochloride identified in § M012.12(l). Adults and children 12 years of age and over: oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 600 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(13) For products containing triprolidine hydrochloride identified in § M012.12(m). Adults and children 12 years of age and over: oral dosage is 2.5 milligrams every 4 to 6 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 4 to 6 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(e) The word “physician” may be substituted for the word “doctor” in any of the labeling statements in § M012.72.

§ M012.74 Labeling of antitussive 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 “cough suppressant” or an “antitussive (cough suppressant).”

(b) Indications. The labeling of the product states, under the heading “Uses,” any of the phrases listed in § M012.74(b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in § M012.74(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) “Temporarily” (select one of the following: “alleviates,” “calms,” “controls,” “decreases,” “quiets,” “reduces,” “relieves,” or “suppresses”) “cough due to” (select one of the following: “minor bronchial irritation” or “minor throat and bronchial irritation”) (select one of the following: “as may occur with,” “associated with,” or “occurring with”) (select one of the following: “A cold” or “the common cold”) “or inhaled irritants.”

(2) “Temporarily” (select one of the following: “alleviates,” “calms,” “controls,” “decreases,” “quiets,” “reduces,” “relieves,” or “suppresses”) “cough” (select one of the following: “as may occur with,” “associated with,” or “occurring with”) (select one of the following: “A cold,” “the common cold,” or “inhaled irritants”).

(3) In addition to the required information identified in §§ M012.74(b)(1) and (2), the labeling of the product may contain any (one or more) of the following statements:

(i) "Cough suppressant which temporarily" (select one of the following: "Alleviates," "controls," "decreases," "reduces," "relieves," or "suppresses") "the impulse to cough."

(ii) "Temporarily helps you cough less."

(iii) "Temporarily helps to" (select one of the following: "Alleviate," "control," "decrease," "reduce," "relieve," or "suppress") "the cough reflex that causes coughing."

(iv) "Temporarily" (select one of the following: "Alleviates," "controls," "decreases," "reduces," "relieves," or "suppresses") "the intensity of coughing."

(v) (Select one of the following: "Alleviates," "Controls," "Decreases," "Reduces," "Relieves," or "Suppresses") (select one of the following: "Cough," "the impulse to cough," or "your cough") "to help you" (select one of the following: "Get to sleep," "sleep," or "rest").

(vi) For products containing chlophedianol hydrochloride, codeine ingredients, dextromethorphan, or dextromethorphan hydrobromide identified in §§ M012.14(a) (1), (2), (3), and (4). "Calms the cough control center and relieves coughing."

(vii) For products containing chlophedianol hydrochloride, dextromethorphan, dextromethorphan hydrobromide, camphor, or menthol identified in §§ M012.14(a) (1), (3), (4) and (b) (1) and (2).

(A) "Nonnarcotic cough suppressant for the temporary" (select one of the following: "alleviation," "control," "decrease," "reduction," "relief," or "suppression") "of cough."

(B) (Select one of the following: "Alleviates," "Controls," "Decreases," "Reduces," "Relieves," or "Suppresses") "cough impulses without narcotics."

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

(1) For oral and topical antitussives. "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor."

(2) For oral and topical antitussives labeled for adults or for adults and children under 12 years of age. "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(3) For oral and topical antitussives labeled only for children under 12 years of age. “Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor.”

(4) Oral antitussives

(i) For products containing codeine ingredients identified in § M012.14(a)(2). “May cause or aggravate constipation.”

(ii) For products containing codeine ingredients identified in § M012.14(a)(2) when labeled only for adults. “Do not take this product if you have a chronic pulmonary disease or shortness of breath unless directed by a doctor.”

(iii) For products containing codeine ingredients identified in § M012.14(a)(2) when labeled only for children under 12 years of age. “Do not give this product to children who have a chronic pulmonary disease, shortness of breath, or who are taking other drugs unless directed by a doctor.”

(iv) For products containing codeine ingredients identified in § M012.14(a)(2) when labeled for use in adults and children under 12 years of age. “Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor.”

(v) For products containing dextromethorphan or dextromethorphan hydrobromide as identified in §§ M012.14(a)(3) and (a)(4) when labeled for adults or for adults and children under 12 years of age. Drug interaction precaution. “Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.”

(vi) For products containing dextromethorphan or dextromethorphan hydrobromide as identified in §§ M012.14(a)(3) and (a)(4) when labeled only for children under 12 years of age. Drug interaction precaution. “Do not use in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product.”

(vii) For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in §§ M012.14(a)(5) and (a)(6). “May cause excitability especially in children.”

(viii) For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in §§ M012.14(a)(5) and (a)(6) when labeled only for children under 12 years of age

(A) "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

(B) "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(C) "Do not use [bullet] with any other product containing diphenhydramine, even one used on skin."

(ix) For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in §§ M012.14(a)(5) and (a)(6) when labeled for use in adults and children under 12 years of age

(A) "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland."

(B) "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(C) "Do not use [bullet] with any other product containing diphenhydramine, even one used on skin."

(5) Topical antitussives

(i) For products containing camphor or menthol identified in §§ M012.14(b)(1) and (2) in a suitable ointment vehicle. "For external use only. Do not take by mouth or place in nostrils."

(ii) For products containing camphor or menthol identified in §§ M012.14(b)(1) and (2) for steam inhalation use. "For steam inhalation only. Do not take by mouth."

(iii) For any product containing camphor or menthol in a suitable ointment vehicle or for steam inhalation use and meets the definition of one of the signal words ("extremely flammable," "flammable," "combustible") as described in 16 CFR 1500.3(b)(10). The labeling contains the appropriate flammability signal word(s) followed by a colon and the statement "Keep away from fire or flame."

(iv) For any product containing camphor or menthol in a suitable ointment vehicle and that does not contain a flammability signal word as described in 16 CFR 1500.3(b)(10). "When using this product, do not [bullet] heat [bullet] microwave [bullet] add to hot water or any container where heating water. May cause splattering and result in burns." [Information highlighted in bold type.]

(v) For any product containing camphor or menthol in a suitable ointment vehicle and that contains a flammability signal word as described in 16 CFR 1500.3(b)(10). "When using this product, do not [bullet] heat [bullet] microwave [bullet] use near an open flame [bullet] add to hot water or any container where heating water. May cause splattering and result in burns." [Information highlighted in bold type.]

(vi) For any product containing camphor or menthol for steam inhalation use. "When using this product, do not [bullet] heat [bullet] microwave [bullet] use near an open flame [bullet] add to hot water or any container where heating water except when adding to cold water only in a hot steam vaporizer. May cause splattering and result in burns." [Information highlighted in bold type.]

(vii) For any product formulated in a volatile vehicle. The labeling contains the following statement under the heading "Other information": "Close container tightly and store at room temperature away from heat."

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

(1) Oral antitussives

(i) For products containing chlophedianol hydrochloride identified in § M012.14(a)(1). Adults: Oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: Consult a doctor.

(ii) For products containing codeine ingredients identified in § M012.14(a)(2). Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could result in serious side effects for your child.

(iii) For products containing dextromethorphan or dextromethorphan hydrobromide identified in §§ M012.14(a)(3) and (4). The dosage is equivalent to dextromethorphan hydrobromide. Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 hours or 30 milligrams every 6 to 8 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 hours or 15 milligrams every 6 to 8 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children 2 to under 6 years of age: Oral dosage is 2.5 to 5 milligrams every 4 hours or 7.5 milligrams every 6 to 8 hours, not to exceed 30 milligrams in 24 hours, or as directed by a doctor. Children under 2 years of age: Consult a doctor.

(iv) For products containing diphenhydramine citrate identified in § M012.14(a)(5). Adults and children 12 years of age and over: oral dosage is 38 milligrams every 4 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 milligrams every 4 hours, not to exceed 114 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(v) For products containing diphenhydramine hydrochloride identified in § M012.14(a)(6). Adults and children 12 years of age and over: oral dosage is 25 milligrams every 4 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(2) Topical antitussives

(i) For products containing camphor identified in § M012.14(b)(1) in a suitable ointment vehicle. The product contains 4.7 to 5.3 percent camphor. “[bullet] see important warnings under ‘When using this product’ [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older: [bullet] rub on the throat and chest in a thick layer [bullet] cover with a warm, dry cloth if desired [bullet] clothing should be loose about throat and chest to help vapors reach the nose and mouth [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(ii) For products containing menthol identified in § M012.14(b)(2) in a suitable ointment vehicle. The product contains 2.6 to 2.8 percent menthol. “[bullet] see important warnings under ‘When using this product’” [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older: [bullet] rub on the throat and chest in a thick layer [bullet] cover with a warm, dry cloth if desired [bullet] clothing should be loose about throat and chest to help vapors reach the nose and mouth [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(iii) For products containing menthol identified in § M012.14(b)(2) in a lozenge. The product contains 5 to 10 milligrams menthol. Adults and children 2 to under 12 years of age: Allow lozenge to dissolve slowly in the mouth. May be repeated every hour as needed or as directed by a doctor. Children under 2 years of age: Consult a doctor.

(iv) For products containing camphor identified in § M012.14(b)(1) for steam inhalation use. The product contains 6.2 percent camphor. “[bullet] see important warnings under ‘When using this product’” [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older (select one of the following, as appropriate):

(A) For products formulated to be added directly to cold water inside a hot steam vaporizer: [bullet] use 1 tablespoonful of solution for each quart of water or 1½ teaspoonsful of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer's directions for using vaporizer, or

(B) For products formulated to be placed in the medication chamber of a hot steam vaporizer: [bullet] place water in the vaporizer and follow manufacturer's directions for using vaporizer [bullet] place solution in the medication chamber only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(v) For products containing menthol identified in § M012.14(b)(2) for steam inhalation use. The product contains 3.2 percent menthol. “[bullet] see important warnings under ‘When using this product’” [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older (select one of the following, as appropriate):

(A) For products formulated to be added directly to cold water inside a hot steam vaporizer: [bullet] use 1 tablespoonful of solution for each quart of water or 1½ teaspoonsful of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer's directions for using vaporizer, or

(B) For products formulated to be placed in the medication chamber of a hot steam vaporizer: [bullet] place water in the vaporizer and follow manufacturer’s directions for using vaporizer [bullet] place solution in the medication chamber only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(e) The word “physician” may be substituted for the word “doctor” in any of the labeling statements in § M012.74.

(f) Exemption from the general accidental overdose warning. The labeling for antitussive drug products containing the active ingredient identified in § M012.14(b)(2) marketed in accordance with § M012.74(d)(2)(iii) is exempt from the requirement in 21 CFR 330.1(g) that the labeling bear the general warning statement "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." The labeling must continue to bear the first part of the general warning in 21 CFR 330.1(g), which states, "Keep this and all drugs out of the reach of children."

§ M012.76 Labeling of bronchodilator 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 "bronchodilator."

(b) Indication. The labeling of the product states the following under the heading "Use": "for temporary relief of mild symptoms of intermittent asthma: [bullet] wheezing [bullet] tightness of chest [bullet] shortness of breath." Other truthful and nonmisleading statements, describing only the indication for use that has been established and listed in § M012.76(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.

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

(1) The following statements shall appear after the subheading "Do not use" [in bold type]:

(i) "[Bullet] unless a doctor said you have asthma."

(ii) "[Bullet] if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product."

(2) The following information shall appear after the subheading "Ask a doctor before use if you have" [in bold type]: "[bullet] ever been hospitalized for asthma [bullet] heart disease [bullet] high blood pressure [bullet] diabetes [bullet] thyroid disease [bullet] seizures [bullet] narrow angle glaucoma [bullet] a psychiatric or emotional condition [bullet] trouble urinating due to an enlarged prostate gland."

(3) The following information shall appear after the subheading "Ask a doctor or pharmacist before use if you are" [in bold type]:

(i) "[Bullet] taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions."

(ii) "[Bullet] taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)."

(4) The following information shall appear after the subheading "When using this product" [in bold type]:

(i) "[Bullet] your blood pressure or heart rate may go up. This could increase your risk of heart attack or stroke, which may cause death." [in bold type]

(ii) "[Bullet] your risk of heart attack or stroke increases if you: [Bullet] have a history of high blood pressure or heart disease [Bullet] take this product more frequently or take more than the recommended dose." [in bold type]

(iii) "[Bullet] avoid foods or beverages that contain caffeine."

(iv) "[Bullet] avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect."

(5) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in §§ M012.16(a), (b), (c), and (f).

(i) The following information shall appear after the subheading "Asthma alert: Because asthma may be life threatening, see a doctor if you" [in bold type]:

(A) "[Bullet] are not better in 60 minutes."

(B) "[Bullet] get worse."

(C) "[Bullet] need more than [insert total number of dosage units that equals 150 milligrams] in 24 hours."

(D) "[Bullet] use more than [insert total number of dosage units that equals 100 milligrams] in 24 hours for 3 or more days a week."

(E) "[Bullet] have more than 2 asthma attacks in a week."

(F) "These may be signs that your asthma is getting worse."

(G) "[Bullet] This product will not give you asthma relief as quickly as an inhaled bronchodilator."

(ii) This "Asthma alert" shall appear on any labeling that contains warnings and shall be the first warning statement under the heading "Warnings."

(6) For products containing epinephrine, epinephrine bitartrate, or racepinephrine hydrochloride identified in §§ M012.16(d), (e), and (g).

(i) The following information shall appear after the subheading "Asthma alert: Because asthma may be life threatening, see a doctor if you" [in bold type]:

(A) "[Bullet] are not better in 20 minutes."

(B) "[Bullet] get worse."

(C) "[Bullet] need more than 12 inhalations in 24 hours."

(D) "[Bullet] use more than 9 inhalations in 24 hours for 3 or more days a week."

(E) "[Bullet] have more than 2 asthma attacks in a week."

(F) "These may be signs that your asthma is getting worse."

(ii) This "Asthma alert" shall appear on any labeling that contains warnings and shall be the first warning statement under the heading "Warnings."

(iii) For products intended for use in a hand-held rubber bulb nebulizer. The following statement shall also appear after the subheading "Do not use" along with the other information in § M012.76(c)(1): "[bullet] if product is brown in color or cloudy."

(7) The following information shall appear after the subheading "Stop use and ask a doctor if" [in bold type]:

(i) "[Bullet] your asthma is getting worse (see Asthma alert)."

(ii) "[Bullet] you have difficulty sleeping."

(iii) "[Bullet] you have a rapid heartbeat."

(iv) "[Bullet] you have tremors, nervousness, or seizure."

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

(1) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in §§ M012.16(a), (b), (c), and (f):

(i) "[Bullet] do not take more than directed" [sentence appears as first bulleted statement under "Directions" and in bold type]

(ii) "[Bullet] adults and children 12 years of age and over: oral dose is 12.5 to 25 milligrams every 4 hours as needed. Do not take more than 150 milligrams in 24 hours."

(iii) "[Bullet] children under 12 years of age: ask a doctor."

(2) For products containing epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride identified in §§ M012.16(d), (e), and (g) for use in a hand-held rubber bulb nebulizer. The ingredient is used in an aqueous solution at a concentration equivalent to 1 percent epinephrine:

(i) "[Bullet] do not use more than directed" [appears as first bulleted statement under "Directions" and in bold type].

(ii) "[Bullet] adults and children 4 years of age and over: 1 to 3 inhalations not more often than every 3 hours. Do not use more than 12 inhalations in 24 hours. The use of this product by children should be supervised by an adult."

(iii) "[Bullet] children under 4 years of age: ask a doctor."

§ M012.78 Labeling of expectorant 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 an "expectorant."

(b) Indications. The labeling of the product states, under the heading "Uses," the following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive"). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in § M012.78(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.

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

(1) "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by a fever, rash, or persistent headache, consult a doctor."

(2) For expectorant drug products labeled for adults or for adults and children under 12 years of age. "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or where cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(3) For expectorant drug products labeled only for children under 12 years of age. "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(d) Directions. The labeling of the product contains the following information under the heading "Directions" for products containing guaifenesin identified in § M012.18: Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams every 4 hours not to exceed 2,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 milligrams every 4 hours not to exceed 1,200 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 50 to 100 milligrams every 4 hours not to exceed 600 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in § M012.78.

§ M012.80 Labeling of nasal decongestant 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 "nasal decongestant."

(b) Indications. The labeling of the product states, under the heading "Uses," the phrase listed in § M012.80(b)(1), as appropriate, and may contain any additional phrases listed in § M012.80(b)(2). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in §§ M012.80(b)(1) and (b)(2), 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) (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in §§ M012.80(b)(1)(i), (ii), and (iii)):

(i) "due to" (select one of the following: "the common cold" or "a cold").

(ii) "due to" (select one of the following: "hay fever," "hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)").

(2) In addition to the information identified in § M012.80(b)(1), the labeling of the product may contain any (one or more) of the following statements:

(i) (Select one of the following: "For the temporary relief of" or "Temporarily relieves") (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Select one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; temporarily relieves sinus congestion and pressure."

(v) "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."

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

(1) Oral nasal decongestants

(i) For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in §§ M012.20(a)(1) and (a)(2) when labeled for adults.

(A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(D) Drug interaction precaution. "Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product."

(ii) For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in §§ M012.20(a)(1) and (a)(2) when labeled for children under 12 years of age.

(A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) “Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor.”

(D) Drug interaction precaution. “Do not use in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child’s prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product.”

(iii) For oral nasal decongestant products labeled for both adults and children under 12 years of age. The labeling of the product contains the warnings identified in § M012.80(c)(1)(i).

(2) Topical nasal decongestants

(i) For products containing any topical nasal decongestant identified in § M012.20(b) when labeled for adults.

(A) “Do not exceed recommended dosage.” [sentence in boldface type]

(B) “This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge.”

(C) “The use of this container by more than one person may spread infection.”

(ii) For products containing levmetamfetamine identified in § M012.20(b)(1) when used in an inhalant dosage form and when labeled for adults. “Do not use this product for more than 7 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, ask a doctor.”

(iii) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in §§ M012.20(b)(2), (b)(3), (b)(4), (b)(5), (b)(6), (b)(7), and (b)(9) when used as nasal sprays, drops, or jellies and when labeled for adults.

(A) “Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor.”

(B) “Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor.”

(iv) For products containing naphazoline hydrochloride identified in § M012.20(b)(5) at a concentration of 0.05 percent. “Do not use this product in children under 12 years of age because it may cause sedation if swallowed.”

(v) For products containing propylhexedrine identified in § M012.20(b)(8) when used in an inhalant dosage form and when labeled for adults. "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(vi) For products containing any topical nasal decongestant identified in § M012.20(b) when labeled for children under 12 years of age. The labeling of the product contains the warnings identified in § M012.80(c)(2)(i).

(vii) For products containing levmetamfetamine identified in § M012.20(b)(1) when used in an inhalant dosage form and when labeled for children under 12 years of age. "Do not use this product for more than 7 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, ask a doctor."

(viii) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in §§ M012.20(b)(2), (b)(3), (b)(4), (b)(5), (b)(6), (b)(7), and (b)(9) when used as nasal sprays, drops, or jellies and when labeled for children under 12 years of age.

(A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product in a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(ix) For products containing propylhexedrine identified in § M012.20(b)(8) when used in an inhalant dosage form and when labeled for children under 12 years of age. "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(x) For topical nasal decongestant products labeled for both adults and for children under 12 years of age. The labeling of the product contains the applicable warnings identified in §§ M012.80(c)(2)(i), (c)(2)(ii), (c)(2)(iii), and (c)(2)(v).

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

(1) Oral nasal decongestants

(i) For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in §§ M012.20(a)(1) and (a)(2). Adults and children 12 years of age and over: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours. Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(2) Topical nasal decongestants

(i) For products containing levmetamfetamine identified in § M012.20(b)(1) when used in an inhalant dosage form. The product delivers in each 800 milliliters of air 0.04 to 0.150 milligrams of levmetamfetamine. Adults: 2 inhalations in each nostril not more often than every 2 hours. Children 6 to under 12 years of age (with adult supervision): 1 inhalation in each nostril not more often than every 2 hours. Children under 6 years of age: ask a doctor.

(ii) For products containing ephedrine, ephedrine hydrochloride, or ephedrine sulfate identified in §§ M012.20(b) (2), (3), and (4)

(A) Nasal drops or sprays—For a 0.5 percent aqueous solution. Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(B) Nasal jelly—For a 0.5 percent water-based jelly. Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours.

(iii) For products containing naphazoline hydrochloride identified in § M012.20(b)(5)

(A) Nasal drops or sprays

(1) For a 0.05 percent aqueous solution. Adults and children 12 years of age and over: 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.025 percent aqueous solution. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(B) Nasal jelly

(1) For a 0.05 percent water-based jelly. Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.025 percent water-based jelly. Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(iv) For products containing oxymetazoline hydrochloride identified in § M012.20(b)(6)

(A) Nasal drops or sprays

(1) For a 0.05 percent aqueous solution. Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(2) A 0.025 percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.027 milligrams of oxymetazoline per three drops or three sprays. Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Use only recommended amount. Do not exceed 2 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) Nasal jelly—For a 0.05 percent water-based jelly. Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(v) For products containing phenylephrine hydrochloride identified in § M012.20(b)(7)

(A) Nasal drops or sprays

(1) For a 1 percent aqueous solution. Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.5 percent aqueous solution. Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(3) For a 0.25 percent aqueous solution. Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(4) A 0.125 percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.135 milligrams of phenylephrine per three drops or three sprays. Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Use only recommended amount. [previous sentence in boldface type] Children under 2 years of age: consult a doctor.

(B) Nasal jelly

(1) For a 1 percent water-based jelly. Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.5 percent water-based jelly. Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(3) For a 0.25 percent water-based jelly. Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(vi) For products containing propylhexedrine identified in § M012.20(b)(8) when used in an inhalant dosage form. The product delivers in each 800 milliliters of air 0.40 to 0.50 milligrams of propylhexedrine. Adults and children 6 to under 12 years of age (with adult supervision): 2 inhalations in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(vii) For products containing xylometazoline hydrochloride identified in § M012.20(b)(9)

(A) Nasal drops or sprays

(1) For a 0.1 percent aqueous solution. Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) A 0.05 percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.054 milligrams of xylometazoline per three drops or three sprays. Children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Use only recommended amount. Do not exceed 3 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) Nasal jelly

(1) For a 0.1 percent water-based jelly. Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.05 percent water-based jelly. Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Children under 6 years of age: consult a doctor.

(viii) Other required statements—For products containing levmetamfetamine or propylhexedrine identified in §§ M012.20(b)(1) or (b)(8) when used in an inhalant dosage form.

(A) "This inhaler is effective for a minimum of 3 months after first use."

(B) "Keep inhaler tightly closed."

§ M012.85 Labeling of permitted combinations of active ingredients

The 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 monographs. If there is no 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, unless otherwise stated in § M012.85(a).

(1) For permitted combinations identified in §§ M012.40(a), (c), (f), (g), (l), (m), (n), (o), (q), and (r) containing an analgesic-antipyretic active ingredient. The analgesic-antipyretic component of the product shall be identified as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to relieve fever, then the analgesic-antipyretic component is identified as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(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 § M012.85(b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in the applicable OTC monographs or listed in § M012.85(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 containing an analgesic-antipyretic active ingredient identified in §§ M012.40(a), (c), (f). (g), (l), (m), (n), (o), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold.

(i) The labeling for the analgesic-antipyretic ingredients states "[bullet] temporarily relieves [bullet] minor aches and pains [bullet] headache" and "[bullet] temporarily reduces fever."

(ii) The labeling for the cough-cold ingredient(s) may follow a separate bullet(s) or may be combined with the relieves part of the indication in § M012.85(b)(1)(i).

(2) For permitted combinations containing an analgesic-antipyretic active ingredient identified in §§ M012.40(a), (c), (f), (g), (m), (q), and (r) when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.

(i) The labeling for the analgesic-antipyretic ingredients states "[bullet] temporarily relieves [bullet] minor aches and pains [bullet] headache."

(ii) The indication(s) for the cough-cold ingredient(s) consists of the labeling for antihistamines in §§ M012.72(b)(1) or (b)(2) and/or nasal decongestants in § M012.80(b)(1)(ii), as appropriate, and the labeling for any other cough-cold combination. This labeling may follow a separate bullet(s) or may be combined with the indication in § M012.85(b)(2)(i).

(3) For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in §§ M012.40(a), (c), (f), (g), (m), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms. The labeling states both indications in §§ M012.85(b)(1) and (b)(2).

(4) For permitted combinations containing an oral anesthetic-analgesic active ingredient identified in §§ M012.40(k), (s), (t), (z), (aa), and (bb). The labeling for the anesthetic-analgesic ingredients in OTC Monograph M022 should be used.

(5) For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § M012.40(u). The labeling for antitussive ingredients in § M012.74(b) should be used.

(6) For permitted combinations containing levmetamfetamine with aromatics identified in § M012.40(v). The labeling for nasal decongestant ingredients in § M012.80(b) should be used.

(7) Other allowable statements. In addition to the required information identified in § M012.85(b), the labeling of the combination drug product may contain any of the "other allowable statements" (if any), that are identified in the applicable OTC monographs, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(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 sections of the applicable OTC monographs, unless otherwise stated in § M012.85(c). For combinations addressed in § M013.20(b)(2) of OTC Monograph M013, when the warnings in OTC Monograph M013 and § M012.85(c) conflict, the warnings in M012.85(c) should be used.

(1) For permitted combinations containing an antitussive and an analgesic-antipyretic identified in §§ M012.40(f), (g), (l), and (m). The labeling states the following warnings:

(i) For products labeled only for adults. The following warning should be used instead of the warnings in § M012.74(c)(1) and OTC Monograph M013: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 7 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(ii) For products labeled only for children under 12 years of age. The following warning should be used instead of the warnings in § M012.74(c)(3) and OTC Monograph M013: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(iii) For products labeled for both adults and for children under 12 years of age. The following warning should be used instead of the warnings in § M012.74(c)(2) and OTC Monograph M013: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 5 days (children) or 7 days (adults) [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(2) For permitted combinations containing an expectorant and an analgesic-antipyretic identified in § M012.40(o). The labeling states the following warnings:

(i) For products labeled only for adults. The warning in § M012.85(c)(1)(i) should be used instead of the warnings in § M012.78(c)(2) and OTC Monograph M013.

(ii) For products labeled only for children under 12 years of age. The warning in § M012.85(c)(1)(ii) should be used instead of the warnings in § M012.78(c)(3) and OTC Monograph M013.

(iii) For products labeled for both adults and for children under 12 years of age. The warning in § M012.85(c)(1)(iii) should be used instead of the warnings in § M012.78(c)(2) and OTC Monograph M013.

(3) For permitted combinations containing a nasal decongestant and an analgesic-antipyretic identified in §§ M012.40(c), (g), (m), (n), (q), and (r). The labeling states the following warnings:

(i) For products labeled only for adults. The following warning should be used instead of the warnings in § M012.80(c)(1)(i)(B) and OTC Monograph M013: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 7 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur."

(ii) For products labeled for only children under 12 years of age. The following warning should be used instead of the warnings in § M012.80(c)(1)(ii)(B) and OTC Monograph M013: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur."

(iii) For products labeled for both adults and children under 12 years of age. The following warning should be used instead of the warnings in § M012.80(c)(1)(iii) and OTC Monograph M013: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 5 days (children) or 7 days (adults) [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur."

(4) For permitted combinations containing an antihistamine combined with an oral antitussive. The labeling states the warning "When using this product [in bold type] [bullet] may cause marked drowsiness." The word "marked" may be deleted from the warning upon petition under the provisions of 21 CFR 10.30 provided adequate data are submitted to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data it contains will be maintained in a permanent file for public review in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(5) For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § M012.40(u). The labeling states the warnings for topical antitussive ingredients in § M012.74(c).

(6) For permitted combinations containing levmetamfetamine with aromatics identified in § M012.40(v). The labeling states the warnings for topical nasal decongestant ingredients in § M012.80(c)(2).

(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 in § M012.85(d). When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC monograph.

(1) For permitted combinations containing an anesthetic/analgesic and/or a demulcent in a liquid dosage form identified in §§ M012.40(k), (s), (t), (w), (x), (y), (z), (aa), and (bb). The labeling states "[optional, bullet] gargle, swish around, or keep in the mouth for at least 1 minute and then swallow. Do not spit out."

(2) For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § M012.40(u). The labeling states the directions for topical antitussive ingredients in § M012.74(d).

(3) For permitted combinations containing levmetamfetamine with aromatics identified in § M012.40(v). The labeling states the directions for topical nasal decongestant ingredients in §§ M012.80(d)(2)(i) and (d)(2)(viii).

Part D—Professional Use

§ M012.90 Professional labeling

The labeling of the product provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredients identified below:

(a) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in §§ M012.16(a), (b), (c), and (f). Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 hours, not to exceed 75 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 0.3 to 0.5 milligram per kilogram of body weight every 4 hours, not to exceed 2 milligrams per kilogram of body weight in 24 hours.

(b) For products containing chlophedianol hydrochloride identified in § M012.14(a)(1). Children 2 to under 6 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(c) For products containing codeine ingredients identified in § M012.14(a)(2).

(1) Children 2 to under 6 years of age: Oral dosage is 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows: For children 2 years of age (average body weight, 12 kilograms), the oral dosage is 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours; for children 3 years of age (average body weight, 14 kilograms), the oral dosage is 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours; for children 4 years of age (average body weight, 16 kilograms), the oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours; for children 5 years of age (average body weight, 18 kilograms), the oral dosage is 4.5 milligrams every 4 to 6 hours, not to exceed 18 milligrams in 24 hours. The manufacturer must relate these dosages for its specific product dosages for its specific product to the use of the calibrated measuring device discussed in § M012.90(c)(3). If age is used to determine the dose, the directions must include instructions to reduce the dose for low-weight children.

(2) Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not exceed the recommended daily dosage.

(3) A dispensing device (such as a dropper calibrated for age or weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose.

(4) Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death.

(d) The following labeling indication may be used for products containing guaifenesin identified in § M012.18 when used as a single ingredient product. “Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis.”

(e) For products containing brompheniramine maleate identified in § M012.12(a). Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(f) For products containing chlorcyclizine hydrochloride identified in § M012.12(b). Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 37.5 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 6 to 8 hours, not to exceed 18.75 milligrams in 24 hours.

(g) For products containing chlorpheniramine maleate identified in § M012.12(c). Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(h) For products containing dexbrompheniramine maleate identified in § M012.12(d). Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(i) For products containing dexchlorpheniramine maleate identified in § M012.12(e). Children 2 to under 6 years: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(j) For products containing diphenhydramine citrate identified in § M012.12(f). Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours.

(k) For products containing diphenhydramine hydrochloride identified in § M012.12(g). Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(l) For products containing doxylamine succinate identified in § M012.12(h). Children 2 to under 6 years of age: oral dosage is 1.9 to 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours.

(m) For products containing phenindamine tartrate identified in § M012.12(i). Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(n) For products containing pheniramine maleate identified in § M012.12(j). Children 2 to under 6 years of age: oral dosage is 3.125 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(o) For products containing pyrilamine maleate identified in § M012.12(k). Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(p) For products containing thonzylamine hydrochloride identified in § M012.12(l). Children 2 to under 6 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours.

(q) For products containing triprolidine hydrochloride identified in § M012.12(m). Children 4 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 4 to 6 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 4 to 6 hours, not to exceed 1.252 milligrams in 24 hours.

(r) For products containing diphenhydramine citrate identified in § M012.14(a)(5). Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 hours, not to exceed 57 milligrams in 24 hours.

(s) For products containing diphenhydramine hydrochloride identified in § M012.14(a)(6). Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 hours, not to exceed 37.5 milligrams in 24 hours.

Part E—Exemption From Prescription Requirements

§ M012.100 Exemption from prescription requirements

The prescription-dispensing requirements of section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)) are not necessary for the protection of the public health with respect to a compound, mixture, or preparation containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams that also includes one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the compound, mixture, or preparation valuable medicinal qualities other than those possessed by codeine alone.

Theresa M. Michele -S

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