DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 1976N–0052N]

RIN 0910–AF34

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of Monograph for Over-the-Counter Nasal Decongestant Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the final monograph (FM) for over-the-counter (OTC) nasal decongestant drug products (drug products used to relieve nasal congestion due to a cold, hay fever, or other upper respiratory allergies) to add phenylephrine bitartrate as generally recognized as safe and effective (GRASE) when used in an effervescent tablet. An effervescent tablet is intended to be dissolved in water before taking by mouth. This proposal is part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments and comments on FDA's economic impact determination by [*insert date 90 days after date of publication in the* **Federal Register**]. Please see section X of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 1976N–0052N and/or RIN number 0910–AF34, by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include Docket No. 1976N–0052N and/or RIN number 0910–AF34 in the subject line of your e-mail message.
- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. 1976N–0052N or Regulatory Information Number 0910–AF34 (RIN) for this rulemaking. All comments received will be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Houda Mahayni, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

A. Advance Notice of Proposed Rulemaking (ANPRM)

1. OTC Cough-Cold Drug Products

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel). That Panel reviewed oral and topical nasal decongestant drug products and found phenylephrine hydrochloride to be a safe and effective ingredient for OTC use (41 FR 38312 at 38399 and 38400). The Cough-Cold Panel did not evaluate phenylephrine bitartrate.

2. OTC Oral Health Care Drug Products

In the **Federal Register** of May 25, 1982 (47 FR 22760), FDA published the report of the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel). That Panel reviewed the safety and effectiveness of two oral nasal decongestant ingredients, phenylephrine hydrochloride and phenylpropanolamine hydrochloride (in lozenge form), and classified these ingredients as Category III (more data needed) (47 FR 22760 at 22911 through 22914). The Oral Cavity Panel did not evaluate phenylephrine bitartrate.

B. Tentative Final Monograph (TFM)

1. OTC Cough-Cold Drug Products

In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA published the TFM for OTC nasal decongestant drug products. The TFM proposed phenylephrine hydrochloride as a monograph ingredient but did not address phenylephrine bitartrate.

2. OTC Oral Health Care Drug Products

In the **Federal Register** of January 27, 1988 (53 FR 2436), FDA published the TFM for OTC oral health care (anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent) drug products. FDA referred the data on the oral nasal decongestant ingredients phenylephrine hydrochloride and phenylpropanolamine hydrochloride to the rulemaking for OTC nasal decongestant drug products because that was the primary rulemaking for these ingredients (53 FR 2436 at 2448 and 2449).

C. Final Monograph (FM)

1. OTC Cough-Cold Drug Products

In the **Federal Register** of August 23, 1994 (59 FR 43386), FDA published the FM for OTC nasal decongestant drug products. The monograph included phenylephrine hydrochloride as GRASE for oral and topical use as a nasal decongestant (§ 341.20(a) and (b)(8) (21 CFR 341.20(a) and (b)(8))). FDA acknowledged that phenylephedrine bitartrate was submitted as an oral nasal decongestant active ingredient in an effervescent combination cold tablets for OTC use. FDA noted that the ingredient was not reviewed by the Cough-Cold Panel or included in its report, or addressed in the TFM for OTC nasal decongestant drug products (59 FR 43386 at 43394 and 43395). FDA reviewed data on phenylephedrine bitartrate submitted in a comment and concluded that the data were inadequate to demonstrate the safety and effectiveness of phenylephrine bitartrate as an OTC oral nasal decongestant ingredient. Consequently, this ingredient was not included in the FM.

2. OTC Oral Health Care Drug Products

FDA has not published an FM for these products.

II. Citizen Petition

A manufacturer submitted a citizen petition (Ref. 1) requesting FDA to amend the OTC nasal decongestant FM to include the ingredient phenylephrine bitartrate as GRASE in an effervescent tablet. The manufacturer stated:

- Domestic and international marketing experiences meet FDA's material time and extent criteria for inclusion in an OTC drug monograph.
- In vitro and in vivo studies demonstrate comparability of phenylephrine bitartrate with phenylephrine hydrochloride, an approved monograph active ingredient.
- Phenylephrine bitartrate would provide consumers a greater choice in combination nasal decongestant/analgesic cough-cold formulations.

The manufacturer requested GRASE status for phenylephrine bitartrate for use as a single ingredient or in combination with any monograph cough-cold active ingredient(s) when delivered in an effervescent tablet.

III. FDA's Comments on the Citizen Petition

A. Marketing History

According to the manufacturer, consumers have used phenylephrine hydrochloride and bitartrate domestically and globally as a nasal decongestant for decades. In terms of domestic marketing experience, the following drug products containing phenylephrine bitartrate have been marketed in the United States: (1) An effervescent product containing aspirin, chlorpheniramine maleate, and phenylephrine bitartrate marketed OTC from 1968 to 1976, before being voluntarily discontinued by its manufacturer, and (2) an inhalation product containing isoproterenol hydrochloride and phenylephrine bitartrate marketed by prescription and later discontinued. Phenylephrine bitartrate

containing products have been marketed outside the United States (Central America, Mexico, Australia, and Spain) since 1978. As of 2002, a total of 1.16 billion tablets have been distributed in these countries (Ref. 1).

Products containing bitartrate are presently sold by prescription in the United States as a salt of hydrocodone, dihydrocodone, and dihydrocodeine. Phenylephrine bitartrate is similar to phenylephrine hydrochloride, which is currently included as an oral nasal decongestant active ingredient in § 341.20(a)(1). Both phenylephrine salts have the same pharmacologic activity and similar side effects. FDA is aware that phenylephrine bitratrate effervescent tablets were marketed in the United States in the 1960s and 1970s and had a similar use and adverse reaction profile as products containing phenylephrine hydrochloride. The citizen petition provides sufficient information of marketing outside the United States since 1978 to allow FDA to determine that phenylephrine bitartrate as a nasal decongestant has been marketed to a material time and to a material extent. In addition, the citizen petition contains recent data demonstration that the phenylephrine bitartrate salt is bioavailable and comparable to the phenylephrine hydrochloride salt.

B. Safety and Effectiveness

1. Review of Adverse Event Databases (AEDs)

The manufacturer conducted a safety review of the FDA and World Health Organization's (WHO) AEDs concerning phenylephrine bitartrate for the period from 1969 to 1997. The review included all dosage forms of phenylephrine but was nonspecific for the phenylephrine salt (e.g., hydrochloride or bitartrate). The review identified 22 reports for phenylephrine bitartrate out of approximately 900 reports for phenylephrine administered orally. There were five reports of ''no drug effect'', two reports of nervousness, and 15

different single events reported such as rash, vomiting, diarrhea, and insomnia. The manufacturer commented that causality and preexisting conditions in the 22 reported subjects could not be established from the available data. The manufacturer noted that:

- The FDA database does not indicate the relationship of adverse events or preexisting medical conditions of consumers to the administration of phenylephrine.
- The WHO database revealed five different single event reports for products containing phenylephrine bitartrate as an active ingredient.
- Reports provided by the manufacturer's affiliate from other countries in which phenylephrine bitartrate products are marketed provided no information on adverse events relative to phenylephrine bitartrate.

FDA finds these data suggest that there are no significant safety concerns reported from the use of phenylephrine bitartrate in the countries where it is currently used. Safety information from various U.S. databases is not available specifically for phenylephrine bitartrate because it has not been marketed for the past 30 years. Safety information from U.S. databases indicate that phenylephrine hydrochloride is safe for OTC use within the label warnings in § 341.80(c)(1) (21 CFR 341.80(c)(1)). Based on their similar pharmacologic activity and side effects, FDA has determined that both phenylephrine salts are safe for OTC use.

2. Pharmacokinetic Study

In a meeting held on February 15, 2002 (Ref. 2), FDA suggested that the manufacturer conduct a bioequivalence study. FDA recommended that the manufacturer follow FDA's Guidance for Industry entitled ''Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General

Considerations'' (the Guidance) (Ref. 3). The Guidance describes a single-dose pharmacokinetic study of both immediate and modified release drug products to demonstrate bioequivalence. FDA generally considers a single-dose study to be more sensitive than a multiple-dose study in assessing the release of the drug substance from the drug product into the systemic circulation. Further, if a multiple-dose study design is necessary, the Guidance recommends performing appropriate dosage administration and sampling to document that ''steady-state'' is attained. At steady-state, the rate of drug leaving the body is equal to the rate of drug entering the body.

The manufacturer submitted an open-label, four-way crossover, multiple-dose study in healthy volunteers to evaluate the pharmacokinetic profiles of the following equivalent phenylephrine doses of phenylephrine hydrochloride and phenylephrine bitartrate in two different dosage forms and different weights because of the different salts forms:

- an effervescent phenylephrine hydrochloride 10 milligram (mg) tablet
- an effervescent phenylephrine bitartrate 15.6 mg tablet
- an encapsulated[1] phenylephrine hydrochloride 10 mg capsule
- an encapsulated phenylephrine bitartrate 15.6 mg capsule

Twenty-five subjects completed the study and were considered evaluable for the pharmacokinetic analysis. All subjects were treated with four oral doses of phenylephrine over a 12-hour period. The first dose was administered at 7 a.m. Subsequent doses were administered 4, 8, and 12 hours later. The analysis provided the mean ratio and 90 percent confidence interval of the derived pharmacokinetic parameters, area under the concentration-time curve

[1] Encapsulated is a capsule dosage form that was termed ''encapsulated'' by the manufacturer in this study.

(AUC) and maximum plasma concentration (Cmax), after single dose and at steady-state for each treatment.

3. FDA's Evaluation of the Pharmacokinetic Study

Bioequivalence may be determined from a multiple-dose study only after a steady-state plasma drug level has been reached. The time needed to reach the steady-state plasma level is related to the elimination half-life of the drug. It takes approximately 6.6 half-lives to reach 99 percent of steady-state plasma level. If steady-state blood levels are going to be used for the determinations of bioequivalence, both drug products must be administered to steady-state. Based on the comparison of the pharmacokinetic parameters obtained, the bioequivalence or lack of bioequivalence may be determined.

The manufacturer did not conduct a single-dose pharmacokinetic study. The manufacturer performed a study in which four doses of the phenylephrine formulations were administered every 4 hours in 1 day. The elimination half-life of phenylephrine is between 2 and 3 hours. Therefore, it takes between 13.2 (2 x 6.6) and 19.8 (3 x 6.6) hours to reach steady-state, at which time blood levels could be obtained to compare and determine bioequivalence. Thus, the study was not designed to achieve steady-state, nor did the manufacturer document that steady-state was reached, which is necessary to establish bioequivalence. Therefore, the study can only demonstrate comparable bioavailability or similarity, but not bioequivalence. Independent scientific study, did not allow enough time between doses.

Table 1 of this document provides a summary of total phenylephrine pharmacokinetic parameters derived from the first-dose data. First-dose data are being considered because attainment of steady-state was not documented and because it is the most robust observation of the data.

TABLE 1.—Summary of Total Phenylephrine Pharmacokinetic Parameters-Derived from First-Dose Data-Mean Ratio, 90 Percent Confidence Interval (CI), and Significance (p=0.05) (n=25)

Treatment Comparison	Actual AUCτ Ratio CI p-value	log AUCτ Ratio CI p-value	Actual C_{max} Ratio CI p-value	log C_{max} Ratio CI p-value
PEB–E[1] vs. PEH–E[2]	0.98 0.93–1.03 0.4298	1.00 0.99–1.00 0.5077	1.00 0.93–1.07 0.991	1.00 0.99–1.01 0.8642
PEB–C[3] vs. PEH–C[4]	0.91 0.87–0.96 0.0050	0.98 0.98–0.99 0.0020	0.90 0.85–0.97 0.0137	0.98 0.97–0.99 0.0062

[1]Phenylephrine bitartrate in an effervescent tablet.
[2]Phenylephrine hydrochloride in an effervescent tablet.
[3]Phenylephrine bitartrate in a capsule.
[4]Phenylephrine hydrochloride in a capsule.

Table 1 of this document shows that, for the effervescent tablet, the mean ratio (log transformed) for both the C_{max} and AUC is 1.00 when comparing phenylephrine hydrochloride to phenylephrine bitartrate. The actual ratios range from 0.98 to 1.0. Therefore, the rate and extent of absorption after the first-dose of the phenylephrine bitartrate effervescent tablet are considered similar to those of the phenylephrine hydrochloride effervescent tablet.

Although the manufacturer did not perform a single-dose or a multiple-dose study (to steady-state), the similarity in the rate and extent of absorption of phenylephrine hydrochloride and phenylephrine bitartrate in the effervescent tablets allows FDA to conclude that the bioavailability of the phenylephrine salts in the effervescent tablets is comparable.

Table 1 of this document shows that, for the encapsulated formulation, the actual mean ratio for AUC and C_{max} are 0.91 and 0.90 for AUC and C_{max} respectively. Because this study was not of optimal design, FDA has concerns about the plasma concentration-time curve that is not available because the second dose was administered. FDA cannot conclude that the in vivo performance of the products are similar because of the magnitude of the difference of the actual mean ratios of 0.90 and 0.91 from 1.0. The encapsulated capsule is bioavailable but not bioequivalent to the effervescent tablet.

IV. FDA's Tentative Conclusions

A. Single Ingredient Products

FDA has tentatively determined that phenylephrine bitartrate has been marketed to a material extent and for a material time as a nasal decongestant with no indication of safety concerns. Based on the ingredient's marketing history, absence of safety concerns, and additional data provided in the manufacturer's citizen petition, FDA has determined that the pharmacokinetic study is acceptable in lieu of a clinical trial because of the similarity in the bioavailability of the two effervescent tablets. Accordingly, FDA acknowledges that the two salts of phenylephrine could be used in the effervescent tablets interchangeably without any clinically significant impact on the performance of the formulations studied. FDA is proposing that phenylephrine bitartrate in an effervescent tablet be GRASE for use as an OTC oral nasal decongestant. Accordingly, FDA is proposing to amend § 341.20(a)(4) of the FM for OTC nasal decongestant drug products to include phenylephrine bitartrate in an effervescent tablet. However, additional pharmacokinetic data are needed to include the phenylephrine bitartrate capsule formulation in the OTC nasal decongestant FM.

B. Combination Products

The combination of single antihistamine, oral nasal decongestant, and analgesic-antipyretic active ingredients is included in 21 CFR 341.40(c) of the Cough-Cold FM. FDA is proposing to include in the FM the combination of chlorpheniramine maleate (antihistamine), phenylephrine bitartrate (oral nasal decongestant), and aspirin (analgesic-antipyretic) in an effervescent tablet. FDA is including only this specific combination product for the following reasons:

- This is the only combination containing phenylephrine bitartrate that has an OTC marketing history in the United States. It was marketed from 1968 to 1976.

- The bitartrate salt form of the OTC nasal decongestant phenylpropanolamine was reviewed by the Cough-Cold Panel and recommended for monograph status as GRASE (41 FR 38312 at 38400 and 38401).

- The rate and extent of absorption of phenylephrine bitartrate effervescent tablet after the first-dose and at steady-state were similar to those of phenylephrine hydrochloride effervescent tablet. Thus, the two phenylephrine salts appear to have comparable bioavailability. A drug-drug interaction study is not necessary for the combination of chlorpheniramine maleate, phenylephrine bitartrate, and aspirin.

FDA does not have data on any other combination products to include them in the FM at this time. FDA is not aware of other combination products containing phenylephrine bitartrate that may have been marketed. To market any other combination product containing phenylephrine bitartrate, manufacturers will need to submit a new drug application deviation (21 CFR 330.11).

C. Monograph Labeling

FDA is proposing the same uses and warnings for phenylephrine bitartrate as appear in § 341.80(b) and (c)(1) for phenylephrine hydrochloride because these are salt of the same ingredient. Based on historical marketing in the United States, more current marketing in foreign countries, and the pharmacokinetic study, FDA is proposing the following doses:

- adults and children 12 years of age and over: 15.6 milligrams every 4 hours, not to exceed 62.4 milligrams in 24 hours
- children 6 to under 12 years of age: 7.8 milligrams every 4 hours, not to exceed 31.2 milligrams in 24 hours
- children under 6 years of age: ask a doctor

FDA proposes that manufacturers include in their product labeling information on the number of tablets and the quantity of water the tablets are to be dissolved in prior to administration.

FDA is also proposing to define effervescent tablet in 21 CFR 341.3 to state:

Effervescent tablet. A tablet 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.

D. Statement About Warnings

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act. This judgment balances the benefits of these drug products against their potential risks. (See 21 CFR 330.10(a).)

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter* v. *Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, Final Rule, 67 FR 72555 (December 6, 2002).

E. USP Monograph

FDA's policy is that for an active ingredient to be included in an OTC drug FM, it is necessary to have publicly available chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. (See the **Federal Register** of April 3, 1989 (54 FR 13480 at 13486), and June 20, 1990 (55 FR 25204 at 25215).) Because phenylephrine bitartrate is not currently standardized and characterized for quality and purity in the official compendium, i.e., the United States Pharmacopoeia (USP)-National Formulary (NF), it will not be included in the FM until such information is available. A proposed compendial monograph for phenylephrine bitartrate was published in the *Pharmacopeial Forum* for May-June 2004 (Ref. 4). When a final compendial monograph is published in the USP-NF, FDA intends to finalize its proposal to include phenylephrine bitartrate in an effervescent tablet in the FM. Interim marketing of phenylephrine bitartrate in an effervescent tablet before an amendment to include this ingredient in the FM is finalized is not allowed and may subject any such products to regulatory action.

V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if the rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes and assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by private sector, of $100,000,000 (adjusted annually for inflation) in any one year.''

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed in this section, FDA has determined that this proposed rule, if finalized, will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed $100

million adjusted for inflation. The current inflation adjusted statutory threshold is about $110 million.

The purpose of this proposed rule is to include phenylephrine bitartrate in the monograph for OTC nasal decongestant drug products. This proposal, when finalized, would allow manufacturers who market products containing this ingredient in foreign countries and manufacturers who would like to market products containing this ingredient in the United States to enter the market place under the OTC drug monograph instead of a new drug application (NDA). Cost savings will occur from marketing without an NDA.

Marketing a new OTC drug product containing phenylephrine bitartrate is optional for any interested manufacturer. The costs would involve the standard startup costs associated with marketing any new product under an OTC drug monograph. Manufacturers will not incur any costs determining how to state the product's labeling because the monograph amendment (and any eventual final rule) will provide that information. Any final rule that issues based on this proposal will not be expected to require any new reporting and recordkeeping activities. Therefore, no additional professional skills would be needed.

FDA considered but rejected several alternatives: (1) Not including phenylephrine bitartrate in the monograph, (2) allowing other combinations, and (3) allowing interim marketing. FDA rejected the first alternative because it considers the data presented supportive of monograph status. FDA rejected the second alternative because it has no data to support other combinations at this time. FDA rejected the third alternative because there currently is no USP monograph for this ingredient. FDA considers it inappropriate to allow interim marketing until there are uniform standards for the ingredient in an

official compendial monograph that all manufacturers can follow, and FDA publishes a notice in the **Federal Register** to allow interim marketing to begin.

This analysis shows that FDA has considered the burden to small entities. FDA does not consider an exemption for small entities necessary because those manufacturers can enter the market place like larger entities anytime after this proposal is finalized. Therefore, FDA certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that the proposed labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the monograph labeling is a ''public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

FDA has determined 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. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the

distribution of power and responsibilities among the various levels of government. Accordingly, FDA tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

IX. Comments

FDA is providing a period of 90 days for interested persons to submit written or electronic comments on the proposed rule to the Division of Dockets Management (see **ADDRESSES**). Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

X. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

XI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 1976N–0052N and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP18.

2. Comment No. MM9.

3. FDA ''Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products–General Considerations,'' October 2000.

4. ‘‘Phenylephrine Bitartrate’’ in *Pharmacopeial Forum*, The United States Pharmacopeial Convention, Inc., Rockville, MD, 30(3):923–924, May-June 2004.

List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 341 be amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 341.3 is amended by adding paragraph (i) to read as follows:

§ 341.3 Definitions.

* * * * *

(i) *Effervescent tablet.* A tablet 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.

3. Section 341.20 is amended by adding paragraph (a)(4) to read as follows:

§ 341.20 Nasal decongestant active ingredients.

* * * * *

(a) * * *

(4) Phenylephrine bitartrate in an effervescent tablet.

* * * * *

4. Section 341.40 is amended by revising paragraphs (b), (c), (e), (g), (i), (j), (m), (n), (p), (q), (r), (s), (t), (x), (y), (aa), and (bb) and by adding paragraph (cc) to read as follows:

§ 341.40 Permitted combinations of active ingredients.

* * * * *

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), and (a)(3) provided that the product is labeled according to § 341.85.

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), and (a)(3) 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 § 341.85.

* * * * *

(e) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), and (a)(3) provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both

the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

* * * * *

(g) Any single antihistamine active ingredient identified in § 341.12(a) through (e) or (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

* * * * *

(i) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) provided that the product is labeled according to § 341.85.

(j) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any single expectorant active ingredient identified in § 341.18 provided that the product is labeled according to § 341.85.

* * * * *

(m) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85.

(n) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any single expectorant active ingredient identified in § 341.18 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 § 341.85.

* * * * *

(p) Any single expectorant active ingredient identified in § 341.18 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) provided that the product is labeled according to § 341.85.

(q) Any single expectorant active ingredient identified in § 341.18 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85.

(r) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85.

(s) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85.

(t) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) may be combined with any single antitussive active ingredient identified in § 341.14(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 § 341.85. 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 § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85.

(y) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85. 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 § 341.20(a)(1), (a)(2), or (a)(3) 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 § 341.85.

(bb) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active

ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and 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 § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(cc) Phenylephrine bitartrate identified in § 341.20(a)(4) may be combined with chlorpheniramine maleate identified in § 341.12(c) and aspirin provided the product is available only in an effervescent tablet and provided that the product is labeled according to § 341.85.

5. Section 341.80 is amended by revising the headings in paragraphs (c)(1)(i) and (c)(1)(ii), and by adding paragraph (d)(1)(iii) to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

* * * * *

(c) * * *

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20(a)(1) through (a)(4) when labeled for adults.* * * *

* * * * *

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine*

bitartrate identified in § 341.20(a)(1) through (a)(4) when labeled for children under 12 years of age. * * *

* * * * *

(d) * * *

(1) * * *

(iii) *For products containing phenylephrine bitartrate identified in § 341.20(a)(4).* Include information on the number of dosage units and the quantity of water the dosage units are to be dissolved in prior to administration as shown in the following table:

Age[1]	Dose[1]
adults and children 12 years of age and over	15.6 milligrams every 4 hours not to exceed 62.4 milligrams in 24 hours
children 6 to under 12 years of age	7.8 milligrams every 4 hours not to exceed 31.2 milligrams in 24 hours
children under 6 years of age	ask a doctor

[1] Headings are not required to appear in the product's labeling.

* * * * *

6. Section 341.85 is amended by revising the headings in paragraphs (a)(1), (b)(1), (b)(2), (b)(3), and (c)(3).

§ 341.85 Labeling of permitted combinations of active ingredients.

* * * * *

(a) * * *

(1) *For permitted combinations identified in § 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), (r), and (cc) containing an analgesic-antipyretic active ingredient.* * * *

* * * * *

(b) * * *

(1) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), (r), and*

(cc) when labeled for relief of general cough-cold symptoms and/or the common cold. * * *

* * * * *

(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), (r), and (cc) when labeled for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.* * * *

* * * * *

(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), (r), and (cc) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.* * * *

* * * * *

(c) * * *

(3) *For permitted combinations containing a nasal decongestant and an analgesic-antipyretic identified in § 341.40(c), (g), (m), (n), (q), (r), and (cc).*

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Dated: October 26, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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