

# DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Food and Drug Administration

### 21 CFR Part 341

[Docket No. 1976N–0052N] (formerly 76N–052N)

RIN 0910–AF34

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

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule 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 (PEB), both individually and in combination drug products in an effervescent dosage form, as generally recognized as safe and effective (GRASE). An effervescent dosage form is intended to be dissolved in water before taking by mouth. This final rule is part of FDA’s ongoing review of OTC drug products.

**DATES:** *Effective Date:* This rule is effective [*insert date 30 days after date of publication in the Federal Register*].

**FOR FURTHER INFORMATION CONTACT:** Michael T. Benson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5484, Silver Spring, MD 20993, 301–796–2090.

**SUPPLEMENTARY INFORMATION:****I. Background***A. Advance Notice of Proposed Rulemaking (ANPR)*

## 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 several active ingredients, including phenylephrine hydrochloride (PEH), to be safe and effective ingredients for OTC use (41 FR 38312 at 38399 and 38400). The Cough-Cold Panel did not evaluate PEB.

## 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, PEH and phenylpropanolamine hydrochloride (both in lozenge form for topical use), and classified these ingredients as Category III (more effectiveness data needed) (47 FR 22760 at 22911 through 22914). The Oral Cavity Panel did not evaluate PEB.

*B. Tentative Final Monograph (TFM)*

## 1. OTC Cough-Cold Drug Product

In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA published the TFM for OTC nasal decongestant drug products. The TFM proposed PEH

as a monograph ingredient, but PEB was not addressed due to lack of available data.

## 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 PEH and phenylpropanolamine hydrochloride in lozenge form for topical use 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) 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 PEH as GRASE for oral and topical use as a nasal decongestant (21 CFR 341.20(a)(1) and (b)(8)). The monograph did not specify specific oral dosage forms. FDA acknowledged that PEB was submitted as an oral nasal decongestant active ingredient in an effervescent combination tablet for OTC use. FDA noted that PEB was not reviewed by the Cough-Cold Panel, or included in its report, and was not addressed in the FM for OTC nasal decongestant drug products (59 FR 43386 at 43394 and 43395). FDA reviewed data on PEB submitted in a comment and concluded that the data were inadequate to demonstrate the safety and effectiveness of PEB in an effervescent dosage form as an OTC oral nasal decongestant ingredient. Consequently, this ingredient was not included in the FM.

On March 20, 2002, a manufacturer submitted a citizen petition to amend the OTC nasal decongestant FM to include the ingredient PEB in an

effervescent tablet as GRASE for use as a single ingredient or in combination with any monograph cough-cold active ingredient. The petition included:

- Domestic and international marketing experience to meet FDA’s material time and extent criteria for inclusion in an OTC drug monograph (see 21 CFR 330.14)
- In vitro and in vivo studies to demonstrate comparability of PEB with PEH, an approved monograph active ingredient
- A proposal that PEB would provide consumers with greater choice in combination nasal decongestant/analgesic cough-cold formulations

In the **Federal Register** of November 2, 2004 (69 FR 63482), FDA published a proposed rule to amend the FM for OTC nasal decongestant products to add PEB in an effervescent tablet as a single ingredient or in combination with aspirin and chlorpheniramine maleate. A drug manufacturer and an individual submitted comments, which included several issues that are discussed in section II of this document.

## **II. The Agency’s Conclusion on the Comments**

(Comment 1) One comment asked FDA to expand the definition of an effervescent dosage form. FDA had proposed the following definition for an 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 releases carbon dioxide when dissolved in water.”

The comment requested that FDA revise the proposed definition of effervescent tablet to permit additional inactive ingredients, claiming that its suggested revision would provide greater formulation flexibility. The comment based its revised definition upon definitions from pharmaceutical texts and reference books, including the United States Pharmacopeia (U.S.P.), the

British/European Pharmacopeia (BP/EP), and other pharmacopeial individual monographs. The comment requested that FDA revise the definition of effervescent tablet as follows: “A tablet intended to be dissolved or dispersed in water before administration. It generally contains, in addition to the active ingredient(s), mixtures of acids/acid salts (citric acid, tartaric acid, malic acid, or any other suitable acid or acid anhydride), which release carbon dioxide when mixed with water. Occasionally, the active ingredient itself could act as the acid or alkali metal compound necessary for effervescent reaction.”

FDA declines the request to revise the definition of effervescent tablet to permit additional inactive ingredients, but is expanding the definition in a different manner to provide manufacturers greater formulation flexibility. FDA’s definition in the OTC nasal decongestant FM is substantially the same as the definitions for effervescent tablets in the U.S.P. (Ref. 1) and for effervescent tablets and granules in the FDA Center for Drug Evaluation and Research (CDER) Data Standards Manual (Ref. 2). All of these definitions describe a dosage form that contains citric acid, tartaric acid, and sodium bicarbonate as inactive ingredients to produce the effervescence, and the product releases gas (carbon dioxide) when added to water.

FDA is not revising the definition in the manner suggested by the comment because the agency has concerns about the comment’s proposed use of the term “any other suitable acid or acid anhydride.” This term is not sufficiently specific to ensure consistency with the current regulatory requirements for inactive ingredients. Under § 330.1(e) (21 CFR 330.1(e)), a product is required to contain only suitable inactive ingredients that meet certain criteria. These inactive ingredients must be safe in the amounts administered and must not interfere with the effectiveness of the preparation or with suitable tests or

assays to determine if the product meets its professed standards of identity, strength, quality, and purity. The comment did not submit data to demonstrate that the additional inactive ingredients it requests are safe in the amounts administered or that they do not interfere with the effectiveness of the preparation or with suitable tests or assays. FDA is not aware of any such data for effervescent dosage forms that contain PEB. FDA is also not aware of PEB as the active ingredient in these products acting as “the acid or alkali metal compound necessary for effervescent reaction.” Accordingly, FDA is not adding this requested information to the definition at this time.

Interested parties should contact U.S.P. for any change in the compendial definition of an effervescent tablet that would apply to all such products. The definition in § 341.3(i) applies only to products containing PEB covered by this FM. Interested parties who wish to include a PEB effervescent dosage form that contains different inactive ingredients than those listed in the definition in this FM may provide FDA specific data on such a product

FDA is expanding the definition of “effervescent tablet” by replacing “effervescent tablet” in § 341.3(i) of the proposed rule with “effervescent dosage form” in this final rule. We are making this change to provide greater formulation flexibility to permit other effervescent dosage forms (e.g., granules and powders) to be marketed. The FDA CDER Data Standards Manual (Ref. 2) defines an effervescent granule as “a small particle or grain containing a medicinal agent in a dry mixture \* \* \*.” The pharmacokinetic data provided for the PEB effervescent tablet dosage form would also support use of an effervescent granule or powder dosage form, based on the smaller particle size of these dosage forms. Accordingly, the definition in § 341.3(i) now reads: “*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.” In conjunction with this change, we have also changed the proposed active ingredient description “phenylephrine bitartrate effervescent tablet” in § 341.20(a)(4) to “phenylephrine bitartrate effervescent dosage form” in this FM.

(Comment 2) One comment requested FDA to allow PEB as an oral nasal decongestant in all combination products containing an oral nasal decongestant when formulated as an effervescent tablet and labeled in accordance with 21 CFR 341.80 and 21 CFR 341.85. The comment contended that PEH is included as a GRASE oral nasal decongestant ingredient in the monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and is included in 17 permitted combinations. The comment further stated that FDA acknowledged in the proposed rule that both phenylephrine salts (bitartrate and hydrochloride) have similar safety and efficacy profiles, and could be used in effervescent tablets interchangeably without any clinically significant impact on the performance of the formulations studied. The comment provided in-vitro data demonstrating comparable recovery of the active ingredient following dissolution in various solution media of effervescent tablets formulated with either PEH or PEB, in the presence or absence of other common cough/cold active ingredients.

FDA agrees with the comment. In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA affirmed the Cough-Cold Panel recommendations for numerous combinations containing an oral nasal decongestant and other active ingredients. PEH was one of those active ingredients. In the proposed rule of the current rulemaking (69 FR 63482 at 63485, November 2, 2004), FDA

acknowledged that the two phenylephrine salts in effervescent tablets could be used interchangeably. The similarity in the rate and extent of absorption of PEH and PEB in the effervescent tablets allows FDA to conclude that the bioavailability of the phenylephrine salts in the effervescent tablets is comparable (69 FR 63482, November 2, 2004). With regard to PEB and other combinations:

- PEH is similarly bioavailable to PEB, as stated previously, and in-vitro dissolution data demonstrate that recovery of phenylephrine from formulations of either salt is virtually indistinguishable (PEH v PEB). FDA believes that PEB would have also been among the ingredients recommended for inclusion in the same combinations as PEH, had the Cough-Cold Panel considered that ingredient. Accordingly, FDA is including PEB in an effervescent dosage form as a permitted active ingredient as follows:

- In the same types of combination products as the other oral nasal decongestant active ingredients under §§ 341.40 (b), (c), (e), (g), (i), (j), (m), (n), (p), (q), (r), (s), (t), (x), (y), (aa), and (bb),
- With labeling for combination products under § 341.85 (b)(1), (b)(2), (b)(3), and (c)(3).

(Comment 3) One comment contended that FDA should not approve PEB for OTC use until an official compendium exists to define the quality and purity of its effervescent dosage form. FDA does not agree with the comment's suggestion. PEB as a drug substance became official in the U.S.P. on August 1, 2005 (Ref. 3). FDA's regulation in 21 CFR 330.14(i) sets forth criteria and procedures for classifying OTC drugs as GRASE and not misbranded. It states that "any active ingredient or botanical drug substance included in a final OTC drug monograph \* \* \* must be recognized in an official USP-NF drug

monograph that sets forth its standards of identity, strength, quality, and purity.” While FDA’s regulation mentions a U.S.P.–N.F. drug monograph for the active ingredient, it does not also require a U.S.P.–N.F. drug monograph for the active ingredient in a specific dosage form. Accordingly, FDA concludes that a U.S.P. compendial monograph for the PEB drug substance is a sufficient basis for including PEB as an active ingredient in an effervescent tablet or other effervescent dosage form in the FM for OTC nasal decongestant drug products.

### **III. Submission of Pharmacokinetic Data for Other Solid Dosage Forms of PEB**

FDA notes in the proposed rule that the rate and extent of absorption after the first dose of PEB capsules are not similar to PEH capsules. FDA is willing to consider pharmacokinetic data in support of other PEB solid dosage forms (e.g., capsule, or noneffervescent tablet, granule, or powder) and invites interested persons to submit such data in the form of a petition under 21 CFR 10.30 to amend the monograph for OTC nasal decongestant drug products.

### **IV. Labeling Change from the Proposed Rule**

At the time of the proposed rule, sinusitis would have been a permitted indication for OTC combination drug products that include PEB in an effervescent dosage form as an oral nasal decongestant. Subsequently, FDA revised the labeling for these products. In the **Federal Register** of October 11, 2005 (70 FR 58974), FDA published a final rule to eliminate the term “sinusitis” from the labeling of OTC nasal decongestant drug products. Accordingly, FDA has revised the introductory language of §§ 341.85(b)(2) and (b)(3) of the proposed rule to replace the term “sinusitis” with “nasal congestion.” Sections 341.85(b)(2) and (b)(3) of the final rule now read as follows:

“§ 341.85 *Labeling of permitted combinations of active ingredients.*

(b)(2) *For permitted combinations containing an analgesic-antipyretic active ingredient \* \* \* when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.*

(b)(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient \* \* \* 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.”*

## **V. Summary of Agency Changes**

1. FDA is changing the definition of “effervescent tablet” in § 341.3(i) to “effervescent dosage form.” In conjunction with this change, FDA is changing the active ingredient description in § 341.20(a)(4) from “Phenylephrine bitartrate in an effervescent tablet” to “Phenylephrine bitartrate in an effervescent dosage form” (see section II, comment 1 of this document).

2. In the proposed rule, FDA proposed to amend § 341.40(b), (c), (e), (g), (i), (j), (m), (n), (p), (q), (r), (s), (t), (x), (y), (aa), and (bb) to exclude PEB in § 341.20(a)(4). Now that FDA is allowing PEB in all of these combinations, there is no need to amend these paragraphs because the existing language therein already refers to all nasal decongestant active ingredients in § 341.20(a).

3. FDA is eliminating proposed § 341.40 (cc) because the combination is now covered by § 341.40(c). With the elimination of proposed § 341.40(cc), the proposed amendments of the headings in § 341.85(a)(1), (b)(1), (b)(2), (b)(3), and (c)(3) to add § 341.40(cc) are no longer needed and are withdrawn. However, the headings in § 314.85(b)(2) and (b)(3) are being revised as discussed in section IV of this document.

## **VI. Analysis of Impacts**

FDA has examined the impacts of this final rule under Executive Order 12866, 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 of anticipated costs and benefits before enacting any rule 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 million (adjusted annually for inflation).

FDA believes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This final 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 final rule 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 final rule, because the final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current threshold after adjustment for inflation is \$115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product.

The purpose of this final rule is to include PEB in the monograph for OTC nasal decongestant drug products. This final rule will 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 PEB 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 provides that information. This final rule is not expected to require any new reporting and recordkeeping activities. Therefore, no additional professional skills will be needed.

FDA considered but rejected the option of not including PEB in the monograph because it considers the data presented supportive of monograph status. The ingredient became official in the U.S.P. on August 1, 2005 (Ref. 3).

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 FM becomes effective. Therefore, FDA certifies that this final 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)).

## **VII. Paperwork Reduction Act of 1995**

FDA concludes that the 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)).

### **VIII. 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.

### **IX. Federalism**

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule will have a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to “construe \* \* \* a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.” Section 751 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that: “\* \* \* no State or political subdivision of a State may establish or continue in effect any requirement— \* \* \* (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*)”

Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See Section 751(b) through (e) of the act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.) This final rule would add PEB, individually and in combination drug products when used in effervescent dosage form, to the FM for OTC nasal decongestant drug products. Although this final rule would have a preemptive effect, in that it would preclude States from promulgating requirements related to these PEB drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule, this preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise. See *Geier v. American Honda Co.*, 529 US 861 (2000).

FDA believes that the preemptive effect of the final rule would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that “when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.” FDA provided the States with an opportunity for appropriate participation in this rulemaking when it sought input from all stakeholders through publication of the proposed rule in the **Federal Register** of November 2, 2004 (69 FR 63482). FDA received no comments from any States on the proposed rulemaking.

In addition, on June 19, 2006, FDA's Division of Federal and State Relations provided notice via fax and email transmission to elected officials of State governments and their representatives of national organizations. The notice provided the States with further opportunity for comment on the rule. It advised the States of the publication of the proposed rule and encouraged State and local governments to review the notice and to provide any comments to Docket No. 1976N-0052N, opened in the November 2, 2004, **Federal Register** notice, by a date 30 days from the date of the notice (i.e., by July 19, 2006), or to contact certain named individuals. FDA received no comments in response to this notice. The notice has been filed in Docket No. 1976N-0052N.

In conclusion, FDA believes that it has complied with all of the applicable requirements under the Executive order and has determined that the preemptive effects of this rule are consistent with Executive Order 13132.

#### **X. Effective Date**

This final rule becomes effective [*insert date 30 days after date of publication in the **Federal Register***].

#### **XI. References**

The following references are on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 under Docket No. 1976N-0052N and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but is not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. *The United States Pharmacopeia 29-National Formulary 24*, The United States Pharmacopeial Convention, Inc., Rockville, MD, pp 3005, 2006.

2. *CDER Data Standards Manual* (see sections entitled “Tablet Effervescent” and “Granule Effervescent”) at <http://www.fda.gov/cder/dsm/DRG/drg00201.htm>.

3. *The United States Pharmacopeia 28–National Formulary 23, Supplement 2*, The United States Pharmacopeial Convention, Inc., Rockville, MD, pp 3520, 2005.

**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, 21 CFR part 341 is amended as follows:

**PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC 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 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.

■ 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 dosage form.

\* \* \* \* \*

■ 4. 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 <sup>1</sup>	Dose <sup>1</sup>
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

<sup>1</sup>Headings are not required to appear in the product's labeling

\* \* \* \* \*

■ 5. Section 341.85 is amended by revising the headings in paragraphs (b)(2) and (b)(3).

**§ 341.85 Labeling of permitted combinations of active ingredients.**

\* \* \* \* \*

(b) \* \* \*

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

\* \* \* \* \*

(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40 (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.\*\*\**

\* \* \* \* \*

Dated: July 24, 2006.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

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