Issued in Washington, DC, on July 19, 2011, by the Commission.

David A. Stawick,

Secretary of the Commission.

Appendices to Process for Review of Swaps for Mandatory Clearing—Commission Voting Summary and Statements of Commissioners

Note: The following appendices will not appear in the Code of Federal Regulations.

Appendix 1—Commission Voting Summary

On this matter, Chairman Gensler and Commissioners Dunn, Sommers, Chilton and O'Malia voted in the affirmative; no Commissioner voted in the negative.

Appendix 2—Statement of Chairman Gary Gensler

I support the final rulemaking to establish a process for the review and designation of swaps for mandatory clearing. One of the primary goals of the Dodd-Frank Wall Street Reform and Consumer Protection Act was to lower risk by requiring standardized swaps to be centrally cleared. The final rule is consistent with the congressional requirement that derivatives clearing organizations be eligible to clear swaps and that the public has an opportunity for input before a swap is subject to mandatory clearing.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 341

[Docket No. FDA–1995–N–0031 (Formerly Docket No. 1995N–0205)]

RIN 0910–AF32

Labeling for Bronchodilators To Treat Asthma; Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the final monograph (FM) for over-the-counter (OTC) bronchodilator drug products to add additional warnings (*e.g.,* an ''Asthma alert'') and to revise the indications, warnings, and directions in the labeling of products containing the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, epinephrine, epinephrine bitartrate, racephedrine hydrochloride, and racepinephrine hydrochloride. FDA is issuing this final rule after considering data and information submitted in response to the Agency's proposed labeling revisions for these products. This final rule is part of FDA's ongoing review of OTC drug products.

DATES: *Effective Date:* This regulation is effective January 23, 2012.

Compliance Date: The compliance date for all products, regardless of annual sales, is January 23, 2012.

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SUPPLEMENTARY INFORMATION:

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I. Changes to the Labeling of OTC Drug Products Used To Treat Asthma

This rulemaking amends the FM for OTC bronchodilator drug products used to treat asthma. The ''Indications,'' ''Warnings'' and ''Directions'' portions of the Drug Facts label are being changed to help consumers better understand how to use these products and when it is appropriate to seek treatment from a doctor for their asthma. The ''Indications'' section now recommends use only for temporary relief of mild symptoms of intermittent asthma. Changes to both the ''Warnings'' and ''Directions'' sections emphasize that consumers should not exceed the recommended dose or duration of use with these drug products. The ''Warnings'' section is being changed to make it clearer that consumers whose symptoms worsen or do not improve should see a doctor. The ''Indications,'' ''Warnings'' and ''Directions'' portions of the Drug Facts label have also been revised to use language that is more readily understood by the average consumer.

II. History of the Development of the 1986 Final Monograph

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published an advance notice of proposed rulemaking (ANPR) under 21 CFR 330.10(a)(6) to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. The ANPR included the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel), the advisory review panel responsible for evaluating data on the active ingredients in this drug class. The Panel recommended that ephedrine and epinephrine preparations be placed in Category I (generally recognized as safe and effective or GRASE) for OTC bronchodilator use (41 FR 38312 at 38370 through 38372).

FDA concurred with the Panel's recommendations and subsequently published the proposed rule in the **Federal Register** of October 26, 1982, (47 FR 47520) and the FM for OTC bronchodilator drug products in the **Federal Register** of October 2, 1986, (51 FR 35326). FDA included the following active ingredients in the FM:

- ''Ephedrine ingredients'' (*i.e.,* ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride)
- ''Epinephrine ingredients'' (*i.e.,* epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride)

In subsequent rulemaking documents for this category, including this final rule, the term ''ephedrine ingredients'' refers to the four active ephedrine ingredients, the term ''epinephrine ingredients'' refers to the three active epinephrine ingredients, and the term ''OTC bronchodilator drug products''

refers to products containing any of these seven active ingredients.

III. Amendments to the 1986 Final Monograph Proposed by FDA

In the **Federal Register** of July 27, 1995, (60 FR 38643), FDA published a proposed rule to amend the FM to remove ephedrine ingredients and to classify them as not GRASE for OTC use. At that time, FDA had reassessed the risks and the benefits of OTC ephedrine drug products based on additional safety data and proposed their removal because of safety concerns. After reviewing the comments received in response to this proposed rule, FDA concluded that ephedrine ingredients should remain in the FM for self-treatment of mild bronchial asthma, and FDA withdrew its proposal to remove ephedrine ingredients from the OTC drug monograph in the **Federal Register** of July 13, 2005, (70 FR 40237).

Also, in the **Federal Register** of July 13, 2005, (70 FR 40237), FDA proposed to amend the FM for OTC bronchodilator drug products with revised labeling for products containing ephedrine and epinephrine ingredients. FDA proposed changes to the Indications, Warnings, and Directions sections of the labeling in 21 CFR 341.76. FDA stated that it considered the labeling revisions to be important for the safe and effective use of OTC bronchodilator drug products by providing better instructions to asthmatics about how to use the product correctly and to minimize risks. The proposed changes were:

1. *Indications:* Revise the indications in § 341.76(b)(1) and (b)(2) to a single indication using the OTC ''Drug Facts'' labeling format in § 201.66 (21 CFR 201.66). The labeling recommends use only for the ''temporary relief of occasional symptoms of mild asthma.''

2. *Warnings:* Revise the entire warnings section into ''Drug Facts'' labeling as follows:

- Add an ''Asthma alert'' section. This proposed section lists specific criteria consumers can use to identify when to seek treatment from a doctor for their asthma (*e.g.,* failure of the product to improve symptoms, need for excessive dosing). The ''Asthma alert'' should appear as the first statement under the heading ''Warnings'' and certain parts of the ''Asthma Alert'' should be in bold type. This new warning replaces the warning previously found in § 341.76(c)(5)(i) for ephedrine ingredients and in § 341.76(c)(6)(ii) for epinephrine ingredients.
- List a number of statements that follow the subheading ''Do not use.'' These statements include the warnings previously found in § 341.76(c)(1), (c)(4), and (c)(6)(iii), where applicable, for products intended for use in a hand-held rubber bulb nebulizer.
- List a number of conditions for which consumers should consult a doctor before using these products under the subheading ''Ask a doctor before use if you have.'' This list includes the conditions previously stated in § 341.76(c)(2), plus several additional conditions.
- Advise consumers to consult a doctor before using the OTC bronchodilator drug product with other specified drugs. This information appears under the subheading ''Ask a doctor or pharmacist before use if you are.'' The list of other specified drugs includes prescription drugs for asthma previously stated in § 341.76(c)(3) as well as a new list of other drugs that could cause side effects when used concurrently with ephedrine or epinephrine ingredients.
- List information that consumers need to know under the heading ''When using this product.'' This information includes the following:

a. Direct consumers' attention to information about the risks associated with increased blood pressure or heart rate by requiring that this information appear in bold type as the first bulleted statement.

b. Side effects that may occur (including side effects currently listed in § 341.76(c)(5)(ii)).

c. Information about risks associated with taking the drug more often than recommended or at higher-than-recommended doses. This information is currently in § 341.76(c)(6)(i) for products containing epinephrine ingredients. FDA proposed to include the information for all products containing either ephedrine or epinephrine ingredients.

d. New information about avoiding certain foods and dietary supplements while using an OTC bronchodilator drug product.

3. *Directions:* Revise the directions in § 341.76(d)(1) and (d)(2) to include the statement ''do not exceed dosage'' [in bold type] as the first bulleted statement under the heading ''Directions.''

IV. FDA's Response to Comments Received About the Proposed Labeling Changes

In response to the amendment to the FM proposed in the **Federal Register** of July 13, 2005, FDA received comments from two consumers, one manufacturer of OTC bronchodilator drug products, and three national associations. One consumer comment discussed dextromethorphan. This comment is not addressed further in this final rule because this ingredient is a cough suppressant rather than a bronchodilator.

(Comment 1) A comment submitted by an asthma patient supported the proposed rule and the continued availability of asthma drugs over the counter (Ref. 1). The comment stated that the proposed rule provides adequate warnings to address both the ''realistic dangers'' (*e.g.,* increased heart rate) and ''remote dangers'' (*e.g.,* seizure) to users. FDA agrees with the comment.

(Comment 2) One comment, from an association of respiratory therapists, stated that patients who suffer from asthma must have adequate instructions and education about drug administration (Ref. 2). The comment also stated that this information should be included with OTC or prescription medication to ensure that consumers receive the full benefits from their drugs and to prevent life-threatening conditions associated with improper use. The comment supported FDA's revisions to the warnings for OTC bronchodilator drug products to enhance labeling for existing products, but urged FDA to reconsider permitting bronchodilator products to remain OTC.

FDA does not plan to remove bronchodilator products from the OTC marketplace. FDA has found that the standards for safety, effectiveness, and labeling for OTC bronchodilator drug products have been met. Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability (21 CFR 330.10(a)(4)(i)). 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 (21 CFR 330.10(a)(4)(ii)). OTC drug product labeling must be clear and truthful and must state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use (21 CFR 330.10(a)(4)(v)). FDA has a reasonable expectation that these drugs provide a clinically meaningful

benefit in the treatment of mild symptoms of intermittent asthma when they are used according to labeled instructions for the temporary relief of wheezing, tightness of chest, and shortness of breath.

In this final rule, FDA has revised the indication to provide the consumer with a better understanding of the use of these drug products. In the July 13, 2005, proposed rule (70 FR 40237), FDA proposed changes to the ''Indications'' section of the labeling in § 341.76(b) (21 CFR 341.76(b)). The indication proposed in that proposed rule was for the ''temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath'' (70 FR 40237 at 40248). This indication was based on the National Asthma Education and Prevention Program (NAEPP) Guidelines of 2002, which defined mild intermittent asthma as having symptoms no more than twice a week during the day or twice a month at night. FDA determined that people with mild intermittent asthma were the only category of asthmatics who should be candidates for OTC bronchodilators and stated that asthmatics with more severe asthma disease (*i.e.,* persistent asthma) should be under the care of a physician for consideration of additional therapy to control the disease (70 FR 40237 at 40240).

Newer NAEPP guidelines on the treatment of asthma published in 2007 (Ref. 3) state that ''mild asthma'' is a persistent form of asthma with symptoms occurring two or more times per week, but not daily. What was previously called ''mild intermittent asthma'' is now classified as ''intermittent asthma'' and is defined as having symptoms no more than twice a week during the day or twice a month at night. Between asthmatic episodes, these asthmatics have no symptoms and can maintain a normal level of activity. FDA is revising the indication for OTC bronchodilators to be consistent with this change in terminology for classifying asthma severity. The revised indication is as follows: ''For temporary relief of mild symptoms of intermittent asthma *e.g.,* wheezing, tightness of chest, and shortness of breath.'' This revised indication conveys the same important information to the consumer as proposed in 2005; that these products should be used on a temporary basis and only for mild symptoms of intermittent asthma, while including a better description of the type of asthma by current guidelines for which OTC products should be used.

(Comment 3) One comment agreed with FDA's proposed labeling changes with one exception (Ref. 4). The comment disagreed with the following warning, contending that the data did not support this statement:

When using this product * * * increased blood pressure or heart rate can occur, which could lead to more serious problems such as heart attack, stroke, and death. Your risk can increase if you take more frequently or more than the recommended dose.

The comment stated that FDA's proposed warning fails to acknowledge that while the available data on ephedrine and epinephrine show that both may increase blood pressure or heart rate, the effect of the increase varies based on the individual's risk factors. Further, the magnitude of the warning is not supported by the literature or adverse event data, and this warning is unnecessarily alarming.

The comment further objected to FDA's warning because it implies that all consumers are at equal risk for complications resulting from increases in heart rate or blood pressure. The comment noted that sympathomimetic drugs (such as ephedrine) may cause modest increases in heart rate and blood pressure, but individual outcomes vary from person to person based on underlying risk factors. Because FDA described adverse event reports associated with taking ephedrine-containing bronchodilator drug products more frequently, or in higher amounts, than the labeled dose in the 2005 proposed rule (70 FR 40237 at 40243), the comment contended that no evidence was presented to link normal use of OTC bronchodilators with any of the events listed in the proposed warning. The comment recommended the following language as being more representative of the data:

When using this product * * * increased blood pressure or heart rate may occur, which could increase your risk of more serious problems, especially if you have risk factors such as a history of high blood pressure or heart disease. Your risk may increase if you take more frequently or more than the recommended dose.

FDA does not agree. FDA stated in the proposed rule (70 FR 40237 at 40243) that based on reports it has received, the risk of adverse events from ephedrine can occur at any dosage and may increase when taking a higher dose or taking more frequent doses than at the recommended dose. In the July 27, 1995, proposed rule to exclude OTC ephedrine drug products from the FM for OTC bronchodilator drug products (60 FR 38643 at 38644), FDA discussed a number of reports of young people abusing OTC ephedrine drug products. In one case, 9 junior high school students took 3 to 8 ephedrine 25 milligram (mg) tablets and experienced rapid heart beats. One female who took 8 tablets had 200 heart beats per minute 2 hours after taking the tablets. In another case, a 22-year-old female took OTC ephedrine tablets (number not reported) and presented to a hospital emergency room with blood pressure of 170/110 millimeters mercury.

FDA also discussed three deaths that occurred. One report involved a 17-year-old male who died after ingesting a toxic or lethal amount of ephedrine. In another case, a 24-year-old male who died of an overdose had a blood level of ephedrine over 30 times the usual therapeutic range. In another case, a 52-year-old-male took 10 to 15 ephedrine tablets (believed to be 50 mg) over the previous 24 hours before he died.

Based on these cases, we disagree with the comment that the risk of adverse reactions is limited mostly to people with risk factors such as a history of high blood pressure or heart disease. As stated in the July 13, 2005, proposed rule (70 FR 40237 at 40243), the risk of adverse events from ephedrine can occur at any dosage, even in healthy individuals who did not take excessive amounts. However, we agree with the comment that those individuals with certain risk factors are at a greater risk. As discussed in the proposed rule, cardiovascular side effects from OTC bronchodilator drug products can include an increase in blood pressure and heart rate, which could lead to more serious problems such as heart attack, stroke, and death (70 FR 40237 at 40242 to 40243). The intent of this warning is to alert all potential users of these products that there are serious risks, even potential death, associated with the use of OTC bronchodilator drug products and that these risks may increase if they take the product more frequently or take more than the recommended dose. We are revising the warning to better convey risk information in clear language to people who have a history of high blood pressure or heart disease. See the language set out in § 341.76(c)(4) in this rule.

(Comment 4) One comment noted FDA's statement in the 2005 proposed rule that, based on differences in composition between OTC ephedrine drug products and dietary supplements containing botanical sources of ephedrine alkaloids, ''adverse event data for dietary supplements containing ephedrine alkaloids may not be completely applicable to ephedrine drug products'' (70 FR 40237 at 40241) (Ref. 4). Emphasizing that FDA's 2004 final rule declaring dietary supplements containing ephedrine alkaloids

adulterated (69 FR 6788) was specific to dietary supplements, the comment expressed concern that the labeling for OTC bronchodilator drug products was being revised based on data from botanically derived ephedrine alkaloids in dietary supplements, which are different from the ephedrine or epinephrine ingredients in OTC bronchodilator drugs. For example, the active ingredients in OTC bronchodilator drugs must meet United States Pharmacopeia standards of identity, strength, quality, and purity, but dietary supplements contain varying amounts and proportions of ephedrine and other ephedrine alkaloids (such as norephedrine, pseudoephedrine, and methylephedrine), depending on the plant species used (70 FR 40237 at 40241).

Although dietary supplements contain ephedrine alkaloids that are not present in OTC ephedrine drug products, ephedrine is the ingredient that was common to both dietary supplements and OTC drug products. As mentioned in the proposed rule, botanically-derived ephedrine alkaloids and the OTC bronchodilator drug product ingredients are related sympathomimetic chemicals that have similar pharmacologic actions. The adverse events associated with dietary supplements that used to contain ephedrine alkaloids may also occur in susceptible individuals taking an OTC bronchodilator drug product containing ephedrine covered by this monograph. FDA considers the known risks associated with dietary supplements that contained ephedrine alkaloids to be important for consideration as part of our analysis in the development of labeling warnings for bronchodilator drug products containing ephedrine, and thus includes those risks in its analysis.

(Comment 5) A comment objected to the inclusion of a warning about ''death'' in the labeling for OTC bronchodilator drug products (Ref. 4). It said that this warning should be reserved for the ''most exceptional circumstances'' and that the existing data did not support the warning. The comment noted that there is no reference to the word ''death'' in the current electronic *Physician's Desk Reference* labeling for OTC products, but cited 51 patient leaflets for prescription products that warn patients specifically about the possibility of death when taking a particular product.

FDA agrees that the term ''death'' in a warning should be used only when it is an accurate representation of existing data. As discussed in comment 3, we have reports of death resulting from taking too much ephedrine. We conclude that the warning is important for safe use of these OTC drug products to alert consumers to the potential consequences of inadequate treatment of asthma and the potential for serious adverse events, such as heart attack, stroke, and death, associated with these products.

(Comment 6) A comment questioned the meaning of the term ''temporary'' in the ''Indication'' statement in § 341.76(b)(1) of the 1995 OTC bronchodilator FM, ''for temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma'' (Ref. 5). The comment asked what the time period associated with ''temporary'' was intended to be and whether these drugs provide temporary relief for all levels of asthma severity.

For bronchodilator drug products, ''temporary'' is defined by the dosing intervals that appear in the directions for use. The temporary effect of ephedrine is expected to be 4 hours and the temporary effect of epinephrine is expected to be 3 hours. If relief is not achieved after taking a dose of the product, consumers should seek the advice of a health professional. FDA notes that the term ''temporary'' is commonly used in OTC drug product labeling to imply short-term rather than permanent relief and to discourage consumers from prolonged use.

To better explain proper use of these products, FDA is revising the ''indication'' statement in this final rule as follows: ''for temporary relief of mild symptoms of intermittent asthma: [bullet] wheezing [bullet] tightness of chest [bullet] shortness of breath'' (see comment 2). People with more severe asthma should consult a physician and ask about other types of asthma relief products.

(Comment 7) One comment addressed the additional ''Indications'' in § 341.76(b)(1)(i) and (b)(ii) of the OTC bronchodilator FM, ''for the temporary relief of bronchial asthma'' and ''eases breathing for asthma patients by reducing spasms of bronchial muscles'' (Ref. 5). The comment stated that this language does not differentiate OTC bronchodilators from other bronchodilators that ''do the job better.'' It was the comment's view that patients may assume that the OTC drug product works the same as prescription products.

FDA's labeling for OTC bronchodilator drug products is intended to help consumers use products safely and effectively in the OTC setting. It is not intended to compare OTC bronchodilators to prescription products. Although OTC labeling is generally not intended to compare or differentiate among various available products, the revised ''Asthma alert'' warning for oral ephedrine does advise the consumer that bronchodilators that have a different route of administration may be advantageous, *i.e.,* inhaled products provide faster asthma relief than oral products (see Comment 10). The indications to which the comment objected in the FM were revised in the proposed rule to amend the FM (70 FR 40237 at 40242). FDA is finalizing the indication in § 341.76(b) to a single statement as follows: ''for temporary relief of mild symptoms of intermittent asthma: [bullet] wheezing [bullet] tightness of chest [bullet] shortness of breath.'' Therefore, the revised indication and ''Asthma alert'' should help consumers to better understand how to use these products.

(Comment 8) A comment addressed the ''Warning'' in § 341.76(c)(1) of the OTC bronchodilator FM, ''do not use this product unless a diagnosis of asthma has been made by a doctor'' (Ref. 5). The comment stated that this warning implies that a diagnosis makes the patient an expert at self-prescribing asthma treatments, but that such a diagnosis offers no information of value to the consumer when using an OTC bronchodilator drug product.

FDA maintains that there is a role for OTC bronchodilator drug products in the treatment of asthma. As conveyed in the labeling, these products are appropriate for consumers for whom a doctor has confirmed the diagnosis of intermittent asthma.

(Comment 9) A comment addressed the ''Warning'' in § 341.76(c)(3) of the OTC bronchodilator FM, ''Do not use this product if you have ever been hospitalized for asthma or if you are taking any prescription drug for asthma unless directed by a doctor'' (Ref. 5). The comment stated that a potential user does not know how hospitalization or prescription drug use will change the effectiveness of an OTC bronchodilator drug product.

FDA designed this warning to address safety concerns; a prior hospitalization or prescription drug use will not change the effectiveness of an OTC bronchodilator drug product. In addition, FDA revised the warnings from the 1995 FM for OTC bronchodilator drug products in the 2005 proposed rule (70 FR 40237 at 40248). The purpose of the warnings is to clearly convey to potential users of OTC bronchodilators that they should seek the advice of a doctor before using any bronchodilator products. The revised two part warning advises

consumers not to use the OTC bronchodilator drug product unless directed by a doctor. Asthmatics who have previously needed hospital care, or are taking a prescription drug to treat asthma, need to consult a doctor before using an OTC bronchodilator.

The warnings in this final rule have been broadened and revised. See the language set out in § 341.76(c)(2) and § 341.76(c)(3) in this rule.

(Comment 10) The same comment also addressed the ''Warning'' in § 341.76(c)(5)(i) of the OTC bronchodilator FM for ephedrine products, ''do not continue to use this product, but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse'' (Ref. 5). The comment stated that if consumers' symptoms do not improve or become worse at any time during treatment, the labeling should advise them to seek immediate medical attention.

FDA agrees and is providing broader labeling information on this issue in the revised ''Asthma alert.'' The new information is intended to help asthmatics understand whether the drug is not working as intended or whether a consumer's condition may be worsening.

The 60-minute timeframe after which a consumer should seek medical attention is specific to ephedrine oral drug products and reflects the time that is needed for the drug to be absorbed from the gastrointestinal tract and to reach therapeutic blood levels. The time is modified to 20 minutes for inhaled drug products.

FDA's new ''Asthma alert'' for ephedrine-containing products is set out in § 341.76(c)(5) in this rule.

FDA has modified the ''Asthma alert'' warning from the warning proposed in the 2005 proposed rule. For ephedrine containing products, the statement, ''this product will not give you asthma relief as quickly as an inhaled bronchodilator'' has been added as the final bulleted statement. Although there are many factors involved, inhaled drugs in general show a faster onset of action than oral drugs (Ref. 6). As discussed previously, oral ephedrine can take 60 minutes to reach therapeutic levels. This statement has been added to the warning to inform the consumer that there are other options for asthma treatment available that can be used in place of oral ephedrine if oral ephedrine does not provide rapid enough symptom relief.

In the ''Asthma alert'' section, two bulleted statements were revised that follow the statement, ''because asthma may be life threatening, see a doctor if you.'' For ephedrine, the statement ''[Bullet] need [insert total number of dosage units that equals 150 milligrams] in any day'' was changed to ''[Bullet] need more than [insert total number of dosage units that equals 150 milligrams] in 24 hours.'' Since 150 mg is the maximum dose of ephedrine that should be used in 24 hours (*i.e.,* one day, see directions), consumers who need more to relieve their symptoms should see a doctor. The terminology ''one day'' may not be clear to consumers as to the exact time frame, so this has been changed to ''24 hours'' to specify the time frame. Also, the statement ''[Bullet] use more than [insert total number of dosage units that equals 100 milligrams] a day for more than 3 days a week'' has been changed to ''[Bullet] use more than [insert total number of dosage units that equals 100 milligrams] in 24 hours for 3 or more days a week.'' The ''day'' time frame is changed to ''24 hours'' and ''for more than 3 days a week'' is changed to ''for 3 or more days a week.'' These changes are made for clarity and do not alter the proposed content of the alert.

Similar changes were made to the ''Asthma alert'' for epinephrine-containing products which is revised to read as set out in § 341.76(c)(6) in this rule.

The ''Asthma alert'' is the type of warning identified in 21 CFR 201.66(c)(5)(ii) [the Drug Facts rule] that has an appropriate subheading that is highlighted in bold type. FDA is amending § 201.66(c)(5)(ii)(B) to cross-reference this new warning.

(Comment 11) One comment addressed the ''Warning'' in § 341.76(c)(6)(ii) of the OTC bronchodilator FM for epinephrine products, ''do not continue to use this product, but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse'' (Ref. 5). The comment noted that while inhaled epinephrine works quickly, the duration of symptom relief is very short. The comment stated that patients are told not to use the drug more frequently than instructed, but not given a reason to comply with the instruction. The comment stated that labeling should explain that an increasing need for medication is a sign of airway swelling that must be treated by a physician. The labeling should tell users that the bronchodilator effect wears off before the next dose may be taken safely and to seek immediate treatment if symptoms are not completely relieved or if they worsen. The labeling should also warn against using inhaled epinephrine in place of, or in addition to, prescription bronchodilators.

In this rule, FDA is requiring new labeling that addresses the concerns expressed in the comment. Consumers are told not to use the drug more frequently than instructed because of an increased risk of serious adverse events. Specifically, the new required labeling will read as set out in § 341.76(c)(4) in this rule.

The labeling also warns to ask a doctor or pharmacist before using any OTC bronchodilator if taking prescription drugs for asthma. In addition, FDA's new labeling addresses the comment's concern that an increasing need for medication is a sign of airway swelling that must be treated by a physician. As discussed in comment 10, FDA's new ''Asthma alert'' for epinephrine-containing products will read as set out in § 341.76(c)(6) in this rule.

FDA believes that the revised Asthma alert as well as the revised warning on the potential for serious adverse events if bronchodilators are not used according to labeled instructions respond to the comment's concern regarding adequate warnings for epinephrine.

V. Additional Consumer-Friendly Changes FDA Made to the Labeling

To make the bronchodilator labeling more consumer friendly and to reach a range of consumers' literacy skills, FDA has made changes to the labeling that do not affect content but make the labeling more understandable to people of all literacy levels. FDA is making these changes so as not to affect the content of the labeling as proposed in the 2005 proposed rule, but to make the labeling clear to ordinary individuals including individuals of low comprehension as stated in § 330.10(a)(4)(v). These changes are as follows:

- As described in comment 10, two bulleted statements in the ''Asthma alert'' section were revised. These follow the statement, ''Because asthma may be life threatening, see a doctor if you.'' For ephedrine, the statement ''[Bullet] need [insert total number of dosage units that equals 150 milligrams] in any day'' was changed to ''[Bullet] need more than [insert total number of dosage units that equals 150 milligrams] in 24 hours'' to clarify the timeframe indicated by a ''day.'' Also, the statement ''[Bullet] use more than [insert total number of dosage units that equals 100 milligrams] a day for more than 3 days a week'' has been changed to ''[Bullet] use more than [insert total number of dosage units that equals 100 milligrams] in 24 hours for 3 or more days a week.'' A similar change was

made to the epinephrine ''Asthma alert.''

• As discussed in comment 3, warnings about increased blood pressure or heart rate have been revised.

• The phrase, ''avoid caffeine-containing foods and beverages'' under the heading ''When using this product'' has been changed to ''avoid foods or beverages that contain caffeine.''

FDA has added a ''Stop use and ask a doctor if'' section by moving warning statements proposed in 2005 under, ''when using this product'' to this new section. The section will read as set out in § 341.76(c)(7) in this rule.

The statement ''your asthma is getting worse (see Asthma alert)'' is taken from the ''Asthma alert'' warning and has been moved to this new section to clarify what the consumer should do if the product is not providing the necessary relief for them. The other three bulleted statements were previously in the labeling section under the heading ''When using this product.'' Moving these statements under this heading does not affect content and may clarify for consumers how they should handle any of these side effects by emphasizing that they should see a doctor.

• Under ''Directions'' for ephedrine and epinephrine, the first bulleted statement, ''do not exceed dosage'' has been changed to ''do not take more than directed'' or ''do not use more than directed,'' respectively.

• The second bulleted statement under ''Directions'' for ephedrine contains the phrase, ''not to exceed 150 mg in 24 hours'' and has been revised to the sentence, ''do not take more than 150 mg in 24 hours.'' The bulleted statement now reads as follows: ''[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.''

• The second bulleted statement under Directions for epinephrine states the dose as 1 to 3 inhalations not more often than every 3 hours. This has been revised by adding, ''do not use more than 12 inhalations in 24 hours'' to be consistent with information provided in the ''Asthma alert.'' The bulleted statement now reads as follows: ''[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.''

VI. FDA's Final Conclusions on Warnings and Other Labeling Information for OTC Bronchodilator Drug Products

A. Implementation Date for New Labeling

FDA has determined in order to provide for safe and effective use of OTC bronchodilator drug products at the earliest possible time because of the safety issues involved with the use of these products that this final rule be implemented within 180 days after its publication. Therefore, on or after 180 days after the date of publication of this final rule in the **Federal Register**, any OTC bronchodilator drug product that is subject to the final rule and that contains nonmonograph labeling or packaging may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Any OTC bronchodilator drug product that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule, and is not in compliance with the regulations, is subject to regulatory action. Further, any OTC drug product that was previously initially introduced or initially delivered for introduction into interstate commerce may not be repackaged or relabeled with the prior monograph labeling for these products after the effective date of this final rule. Manufacturers are encouraged to comply voluntarily as soon as possible.

B. 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 regulation 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 regulations 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 the December 6, 2002, (67 FR 72555), final rule entitled ''Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use.''

VII. Analysis of Impacts

A. Introduction and Summary

1. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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). The Agency believes that this final rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the requirements are likely to impose a burden on a substantial number of affected small entities, the Agency projects that the final rule will have a significant economic impact on a substantial number of small entities and has conducted an Initial Regulatory Flexibility Analysis as required under the Regulatory Flexibility Act.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

2. Summary

The purpose of this final rule is to revise the labeling of the ''Indications,'' ''Warnings,'' and ''Directions'' sections for over-the-counter (OTC) single-ingredient ephedrine and epinephrine bronchodilators. The required revised labeling would indicate the condition (mild symptoms of intermittent asthma) for which the product is intended and would warn consumers about when to seek medical assistance. The final rule would also use language that is more readily understood by the average consumer. The revised labeling may lead consumers to seek medical care and to improved asthma management. Thus, the estimated benefits of the final rule may come from reduced medical costs associated with adverse events arising from the misuse or abuse of the product. The estimated annual benefits range from $14.0 million to $69.3 million. One-time labeling costs from personnel, reallocation time, materials, and inventory disposal range from $0.7 million to $4.1 million. In addition, costs may arise from increased physician and medication expenses paid by consumers who may switch to managed care. The estimated annual costs from additional medical care range from $1.3 million to $2.5 million. Annualized over 20 years, the estimated total costs range from $1.3 million to $2.8 million with a 3-percent discount rate, and from $1.3 million to $2.9 million with a 7-percent discount rate. Annualized over 20 years, the estimated net benefits (estimated benefits minus estimated costs) from the regulation range from $11.2 million to $68.0 million with a 3-percent discount rate and from $11.1 million to $68.0 million with a 7-percent discount rate.

B. Need for Regulation

The Centers for Disease Control and Prevention (CDC) reported that in 2009, 7.7 percent (or 17.5 million) of non-institutionalized adults and 9.6 percent (7.1 million) of children suffer from asthma in the United States. Within population subgroups, asthma prevalence is higher among females, children of non-Hispanic Black and Puerto Rican race or ethnicity, and persons with family income below the poverty level (Ref. 7). In 2006, asthma was listed as one of the top five most costly conditions in the United States (Ref. 8). Asthma leads to direct health care costs and indirect costs such as mortality and lost productivity that pose a high burden on society. For example, in 2007, there were 1.75 million asthma-related emergency department visits and 456,000 asthma hospitalizations (Ref. 7), and in 2009, there were 3,447 persons who died of asthma (Ref. 9).

A study found that 5 to 10 percent of individuals with asthma use nonprescription bronchodilators as monotherapy for the treatment of asthma (Ref. 10). Current references for managing asthma acknowledge that once asthma has been professionally diagnosed, patients with mild cases of asthma may use OTC bronchodilators and patients who have more frequent or serious symptoms should be referred to a prescription long-term controller. While the Handbook of Nonprescription Drugs lists epinephrine and ephedrine as the nonprescription bronchodilators available for the treatment of asthma (Ref. 11), the National Heart, Lung and Blood Institute's guidelines for the diagnosis and management of asthma does not recommend epinephrine or ephedrine as a medication of choice for quick-relief of asthma (Ref. 3). (See discussion under IV. FDA's Response to Comments Received About the Proposed Labeling Changes, Comment 2.)

There have been concerns that self-diagnosis and self-treatment of asthma along with illicit use or misuse of OTC single-ingredient ephedrine and epinephrine bronchodilators can lead to serious clinical consequences, which may include death. Studies indicate that approximately 20 percent of individuals using OTC epinephrine inhalers have mild-to-moderate persistent asthma, and should not be using OTC products but be under the supervision of a physician (Ref. 12). The American Association of Poison Control Centers National Poison Data System (NPDS), which collects data on adverse event exposure and information calls associated with pharmaceutical products, reported 1,035 cases associated with exposure to non-selective beta agonists in 2008 (Ref. 13). Although in most of these cases the reason for exposure was reported to be unintentional, 350 of these cases had to be treated in a health facility. Furthermore, other studies report abuse of epinephrine inhalers among high school students (Ref. 14) and fatal cases of asthma in which individuals were using OTC epinephrine (Ref. 15).

The use of OTC bronchodilators appears to be associated with certain demographic characteristics such as low income or educational attainment. For example, a study that drew participants from Northern California found that 60 percent of subjects who had used only OTC bronchodilator to treat asthma did not have any health insurance or a primary caregiver for the management of asthma (Ref. 16). Furthermore, another study reports that overuse of inhaled beta-agonists is associated with lower educational level (Ref. 17).

Executive Order 12866 directs agencies to assess the need for any regulatory action and to provide an explanation of how the regulation will meet that need. FDA is responsible for protecting the public health and for helping the public get the accurate, science-based information they need to use medicines to maintain and improve their health. FDA concludes that current labeling of single ingredient ephedrine and epinephrine products available over-the-counter provide inadequate information. The revised labeling would provide consumers access to information that may enable them to better assess the risk of taking OTC bronchodilators and to possibly improve the management of asthma.

C. Benefits

The estimated benefits of the final rule would derive from a reduction in the number of adverse events, namely hospitalizations, emergency department (ED) visits, physician visits, and mortality, associated with self-medication or mismanagement of asthma medication that may be prevented with revised information or with the help of professional guidance.

FDA estimates the number of preventable events based on the range of individuals with asthma that use OTC bronchodilators as monotherapy, which is between 5 percent (Low) and 10 percent (High) (Ref. 10). Table 1 of this document presents the number of preventable events by category. The analysis assumes that the percent of ambulatory or ED visits related to medication adverse effects approximates the percent of events that may be preventable due to mismanagement or misuse of the medication, and that adults and children face the same incidence rates or likelihood of experiencing each of these events. (See Appendix A for a description on how these are estimated.)

TABLE 1—ESTIMATED PREVENTABLE EVENTS

Description [a]	Length of visit	Number of events	
		Low	High
Ambulatory Visits	0.8 hr	282	564
Emergency Department (ED) Visits	3.0 hrs	67	134
Hospital Stays:			
Inpatient	3.4 days	4	7
Emergency Department (ED).[b]	4.0 days	13	27
Statistical Lives Saved		2	9

Notes: [a] See Appendix A for calculations.
[b] ED hospital length of stay includes 4.93 hours of estimated ED wait time. Sources: Refs. 10–12, 15, 18–25.

Using information of the average length of hospital stays (3.4 days, Ref. 18), ED wait time (3.0 hours and 4.93 hours for ED visits that result in discharge and hospital admissions, respectively, Ref. 19) and time spent in a physician's visit (0.8 hour, Ref. 20), the benefits from the estimated preventable events are valued using median or average costs on physician visits ($155/visit, Ref. 26), ED visits ($569/visit, Ref. 27) and hospital stays ($1,400/day, Ref. 28). We also include part of the indirect benefits: namely, averted loss of work time, using the 2009 median hourly wage of $15.95 plus benefits (equal to $20.73) as reported by the Bureau of Labor Statistics (Ref. 29). Estimates for the loss of work time are determined assuming 8-hour work days, *i.e.,* 3 days in the hospital would be considered 24 hours of lost work. FDA notes that an appropriate method to value the indirect costs of illness would be either a revealed or stated preference measure of willingness to pay. Because we do not have such a measure for these events, we used the value of lost work-time, which likely leads to a lower bound of the estimate of the indirect benefits. Estimated statistical lives saved are valued using Environmental Protection Agency (EPA)'s value of a statistical life (VSL) adjusted for inflation, $7.9 million/life (Ref. 30). The total estimated benefits range from $13.98 million to $69.33 million (see table 2 of this document).

TABLE 2—ESTIMATED PREVENTED EVENTS AND ASSOCIATED ESTIMATED BENEFITS

Description	Time	Cost	Number of events		Estimated benefit [a]	
			Low	High	Low ($000)	High ($000)
Ambulatory Visits		$155/visit	282	564	43.71	87.43
Emergency Department (ED) Visits.		$569/visit	67	134	38.04	76.09
Hospital Stays:						
Inpatient	3.4 days	$1,400/day	4	7	21.04	42.08
ED	4.0 days	$1,400/day	13	27	75.19	150.38
Loss of Work Time:						
Ambulatory Visits	0.8 hr	$20.73/hr[b]	282	564	4.58	9.16
ED Visits	3.0 hrs	$20.73/hr[b]	67	134	3.19	6.38
Hospital Stays:						
Inpatient	27.2 hrs[c]	$20.73/hr[b]	4	7	2.11	4.22
ED	32.1 hrs[c]	$20.73/hr[b]	13	27	8.91	17.82
Statistical Lives Saved		$7.9 Mil/life	2	9	$13,788	$68,941
Total Estimated Benefits					$13,985	$69,334

Notes: [a] Statistical Lives Saved are valued in millions of dollars.
[b] Median hourly wage of $15.95 plus benefits.
[c] Time estimates for loss of work related to hospital stays assume 8-hour work days.

D. Costs

The estimated costs come from labeling costs and additional costs borne by those consumers who switch to prescription medication or other OTC products within the same therapeutic class.

1. Relabeling Costs

Based on Universal Product Code (UPC) counts of the number of OTC products listed in the Red Book and where ephedrine or epinephrine is the single-active ingredient, the number of OTC bronchodilators has decreased from 19 UPCs in 2000 to 13 in 2010. While inhalers are the most prevalent form, OTC bronchodilators are also available in capsules and tablets. FDA estimates that approximately seven manufacturers and distributors market five different brands that are sold in 13 product-form variations or UPCs (see table 3 of this document).

TABLE 3—ESTIMATED NUMBER OF OVER-THE-COUNTER SINGLE-INGREDIENT EPHEDRINE AND EPINEPHRINE BRANDS AND MANUFACTURERS

	2000	2004	2010
No. of Brands [a]	5	5	5
Form: Aerosol	3	3	3
Form: Capsule	1	1	1
Form: Tablet	1	1	1
No. of UPCs	19	15	13
Form: Aerosol	11	8	7
Form: Capsule	5	4	4
Form: Tablet	3	3	2
No. of Manufacturers and Distributors [a]	8	6	7

Note: [a] A brand, manufacturer or distributor is counted only once.
Source: Calculations based on the Red Book, Refs. 31–33.

FDA estimates the costs of the required labeling change using a model developed by a contractor, RTI International (RTI). The labeling cost model was based on an earlier model developed by RTI for FDA to estimate the cost of food label changes (Ref. 34). The required change would revise the ''Indications,'' ''Warnings'' and ''Directions'' sections of the Drug Fact label, and would be deemed minor. (See discussion under IV. FDA's Response to Comments Received About the Proposed Labeling Changes.) The required compliance period is 6 months and it would affect 100 percent of the OTC single ingredient ephedrine and epinephrine UPCs.

RTI's labeling cost estimates are based on the 6-digit North American Industry Classification System (NAICS) that corresponds to Pharmaceutical Preparation Manufacturing of Bronchial Remedies (NAICS code 325412). Labeling costs include labor, material, inventory and recordkeeping. Since FDA provides the design of the label, the labeling cost model assumes there are no costs associated with analytical tests, market tests or label design. The estimated one-time relabeling cost ranges from $0.75 million to $4.1 million (see table 4 of this document).

TABLE 4—ESTIMATED LABELING COST

Cost factor	Low ($000)	Midpoint ($000)	High ($000)
Labor	206	729	1,354
Materials	45	112	230
Inventory	486	1,015	2,481
Recordkeeping	9	18	22
Total Labeling Cost	746	1,873	4,087

2. Switching Costs

Since the revised labeling requirement advises consumers that moderate and severe cases of asthma and all cases of persistent asthma should be under the supervision of a physician and that inhalers provide faster relief, this may have two possible effects on users of OTC ephedrine products with mild-to-severe asthma. Some individuals may respond to this new advice and seek medical help that gets them under a managed care plan. While some of these individuals may seek a physician and switch to prescription medicine as a result, others may substitute other OTC products within the same therapeutic class. FDA does not estimate the number of switchers within the same class and assumes that all switchers will seek a physician and switch to prescription medicine. This estimate may be considered an upper bound of the costs as nonprescription medicine is, on average, lower than prescription medicine.

FDA uses 13 percent as the proxy for the proportion of patients with asthma that may respond to the labeling change and switch to prescription medicine, which is based on a study that reported that 13 to 22 percent of prescription drug spending is attributable to purchases made by consumers who asked for the advertised drug after exposure to television or radio advertisements (Ref. 35). The implied assumption is that consumers who read the labeling would respond to the new ''Indications,'' ''Warnings'' and ''Directions'' sections by then visiting a physician to be placed under a managed care plan or by switching to a new OTC medication as if they were responding to advertisements. The estimated number of switchers is 446 to 892. The range of switchers is estimated by taking the population at risk (245,870 and 491,740 for Low and High, respectively) and weighting it by the percent of the physician visits from patients with asthma (1.4 percent) and the percent of the physician visits due to advertising (13 percent).

The additional annual estimated costs of switching to prescription care is calculated using the difference in total medical expenditures of current asthma users without preventive prescription care ($4,721, Ref. 36) and with preventive prescription care ($7,586, Ref. 36), and the estimated number of switchers. The total estimated cost of switching is calculated by multiplying the additional estimated cost from switching to preventive prescription care ($2,865) times the estimated number of individuals switching to preventive care. The total estimated cost from switching ranges from $1,278,000 to $2,555,000.

3. Estimated Total Costs

The estimated total costs include one-time labeling costs plus annual switching costs. Annualized over 20

years, total estimated costs range from $1.3 million to $2.8 million with a 3-percent discount rate and from $1.3 million to $2.9 million with a 7-percent discount rate (see table 5 of this document).

TABLE 5—TOTAL ESTIMATED COST

Description	Low ($000)	High ($000)
Annual Cost:		
Switching Cost	1,278.00	2,555.00
One-Time Cost:		
Labeling Cost	745.57	4,086.83
Annualized Cost		
3 Percent ...	1,326.65	2,821.70
7 Percent ...	1,343.77	2,915.53

E. Summary of Costs and Benefits

The net benefits are determined based on the various combinations (Low and High) of costs and benefits and annualizing over 20 years assuming a 3 and 7 percent discount rate, separately. Annualized over 20 years, the minimum and maximum estimated net benefits range from $11.2 million to $68.0 million with a 3 percent discount rate, and from $11.1 million to $68.0 million with a 7 percent discount rate (see table 6 of this document).

TABLE 6—ESTIMATED ANNUALIZED NET BENEFITS

Benefits	Cost		Net benefits	
	Low	High	Low	High
	Annualized at 3% over 20 years			
$13,985	$1,327	$2,822	$12,658	$11,163
69,334	1,327	2,822	68,008	58,171
	Annualized at 7% over 20 years			
13,985	1,344	2,916	12,641	11,069
69,334	1,344	2,916	67,991	58,265

Notes: Estimates are in $000s. Net Benefits are benefits minus costs.

Current asthma prevalence rates (percents of the population affected shown in parentheses) between population subgroups show that females (9.3) have higher current asthma prevalence than males (7.0), and that children (9.6) have higher asthma prevalence than adults (7.7). Compared with white persons (7.8), the prevalence is higher among black (11.1) and lower among Asians (5.3). Moreover, those with family income below the Federal poverty level have higher asthma prevalence (11.6) than those with incomes in the near poor (8.5), and not poor (7.3) categories (Ref. 7). While the estimated benefits are calculated based on average characteristics of an asthma individual, it is likely that those sub-groups, *e.g.,* children and the poor, with high prevalence rates may benefit the most from the regulation.

Several factors such as growing asthma prevalence and educational programs geared to improving asthma management and care may impact the market for OTC epinephrine and ephedrine bronchodilators. Current asthma treatment and management guidelines (Ref. 3) do not recommend OTC ephedrine and epinephrine as the standard of care and this may impact the demand for epinephrine and ephedrine bronchodilators and their substitutes, *e.g.,* other OTC bronchodilators or prescription medication within the same therapeutic class. Moreover, the expected withdrawal of chlorofluorocarbon (CFC) inhalers may affect the sale of OTC epinephrine and ephedrine bronchodilators. FDA is uncertain on the impact of these effects on the overall market for OTC bronchodilators in the coming years, but at best, the benefits from preventable adverse events or improved asthma management due to the revised labeling may offset the additional cost of switching to prescription medication and managed care.

F. Analysis of Regulatory Alternatives to the Final Rule

The final rule seeks to change the labeling to make it more understandable to the average reader and to warn users when to seek medical assistance. Changes would also include information that alternative medication may provide faster relief. The final rule establishes an implementation period of 180 days from publication.

The following alternatives were identified: (1) Extend the compliance period, and (2) require more labeling. The compliance periods were 12 and 18 months. Another alternative would be to require additional labeling changes that would be considered ''Major.'' This type of labeling change would involve multiple color changes that would require a label redesign such as substantial changes or elimination of a claim, caution statement or disclaimer. Table 7 of this document presents the relabeling costs associated with these alternatives. Extending the implementation period would lower the costs under both minor and major labeling changes. Extending the period, however, would also postpone the period in which benefits may be observed.

TABLE 7—ESTIMATED LABELING COSTS UNDER ALTERNATIVES TO FINAL RULE

Compliance period (months)	Labeling change					
	Minor			Major		
	Low ($000)	Midpoint ($000)	High ($000)	Low ($000)	Midpoint ($000)	High ($000)
6	746	1,873	4,087	1,200	2,813	5,851
12	429	1,063	1,840	870	1,974	3,550
18	244	656	1,164	540	1,267	2,308

G. Regulatory Flexibility Analysis

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. This analysis serves as the Initial Regulatory Flexibility Analysis as required under the Regulatory Flexibility Act.

1. Description and Number of Affected Small Entities

The Small Business Administration (SBA) uses different definitions of what a small entity is for different industries. Using 2009 SBA size standard definitions, a firm categorized in NAICS code 315412 (Pharmaceutical Preparations) is considered small if it employs fewer than 750 persons (Ref. 37). Using the most currently available data on the number of establishments by employee size from the 2007 Economic Census (Ref. 38) shows that the majority of the establishments have employee sizes by which they would be considered small (see table 7). Using data at the establishment level implicitly assumes that the typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm.

2. Economic Effect on Small Entities

FDA uses data on the total value of shipments by employment size from the 2007 Economic Census (Ref. 38) to determine the unit labeling cost as a percent of the total value of shipments for a typical manufacturer. The average value of shipments is presented for all establishments in NAICS code 325412 and for establishments employing 1–10, 11–499 and over 500 employees, separately. The average value of shipments for entities that employ up to 10 workers is $1,433,000 while for entities with more than 500 employees it is over $1,160 million. It is estimated that the average one-time labeling cost per UPC as a percent of average value of shipments for small entities may be between 0 and 22 percent (see table 8 of this document). The Agency tentatively concludes that this rule would have a significant impact on a substantial number of small entities, but the impact is uncertain.

TABLE 8—ESTIMATED IMPACT OF THE FINAL RULE ON SMALL BUSINESS ENTITIES

Establishments (NAICS 325412)			Value of shipments ($000)		Percent cost per UPC of average value of shipment		
Employees	Count	Percent	Total	Average	Low	Midpoint	High
0–10	408	41	$584,656	1,433	4.00	10.05	21.94
11–499	508	51	55,256,380	108,772	0.05	0.13	0.29
500+	75	8	87,035,221	1,160,470	0.00	0.01	0.03

Source: Pharmaceutical Preparations (NAICS 325412), 2007 Economic Census (Ref. 38).

3. Additional Flexibility Considered

In this section, we discuss alternatives that would present reductions in costs which would be channeled through small entities.

a. *Alternative 1: Exempt small-sized manufacturers from labeling requirement.* Exempting small-sized manufacturers from the labeling requirement would result in a one-time saving of 10 to 22 percent of the value of shipments (see table 8 of this document). However, assuming that the majority of the consumers purchase from small-size firms, it is uncertain that the estimated public health benefits discussed above would be observed.

b. *Alternative 2: Expand the compliance period for small businesses.* FDA considers expanding the compliance period to 12 and 18 months for manufacturers employing up to 10 workers. Table 9 of this document shows that the longer the compliance period, the lower the costs, and that costs may be reduced to 1 and 6 percent under the 18-month compliance period. The longer the compliance period, however, the longer it may take to observe benefits.

TABLE 9—PERCENT COST OF AVERAGE VALUE OF SHIPMENT FOR SMALL ENTITIES

Compliance period (months)	Number of employees	Average Value of shipments ($000)	Percent cost of average value of shipment		
			Low	Midpoint	High
6	0–10	$1,433	4.0	10.1	21.9
12	0–10	1,433	2.3	5.7	9.9
18	0–10	1,433	1.3	3.5	6.2

VIII. 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 labeling statements are 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)).

IX. 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.

X. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. 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.'' The sole statutory provision giving preemptive effect to the final rule is section 751 of the act (21 U.S.C. 379r). We believe that we have complied with all of the applicable requirements under the Executive order and have determined that the preemptive effects of this rule are consistent with Executive Order 13132.

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. FDA–1995–N–0031 (formerly Docket No. 1995N–0205), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

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2. Comment No. C127, Docket No. 1995N–0205, Division of Dockets Management.
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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

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 parts 201 and 341 are amended as follows:

PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Section 201.66 is amended by revising paragraph (c)(5)(ii)(B) to read as follows:

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

* * * * *

(c) * * *

(5) * * *

(ii) * * *

(B) Allergic reaction and asthma alert warnings. Allergic reaction warnings set forth in any applicable OTC drug monograph or approved drug application for any product that requires a separate allergy warning. This warning shall follow the subheading ''Allergy alert:'' The asthma alert warning set forth in §§ 341.76(c)(5) and 341.76(c)(6) of this chapter. This warning shall follow the subheading ''Asthma alert:''

* * * * *

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

■ 3. 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.

■ 4. Section 341.76 is amended by revising paragraphs (b), (c), and (d) to read as follows:

§ 341.76 Labeling of bronchodilator drug products.

(b) *Indication.* The labeling of the product states the following under the heading ''Use'': ''for temporary relief of mild symptoms of intermittent asthma: [bullet] [1] 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 this paragraph (b) may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act relating to misbranding and the prohibition in section 301(d) of the Federal Food, Drug, and Cosmetic Act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the Federal Food, Drug, and Cosmetic 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''.

[1] See § 201.66(b)(4) of this chapter for the definition of ''bullet.''

(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 § 341.16(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 § 341.16(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 paragraph (c)(1) of this section: ''[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 heart beat''.

(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 § 341.16(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 § 341.16(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''.

* * * * *

Dated: July 15, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

Note: The following appendices will not appear in the Code of Federal Regulations.

Appendices

Appendix A. Definitions

Population at Risk: Population with asthma x percent of individuals with asthma using OTC bronchodilators as monotherapy x percent of individuals with mild-to-moderate asthma using OTC epinephrine inhalers

Physician visits: Population at risk x percent of total ambulatory visits related to asthma x percent of ambulatory visits due to medication adverse effects

Emergency Department (ED) Visits: Population at risk x percent of ED visits related to asthma x percent of ED visits related to medication adverse effects x percent of ED visits of patients with acute asthma that were discharged

Inpatient Hospital Stays: Population at risk x percent of total ambulatory visits related to asthma x percent of hospital discharges due to asthma x percent of adverse effects related to medication

ED Hospital Stays: Population at risk x percent of ED visits related to all asthma conditions that resulted in hospitalizations x percent of ED visits related to medication adverse effects x percent of ED visits of patients with acute asthma that were admitted

Lives Saved: Mortality due to asthma x percent of individuals with mild-to-moderate asthma using non-prescription OTC ephedrine x percent of fatal asthma deaths where patient used was using epinephrine.

Note: See Appendix B for values and sources.

Appendix B. Values and Sources Used for Estimated Benefits Calculations

	Value	Source
Individuals with Asthma that use OTC Bronchodilators as Monotherapy	5–10%	Ref. 10
Individuals with Mild-to-moderate Asthma Using OTC Epinephrine Inhalers	20%	Ref. 12
Individuals with Acute Asthma Visiting the ED and Requiring Admission	20–30%	Ref. 21
Fatal Asthma Cases and Use of OTC Epinephrine	5%	Ref. 15
Population with Asthma (Adults and Children)	24,587,000	Refs. 22, 23
Total Ambulatory Visits	994,321,000	Ref. 24
Total Ambulatory Visits, Asthma	13,872,000	Ref. 24
Total Visits, Injury-related	106,451,000	Ref. 24
Total Visits, Injury-related due to Medication Adverse Effects	8,752,000	Ref. 24
Total ED Visits	116,802,000	Ref. 25
Total ED Visits, Asthma	1,750,000	Ref. 25

	Value	Source
Total ED Visits, Injury-related	39,395,000	Ref. 25
Total ED Visits, Injury-related due to Medication Adverse Effects	716,000	Ref. 25
Total ED Visits, Admitted	14,641,000	Ref. 25
Total ED Visits, Admitted with Asthma	158,000	Ref. 25
Total Hospital Discharges	34,369,000	Ref. 18
Total Hospital Discharges, Asthma	456,000	Ref. 18
Mortality, Asthma	3,447	Ref. 11

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 882

[Docket No. FDA–2011–N–0466]

Medical Devices; Neurological Devices; Classification of Repetitive Transcranial Magnetic Stimulation System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is classifying the repetitive transcranial magnetic stimulation (rTMS) system into class II (special controls). The Agency is classifying this device type into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of these devices.

DATES: This final rule is effective August 25, 2011.

FOR FURTHER INFORMATION CONTACT: Ann H. Costello, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 2460, Silver Spring, MD 20993–0002, 301–796–6493.

SUPPLEMENTARY INFORMATION:

I. What is the background of this rulemaking?

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976, the date of enactment of the Medical Device Amendments of 1976, generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless the device is classified or reclassified into class I or class II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act (21 U.S.C. 360c(i)), to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 of FDA's regulations (21 CFR part 807).

Section 513(f)(2) of the FD&C Act provides that any person who submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified may, within 30 days after receiving an order classifying the device in class III under section 513(f)(1), request FDA to classify the device under the criteria set forth in section 513(a)(1). FDA must, within 60 days of receiving such a request, classify the device by written order. This classification will be the initial classification of the device type. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the **Federal Register** announcing this classification (section 513(f)(2) of the FD&C Act).

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on April 27, 2007, classifying the NeuroStar® TMS System for the treatment of major depressive disorder in patients who have failed to receive benefit from one antidepressant trial into class III, because it was not substantially equivalent to a device that was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or a device that was subsequently reclassified into class I or class II. On May 23, 2007, Neuronetics, Inc., submitted a petition requesting classification, under section 513(f)(2) of the FD&C Act, of the NeuroStar® TMS System for the treatment of major depressive disorder in patients who have failed to receive benefit from one antidepressant trial. The manufacturer recommended that the device be classified into class II (Ref. 1).

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the petition in order to classify the device under the criteria for classification set forth in 513(a)(1) of the FD&C Act. FDA classifies devices into class II if general controls, by themselves, are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the petition, FDA determined that the rTMS system can be classified into class II with the establishment of special controls. FDA believes that these special controls, in addition to general controls, are adequate to provide reasonable assurance of the safety and effectiveness of the device. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a guidance document entitled ''Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation System,'' which will serve as the special control for rTMS systems.

The device is assigned the generic name ''Repetitive Transcranial Magnetic Stimulation System.'' A repetitive transcranial magnetic stimulation system is an external device that delivers transcranial repetitive pulsed magnetic fields of sufficient magnitude to induce neural action potentials in the prefrontal cortex to treat the symptoms of major depressive disorder without inducing seizure in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy.

FDA has identified the risks to health associated with this type of device as follows:

- Failure to identify correct patient population;
- Ineffective treatment;
- Seizure;
- Scalp discomfort, scalp burn, or other adverse effects;
- Magnetic field effects on functioning of other medical devices;
- Adverse tissue reaction;
- Hazards associated with electrical equipment;
- Hazards caused by electromagnetic interference and electrostatic discharge hazards; and
- Hearing loss.

FDA believes that the class II special controls guidance document will aid in