Guidance for Industry

Labeling for Bronchodilators: Cold, Cough, Allergy, Bronchodilator, And Antiasthmatic Drug Products for Over-the-Counter Human Use

(Small Entity Compliance Guide)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2012
OTC

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to help small businesses understand and comply with the Food and Drug Administration's (FDA's) labeling regulations for certain over-the-counter (OTC) bronchodilator drug products marketed without an approved application.[2] On July 26, 2011, we published the final rule "Labeling for Bronchodilators to Treat Asthma; Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use" (2011 bronchodilator final rule; 76 FR 44475). The 2011 bronchodilator final rule requires that certain OTC bronchodilator drug products bear specific labeling to promote their safe and effective use. This guidance was prepared in accordance with section 212 of the Small Business Regulatory Fairness Act (Public Law 104-121).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Nonprescription Regulation Development in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). Approved applications under section 505 include both new drug applications and abbreviated new drug applications. This guidance does not address those drug products that are marketed under approved applications.

II. SUMMARY OF THE REGULATION AND THIS GUIDANCE

In the *Federal Register* of July 13, 2005 (70 FR 40237), we published a proposed rule that included labeling for OTC bronchodilator drug products. The rule proposed an additional warning (an *Asthma Alert*), and revised the indications, warnings, and directions in the labeling of OTC bronchodilator drug products. We reviewed information submitted in response to the proposed rule and other pertinent information to establish our requirements.

In the *Federal Register* of July 26, 2011, we published a final rule that revised and finalized the Drug Facts labeling for OTC bronchodilators (21 CFR 341.76). The compliance date for all drug products subject to this final rule was January 23, 2012.

III. QUESTIONS AND ANSWERS

Question 1: What active ingredients are included in this rule?

Answer: The 2011 bronchodilator final rule lists all permitted active ingredients for OTC bronchodilator drug products, as set forth in 21 CFR 341.16. The monograph, as amended by the final rule, permits use of four single active ingredients in an oral dosage form and three single active ingredients used in a hand-held rubber bulb nebulizer. These ingredients are listed below.

For oral dosage forms, the permitted single *ephedrine active ingredients* category includes four active ingredients:

1. Ephedrine
2. Ephedrine hydrochloride
3. Ephedrine sulfate
4. Racephedrine hydrochloride

For inhaled dosage forms using a hand-held rubber bulb nebulizer, the permitted single *epinephrine active ingredients* category includes three active ingredients:

1. Epinephrine
2. Epinephrine bitartrate
3. Racepinephrine hydrochloride

Question 2: Is my drug product subject to the 2011 bronchodilator final rule?

Answer: Your OTC bronchodilator drug product is subject to this rule if it meets both of the following conditions:

- Contains any of the active ingredients listed under 21 CFR 341.16 (i.e., the seven ephedrine and epinephrine active ingredients listed in the answer to question 1 above).

- Is marketed under the OTC bronchodilator monograph (21 CFR part 341, Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use).

Question 3: When must I be in compliance with this rule?

Answer: The compliance date for all drug products, regardless of the size of your business or annual sales, was January 23, 2012.

Question 4: Does this rule apply to OTC bronchodilator drug products that are marketed under a new drug application (NDA)?

Answer: No, this rule does not apply to NDA drug products. NDA drug products, including formulations of epinephrine in a metered dose inhaler,[3] are subject to premarket review and approval.

Question 5: What combinations of active ingredients are included in this rule?

Answer: Combinations of active ingredients that are permitted in cold, cough, allergy, bronchodilator, and antiasthmatic drug products are found under 21 CFR 341.40. The current regulations do not allow combinations of two or more bronchodilator ingredients, or combinations of bronchodilators with nonbronchodilator active ingredients.

Question 6: What Drug Facts labeling does the 2011 bronchodilator final rule require for my drug products?

Answer: See Table 1 that provides:

- The exact language that must be used in warnings and other labeling statements of Drug Facts

- Some language differences between the labeling of drug products that contain ephedrine active ingredients and epinephrine active ingredients

- Updated **Asthma Alert** language

- Updated Drug Facts content and formatting requirements consistent with 21 CFR 201.66

[3] See the final rule "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Monograph for OTC Bronchodilator Drug Products" (61 FR 25142).

In addition, bronchodilator drug products must comply with the labeling requirements in 21 CFR part 201 that apply to OTC drugs in general.

Table 1. Summary of Labeling Required for OTC Bronchodilator Drug Products Subject to the 2011 Bronchodilator Final Rule

Drug Facts Heading	Specific Language Required	
Use	Labeling for all bronchodilators: "• for temporary relief of mild symptoms of intermittent asthma: • wheezing • tightness of chest • shortness of breath"	
Warnings **Asthma Alert**	Labeling for ephedrine active ingredients: **"Asthma alert: Because asthma may be life threatening, see a doctor if you [in bold type]** • are not better in 60 minutes • get worse • need more than [insert total number of dosage units that equals 150 mg] in 24 hours • use more than [insert total number of dosage units that equals 100 mg] in 24 hours for 3 or more days a week • have more than 2 asthma attacks in a week These may be signs that your asthma is getting worse. • This product will not give you asthma relief as quickly as an inhaled bronchodilator."	Labeling for epinephrine active ingredients: **"Asthma alert: Because asthma may be life threatening, see a doctor if you [in bold type]** • are not better in 20 minutes • get worse • need more than 12 inhalations in 24 hours • use more than 9 inhalations in 24 hours for 3 or more days a week • have more than 2 asthma attacks in a week These may be signs that your asthma is getting worse."

continued

Table 1, continued

Drug Facts Heading	Specific Language Required	
Warnings **Do not use**	Labeling for ephedrine active ingredients: "• unless a doctor said you have asthma • if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product."	Labeling for epinephrine active ingredients: "• unless a doctor said you have asthma • if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product. • if product is brown in color or cloudy"
Warnings **Ask a doctor before use if you have**	Labeling for all bronchodilators: "• ever been hospitalized for asthma • heart disease • high blood pressure • diabetes • thyroid disease • seizures • narrow angle glaucoma • a psychiatric or emotional condition • trouble urinating due to an enlarged prostate gland"	
Warnings **Ask a doctor or pharmacist before use if you are**	Labeling for all bronchodilators: "• taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions • taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)"	

continued

Table 1, continued

Drug Facts Heading	Specific Language Required	

Warnings **When using this product**	Labeling for all bronchodilators:
	"• **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]**
	• **your risk of heart attack or stroke increases if you:**
	  • **have a history of high blood pressure or heart disease**
	  • **take this product more frequently or take more than the recommended dose [in bold type]**
	• avoid foods or beverages that contain caffeine
	• avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect"	

Warnings **Stop use and ask a doctor if**	Labeling for all bronchodilators: "• your asthma is getting worse (see Asthma Alert) • you have difficulty sleeping • you have a rapid heart beat • you have tremors, nervousness, or seizure"	
Directions	Labeling for ephedrine active ingredients: "• **do not take more than directed [in bold type]** • adults and children 12 years of age and over: oral dose is 12.5 mg to 25 mg every 4 hours as needed. Do not take more than 150 mg in 24 hours. • children under 12 years of age: ask a doctor"	Labeling for epinephrine active ingredients: "• **do not use more than directed [in bold type]** • adults and children 4 years of age and over: oral dose is 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. • children under 4 years of age: ask a doctor"

Question 7: Do I need preapproval from the FDA to market drug products with the labeling revisions required by this rule?

Answer: No. Provided that your drug product and its labeling are modified to comply with the current monograph for OTC bronchodilator drug products, you do not need preapproval of the labeling.

Question 8: Do I need to update my listing information, reflecting this revised labeling, with the FDA?

Answer: Yes. Labeling that is revised to meet the requirements of this rule should be submitted to the FDA through the drug listing process. Any updates must be submitted every June and December (section 510(j)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)).[4] However, registrants (and, if applicable, private label distributors) are encouraged to submit updates through the registration and listing system more frequently, as changes occur. Information on this process can be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm.

Question 9: What will happen if my drug product fails to comply with this rule by the compliance date?

Answer: If your drug product fails to comply with this rule by the appropriate compliance date, it will be deemed to be misbranded under section 502(j) of the FD&C Act (21 U.S.C. 352(j)) as well as potentially in violation of other sections of the Act, and will be subject to regulatory action.

Question 10: If I have questions about whether my drug product is subject to this rule, how to comply with the rule, or any related issues, whom should I contact at the FDA?

Answer: You should contact the Division of Nonprescription Regulation Development. Contact information is available at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm093452.htm.

Question 11: Where can I find a copy of the *Federal Register* notice that contains the final rule?

Answer: You can access the final rule at: http://www.regulations.gov/#!documentDetail;D=FDA-1995-N-0031-0005. You also can access additional information about the rulemaking history for the OTC bronchodilator drug product monograph on FDA's Web site at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm070900.htm.

[4] See 21 CFR 207.21(b).