
Guidance for Industry

Topical Acne Drug Products for Over-the-Counter Human Use — Revision of Labeling and Classification of Benzoyl Peroxide as Safe and Effective

Small Entity Compliance Guide

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

**June 2011
OTC**

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TABLE OF CONTENTS

I.	INTRODUCTION.....	2
II.	BACKGROUND	3
III.	SUMMARY OF THE REGULATION.....	3
IV.	PERMITTED ACTIVE INGREDIENTS, WARNINGS, AND DIRECTIONS	4
V.	QUESTIONS AND ANSWERS.....	7

Guidance for Industry¹
Topical Acne Products for Over-the-Counter Human Use —
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and Classification of Benzoyl Peroxide as Safe and Effective
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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 FDA's regulation regarding over-the-counter (OTC) topical acne drug products published in the *Federal Register* on March 4, 2010 (75 FR 9767). The final rule makes the following changes to the OTC regulations at 21 CFR 333, subpart D:

- Adds benzoyl peroxide as a generally recognized as safe and effective (GRASE) active ingredient in OTC topical acne drug products
- Sets forth new warnings and a direction that must be included in labeling of OTC topical acne drug products that contain benzoyl peroxide
- Revises labeling requirements for *all* OTC topical acne drug products, to ensure consistency with the standardized Drug Facts formatting and requirements set forth in 21 CFR 201.66

FDA has prepared this guidance 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 Office of Drug Evaluation IV in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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II. BACKGROUND

In the *Federal Register* of January 15, 1985 (50 FR 2172), FDA published a proposed rule allowing for the use of a number of active ingredients, including benzoyl peroxide (2.5 to 10%), in OTC topical acne drug products.

Based on safety concerns raised after publication of the 1985 proposed rule, FDA proposed to classify benzoyl peroxide as category III, which meant that more data were needed to properly classify benzoyl peroxide as a GRASE active ingredient (56 FR 37622, August 7, 1991). Shortly after proposing to classify benzoyl peroxide as category III, FDA issued a final rule for OTC topical acne products that permitted the use of the other active ingredients included in the 1985 proposed rule — resorcinol, resorcinol monoacetate, salicylic acid, and/or sulfur in certain concentrations and combinations (56 FR 41008, August 16, 1991).

Since 1991, new data have been submitted to address the safety concerns regarding benzoyl peroxide. After reviewing the data, FDA concluded that benzoyl peroxide can be adequately labeled to minimize risks while delivering effective acne treatment. The final rule, published on March 4, 2010, and effective on March 4, 2011, reflects these conclusions. Note that although the final rule is effective on March 4, 2011, compliance dates for specific requirements under the final rule vary depending upon the active ingredient and volume of annual sales, as discussed in section V (QUESTIONS AND ANSWERS), Question 4.

III. SUMMARY OF THE REGULATION

FDA issued the March 4, 2010, final rule to classify benzoyl peroxide (in concentrations of 2.5 to 10%) as a permitted active ingredient in OTC topical acne drug products. In the final rule, FDA concludes that benzoyl peroxide may be used in OTC topical acne products based on our review of studies on genotoxicity, tumor promotion with chemical/ultraviolet initiation, animal carcinogenicity, and photocarcinogenicity, as well as the related epidemiological data.

In addition to adding benzoyl peroxide to the monograph as a permitted active ingredient, the March 4, 2010, final rule adds specific warnings (regarding potential sensitivity and/or irritation) and a new “direction for use” (regarding the use of sunscreen after treatment with benzoyl peroxide products) required in the labeling for OTC topical acne products that contain benzoyl peroxide.

The final rule also requires the use of new warnings and directions in the labeling of all OTC acne drug products (including those products that contain benzoyl peroxide). These changes ensure that the labeling for OTC topical acne products meets the standardized OTC drug labeling content and format requirements in 21 CFR 201.66, which had not yet been established when the monograph for OTC topical acne products (allowing for the use of resorcinol, resorcinol monoacetate, salicylic acid, and/or sulfur as active ingredients) was published in 1991.

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IV. PERMITTED ACTIVE INGREDIENTS, WARNINGS, AND DIRECTIONS

The final rule lists all permitted active ingredients for OTC topical acne products, and their respective permissible concentrations and ingredient combinations, as set forth in 21 CFR 333.310 and 21 CFR 333.320. The monograph, as amended by the final rule, permits use of three single active ingredients and two combinations of active ingredients, which are listed below.

Permitted single active ingredient products:

- **Benzoyl peroxide** in concentrations of 2.5 to 10 percent.
- **Salicylic acid** in concentrations of 0.5 to 2 percent.
- **Sulfur** in concentrations of 3 to 10 percent.

Permitted combination active ingredient products.

- **Resorcinol** in 2 percent concentration in combination with **sulfur** in concentrations of between 3 and 8 percent.
- **Resorcinol monoacetate** in 3 percent concentration in combination with **sulfur** in concentrations of between 3 and 8 percent.

The final rule also revises the labeling requirements for OTC topical acne products, as set forth in 21 CFR 333.350. Table 1 provides warnings and directions required in labeling of all OTC topical acne products marketed under the monograph as amended by the final rule. Table 2 provides additional warnings and directions required in labeling of OTC topical acne products that contain benzoyl peroxide, sulfur, or a combination of active ingredients.

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**Table 1. Summary of Warnings and Directions Required for
All OTC Topical Acne Ingredients**

Active Ingredient(s)	Warnings	Directions
All	<p>For external use only</p> <p>When using this product</p> <ul style="list-style-type: none"> ● skin irritation and dryness is more likely to occur if you use another topical acne medication at the same time. If irritation occurs, only use one topical acne medication at a time. 	<ul style="list-style-type: none"> ● clean the skin thoroughly before applying this product ● cover the entire affected area with a thin layer one to three times daily ● because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor ● if bothersome dryness or peeling occurs, reduce application to once a day or every other day. <p>Products, such as soaps and masks, which are applied and removed should include appropriate directions in addition to the directions set forth above. For example, the second bullet of the standard directions listed above may be revised to read “cover the entire affected area with a thin layer <u>and rinse thoroughly</u> one to three times daily.”</p> <p>In addition to the required directions, all OTC topical acne products marketed under the monograph may contain the following optional direction: <i>“Sensitivity Test for a New User. Apply product sparingly to one or two small affected areas during the first 3 days. If no discomfort occurs, follow the directions stated (select one of the following: ‘elsewhere on this label,’ ‘above,’ or ‘below’).”</i></p>

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Table 2. Additional Required Warnings and Directions for OTC Topical Acne Products Containing Benzoyl Peroxide, Sulfur, or a Combination of Active Ingredients

Active Ingredient(s)	Additional Required Warnings	Additional Required Directions
Benzoyl peroxide	<p>Do not use if you</p> <ul style="list-style-type: none"> ● have very sensitive skin ● are sensitive to benzoyl peroxide <p>When using this product</p> <ul style="list-style-type: none"> ● avoid unnecessary sun exposure and use a sunscreen ● avoid contact with the eyes, lips, and mouth ● avoid contact with hair and dyed fabrics, which may be bleached by this product ● skin irritation may occur, characterized by redness, burning, itching, peeling, or possibly swelling. Irritation may be reduced by using the product less frequently or in a lower concentration. <p>Stop use and ask a doctor if</p> <ul style="list-style-type: none"> ● irritation becomes severe 	<ul style="list-style-type: none"> ● if going outside, apply sunscreen after using this product. If irritation or sensitivity develops, stop use of both products and ask a doctor.
Sulfur	<p>Do not use on</p> <ul style="list-style-type: none"> ● broken skin ● large areas of the skin <p>When using this product</p> <ul style="list-style-type: none"> ● apply only to areas with acne 	
Combinations of active ingredients	<p>Do not use on</p> <ul style="list-style-type: none"> ● broken skin ● large areas of the skin <p>When using this product</p> <ul style="list-style-type: none"> ● apply only to areas with acne ● rinse right away with water if it gets in eyes <p>Stop use and ask a doctor</p> <ul style="list-style-type: none"> ● if skin irritation occurs or gets worse 	

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V. QUESTIONS AND ANSWERS

Question 1: Is the product I manufacture subject to this rule?

Answer: If you manufacture an OTC topical drug product to treat acne, your drug product is subject to this rule if your product:

- Contains any of the active ingredients listed above under § 333.310 (i.e., benzoyl peroxide, resorcinol, resorcinol monoacetate, salicylic acid, sulfur) or a combination of these ingredients permitted under § 333.320
- Is marketed under the OTC acne monograph (21 CFR part 333, subpart D)

Question 2: Does this rule apply to OTC products marketed under a new drug application (NDA)?

Answer: No, this rule does not apply to NDA products. The labeling of products marketed under an NDA is subject to prior review and approval by FDA.

Question 3: I manufacture a product containing one or more of the specified ingredients, but with annual sales of less than \$25,000. Is my drug product subject to this rule?

Answer: Yes, the final rule applies to products with annual sales of less than \$25,000, but the compliance dates are dependent upon the active ingredient used in the product (see below).

Question 4: When must I be in compliance with this rule?

Answer: The exact compliance date for your product will depend on the active ingredient and volume of annual sales, as shown below:

- March 4, 2011: Products containing benzoyl peroxide with annual sales of \$25,000 or more
- March 2, 2012: Products containing benzoyl peroxide with annual sales of less than \$25,000
- March 4, 2015: Products containing resorcinol, resorcinol monoacetate, salicylic acid, and/or sulfur, regardless of annual sales

Question 5: This final rule also updated the labeling requirements for all OTC topical acne products for consistency with 21 CFR 201.66. What is 21 CFR 201.66 about?

Answer: In addition to finalizing the OTC topical acne monograph by resolving the status of the active ingredient, benzoyl peroxide, the final rule also updates the monograph labeling for products containing any of the active ingredients in the monograph. These changes were made to improve the compatibility of the acne monograph labeling language with the Drug Facts formatting requirements in 21 CFR 201.66.

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Question 6: Where should the new labeling appear in the package?

Answer: The relevant, required language shown in tables 1 and 2 should be included in the Warnings and Directions section of Drug Facts, respectively, on the carton labeling. We do not require a consumer package insert in this rule.

Question 7: Do I need preapproval from FDA of the new labeling/principal display panel (PDP) before I begin to use it?

Answer: No. Provided that the product and its labeling comply with the monograph for topical OTC acne drugs, you do not need preapproval of the labeling.

Question 8: Do the new labeling requirements apply to all topical formulations containing the active ingredients included in this final rule?

Answer: Yes, this final rule applies to all OTC topical acne products, whether a gel, lotion, cream, mask, face wash, rinse, or other forms to be applied to the skin. In addition, this final rule applies whether the topical OTC acne product is intended to be left on the skin or applied and then rinsed off.

Question 9: What will happen if I fail to comply with this rule by the compliance date?

Answer: If you fail to comply with this rule by the appropriate compliance date (see question 4, above), your drug product will be deemed an unapproved new drug under section 505(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(a)) and misbranded under section 502(f)(1) and (f)(2) of the FD&C Act (21 U.S.C. 352(f)(1) and 352(f)(2)). As a result, your drug may be subject to regulatory enforcement action.

Question 10: Do I need to update my listing information, reflecting this revised labeling, with FDA?

Answer: Yes. Labeling that is revised to meet the requirements of this rule should be submitted to FDA through the drug listing process. Any updates must be submitted every June and December (section 510(j)(2) of the FD&C Act; 21 CFR 207.21(b)). 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>.

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Question 11: If I have questions about whether the drug product I manufacture is subject to this rule, how to comply with the rule, or any related issues, whom should I contact at FDA?

Answer: You should contact the Division of Nonprescription Regulation Development, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5426, Silver Spring, MD 20993, 301-796-2090.

Question 12: 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-1981-N-0114-0001>. You also can access additional information about the rulemaking history for the OTC acne drug product monograph on FDA's Web site, at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm069967.htm>.