

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration.

21 CFR Part 341

[Docket No. 76N-052G]

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Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Partial Final Rule for Combination Drug Products Containing a Bronchodilator

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that cough-cold combination drug products containing any oral bronchodilator active ingredient in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient are not generally recognized as safe and effective and are misbranded for over-the-counter (OTC) use. FDA is issuing this final rule after receiving no public comments on the agency's proposed nonmonograph status of these specific combination drug products, which was issued in the form of a tentative final monograph for OTC cough-cold combination drug products. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

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

FOR FURTHER INFORMATION CONTACT: Cazemiro R. Martin, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, **301-827-2222**.

SUPPLEMENTARY INFORMATION:
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I. Background

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic (cough-cold) drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. The Panel placed the combination of an oral bronchodilator with either an analgesic-antipyretic, anticholinergic, antihistamine, or antitussive (when the product is labeled only for cough associated with asthma) ingredient in Category II (not generally recognized as safe and/or effective) (41 FR 38312 at 38326).

The agency concurred with the Panel in the tentative final monograph for cough-cold combination drug products (53 FR 30522 at 30556, August 12, 1988). The agency also classified the combination of caffeine and ephedrine or pseudoephedrine in Category II (53 FR 30522 at 30557). No comments on these specific combinations were submitted in response to the tentative final monograph.

The current monograph oral bronchodilator active ingredients are ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride (21 CFR 341.16(a), (b), (c), and (f)). The agency is not aware of any OTC drug products currently marketed containing an oral bronchodilator active ingredient in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient.

II. The Agency's Conclusion

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. The Panel evaluated the submitted data on active ingredients in combination products from the standpoint of safety and effectiveness

and, based on its evaluation, recommended specific combinations of ingredients from the same and different pharmacologic groups. The Panel classified a number of cough-cold combinations as Category II (41 FR 38312 at 38326) and considered medical rationale and drug interaction in making these recommendations.

In the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30556 to 30557), the agency agreed with the Panel's recommended Category II status of any oral bronchodilator active ingredient in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient. The agency invited interested persons to submit written comments and new data demonstrating the safety and effectiveness of those conditions not classified in Category I (53 FR 30522 at 30560). The agency did not receive any comments in response to its request for such information concerning the proposed Category II status of any of the above-mentioned OTC cough-cold combination drug products containing an oral bronchodilator.

Accordingly, in this final rule the agency is finalizing the nonmonograph status of any oral bronchodilator active ingredient in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient. Thus, any drug product labeled, represented, or promoted for use as an OTC cough-cold combination drug that contains any oral bronchodilator active ingredients in combination with any of these specific active ingredients may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352). These specific combination drug products can not be marketed for OTC cough-cold use unless they are the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). Any OTC cough-cold combination drug product included in new § 310.545(a)(6)(iv)(D) that is initially introduced or initially delivered for introduction into interstate commerce after the effective date stated in

§ 310.545(d)(33) of this final rule that is not in compliance with the regulations is subject to regulatory action.

III. Analysis of Impacts

The agency did not receive any comments in response to its request in the tentative final monograph (53 FR 30522 at 30560) for specific comment on the economic impact of this rulemaking. FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

The purpose of this final rule is to declare any oral bronchodilator active ingredient in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient as not generally recognized as safe and effective. The agency does not believe that any of these combination drug products are currently marketed OTC. Therefore, this final rule should have no economic impact on any manufacturer.

Under the Unfunded Mandates Reform Act, FDA is not required to prepare a statement of costs and benefits for this final rule because this final rule is not expected to result in an expenditure that would exceed \$100 million adjusted for inflation in any one year.

The agency certifies that the final rule will not have a significant impact on a substantial number of small entities.

IV. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that is categorically excluded from the preparation of an environmental assessment because these actions, as a class, will not result in the production or distribution of any substance and therefore will not result in the production of any substance into the environment.

V. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216,241,242(a), 262, 263b-263n.

2. Section 310.545 is amended by adding paragraph (a)(6)(iv)(D), by revising paragraph (d) introductory text, by adding and reserving paragraph (d)(32), and by adding paragraph (d)(33) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(iv) * * *

(D) Approved as of *[insert date 30 days after date of publication in the **Federal Register**]*.

Any oral bronchodilator active ingredient (e.g., ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, or any other ephedrine salt) in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient.

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(33) of this section.

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(32) [Reserved]

(33) [Insert date 30 days after date of publication in the **Federal Register**], for products subject to paragraph (a)(6)(iv)(D) of this section.

Dated: 9/20/01
September 20, 2001.



Margaret M. Dotzel,
Associate Commissioner for Policy.

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