

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Part 310

[Docket No. 78N-036L]

RIN 0910-AA01

**Status of Certain Additional Over-the-Counter Drug Category II and III Active  
Ingredients**

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

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule stating that the stimulant laxative ingredients aloe (including aloe extract and aloe flower extract) and cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract) in over-the-counter (OTC) drug products are not generally recognized as safe and effective or are misbranded. This final rule is part of FDA's ongoing OTC drug product review.

**DATES:** This rule is effective [*insert date 180 days after date of publication in the Federal Register*].

**FOR FURTHER INFORMATION CONTACT:** Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2307.

**SUPPLEMENTARY INFORMATION:**

## I. Background

In the **Federal Register** of November 7, 1990 (55 FR 46914), FDA published under 21 CFR 330.10(a)(7)(ii) a final rule on the status of certain OTC drug category II and III active ingredients. That final rule declared as not generally recognized as safe and effective certain active ingredients that had been proposed as nonmonograph (category II or III) under the agency's OTC drug review. The periods for submission of comments and new data following the publication of a notice of proposed rulemaking had closed and no significant comments or new data had been submitted to upgrade the status of these ingredients. In each instance, a final rule for the class of ingredients involved had not been published to date.

In the **Federal Register** of June 19, 1998 (63 FR 33592), FDA reopened the administrative record and reclassified the stimulant laxative ingredients aloe, bisacodyl, cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract), and senna (including sennosides A and B) from category I (monograph) to category III (more data needed). The agency requested mutagenicity, genotoxicity, and carcinogenicity data on aloe and cascara sagrada ingredients and carcinogenicity data on bisacodyl and senna. The agency recommended that persons interested in testing these drugs consult the agency before initiating any studies and stated that these ingredients would be placed in category II (nonmonograph) in a final rule if data were not provided. The agency has received data on bisacodyl and senna, which will be discussed in future issues of the **Federal Register**. However, no comments or data were submitted for aloe or cascara sagrada ingredients.

Accordingly, aloe and cascara sagrada ingredients will not be included in the final monograph for OTC laxative drug products because they have not been shown to be generally recognized as safe and effective for their intended use. These ingredients should be eliminated from OTC laxative drug products 180 days after the date of publication of this final rule, regardless of whether further testing is undertaken to justify future use.

The agency points out that publication of this final rule does not preclude a manufacturer's testing an ingredient. New, relevant data can be submitted to the agency at a later date as the subject of a new drug application that may provide for prescription or OTC marketing status. (See part 314 (21 CFR part 314).) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in an appropriate citizen petition to amend a monograph. (See § 10.30 (21 CFR 10.30).)

## **II. The Agency's Final Conclusions**

Based on the lack of data and information and the failure of interested persons to submit any new data from carcinogenicity studies, the agency has determined that the stimulant laxative ingredients aloe (including aloe extract and aloe flower extract) and cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract) should be deemed not generally recognized as safe and effective for OTC use before a final monograph is established for OTC laxative drug products. The agency is reclassifying these ingredients to category II (nonmonograph) and is adding them to the list of stimulant laxative ingredients for which the data are inadequate to establish general recognition of safety and effectiveness for such use in § 310.545(a)(12)(iv) (21 CFR 310.545(a)(12)(iv)) at new § 310.545(a)(12)(iv)(C).

Accordingly, any drug product containing any of these aloe or cascara sagrada ingredients and labeled for OTC laxative use will be considered nonmonograph and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations is required for marketing. This applies to any OTC drug product containing any of these aloe or cascara sagrada ingredients and labeled for laxative use that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule. Further, any OTC drug product that was previously initially introduced or initially delivered for introduction into interstate commerce cannot

be repackaged or relabeled after the effective date of the rule. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

### III. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), 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 of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency concludes that this final rule is consistent with the principles set out in the Executive order and in these two statutes. In accordance with Executive Order 12866, FDA previously analyzed the potential economic effects of this final rule. As stated in the proposal (63 FR 33592 at 33594), the agency believed then that the rule would not be a significant regulatory action as defined by the Executive order. The agency has not received any new information or comments altering its previous expectations. Further, since this final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation, FDA need not prepare additional analyses under the Unfunded Mandates Reform Act.

The purpose of this final rule is to act on the nonmonograph status of certain stimulant laxative ingredients in advance of finalization of other monograph conditions in order to expedite completion of the OTC drug review. Products containing these ingredients will need to be reformulated to delete and/or replace the ingredient(s) with another laxative active ingredient. There are a number of acceptable laxative active ingredients in proposed part 334 (50 FR 2124 at 2152, January 15, 1985) that could be used. The reformulated products will also require relabeling.

The agency's Drug Listing System (DLS) identifies approximately 15 OTC laxative drug products that contain aloe (including aloe extract and aloe flower extract) and 160 OTC laxative drug products that contain cascara sagrada ingredients. Six products contain both aloe and cascara or casanthranol and appear on both lists. Approximately 125 products contain casanthranol and docusate sodium, a proposed monograph laxative ingredient. These combination products could be reformulated to eliminate the casanthranol, replace the casanthranol with sennosides A and B or sodium carboxymethylcellulose (proposed monograph combinations with docusate sodium in § 334.30(i)(3) and (j) (58 FR 46589 at 46595, September 2, 1993)), or possibly increase the quantity of docusate sodium in the product, in conformance with the proposed monograph.

The cost to reformulate a product will vary greatly, based on: The nature of the change in formulation, the product, the process, and the size of the firm. Based on the reformulation options discussed previously in this document, most firms should not need to change their dosage form. However, they will have to redo the validation (product, process, new supplier), conduct stability tests, and change master production records in order to ensure compliance with current good manufacturing practice. (See section 501(a)(1)(B) of the act (21 U.S.C. 351(a)(1)(B)) and parts 210 and 211) (21 CFR parts 210 and 211).)

The DLS indicates that approximately 35 manufacturers and 70 distributors/repackers/relabelers market these 170 products. Most firms have only one or two products and should not incur substantial economic expense should they choose to reformulate or discontinue their

product(s). The 35 manufacturers will incur the majority of the costs to reformulate and relabel products.

The agency estimates the range of reformulation costs is from \$100,000 to \$500,000 per product. As most affected firms have only one or two products containing these ingredients, the midpoint of the cost estimate for reformulation implies total costs of \$300,000 to \$600,000 per firm. If all manufacturers decide to reformulate, about 56 products would be affected. Using the midpoint of the estimated cost to reformulate (\$300,000) implies total costs of \$16.8 million. However, the agency believes the total costs will be lower because not all firms will choose to reformulate. Some firms may choose to discontinue a product line if sales are too low to justify the added cost of reformulation and/or they may place their market emphasis on other OTC laxative drug products. The lost sales from the products containing nonmonograph ingredients may be offset by sales of the substitute products containing monograph ingredients. In addition, firms have been aware of the proposed nonmonograph status of these products since 1998 and have not submitted data to the agency. While this final rule may cause firms to discontinue marketing or to reformulate some products prior to issuance of the final monograph, these firms have known for some time that if adequate data were not submitted to support safety, cessation of marketing of the current products would be required, in any event, when the final monograph is published.

The agency estimates that the average cost to relabel OTC drug products is about \$3,600. The agency is unsure of how many products will require new labeling. If all of the 170 products are reformulated and are still marketed, then the one-time costs to relabel would be \$612,000. The estimated total one-time reformulation and relabeling cost would be \$17.8 million.

The agency considered but rejected not acting on these ingredients in advance of the finalization of other monograph conditions. As firms have not submitted the requested safety data, these ingredients will not be included in the final monograph when completed. The agency has determined that there is no reason to allow continued marketing of OTC laxative drug products containing any of these ingredients. Consumers will benefit from the early removal from the

marketplace of products containing ingredients for which safety has not been established. Consumers can then purchase products containing only ingredients proposed for monograph status. Manufacturers who choose to reformulate or replace affected products will be able to use alternate ingredients, as discussed previously in this document, that are proposed as monograph conditions without incurring any additional expense of clinical testing for those ingredients.

Because these products must be manufactured in compliance with the pharmaceutical current good manufacturing practices (parts 210 and 211), all firms have the necessary skills and personnel to perform the tasks of reformulation, validation, and relabeling either in-house or by contractual arrangement. No additional professional skills are needed. No other Federal rules duplicate, overlap, or conflict with this rule.

The agency has considered the burden to small entities and identified reformulation options available to them. Nevertheless, some entities may incur significant impacts, especially private label manufacturers that provide labeling for a number of the affected products. This economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

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

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### **V. Environmental Impact**

The agency 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.

#### **VI. 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 Executive 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 paragraphs (a)(12)(iv)(C) and (d)(30) to read as follows:

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

(a) \* \* \*

(12) \* \* \*

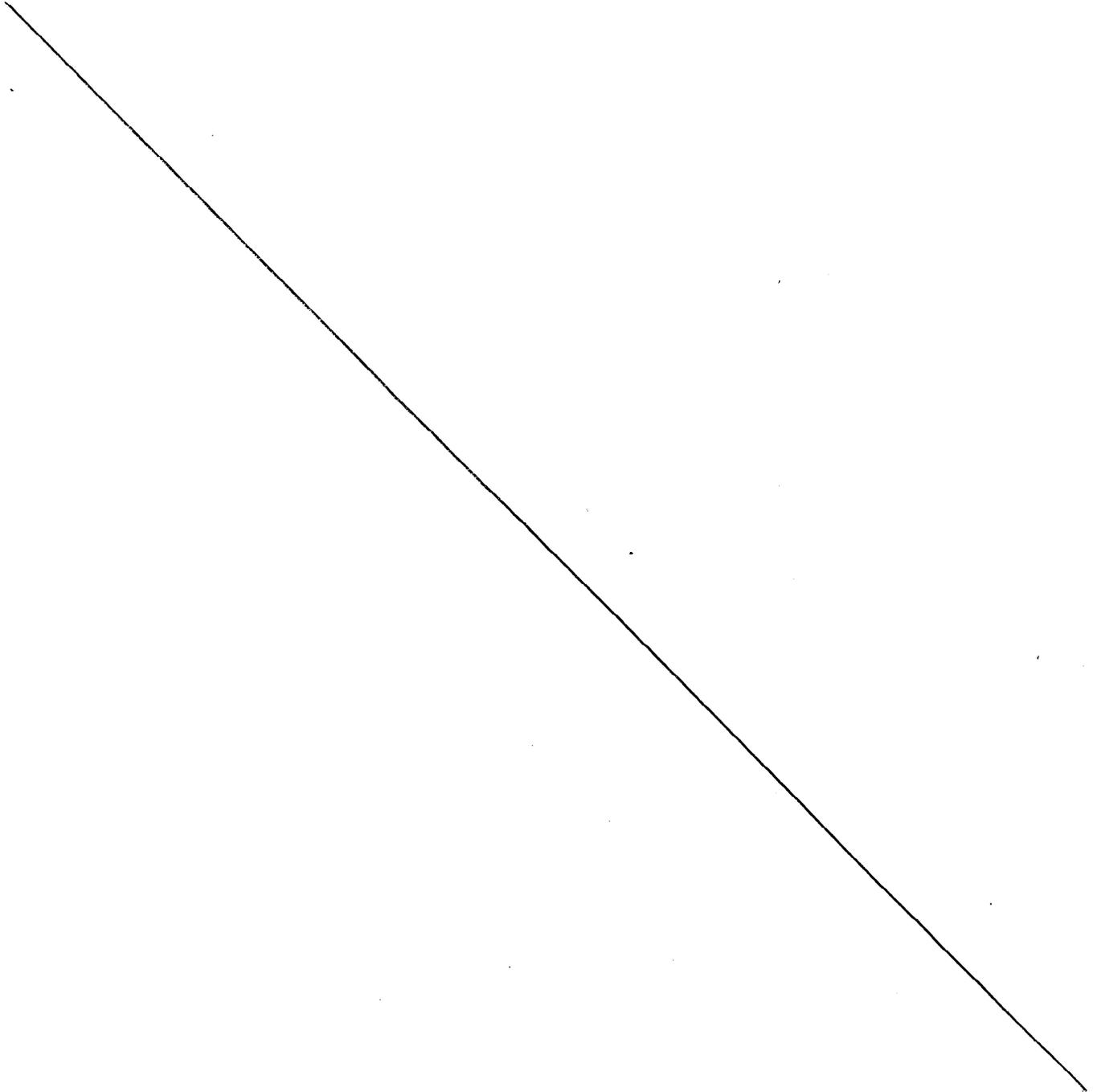
(iv)(C) *Stimulant laxatives—Approved as of [insert date 180 days after date of publication in the Federal Register].*

Aloe ingredients (aloe, aloe extract, aloe flower extract)

Cascara sagrada ingredients (casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluidextract).

\* \* \* \* \*

(d) \* \* \*



(30) [Insert date 180 days after date of publication in the **Federal Register**], for products

subject to paragraph (a)(12)(iv)(C) of this section.

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\* \* \* 4/29/02 \*

Dated: \_\_\_\_\_  
April 29, 2002.

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Margaret M. Dotzel,  
Associate Commissioner for Policy.

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