

**§ 71.1 [Amended]**

2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9D, Airspace Designations and Reporting Points, dated September 10, 1997, and effective September 16, 1997, is amended as follows:

*Paragraph 6005 Class E airspace areas extending upward from 700 feet or more above the surface of the earth.*

**Spruce Creek Airport**

(Lat. 29°04'49" N, long. 81°03'27" W)

**Ormond Beach Municipal Airport**

(Lat. 29°18'04" N, long. 81°06'50" W)

That airspace extending upward from 700 feet or more above the surface of the earth within a 10-mile radius of Daytona Beach International Airport, within a 6.4-mile radius of Spruce creek Airport and within a 7.3-mile radius of Ormond Beach Municipal Airport.

\* \* \* \* \*

Issued in College Park, Georgia, on June 10, 1998.

**Nancy B. Shelton,**

*Acting Manager, Air Traffic Division,  
Southern Region.*

[FR Doc. 98-16354 Filed 6-18-98; 8:45 am]

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Food and Drug Administration****21 CFR Parts 310 and 334**

[Docket No. 78N-036L]

RIN 0910-AA01

**Laxative Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final Monograph**

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

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Food and Drug Administration (FDA) is reopening the administrative record and proposing to amend the tentative final monograph (proposed rule) for over-the-counter (OTC) laxative drug products to reclassify the stimulant laxative ingredients aloe, bisacodyl, cascara sagrada, and senna (including sennosides A and B) from Category I (generally recognized as safe and effective and not misbranded) to Category III (further testing is required). FDA is issuing this proposed rulemaking after considering data and information on the safety of bisacodyl, senna, and two related stimulant

laxative ingredients, danthron and phenolphthalein. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Submit written comments by September 17, 1998. Written comments on the agency's economic impact determination by September 17, 1998. New data by June 21, 1999. Comments on the new data by August 19, 1999.

**ADDRESSES:** Submit written comments and new data to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

**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 March 21, 1975 (40 FR 12902), 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 laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these classes. In the advance notice of proposed rulemaking, the Panel recommended Category I status for the OTC stimulant laxative ingredients aloe, bisacodyl, cascara sagrada preparations, danthron, phenolphthalein, and senna preparations (40 FR 12902 at 12908 to 12910). The agency concurred with the Panel's Category I classification of these ingredients in the tentative final monograph published in the *Federal Register* of January 15, 1985 (50 FR 2124 at 2152 to 2156).

**II. Danthron and Phenolphthalein**

In the *Federal Register* of September 2, 1997 (62 FR 46223), the agency reopened the administrative record for this rulemaking, discussed the carcinogenic risk of danthron and phenolphthalein, and proposed to reclassify these two anthraquinone laxative ingredients from Category I to Category II (not generally recognized as safe and effective or misbranded). The agency is evaluating the data and comments submitted in response to that proposal and will discuss this subject

further in a future issue of the *Federal Register*.

**III. Bisacodyl**

The FDA Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) has recommended that the anthraquinone laxatives (aloe, cascara sagrada, and senna) and bisacodyl be tested in the standard battery of genotoxicity tests and under the test conditions by which phenolphthalein was found to be positive (Ref. 1). Phenolphthalein and bisacodyl are diphenylmethane derivatives with a similar chemical structure and pharmacological characteristics. The CAC recommended the Syrian Hamster Embryo (SHE) cell transformation assay as an early screen for bisacodyl and, based on its results, either the p53 transgenic mouse assay or another in vivo alternative assay, as appropriate, follow. Two-year carcinogenicity studies would then be contingent upon the results of these assays.

The agency has informed industry that additional testing for bisacodyl will be necessary (Ref. 2). Subsequently, industry submitted data from two mutagenicity studies (Ames test and rat bone marrow micronucleus assay) and a chromosomal aberration study in Chinese hamster ovary cells. The agency has reviewed these studies and determined that the results of all of the tests were negative (Ref. 3). Phenolphthalein was tested in two of these tests and was found negative in one (Ames test). However, findings from further studies indicated that phenolphthalein presents a potential carcinogenic risk. Thus, because of the chemical similarity of bisacodyl to phenolphthalein and the lack of previous carcinogenicity testing of bisacodyl, the agency is requesting that bisacodyl undergo further testing to assess its carcinogenic potential. Industry has completed dose range finding studies intended to select bisacodyl doses for a 6-month oral gavage carcinogenicity study in the p53 transgenic mouse (Ref. 4).

**IV. Senna**

The agency has reviewed metabolic, genotoxicity, and carcinogenicity data on senna and its components (Ref. 5). Senna contains a number of components, including but not limited to: Sennosides A and B, sennosides C and D, rhein (including rhein anthrone-8-monoglucoside and rhein-8-monoglucoside), chrysophanol, emodin, and aloe-emodin. The metabolic studies show that varying amounts of senna and its metabolites are absorbed into the

systemic circulation. The data do not present conclusive absorption information, nor indicate whether any of the metabolites present a safety hazard, if absorbed.

The agency believes that there are sufficient mutagenicity (Ames test) data in the literature on the senna extracts sennosides A and B, aloë-emodin, chrysophanol, and emodin. The data indicate that sennosides A and B are negative, while the senna extracts aloë-emodin, emodin, and chrysophanol are positively genotoxic (Ref. 5). Thus, senna preparations containing any of these components (or kaempferol or quercetin) may have mutagenic properties. These potentially mutagenic anthrones are found in the dried leaves and pods of senna. Therefore, until manufacturers can show that commercially available senna preparations do not contain mutagenic/genotoxic components, the agency is unable to state that sennosides A and B do not pose a relative risk to humans.

The agency also reviewed a 2-year carcinogenicity study with sennosides in the rat (Ref. 6). However, the agency found this study deficient because of the limited and incomplete histopathologic examination of tissues (Ref. 5). The agency concludes that further testing is necessary to assess the carcinogenic potential of senna products. In these studies, specific analysis of the test substance should be done to enable quantitative estimation of each component of the preparation. The senna dose selection should be based on a 1-month dose ranging study for an alternative assay or a 3-month dose ranging study for a 2-year carcinogenicity study in the rodent species and strains selected for the carcinogenicity studies. Histopathologic examination of all tissues from all groups of animals should be conducted (Ref. 5).

#### V. Aloe and Cascara Sagrada Preparations

Aloe and cascara sagrada are other anthraquinone ingredients. Cascara sagrada ingredients included in the tentative final monograph are casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract (50 FR 2124 at 2152). The agency has not received any mutagenicity, genotoxicity, or carcinogenicity data for these ingredients. The agency concludes that these ingredients need to have these types and other toxicity data using tests similar to those used and found positive for phenolphthalein.

#### VI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. MM13, Docket No. 78N-036L, Dockets Management Branch.
2. Letter from D. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association (NDMA), coded LET111, Docket No. 78N-036L, Dockets Management Branch.
3. Letter from D. Bowen, FDA, to L. Totman, NDMA, coded LET175, Docket No. 78N-036L, Dockets Management Branch.
4. Comment No. C178, Docket No. 78N-036L, Dockets Management Branch.
5. Letter from D. Bowen, FDA, to J. Conover, The Purdue Frederick Co., coded LET173, Docket No. 78N-036L, Dockets Management Branch.
6. Comment No. LET113, Docket No. 78N-036L, Dockets Management Branch.

#### VII. Summary of the Agency's Changes to the Proposed Rule

The agency is proposing to reclassify the stimulant laxative ingredients aloë, bisacodyl, cascara sagrada (including casanthranol), and senna (including sennosides A and B) from Category I (monograph) to Category III (more data needed). The agency recommends that persons interested in testing these drugs consult the agency about carcinogenicity study requirements and protocols before initiating any studies. If these data are not provided or are inadequate for any of these ingredients, these ingredients will be placed in Category II (nonmonograph) in a final rule. The agency will add any of these ingredients that become nonmonograph to the list of stimulant laxatives in § 310.545(a)(12)(iv) (21 CFR 310.545(a)(12)(iv)) in new § 310.545(a)(12)(iv)(C). The agency will also amend proposed §§ 334.18, 334.30, 334.32, 334.60, 334.66, and 334.80 to remove any of these ingredients and their labeling if any of these ingredients are not included in the final monograph.

#### VIII. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). 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.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this proposed rule is to establish conditions under which the OTC stimulant laxative ingredients aloë, bisacodyl, cascara sagrada, and senna are or are not generally recognized as safe and effective. If the ingredients are determined to be safe and effective, no product reformulation will be necessary. If the ingredients are not determined to be safe and effective, product reformulation will be needed. There are a number of other laxative ingredients in proposed part 334 (50 FR 2124 at 2152) or one of these ingredients, if found safe and effective, that could be used if product reformulation becomes necessary.

The cost to reformulate a product will vary greatly depending on the nature of the change in formulation, the product, the process, and the size of the firm. Because of the large number of monograph active ingredients available for substitution, no manufacturer should need to change its dosage form; however, a manufacturer would have to redo the validation (product, process, new supplier), conduct stability tests, change master production records, and, for some dosage forms, conduct palatability tests. Competitive market forces and increased public awareness of a potential safety hazard of these ingredients would most likely lead all manufacturers to move to alternative products over time.

Manufacturers of these products will also incur costs to relabel their products to reflect the new formulation. The agency obtained estimates of relabeling costs for the type of changes required by this proposed rule ranging from \$2,700 to \$10,000 per standard stock keeping unit (SKU) (individual products, packages, and sizes) for nationally branded products and from \$500 to \$1,500 per SKU for private label products. The agency estimates the number of SKU's that will need to be relabeled as a result of reformulation as between 500 and 1,000, depending if

some or all of the involved ingredients are not included in the final monograph for OTC laxative drug products. Most of these label changes will be made by private label manufacturers that tend to use simpler and less expensive labeling.

Finally, some manufacturers that do not reformulate and validate their products by the effective date of the final rule may incur a loss of revenue. Nevertheless, because of the large number of substitute products that are available, many in the same dosage form, there should be no significant drop in the overall consumption of laxative drug products. Some manufacturers already have other laxative products. If products need to be reformulated eventually, manufacturers will be able to retain the same brand names. Consumer loyalty to these brands should lessen the revenue losses to these firms.

Because these products must be manufactured in compliance with the pharmaceutical current good manufacturing practices (21 CFR 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. The rule will not require any new reporting and recordkeeping activities. No additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with this rule.

**Small business impact.** The U.S. Small Business Administration designates an entity as small if it employs less than 750 employees. The agency does not believe that any small firms will be conducting genotoxicity or carcinogenicity studies on any of the laxative ingredients included in this proposal. Small firms that may have to reformulate their products could incur significant costs as a result of this rule. The agency is attempting to reduce this burden by keeping industry informed of the findings of new research on these products through public meetings and letters to manufacturers of products containing these ingredients. In this manner, manufacturers should be aware of which ingredients are likely to be included or excluded from the final monograph and can make their marketing decisions accordingly.

The agency considered but rejected the following alternatives: (1) Fewer testing requirements, and (2) an exemption from coverage for small entities. The agency does not consider either of these approaches acceptable because they do not assure that consumers will have safe and effective OTC laxative drug products at the

earliest possible time. The agency does not believe that there are any significant alternatives to the proposed rule that would adequately provide for the safe and effective use of these OTC drug products.

The agency expects that this proposed rule will not be economically significant under Executive Order 12866, nor would it impose an Unfunded Mandate (as that term is described in the Unfunded Mandate Act). The agency also believes that it is undertaking steps to reduce the burden to small entities. Nevertheless, some entities may incur significant impacts, especially manufacturers that may have to reformulate their products and, to a lesser extent, private label manufacturers that provide labeling for a number of the affected products. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

Finally, the agency specifically invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC laxative drug products containing aloe, bisacodyl, cascara sagrada, and senna, particularly the costs associated with reformulation. Comments regarding the impact of this rulemaking on OTC laxative drug products containing any of these ingredients should be accompanied by appropriate documentation. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

#### IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that labeling requirements related to this proposed rule 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, this proposed rulemaking involves labeling that is 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)).

#### X. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

#### XI. Request for Comments

Interested persons may, on or before September 17, 1998, submit written comments on the proposed regulation to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before September 17, 1998. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Interested persons may also submit new data demonstrating the safety of any of those conditions not classified in Category I on or before June 21, 1999. Written comments on the new data may be submitted on or before August 19, 1999. Three copies of all data and comments should be submitted as stated previously, and received data and comments may be seen as stated previously. In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 19, 1999. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner of Food and Drugs finds good cause has been shown that warrants earlier consideration.

#### List of Subjects

##### 21 CFR Part 310

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

##### 21 CFR Part 334

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, it is proposed that 21 CFR parts 310 and 334 (as proposed in the **Federal Register** of January 15, 1985 (50 FR 2124), September 2, 1993 (58 FR 46589), and September 2, 1997 (62 FR 46223)) be 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, 356, 357, 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 new paragraphs (a)(12)(iv)(C) and (d)(30), and by revising paragraph (d) introductory text to read as follows:

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

- (a) \* \* \*
- (12) \* \* \*

(iv)(C) *Stimulant laxatives*—  
Approved as of (date of publication in the **Federal Register**).

Aloe

Bisacodyl

Cascara sagrada in any form (e.g., casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluidextract)

Senna in any form (e.g., senna fluidextract, senna fruit extract, senna leaf powder, senna pod concentrate, senna syrup, or sennosides A and B)

\* \* \* \* \*

(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)(30) of this section.

\* \* \* \* \*

(30) (Date 6 months after date of publication in the **Federal Register**), for products subject to paragraph (a)(12)(iv)(C) of this section.

**PART 334—LAXATIVE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE**

3. The authority citation for 21 CFR part 334 is revised to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

**§ 334.18 [Amended]**

4. Section 334.18 *Stimulant laxative active ingredients* is amended by removing paragraphs (a), (b), (c)(1) through (c)(5), and (f) and redesignating paragraphs (d) and (e) as paragraphs (a) and (b), respectively.

**§ 334.30 [Amended]**

5. Section 334.30 *Permitted combinations of active laxative ingredients* is amended by removing and reserving paragraphs (c), (e), (g), (h), and (i).

**§ 334.32 [Amended]**

6. Section 334.32 *Bowel cleansing systems* is amended by removing and reserving paragraph (a).

**§ 334.60 [Amended]**

7. Section 334.60 *Labeling of stimulant laxative drug products* is amended by removing paragraphs (b)(3), (d)(1) through (d)(7), (d)(10), and (d)(11), by removing and reserving paragraph (c), and by redesignating paragraphs (d)(8) and (d)(9) as paragraphs (d)(1) and (d)(2), respectively.

**§ 334.66 [Amended]**

8. Section 334.66 *Labeling of bowel cleansing systems identified in § 334.32* is amended in paragraph (a) by removing “§ 334.32(a)” and adding in its place “§ 334.32” and by removing and reserving paragraphs (c)(1) and (d)(3)(iii)(A).

**§ 334.80 [Amended]**

9. Section 334.80 *Professional labeling* is amended in paragraph (a)(2) by removing the words “or bisacodyl identified in § 334.18(b)”, by removing paragraphs (a)(4) and (c)(5) through (c)(10), and by adding the word “or” after “§ 334.16(a)” in paragraph (a)(2), and by redesignating paragraphs (c)(11), (c)(12), and (c)(13) as paragraphs (c)(5), (c)(6), (c)(7), respectively.

Dated: June 9, 1998.

**William K. Hubbard,**  
*Associate Commissioner for Policy Coordination.*

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BILLING CODE 4160-01-F

**DEPARTMENT OF THE TREASURY**

**Internal Revenue Service**

**26 CFR Part 1**

[REG-209035-86]

RIN 1545-A132

**Foreign Liquidations and Reorganizations**

**AGENCY:** Internal Revenue Service (IRS), Treasury.

**ACTION:** Amendment to notice of proposed rulemaking.

**SUMMARY:** This document removes from an existing (1991) notice of proposed rulemaking the special (August 26, 1991) effective date rule for the definition of the all earnings and profits amount. The IRS and the Treasury Department believe that issues regarding the all earnings and profits amount should be studied; thus, when final

regulations under section 367(b) are issued with respect to the all earnings and profits amount, such regulations will have a prospective effective date. This modification may affect domestic corporations in connection with an acquisition of a foreign corporation in a liquidation described in section 332 or in an asset acquisition described in section 368(a)(1).

**DATES:** Written comments must be received by September 17, 1998.

**ADDRESSES:** Send submissions to: CC:DOM:CORP:R (REG-209035-86), Room 5228, Internal Revenue Service, POB 7604, Ben Franklin Station, Washington, DC 20044. In the alternative, submissions may be hand delivered between the hours of 8 a.m. and 5 p.m. to: CC:DOM:CORP:R (REG-209035-86), Courier's Desk, Internal Revenue Service, 1111 Constitution Ave. NW., Washington, DC.

**FOR FURTHER INFORMATION CONTACT:** Philip L. Tretiak at (202) 622-3860 (not a toll-free call).

**SUPPLEMENTARY INFORMATION:**

**Background**

Section 367(b) was enacted in its current form by the Tax Reform Act of 1976. On December 27, 1977, proposed and temporary regulations §§ 7.367(b)-1 through 7.367(b)-12 were adopted (TD 7530, 1978-1 C.B. 92). Prior to the issuance of a notice of proposed rulemaking in 1991 (the 1991 proposed regulations), discussed below, the regulations under section 367(b) were amended on several occasions. The 1991 proposed regulations, which were published in the **Federal Register** on August 26, 1991 (56 FR 41993), propose to completely revise the regulations under section 367(b), as well as the rules under section 367(a) with respect to certain transfers of stock or securities by U.S. persons to foreign corporations. Section 1.367(b)-6(a) of the proposed regulations provides that the rules contained in the section 367(b) proposed regulations will be effective for exchanges that occur on or after the date that is 30 days after final regulations are published. However, an exception to the general effective date provides that § 1.367(b)-2(d) (relating to the definition and computation of the “all earnings and profits amount”) is effective for exchanges that occur on or after August 26, 1991.

A package of final regulations, published elsewhere in this issue of the **Federal Register**, contains final rules with respect to the section 367(a) portion of the 1991 proposed regulations (to the extent that such rules were not previously finalized) and final