§ 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)

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.

For Further Information Contact:
Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

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 aloes, 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) 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.


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, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

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III. Bisacodyl

The FDA Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) has recommended that the anthraquinone laxatives (aloes, 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 (H4Y) 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, rhei (including rhei anthrone-8-monoglucoside and rhei-6- 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, aloe-emodin, chrysophanol, and emodin. The data indicate that sennosides A and B are negative, while the senna extracts aloe-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 species and strains selected for the 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.

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 fluid extract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluid extract (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 of 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.

3. Letter from D. Bowen, FDA, to L. Totman, NDMA, coded LET175, 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 aloe, bisacodyl, cascara sagrada (including casanthranol), and senna (including sennosides A and B) from Category I (monograph) to 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.

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 aloe, 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 reformation 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 that provide labeling for 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 ruling 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.), neither 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:


2. Section 310.545 is amended by adding new paragraphs (a)(2)(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) * * *

(ii) Stimulant laxatives—

Approved as of (date of publication in the Federal Register).

Aloe

Bisacodyl

Cascara sagrada in any form (e.g., casanthanol, cascara fluid extract

aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluid extract)

Senna in any form (e.g., senna fluid extract, 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)(2)(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:


§ 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).