

repair on the unsafe condition addressed by this AD; and, if the unsafe condition has not been eliminated, the request should include specific proposed actions to address it.

Compliance: Required as indicated, unless accomplished previously.

To prevent evacuee overload of the slide/raft, and consequent impeded evacuation and injury to the evacuees, accomplish the following:

(a) Within 180 days after the effective date of this AD, modify the sliding surfaces of the door 1 left and door 1 right evacuation slide/rafts, in accordance with Boeing Alert Service Bulletin 777-25A0035, dated December 2, 1996.

Note 2: The Boeing alert service bulletin references Air Cruisers Company Service Bulletin S.B. 777-107-25-02, dated October 29, 1996, as an additional source of service information.

(b) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, Seattle Aircraft Certification Office (ACO), FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, Seattle ACO.

Note 3: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Seattle ACO.

(c) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Issued in Renton, Washington, on August 26, 1997.

John J. Hickey,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 97-23173 Filed 8-29-97; 8:45 am]

BILLING CODE 4910-13-U

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 for over-the-counter (OTC) laxative drug products to reclassify the stimulant laxative ingredients danthron and phenolphthalein from Category I (generally recognized as safe and effective and not misbranded) to Category II (not generally recognized as safe and effective or misbranded) and adding these ingredients to a list of nonmonograph active ingredients. FDA is issuing this proposed rulemaking after considering data and information on the safety of danthron and phenolphthalein. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Submit written comments by October 2, 1997. Written comments on the agency's economic impact determination by October 2, 1997. FDA is proposing that any final rule based on this proposal be effective on the date of its publication in the **Federal Register**.

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

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

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

Following publication of the laxative tentative final monograph in 1985, FDA became aware of studies concerning the potential carcinogenic risk of danthron. In January 1987, a leading U.S. pharmaceutical manufacturer informed FDA that it would voluntarily cease manufacture and distribution of products containing danthron. The company's decision was partly in response to published studies in Britain and Japan that strongly suggested that chronic administration of high doses of danthron to rats and mice resulted in development of intestinal and liver tumors and that danthron is, therefore, a potential carcinogen in humans (Refs. 1 and 2). Danthron, in common with other anthraquinone compounds, has also been shown to exhibit a positive mutagenic effect in some in vitro models (Refs. 3 and 4). FDA subsequently initiated a recall that extended to the retail/dispensing level of all danthron-containing drug products, by sending a recall letter to all registered drug firms and distributors (Ref. 5). FDA stated that "danthron toxicity in humans has not been specifically demonstrated, but because of potential risk, FDA has requested an immediate halt to all manufacturing, relabeling, repackaging, and further distribution of human drug products containing danthron as an ingredient" (Ref. 6). The agency notes that, although danthron was removed from OTC laxative drug products in 1987, it was not specifically included in part 310 (21 CFR part 310) as a new drug. Therefore, in this rulemaking, the agency is proposing to amend § 310.545 to include danthron as a nonmonograph ingredient.

III. New Information on Phenolphthalein

Recently, FDA became aware of data indicating that phenolphthalein is a potential carcinogen in humans. Under the direction of the National Institute of Environmental Health Science (NIEHS) through the National Toxicology Program (NTP), phenolphthalein was studied for its carcinogenic potential in rats and mice. The National Cancer Institute (NCI) nominated phenolphthalein for study because of its widespread chronic use in OTC laxative drug products and the lack of adequate testing for carcinogenicity in experimental animals. The preliminary findings were reported in a 1995 NTP draft technical report (NTP TR 465, NIH publication No. 95-3390), which indicated that phenolphthalein demonstrated evidence of carcinogenic

activity in rats and mice. The final version of this report was published in November 1996 (NTP TR 465, NIH publication No. 97-3390) (Ref. 7).

In these studies, male and female F344/N rats and B6C3F1 mice were exposed to phenolphthalein (98 percent to 99 percent pure) in feed for 14 days, 13 weeks, or 2 years. Genetic toxicology studies in *Salmonella typhimurium* (Ames test), cultured Chinese hamster ovary (CHO) cells, and mouse peripheral blood cells were also conducted. Phenolphthalein was not mutagenic in the Ames test and was inactive in the CHO cell sister chromatid exchange assay. It was, however, clastogenic in a CHO cell chromosomal aberration test in the presence of metabolic activation and in the mouse micronucleus assay.

In the 2-year carcinogenicity studies, groups of 50 male and female rats were given 0, 12,000, 25,000, or 50,000 parts per million (ppm) phenolphthalein in feed for 2 years (equivalent to average daily doses of approximately 500, 1,000, or 2,000 milligrams (mg) phenolphthalein/kilogram (kg) body weight to males and 500, 1,000, or 2,500 mg/kg to females). Groups of 50 male and female mice were given 0, 3,000, 6,000, or 12,000 ppm phenolphthalein in feed for 2 years (equivalent to average daily doses of approximately 300, 600, 1,200 mg phenolphthalein/kg body weight to males and 400, 800, 1,500 mg/kg to females).

From these 2-year feeding studies, NTP concluded that there was clear evidence of carcinogenic activity of phenolphthalein in male rats based on the markedly increased incidences of benign pheochromocytoma of the adrenal medulla and renal tubule adenomas or adenomas and carcinomas. There was some evidence of carcinogenic activity of phenolphthalein in female rats based on the increased incidences of benign or benign and malignant pheochromocytoma of the adrenal medulla. There was clear evidence of the carcinogenic activity of phenolphthalein in male mice based on the increased incidences of histiocytic sarcoma and malignant lymphoma of thymic origin. There was clear evidence of carcinogenic activity of phenolphthalein in female mice based on the increased incidences of histiocytic sarcoma, malignant lymphoma of all types, lymphoma of thymic origin, and benign sex-cord stromal tumors of the ovary. Thus, the 1995 NTP draft technical report on the carcinogenicity studies of phenolphthalein concluded that phenolphthalein has carcinogenic activity in rodents.

FDA held a public meeting on December 18, 1995 (Ref. 8), to discuss the 1995 NTP draft technical report with representatives of NTP and manufacturers of phenolphthalein-containing laxative drug products. Additional data were presented that suggested a genotoxic mechanism and demonstrated similar human and rodent metabolic pathways.

Subsequently, on April 2, 1996 (Ref. 9), information from the December 1995 public meeting and the 1995 NTP draft technical report were discussed at an FDA Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) meeting. A majority of the CAC members agreed that the carcinogenicity studies as conducted provided a valid assessment of the carcinogenic potential of phenolphthalein and that the studies addressing genotoxic potential and comparative metabolism and exposure provided information of potential relevance to human risk. The CAC indicated that phenolphthalein is a likely genotoxin for the rodent, but adequate data were not available to make a clear assessment for humans. The CAC concluded that further evaluation of the safety of phenolphthalein should be done following the completion of NTP's pending studies of phenolphthalein including in the p53 transgenic mouse.

In a May 10, 1996, letter (Ref. 10), FDA informed laxative manufacturers of the NTP findings and the CDER CAC recommendations, and requested more safety data for certain stimulant laxative ingredients. FDA indicated that additional testing for the OTC stimulant laxative ingredients aloe, bisacodyl, cascara sagrada ingredients, and senna preparations would be necessary.

NTP recently completed additional studies on phenolphthalein (Ref. 11) and prepared draft manuscripts of the findings for publication (Ref. 12). This new information and the previous findings were the subject of an April 30, 1997, CAC meeting (Ref. 13) (the April 30, 1997, meeting). The studies involve five areas: Human epidemiology, in vivo rodent metabolism and distribution, in vitro free radical metabolism, in vitro cell transformation and mutagenicity in Syrian hamster embryo (SHE) cells, and tumorigenicity and micronucleus studies in p53 deficient mice.

The CAC members voted that the p53 heterozygous mice studies demonstrate that phenolphthalein may be carcinogenic through a genotoxic mechanism. There was a clear dose-dependent increase in the incidence of thymic lymphoma in the p53 assay, confirming one of the primary tumors of

concern to the CAC based on its original evaluation of the 2-year assay data. These tumors occurred at doses that showed no other signs of toxicity.

The CAC believed that several of the assays and data support a genotoxic mechanism. Phenolphthalein was positive in chromosome aberration tests and showed chromosomal abnormality and hypoxanthine phosphoribosyltransferase (hprt) mutations in the SHE cell assay. Nontoxic doses caused cell transformation, mutations, and chromosome aberration. Phenolphthalein was also positive in the peripheral blood micronucleus assay in p53 mice. The micronucleus assay showed that even at the low doses (about 15 times the human exposure), the micronuclei response occurred with increased duration of treatment. It might be expected with a free radical generator, such as phenolphthalein, and based on the observations in mice, that it will take time, at lower concentrations, for lesions to occur and be detected. Thus, it appears that this genotoxic event may not be observed with short term phenolphthalein use. The p53 protein accumulation in the nucleus of thymic lymphoma cells of the original bioassay, coupled with the deletion of the wild type p53 allele in the thymic lymphomas of p53 mice, are indicative of interaction with the p53 gene as a target site. In vivo, repeated exposure resulted in micronuclei in both the original bioassay and in p53 mice studies. The exposures used to demonstrate these in vivo and in vitro genotoxic effects were in the range of those that could occur with human laxative use.

Based on the totality of the evidence that has been evaluated thus far, FDA considers use of phenolphthalein a potential risk to humans. These findings of rodent carcinogenicity and genotoxicity in several test systems indicate that chronic use could lead to damage to the human genome (including p53, which is known to be a tumor suppressor gene) and could increase the risk of malignancy. Some human cancers are associated with alterations in the p53 gene. Such genetic damage and increased risk could occur at phenolphthalein doses that are likely to be used by humans. Because of this concern, the agency is proposing to declare all drug products containing phenolphthalein to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). Accordingly, products without a new drug application would be subject to regulatory action under, among others,

sections 502 (misbranding) and 505 (new drug) of the act (21 U.S.C. 352 and 355). The agency also notes that there is no evidence (Ref. 14) to suggest that there are any adverse effects from the abrupt discontinuation of phenolphthalein cathartics.

On May 13, 1997 (Ref. 15), the agency informed known manufacturers of phenolphthalein drug products and trade associations that the NTP data discussed at the April 30, 1997, meeting (Ref. 13) were available for public examination in FDA's Dockets Management Branch. At that time, the agency notified interested persons that 30 days would be provided for comment on the NTP data. The agency is now providing an additional 30 days in response to this notice.

The NTP data and the transcript of the April 30, 1997, meeting are available for public examination between 9 a.m. and 4 p.m., Monday through Friday, in the Dockets Management Branch (address above). Copies of the NTP data and the transcript of the April 30, 1997, meeting may be requested (by mail or fax) from the Freedom of Information Staff (HFI-35), 5600 Fishers Lane, rm. 12A-16, Rockville, MD 20857, 301-443-6310 or FAX 301-443-1726. Requests should specify the date of the meeting, name of the committee, a description of the document(s) requested, and the docket number found in brackets in the heading of this document.

IV. 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. Mori, H. et al., "Induction of Intestinal Tumors in Rats by Chrysazin," *British Journal of Cancer*, 52:781-783, 1985, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

2. Mori, H. et al., "Carcinogenicity of Chrysazin in Large Intestine and Liver in Mice," *Japanese Journal of Cancer Research*, 77:871-876, 1986, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

3. Brown, J. P., and R. J. Brown, "Mutagenesis by 9,10-Anthraquinone Derivatives and Related Compounds in Salmonella Typhimurium," *Mutation Research*, 40:203-224, 1976, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

4. Tikkanen, L., T. Matsushima, and S. Natori, "Mutagenicity of Anthraquinones in Salmonella Typhimurium," *Mutation Research*, 116:297-303, 1983, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

5. FDA Drug Recall Letter Concerning Danthron-containing Drug Products, in OTC

Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

6. FDA Press Release on Danthron Drug Products, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

7. "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Phenolphthalein in F344/N Rats and B6C3F1 Mice (Feed Studies)," NTP TR 465, NIH Publication No. 97-3390, Comment No. RPT8, Docket No. 78N-036L, Dockets Management Branch.

8. Comment No. MM11, Docket No. 78N-036L, Dockets Management Branch.

9. Comment No. MM12, Docket No. 78N-036L, Dockets Management Branch.

10. Letter from D. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET111, Docket No. 78N-036L, Dockets Management Branch.

11. Comment No. RPT7, Docket No. 78N-036L, Dockets Management Branch.

12. Letter from the National Institute of Environmental Health Sciences, to D. L. Bowen, FDA, coded LET167, Docket No. 78N-036L, Dockets Management Branch.

13. Comment No. MM13, Docket No. 78N-036L, Dockets Management Branch.

14. Weiss, B., and G. Wood, "Laxative Abuse Causing Gastrointestinal Bleeding," *The Journal of Family Practice*, 15:177-181, 1982.

15. Letters from D. L. Bowen, FDA, to Nonprescription Drug Manufacturers Association and various manufacturers, coded LET137 through 165, Docket No. 78N-036L, Dockets Management Branch.

V. Summary of the Agency's Changes to the Proposed Rule

1. Based on new data and information, the agency is proposing to reclassify the stimulant laxative ingredients danthron and phenolphthalein from Category I (monograph) to Category II (nonmonograph).

2. As a result of this reclassification, the agency would add danthron and phenolphthalein to the list of stimulant laxatives in § 310.545(a)(12)(iv). The current list in that section is redesignated as § 310.545(a)(12)(iv)(A) and danthron and phenolphthalein are being included in new § 310.545(a)(12)(iv)(B).

VI. Analysis of Impacts

FDA has examined the impacts of the 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 danthron and phenolphthalein are not generally recognized as safe and effective. Cessation of marketing of OTC laxative drug products containing danthron occurred in 1987. Therefore, no reformulation or relabeling will be necessary for this ingredient.

Products containing phenolphthalein will need to be reformulated to replace the ingredient with another laxative active ingredient. There are a number of laxative ingredients in proposed part 334 (50 FR 2124 at 2152) that could be used.

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. The agency is aware, however, that most companies have either changed and are marketing reformulated products, are in the process of reformulating their products, or have decided to discontinue marketing products containing phenolphthalein.¹ Competitive market forces and increased public awareness of the potential safety hazard of phenolphthalein would most likely lead

¹ The agency's drug listing data base lists 60 manufacturers of products containing phenolphthalein; however, this number does not reflect the recent changes that have taken place in the market. Because many manufacturers have reformulated or discontinued production of their phenolphthalein products, FDA believes that not more than 20 manufacturers still produce phenolphthalein products.

all manufacturers to move to alternative products over time.

Manufacturers 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 rule ranging from \$2,700 to \$10,000 per standard stock keeping unit (SKU) (individual products, package and size) for nationally branded products and from \$500 to \$1,500 per SKU for private label products. Because of the large number of products that have recently been reformulated, the agency cannot accurately calculate the number of SKU's that will need to be relabeled, but estimates the number to be approximately 300. Most of these label changes will be for private label products.

Finally, some manufacturers that have not reformulated and validated their products by the effective date of the final rule may incur a loss in revenue. Nevertheless, because of the large number of substitute products, many in the same dosage form, there should be no significant drop in the overall consumption of laxative products. Some manufacturers of phenolphthalein laxative drug products also manufacture substitute products, some under the same brand name. Consumer brand loyalty should lessen the revenue losses to these firms.

The agency is aware of only one phenolphthalein dosage form, a flavored chewable tablet, which does not currently have an adequate number of substitutes in the same dosage form. Sales of this dosage form by all manufacturers were about \$20 million in 1995 (most attributed to one large manufacturer), comprising about 3 percent of the total retail market for laxative products.² Manufacturers of this dosage form may incur greater revenue losses than those making other dosage forms, until an acceptable substitute product is reformulated. The agency requests additional information on the likelihood and economic costs of such reformulation alternatives.

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.

²Based on data obtained from A.C. Nielsen, a recognized provider of market research and business information.

No additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with this rule.

Small business impact. The agency believes that no more than 20 firms are still producing phenolphthalein products and assumes that the size distribution of these firms is comparable to that for the entire drug industry, implying that 87 percent of the establishments are small. (Based on U.S. Census data on the total number of establishments for Standard Industrial Classification 2834, Pharmaceutical Preparations. The U.S. Small Business Administration designates an entity as small if it employs less than 750 employees.)

Small firms that have not yet reformulated their phenolphthalein products may incur significant costs as a result of this rule. The agency has attempted to reduce this burden by keeping industry informed of the findings of the new research on these products through public meetings and letters to manufacturers of phenolphthalein products.

The agency considered but rejected the following alternatives: (1) A longer effective date, 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.

Based on the agency's understanding that most manufacturers have already reformulated or otherwise are in the process of reformulating, 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 has undertaken steps to reduce the burden to small entities.

Nevertheless, some entities may incur significant impacts, especially manufacturers that still must reformulate their phenolphthalein products and, to a lesser extent, private label manufacturers that provide labeling for a number of the affected products. Danthron was removed from OTC laxative drug products in 1987 and has not been available for approximately 10 years. Therefore, it is unlikely that reclassification of danthron as a nonmonograph ingredient would have any economic impact. 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 phenolphthalein, particularly the costs associated with reformulation. Comments regarding the impact of this rulemaking on OTC laxative drug products containing this ingredient 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.

VII. Comment Period and Effective Date

Under 5 U.S.C. 553(d) and § 10.40(c)(4) (21 CFR 10.40(c)(4)), the effective date of a final rule may not be less than 30 days after the date of its publication in the **Federal Register**, except when the regulation grants an exemption or relieves a restriction, or the Commissioner of Food and Drugs (the Commissioner) finds and states in the notice of good cause for an earlier effective date. In addition, under § 10.40(b)(2), the agency generally provides the public 60 days to comment on a proposed rule, although the Commissioner may shorten or lengthen this time period for good cause.

FDA is limiting the comment period in this proceeding to 30 days, and is proposing to make any final rule that issues in this proceeding relating to danthron or phenolphthalein effective on the date of publication. FDA is taking both of these actions for the same reasons.

Manufacturers have been aware for over 1 year (via three public meetings) of the public health concerns associated with the NTP study. Accordingly, many manufacturers have already reformulated their drug products. In addition, on May 13, 1997, the agency informed manufacturers of phenolphthalein drug products and trade associations, by letter, that the NTP data and the conclusions reached at the April 30, 1997, joint CAC and NTP meeting would likely have a direct impact on the rulemaking for OTC laxative drug products. That letter also provided notice of the availability of the data and invited comment on the data. By the time the final rule publishes, manufacturers will have had sufficient notice and an ample opportunity to comment on the information regarding

the concerns associated with phenolphthalein. Finally, the agency considers the phenolphthalein portion of this proposed rule to be a pressing public health concern because the ingredient is still being used in some drug products and genetic damage and risk of malignancy could occur at doses that are likely to be used by humans.

FDA therefore finds that there is good cause for a 30-day comment period and an immediate effective date.

VIII. 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)).

IX. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) 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.

X. Request for Comments

Interested persons may, on or before October 2, 1997 submit written comments on this proposed rule to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before October 2, 1997. Three copies of all comments or objections are to be submitted, except that individuals may submit one copy. Comments should 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 and objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

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)) be amended as follows:

PART 310—NEW DRUGS

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.545 is amended by redesignating the text of paragraph (a)(12)(iv) as (a)(12)(iv)(A), by adding new (a)(12)(iv)(B) heading and paragraphs (a)(12)(iv)(B) and (d)(29), and by revising paragraph (d) introductory text and paragraph (d)(1) to read as follows:

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

(a) * * *

(12) * * *

(iv)(A) *Stimulant laxatives*—
Approved as of May 7, 1991. * * *

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

Danthron

Phenolphthalein

* * * * *

(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)(29) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3) through (a)(4), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i) through (a)(12)(iv)(A), (a)(14) through (a)(15)(i), and (a)(16) through (a)(18) of this section.

* * * * *

(29) September 2, 1997 for products subject to paragraph (a)(12)(iv)(B) of this section.

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

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

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (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 (e) and (g) and redesignating paragraphs (f) and (h) as paragraphs (e) and (f), respectively.

§ 334.30 [Amended]

5. Section 334.30 *Permitted combinations of active laxative ingredients* is amended by removing paragraph (e)(4) and removing and reserving paragraph (h)(2).

§ 334.32 [Amended]

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

§ 334.60 [Amended]

7. Section 334.60 *Labeling of stimulant laxative drug products* is amended by removing paragraph (c)(2) and redesignating paragraph (c)(3) as paragraph (c)(2) and by removing paragraphs (d)(9) and (d)(11) and redesignating paragraphs (d)(10), (d)(12), and (d)(13) as paragraphs (d)(9), (d)(10), and (d)(11), respectively.

§ 334.66 [Amended]

8. Section 334.66 *Labeling of bowel cleansing systems identified in § 334.32* is amended by removing the words "and (b)" in paragraph (a) and by removing and reserving paragraphs (c)(2) and (d)(3)(iii)(B).

Dated: August 20, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–23122 Filed 8–29–97; 8:45 am]

BILLING CODE 4160–01–F

NATIONAL INDIAN GAMING COMMISSION

25 CFR Part 502

Indian Gaming Regulatory Act of 1988; Definitions

AGENCY: National Indian Gaming Commission.

ACTION: Advance notice of proposed rulemaking.