(c) Establishments that have drug products in commercial distribution, which are not listed on the Compliance Verification Report, shall submit these drug product listings to FDA on Form FDA-2657 (and Form FDA-2658, when reporting for a private label distributor), in accordance with 207.20, 207.21, 207.22, 207.25, and 207.30.

Dated: June 30, 1993.

Michael R. Taylor,

*Deputy Commissioner for Policy.*

[FR Doc. 93-21245 Filed 8-31-93; 8:45 am]

BILLING CODE 4160-01-F

## 21 CFR Part 334

[Docket No. 78N-036L]

RIN 0905-AA06

## 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 issuing a notice of proposed rulemaking to amend the tentative final monograph for over-the-counter (OTC) laxative drug products to include conditions under which docusate salts, i.e., docusate calcium, docusate potassium, and docusate sodium, are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel), public comments on the advance notice of proposed rulemaking that was based on those recommendations, and a comment submitted in response to the tentative final monograph for OTC laxative drug products that was published in the Federal Register of January 15, 1985 (50 FR 2124). This proposal is part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by December 31, 1993. New data by September 2, 1994. Comments on the new data by November 2, 1994. Written comments on the agency's economic impact determination by December 31, 1993.

**ADDRESSES:** Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

**SUPPLEMENTARY INFORMATION:** 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 Panel, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. The agency's proposed regulation, in the form of a tentative final monograph, for OTC laxative drug products was published in the Federal Register of January 15, 1985 (50 FR 2124).

In the advance notice of proposed rulemaking, the Panel recommended that docusate calcium [1], docusate potassium [2], and docusate sodium [3] in the recommended dosages be classified in Category I (generally recognized as safe and effective) as OTC stool softener laxatives (40 FR 12902 at 12912). Subsequently, FDA became aware of information in animal studies implicating docusate sodium as a potential animal teratogen (Refs. 1, 2, and 3), thereby raising questions about the Panel's conclusions and recommendations for these laxative ingredients. Because evaluation of the animal studies had not been completed when FDA published the tentative final monograph on OTC laxative drug products in 1985, the agency did not discuss docusate salts and stated that a separate document would be published to address the status of these ingredients (50 FR 2124 at 2125). The agency has completed its evaluation of these animal studies and is now proposing that these docusate salts are safe and effective for OTC laxative use.

In response to the advance notice of proposed rulemaking, seven manufacturers, one university, and one individual submitted comments concerning docusate salts. These comments are also addressed in this document. Copies of the comments received are on public display in the Dockets Management Branch (address above).

The chemical name for docusate sodium is butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (Ref. 4). Docusate calcium, docusate potassium, and docusate sodium are chemically identical, with the exception of the substitution of a calcium or potassium salt for the sodium salt. The agency is unaware of any data demonstrating that the substitution of the calcium or potassium ion for the sodium ion in the docusate formulation would have a significant effect on the biological activity of the docusate anion. The agency believes that any toxicological effects are due to the organic portion of the molecule, and not to the calcium, potassium, or sodium portion.

Oral administration of docusate calcium and docusate sodium has been studied in pregnant rats (Ref. 1). Ingestion of docusate calcium at levels of 1,500 to 2,000 milligrams per kilogram (mg/kg) body weight or docusate sodium at levels of 2,000 mg/kg by pregnant rats throughout gestation days 6 through 15 resulted in increased fetal resorptions and produced significant incidences of fetal malformations, consisting primarily of exencephaly frequently associated with spina bifida and microphthalmia. However, 2,000 mg/kg of docusate calcium was not teratogenic when ingested for shorter periods of time (days 6 to 8, 8 to 10, or 10 to 12) during gestation.

In the same study, gavage dosing of docusate calcium at 750 mg/kg per day (mg/kg/day) during days 6 to 15 of gestation resulted in fetal resorptions and skeletal abnormalities, primarily incomplete ossification of cranial bones. In most instances, mean maternal weight gain was somewhat reduced after gavage doses of 750 mg/kg. Docusate calcium administered by gavage to pregnant rats at 1,000 and 1,500 mg/kg during various 3-day periods of gestation was not teratogenic but did cause fetal resorption and maternal deaths. The data from these teratology studies in the rat support a no-effect level of 500 mg/kg of docusate calcium, which is 100 times the human laxative dose of 300 mg/day.

[1] The Panel designated this ingredient "dioctyl calcium sulfosuccinate." However, docusate calcium is currently the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1992."

[2] The Panel designated this ingredient "dioctyl potassium sulfosuccinate." However, docusate potassium is currently the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1992."

[3] The Panel designated this ingredient "dioctyl sodium sulfosuccinate." However, docusate sodium is currently the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1992."

A teratology study of docusate calcium in dogs was inconclusive (Ref. 2). Pregnant dogs received 0, 50, or 200 mg/kg of docusate calcium in capsules during gestational days 14 through 30. Fetuses were surgically delivered on the 55th day of gestation and examined for gross external, internal soft tissue, and skeletal malformations. There were some minor fetal skeletal malformations in the 50 mg/kg group. However, because of the lack of good controls, it could not be determined whether these were embryotoxic effects of docusate calcium or reflected normal skeletal variations in this strain. The toxic effects in the 200 mg/kg treated group included resorptions, fetal weight loss, and malformations. However, at this dose, it was not possible to distinguish the teratogenic effects of the docusate calcium from the effects of general maternal toxicity.

A three-generation reproduction dietary exposure study of docusate sodium at levels of 0, 0.5, and 1 percent in the diet was conducted in rats (Ref. 3). Mothers received 0.5 percent (approximately 440 mg/kg/day) or 1 percent (approximately 890 mg/kg/day) of docusate sodium prior to the first mating. Successive generations were divided into two groups: (1) Mothers who were fed docusate sodium continuously, and (2) mothers who stopped receiving docusate sodium 24 hours prior to expected delivery and did not receive any throughout lactation. Pups from group one mothers exhibited decreased mean body weight and increased mortality prior to weaning compared to pups from group two mothers. No malformations were noted among any of the pups. However, because it was not reported whether the births were supervised, it was not possible to rule out the possibility that the mothers ate any deformed pups. No maternal toxicity from docusate sodium was noted. The agency was unable to assign a no-effect level for docusate sodium in this study because preweaning deaths occurred at the lowest dose level tested. The design of the study was inadequate to determine whether docusate sodium was directly or indirectly toxic to pups because the docusate may have altered the taste of the milk, which the pups then refused to drink, or because the mothers were not secreting milk.

The possibility exists in these rat studies that docusate sodium produced teratogenic and reproductive effects in rats by interfering with pantothenic acid by blocking its absorption or perhaps its utilization. Pantothenic acid deficiency in pregnant rats has been associated with resorptions and malformations, most frequently exencephaly and eye malformations. These fetal effects can occur in the absence of obvious signs of toxicity in pregnant rats. A possible mechanism by which docusate calcium and docusate sodium create a deficiency of pantothenic acid has been ascribed to micellar entrapment of pantothenate in the small intestine by high levels of docusate. One unresolved matter, however, was that concentrations of pantothenic acid were not determined in maternal liver or in the fetus, so it was not known if a general deficiency state was created or if the docusate interfered with the cellular activities of pantothenic acid in the fetus.

FDA considered the above data as suggesting that docusate salts were teratogenic in animals, thereby suggestive of possible human effects. Therefore, FDA convened a panel of scientists from other agencies within the Federal government to review the available data, information, and views concerning the teratogenicity and reproductive toxicity of docusate salts. The Dioctyl Sodium Sulfosuccinate Scientific Review Panel (the DSS Panel) issued its report in March 1984 (Ref. 5) with the following conclusions:

(1) Docusate calcium, docusate potassium, and docusate sodium should not be considered potential human teratogens.

(2) The findings of the three-generation reproduction study of docusate sodium in rats (in which treatment was continued through lactation and a significant decrease in pup survival was observed during lactation) provide grounds for concern that should be explored further.

(3) There was no compelling reason to alter the accepted 1,000-fold safety factor (used for teratogens by FDA) based on the data reviewed.

(4) For therapeutic uses of docusate sodium, a safety margin of nearly 120-fold is adequate.

(5) The data suggest that docusate sodium has the potential to produce adverse reproductive effects in the laboratory animals treated with large doses, but it appears the human risk is very low.

The DSS Panel, therefore, recommended conduct of the following studies:

(1) A standard FDA three-generation reproductive study of docusate sodium using rats and mice and including pair-fed and untreated controls.

(2) Additional pharmacokinetics and biotransformation studies of docusate sodium to include a determination of the occurrence of docusate sodium and its metabolites in breast milk.

(3) Continued epidemiologic surveillance of pregnancy outcome in women treated with docusate salts.

Subsequently, FDA amended its proposed requirements to:

(1) Defer the reproduction study in mice, pending completion and evaluation of the reproduction study in rats, (2) delete the pair-fed controls in the reproduction study, and (3) require performance of a pharmacokinetic study if toxic effects in rat pups during lactation were confirmed.

A final report of the rat reproduction study was submitted to the agency as a citizen petition to reopen the administrative record for this rulemaking (Ref. 6). In this study, docusate sodium was administered in the diet to three successive generations of male and female rats with 30 rats per sex per group (30/sex/group) at levels of 0.0, 0.1, 0.5, and 1 percent. The males in the original parental group (F0) were exposed to the diets for at least 10 weeks and the females were exposed for 2 weeks prior to mating that produced the F1 litters. All descendant animals were exposed to the test material in utero, while nursing, continuously from weaning throughout mating, gestation, and lactation. The exceptions were the F3 litters that were sacrificed after weaning and animals from other generations that were culled or not selected for parents of the succeeding generation. The report included summaries and individual data on mean body weight, body weight gain, food consumption, and compound consumption for males and females during the premating phases; group mean and individual body weight and food intake data and compound consumption for females during gestation and lactation; male fertility indices, summary and individual litter data through day 21 of lactation, and gross pathological observations of all adults and the F3 weanlings.

After reviewing these data, the agency concluded that docusate sodium administered in the diet to three successive generations of rats at levels of 0.5 percent and 1 percent caused a reduction in body weights for parental males of all generations and for F1 and F2 females. In addition, the pup weights were lower than those of the controls. There was no evidence of effects on growth or reproductive performance except for the isolated incidence of an increased number of pups born dead (stillbirths) in the F3 litters of the 1 percent group, and some pups in the F2 and F3 litters had suckling problems.

The high percentage (90 percent or greater) of pup survival to weaning in this study might be attributed to the

high quality of the conduct of the study and the analysis of the diet for pantothenic acid content to ensure that the level of the vitamin was optimal. After further evaluation, the agency concluded that the teratogenicity seen in earlier studies of docusate calcium and docusate sodium in this species (Ref. 3) was due specifically to a surfactant induced deficiency of the B vitamin calcium pantothenate.

To address the question of human risk involving use of docusate sodium and a possible pantothenic acid deficiency, the agency examined the literature to determine if there was any evidence of this problem. The agency was unable to find any clinical evidence in the literature that showed pantothenic acid deficiency or possible toxicity problems, even to a moderate degree. The distribution of pantothenic acid in foods is so widespread that an occurrence of a deficiency of the vitamin is probably extremely rare (Refs. 7 and 8). In fact, evidence of dietary deficiency of pantothenic acid alone has not been clinically recognized in man. A deficiency syndrome has been experimentally induced in human volunteers by administration of a metabolic antagonist, omega-methylpantothenic acid, imposed on a pantothenic acid-deficient diet. However, it has been impossible to induce an isolated deficiency of the vitamin in less than at least 9 months on a natural diet alone (Ref. 8). The customary intake of pantothenic acid from ordinary foods in the United States is approximately 5 to 20 mg/day (Ref. 8). The estimated safe and adequate daily dietary intake of pantothenic acid for adults is estimated to be 5 to 10 mg/day (Ref. 8). Therefore, the probability of observing pantothenic acid deficiency in the United States is considered to be extremely low.

A search of the literature from 1985 through 1991 has revealed no articles suggesting teratogenic or reproductive problems associated with docusate salts. Results of epidemiologic surveillance of pregnancy outcome in women treated with docusates have been inconclusive, supporting neither safety nor increased risk of birth defects (Ref. 9).

The usual daily human dose of docusate sodium as a laxative is 50 to 500 mg/day (Ref. 10), which is 1 to 10 mg/kg/day based on the FDA standard of an average adult weight of 50 kg. The no adverse effect level from teratology studies in rats is 500 mg/kg/day; for reproductive toxicity it is about 50 to 150 mg/kg/day. After considering these data, the agency has determined that the human dosages of docusate salts proposed in this tentative final monograph do not pose reproductive or teratological problems and that these ingredients can be generally recognized as safe and effective OTC laxatives. The agency is amending § 334.20 to include docusate salts as stool softener laxatives. In addition to the specific labeling proposed for these ingredients in § 334.62 in this document, docusate salts will also be required to bear the labeling proposed for all laxative drug products in § 334.50 (50 FR 2124 at 2153). Section 334.50 limits use of the product to "relief of occasional constipation" and proposes the following warnings: (1) "Do not use laxative products when abdominal pain, nausea, or vomiting are present unless directed by a doctor," (2) "If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a doctor before using a laxative," (3) "Laxative products should not be used for a period longer than 1 week unless directed by a doctor," (4) "Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition. Discontinue use and consult your doctor," (5) "Do not use this product if you are on a low salt diet unless directed by a doctor" for products containing more than 5 milliequivalents (115 mg) of sodium in the maximum recommended daily dose, and (6) "Do not use this product if you have kidney disease unless directed by a doctor" for products containing more than 25 milliequivalents (975 mg) of potassium in the maximum recommended daily dose. (In the Federal Register of April 25, 1991 (56 FR 19222), the agency proposed to amend the general labeling provisions for OTC drug products to provide uniform sodium content labeling for all orally administered OTC drug products. Should that proposed amendment be published as a final rule, any existing requirements relating to sodium labeling in the laxative monograph will be superseded.) The agency believes that the proposed labeling will provide for the safe and effective OTC use of docusate salts. Accordingly, in this amendment to the tentative final monograph for OTC laxative drug products, the agency is proposing that docusate calcium (oral dosage forms), docusate potassium (rectal enema dosage form), and docusate sodium (oral dosage forms) be classified as Category I stool-softener laxative ingredients at the dosages discussed below.

## References

(1) Hoechst-Roussel Pharmaceuticals,Inc., "Teratogenic Evaluation of Larger Oral Dosages of Dioctyl Calcium Sulfosuccinate (and Dioctyl Sodium Sulfosuccinate) in the Rat," Experiment 0972–45, OTC Vol. 090043 Docket No. 78N–036L, Dockets Management Branch.

(2) International Research and Development Corp. for Hoechst-Roussel Pharmaceuticals, Inc., "DCS Teratology Study in Beagle Dogs," in the final report of the Dioctyl Sodium Sulfosuccinate Scientifi Review Panel, app. 4, Attachment 62, March 1984, Docket No. 84N-0184, Dockets Management Branch.

(3) American Cyanamid Co., "Aerosol OT Successive Generation Studies in Rats," Report No. 70–239, OTC Vol. 090093, Docke No. 78N–036L, Dockets Management Branch

(4) "USAN and the USP Dictionary of Dru Names," edited by C. A. Fleeger, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 220, 1992.

(5) Final Report of the Dioctyl Sodium Sulfosuccinate Scientific Review Panel, "Reproductive Toxicity of Dioctyl Sodium and Calcium Sulfosuccinate—A Report to th Acting Commissioner of Food and Drugs," March 1984, Docket No. 84N–0184, Dockets Management Branch.

(6) Comment No. CP6, Docket No. 78N–036L, Dockets Management Branch.

(7) Shils, M. E., and V. R. Young, "Moder Nutrition in Health and Disease," 7th ed., L & Febiger, Philadelphia, pp. 383–387, 1988.

(8) Gennaro, A., editor, "Remington's Pharmaceutical Sciences," 18th ed., Mack Publishing Co., Easton, PA, pp. 1016–1017, 1990.

(9) Rosa, F. W., "Birth Defect Diagnoses with First Trimester Docusate Exposures in Michigan Medicaid Data," draft of unpublished study, dated June 2, 1987, in OTC Vol. 090TFM2, Docket No. 78N–036L, Dockets Management Branch.

(10) "USP DI, Drug Information for the Health Care Professional," Vol. 1, 13th ed., United States Pharmacopeial Convention, Inc., Washington, pp. 1717–1759, 1993.

## I. The Agency's Tentative Conclusions on The Comments

1. One comment requested that the Panel's recommendation in § 334.20(c) which provides for an oral dosage form of docusate sodium, be amended to provide for a rectal dosage form of this ingredient. The comment argued that the Panel provided for a rectal dosage form of docusate potassium in § 334.20(b) and concluded that the calcium, potassium, and sodium docusate salts are safe and effective in the amounts usually taken orally or rectally in laxative drug products (40 F 12902 at 12912). The comment concluded that the monograph should provide for the same rectal dosage of docusate sodium in § 334.20(c) as present for docusate potassium in § 334.20(b).

The agency has reviewed the Panel's recommendations regarding oral and rectal dosage forms of docusate salts (4 FR 12902 at 12941). The Panel recommended as Category I an oral

dosage for docusate calcium and docusate sodium of 50 to 360 mg daily for adults and children over 12 years of age. For docusate calcium, the Panel recommended an oral dosage of 50 to 150 mg daily for children 2 to 12 years of age, and 25 mg daily for infants under 2 years of age. For docusate sodium, the recommended dosage was 50 to 150 mg daily for children 2 to 12 years of age, and 20 to 25 mg for infants under 2 years of age. The Panel also recommended as Category I a rectal dosage of docusate potassium of 50 to 250 mg daily for adults and children over 12 years of age, and 100 mg daily for children 2 to 12 years of age.

As discussed above, docusate calcium, docusate potassium, and docusate sodium are chemically identical, with the exception of the substitution of a calcium or potassium salt for the sodium salt. The data on the marketed products submitted to the Panel included information only on oral dosage forms for docusate calcium and docusate sodium, and on rectal enema dosage forms for docusate potassium. The agency is unaware of any data demonstrating that the substitution of the calcium or potassium ion for the sodium ion in the docusate formulation would have a significant effect on the biological activity of the docusate anion. The agency is aware of several products in which docusate potassium is marketed in an oral dosage form (Refs. 1 and 2) and no products in which docusate calcium is marketed in a rectal dosage form (Refs. 2 and 3). Although the American Drug Index lists three products in which docusate sodium is marketed in a rectal dosage form (Ref. 3), the manufacturers of these products state that the products are not currently marketed (Refs. 4, 5, and 6). No safety or effectiveness data have been submitted for any of these products and, in addition, no data have been submitted to show that the individual docusate salts are therapeutically equivalent when used interchangeably in oral or rectal dosage forms. Thus, the agency concludes that safety and effectiveness have been established only for the docusate salt dosage forms recommended by the Panel, and these are the only dosage forms being included in this tentative final monograph. Manufacturers of docusate salt products in other dosage forms, as noted above, need to submit data on these products to support the use of the various docusate salts interchangeably in both oral and rectal dosage forms. Such data should address the safety of the docusate salt in the dosage form not included in the monograph and the pharmacologic/therapeutic equivalence of the specific docusate salt(s) in both oral and rectal dosage forms. The agency invites interested persons to submit such data for consideration.

## References

(1) "Physicians' Desk Reference forNonprescription Drugs," 14th ed., Medical Economics Data, Montvale, NJ, pp. 668–669, 1993.

(2) Curry, C. E., and D. Tatum-Butler, "Laxative Products" in "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, pp. 343–378, 1990.

(3) Billups, N. F., and S. M. Billups, editors, "American Drug Index," 36th ed., J. B. Lippincott Co., St. Louis, pp. 204–205,1991.

(4) Memorandum of telephone conversation between L. Gilbert, WebconPharmaceuticals, and D. Hernanedz, FDA, dated September 14, 1992, in OTC Vol. 090TFM2, Docket No. 78N–036L, Dockets Management Branch.

(5) Memorandum of telephone conversation between S. Kolakowsky, Carter Products, and D. Hernandez, FDA, dated September 14, 1992, in OTC Vol. 090TFM2, Docket No. 78N–036L, Dockets Management Branch.

(6) Memorandum of telephone conversation between S. Scheindlin, Lemmon Co., and D. Hernandez, FDA, dated September 14, 1992, in OTC Vol. 090TFM2, Docket No. 78N–036L, Dockets Management Branch.

2. Several comments objected to the wording of the drug interaction precaution recommended by the Panel in § 334.62(b), which states: "Do not take this product if you are presently taking a prescription drug or mineral oil." One comment argued that this drug interaction precaution was unnecessarily discriminatory and should be deleted because many food products that are consumed daily contain natural and synthetic emulsifiers, surfactants, and "softening agents" that may cause interactions with oral prescription drugs or mineral oil. Two of the comments argued that unless specific adverse drug interactions can be proven, it is not appropriate to require a general precaution statement. Another comment argued that it would be more useful to the consumer if known specific drugs, such as mineral oil, that interact with stool softeners were listed rather than using a general warning against the use of stool softeners with prescription drugs. Three of the comments urged that the drug interaction precaution in § 334.62(b) be further amended to add the statement "* * * except on the advice of a physician," because doctors often recommend the concomitant use of a laxative product to counteract the constipation problem that may occur with some prescription drugs. One comment further suggested that the negatively worded drug interaction precaution be revised to read, "Consult your physician if you are taking mineral oil," because this positively worded statement would help consumers avoid the chance of a drug interaction.

The agency does not consider the drug interaction precaution statement in § 334.62(b) to be discriminatory because the laxative monograph sets forth conditions for the safe and effective use of ingredients for drug and not food use. Although foods may contain surfactants such as those found in stool softener laxatives, these ingredients are generally present in foods in much lower amounts than in laxatives and, therefore, pose a much lower risk of interaction with drugs.

The Panel suggested a possible interaction between the stool softener ingredients and prescription drugs significant enough to justify a warning and stated that docusate sodium possesses potent detergent properties that may facilitate gastrointestinal or hepatic uptake of other drugs, thereby potentiating their activities (40 FR 12902 at 12912). The agency, however, has been unable to verify that any detrimental interaction occurs. A search of scientific literature reveals no conclusive data or information to substantiate this suggested problem (Refs. 1 through 7). One pilot bioavailability study (Ref. 7) suggested that there is a reduction in tetracycline availability due to docusate sodium, but the results were not statistically significant in this small study. The agency invites any interested person to submit data showing an interaction between docusate salts and any prescription drug for the agency's consideration.

The agency agrees with the Panel that the absorption of mineral oil may be enhanced by docusate sodium and these agents should not be taken concurrently (40 FR 12902 at 12912).

The agency disagrees with the suggestion that the negatively worded drug interaction precaution "Do not take this product if * * *" would be more helpful to consumers if reworded to read, "Consult your physician if * * *," because the key advice is that consumers should not take the drug under certain circumstances. The wording suggested by the comment could easily mislead consumers into thinking that they should take the product first and consult their physician later. The agency agrees, however, that the drug interaction precaution should be expanded to allow concomitant use of stool softeners with mineral oil if

deemed necessary by a doctor. In an effort to make the labeling clearer and easier to understand, the phrase suggested by several comments "* * * except on the advice of a physician" has been simplified and reworded to "* * * unless directed by a doctor." Accordingly, in this tentative final monograph, this drug interaction precaution is revised to read: "Drug interaction precaution: Do not take this product if you are presently taking mineral oil, unless directed by a doctor."

**References**

(1) Brunton, L. L., "Agents AffectingGastrointestinal Water Flux and Motility, Digestants, and Bile Acids" in "The Pharmacological Basis of Therapeutics, 8th ed., edited by A. G. Gilman, et al., Pergamon Press Co., Inc., New York, pp. 914–932, 1990.

(2) Osol, A., R. Pratt, and A. Gennaro, "The United States Dispensatory," 27th ed., J. B. Lippincott Co., Philadelphia, pp. 438–439, 1973.

(3) Curry, C. E., and D. Tatum-Butler, "Laxative Products" in "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, pp. 343-378, 1990.

(4) "USP DI, Drug Information for the Health Care Professional," Vol. I, 13th ed., United States Pharmacopeial Convention, Inc., Washington, pp. 1717–1759, 1993.

(5) "Drug Evaluations," 6th ed., American Medical Association, Chicago, p. 982, 1986.

(6) Gennaro, A., editor, "Remington'sPharmaceutical Sciences," 18th ed., Mack Publishing Co., Easton, PA, pp. 1016–1017, 1990.

(7) Shah, V. P., et al., "Influence of Dioctyl Sodium Sulfosuccinate on the Absorption of Tetracycline," Biopharmaceutics and Drug Disposition, 7:27–33, 1986.

3. One comment expressed concern about the Panel's Category I classification of docusate sodium in combination with stimulant laxatives in § 334.32(a), which included as oral dosage forms: (1) Docusate sodium and casanthranol, (2) docusate sodium and danthron, (3) docusate sodium and phenolphthalein, (4) docusate sodium and senna concentrate, and (5) docusate calcium and danthron. The comment cited three references that discuss the potential dangers of such combinations (Refs. 1, 2, and 3). The comment felt that the Panel's report was well-researched, but expressed surprise that these references were not mentioned.

The agency has reviewed the references cited by the comment and notes that they were not reviewed by the Panel. The article by Smith (Ref. 1) deals with possible damage to the myenteric plexus from long-term administration of anthraquinone laxatives and does not address any problems or dangers arising from the administration of combinations of docusate sodium and stimulant laxatives. The other two references (Refs. 2 and 3) both quote the same study in which the oral LD50 for danthron (1,8-dihydroxyanthraquinone) in rats was lowered from over 22 mg/kg when administered alone to 9 mg/kg when administered in combination with an unspecified amount of docusate sodium. The study concludes that this effect can only be due to increased absorption of danthron because the animals died with symptoms of systemic toxicity.

A well-designed, well-controlled study by Case, Smith, and Nelson (Ref. 4) in mice shows considerably higher LD50 values of 7 grams per kilogram (g/kg) for danthron, 2.64 g/kg for docusate sodium, and 3.42 g/kg for a danthron/docusate sodium mixture (1:2 ratio). This study attributes the lower LD50 values cited in the two earlier studies (Refs. 2 and 3) to a typographical error in the original study. Case, Smith, and Nelson point out that the mg/kg values are more logical and in closer agreement with current findings if read in terms of g/kg rather than mg/kg. Case, Smith, and Nelson also conducted a 1-year chronic toxicity study in dogs (Ref. 4). No toxic effects and no evidence of any changes in the myenteric plexus at levels of 15 mg/kg/day of danthron in combination with 30 mg/kg/day of docusate sodium were shown. Because these levels are considerably lower than the g/kg amounts discussed above, the agency concludes that the comment's concerns have been adequately addressed by subsequent reports in the literature.

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 the development of intestinal and liver tumors and that danthron is, therefore, potentially a carcinogen in man (Refs. 5 and 6). Danthron, in common with other anthraquinone compounds, has also been shown to exhibit a positive mutagenic effect in some in vitro models (Refs. 7 and 8). FDA subsequently initiated a total recall to the retail-dispensing level of all danthron-containing drug products, by sending a recall letter to all registered drug firms and distributors (Ref. 9). 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" (Ref. 10). Accordingly, FDA is not including the combination of docusate sodium and danthron in this tentative final monograph. The other four docusate salt and stimulant laxative combination products mentioned by the comment and recommended as Category I by the Panel are being proposed for inclusion in the monograph in the absence of specific data indicating a safety problem.

**References**

(1) Smith, B., "Effect of Irritant Purgatives on the Myenteric Plexus in Man and the Mouse," Gut, 9:139–143, 1968.

(2) Smith, B., "The Neuropathology of the Alimentary Tract," The Williams and Wilkins Co., Baltimore, pp. 92–98, 1972.

(3) Godfrey, H., "Dangers of Dioctyl Sodium Sulfosuccinate in Mixtures," Journal of the American Medical Association, 215:643, 1971.

(4) Case, M. T., J. K. Smith, and R. A. Nelson, "Acute Mouse and Chronic Dog Toxicity Studies on Danthron, Dioctyl Sodium Sulfosuccinate, Paloxalkol and Combinations," Drug and Chemical Toxicology, 1:89–101, 1977.

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(8) Tikkanen, L., T. Matsushima, and S. Natori, "Mutagenicity of Anthraquinones in the Salmonella Preincubation Test," Mutation Research, 116:297–303, 1983.

(9) FDA drug recall letter concerningdanthron-containing drug products, in OTC Vol. 090TFM2, Docket No. 78N–036L, Dockets Management Branch.

(10) FDA press release on danthron drug products, in OTC Vol. 090TFM2, Docket No. 78N–036L, Dockets Management Branch.

4. One comment requested that recommended § 334.32(b)(1) be amended to provide for a combination of docusate sodium and glycerin in a rectal dosage form, in addition to the combination of docusate potassium and glycerin recommended by the Panel. The comment argued that historically docusate sodium is the best-known and most widely used of the docusate salts, that it is pharmaceutically compatible with glycerin, and that it is no less effective and no more toxic than docusate potassium.

The agency is unaware of any data demonstrating that the substitution of the sodium ion for the potassium ion in

the docusate formulation would have a significant effect on the biologic activity of the docusate anion (see comment 1). However, no data have been submitted to support the assumption that the effectiveness of docusate sodium would be comparable to docusate potassium in a combination rectal dosage formulation with glycerin or that the toxicity would not be increased. Therefore, the agency is not including in this tentative final monograph the rectal dosage form combination recommended by the comment. The agency is including in this tentative final monograph the two rectal enema dosage combinations classified by the Panel as Category I: (1) Docusate potassium and glycerin, and (2) docusate potassium and sorbitol.

## II. The Agency's Tentative Conclusions and Adoption of The Panel's Report

### *A. Summary of Ingredient Categories and Testing of Category II and III Conditions*

1. Summary of Ingredient Categories

The agency has reviewed the docusate salt active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's Category I classification of docusate calcium and docusate sodium in oral dosage forms and docusate potassium in a rectal dosage form for use as OTC laxative drug products. As a convenience to the reader, the following list is included as a summary of the Panel's recommendations and the agency's proposed categorization of stool softener active ingredients.

| Active ingredient | Panel | Agency |
|---|---|---|
| Docusate calcium | I | I |
| Docusate potassium | I | I |
| Docusate sodium | I | I |

2. Testing of Category II and Category III Conditions

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any docusate salt condition not included in this tentative final monograph by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

### *B. Summary of the Agency's Changes*

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph conditions for docusate salt ingredients with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The wording of the drug interaction precaution recommended by the Panel in § 334.62(b) has been revised to read: "Drug interaction precaution: Do not take this product if you are presently taking mineral oil, unless directed by a doctor." (See comment 2.)

2. The agency is not including in this tentative final monograph the combinations of docusate calcium or docusate sodium and danthron because of a 1987 recall of all danthron-containing products based on evidence of potential carcinogenicity in humans. (See comment 3.)

3. The Panel recommended dosages for children under 2 years of age for docusate calcium and docusate sodium. The agency, however, in the tentative final monograph for OTC laxative drug products (50 FR 2124 at 2148) proposed that dosages for children under 2 years of age not appear in the OTC labeling because of the concern that constipation in infants may be a sign of a more serious condition that should be properly diagnosed by a doctor. Therefore, dosages for children under 2 years of age for docusate calcium and docusate sodium are being included in this tentative final monograph only under professional labeling.

4. The Panel recommended docusate sodium and senna concentrate as a permitted active ingredient combination (40 FR 12902 at 12921). However, in the tentative final monograph for OTC laxative drug products, the dosages for senna preparations were revised to provide dosages for sennosides A and B only (50 FR 2124 at 2140 and 2141). Therefore, sennosides A and B are being used to describe this combination in this amendment.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC laxative drug products, is a major rule.

In the economic assessment, the agency also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96-354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC laxative drug products is not expected to pose such an impact on small businesses. All conditions reviewed by the Panel are proposed for inclusion in the monograph except one condition that was removed from the market in 1987. Only some minor relabeling will be necessary. This will be a one-time expense when the final monograph is issued. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on laxative drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC laxative drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on OTC laxative drug products containing docusate salts as active ingredients, a period of 120 days from the date of publication of this proposed rule in the Federal Register is being provided for comments and data on this subject to be developed and submitted. 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.

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.

Interested persons may, on or before December 31, 1993, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the

Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 31, 1993. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests 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. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled hearing will be announced in the **Federal Register.**

Interested persons, on or before September 2, 1994, may also submit in writing new data demonstrating safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before November 2, 1994. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47740). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addresssed to the Dockets Management Branch (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only comments and data submitted prior to the closing of the administrative record on November 2, 1994. 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 in 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 part 334 (as proposed in the **Federal Register** of January 15, 1985, 50 FR 2124) be amended as follows:

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

1. The authority citation for 21 CFR part 334 is revised 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).

2. Section 334.20 is amended by adding text to read as follows:

**§ 334.20 Stool softener laxative active ingredients.**

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.62(d):

(a) Docusate calcium.

(b) Docusate potassium.

(c) Docusate sodium.

3. Section 334.30 is amended by adding new paragraphs (i), (j), and (k) to read as follows:

**§ 334.30 Permitted combinations of active laxative ingredients.**

* * * * *

(i) The following stool softener laxative ingredient may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§ 334.60 and 334.62:

(1) Docusate sodium identified in § 334.20(c) and casanthranol identified in § 334.18(c)(1).

(2) Docusate sodium identified in § 334.20(c) and phenolphthalein identified in § 334.18(g).

(3) Docusate sodium identified in § 334.20(c) and sennosides A and B identified in § 334.18(h).

(j) The following stool softener laxative ingredient may be combined with the following bulk-forming laxative ingredient provided the combination is labeled according to §§ 34.52 and 334.62: Docusate sodium identified in § 334.20(c) and sodium carboxymethylcellulose identified in § 334.10(b)(2).

(k) The following stool softener laxative ingredient may be combined with the following hyperosmotic laxative ingredients provided the combination is labeled according to §§ 334.54 and 334.62:

(1) Docusate potassium identified in § 334.20(b) and glycerin identified in § 334.12(a).

(2) Docusate potassium identified in § 334.20(b) and sorbitol identified in § 334.12(b).

4. Section 334.62 is amended by adding text to paragraphs (c) and (d) to read as follows:

**§ 334.62 Labeling of stool softener laxative drug products.**

* * * * *

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of the product contains the following statement under the heading "Drug Interaction Precaution": "Do not take this product if you are presently taking mineral oil, unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing docusate calcium identified in § 334.20(a).* Adults and children 12 years of age and over: oral dosage is 50 to 360 milligrams. Children 2 to under 12 years of age: oral dosage is 50 to 150 milligrams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(2) *For products containing docusate potassium identified in § 334.20(b).* Adults and children 12 years of age and over: rectal enema dosage is 50 to 250 milligrams in a single daily dose. Children 2 to under 12 years of age: rectal enema dosage is 100 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(3) *For products containing docusate sodium identified in § 334.20(c).* Adults and children 12 years of age and older: oral dosage is 50 to 360 milligrams. Children 2 to under 12 years of age: oral dosage is 50 to 150 milligrams. This dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

5. Section 334.80 is amended by revising the introductory text and by adding paragraphs (c)(12) and (c)(13) to read as follows:

**§ 334.80 Professional labeling.**

The labeling of the product provided to health professionals (but not to the general public) contains the following information in addition to the labeling identified in §§ 334.50, 334.52, 334.54, 334.56, 334.58, 334.60, and 334.62.

* * * * *

(c) * * *

(12) *For products containing docusate calcium identified in § 334.20(a).* Children under 2 years of age: oral dosage is 25 milligrams in a single daily dose or in divided doses.

(13) *For products containing docusate sodium identified in § 334.20(c).* Children under 2 years of age: oral dosage is 20 to 50 milligrams in a single daily dose or in divided doses.

Dated: August 26, 1993.

**Michael R. Taylor,**

*Deputy Commissioner for Policy.*

[FR Doc. 93-21368 Filed 9-1-93; 8:45 am]

BILLING CODE 4160-01-F

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 372

[OPPTS-400079A; FRL-4643-7]

### Chromium, Nickel, and Copper in Stainless Steel, Brass, and Bronze; Toxic Chemical Release Reporting; Community Right-To-Know; Extension of Comment Period

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice of extension of comment period.

**SUMMARY:** EPA is extending the comment period for a denial of petition published in the **Federal Register** of June 29, 1993. The document denied three petitions to exempt reporting of chromium in stainless steel, nickel in stainless steel, and chromium, nickel, and copper in stainless steel, brass, and bronze from the list of toxic chemicals subject to section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA). The original comment period ended August 30, 1993; the comment period is extended until November 1, 1993.

**DATES:** Written comments must be received by November 1, 1993.

**ADDRESSES:** Written comments must be submitted in triplicate to: OPPT Docket Clerk, TSCA Document Receipt Office (TS-790), Office of Pollution Prevention and Toxics, Environmental Protection Agency, Rm. E-G99, 401 M St., SW., Washington, DC 20460, Attention: Docket Control Number OPPTS-400079.

**FOR FURTHER INFORMATION CONTACT:** Maria J. Doa, Petitions Coordinator, Emergency Planning and Community Right-to-Know Information Hotline, Environmental Protection Agency, Mail Stop OS-120, 401 M St., SW., Washington, DC 20460, Toll free number: 800-535-0202, Toll number: 703-412-9877, TDD Toll free number: 800-553-7672.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of June 29, 1993 (58 FR 34738), EPA denied three petitions to exempt reporting of: (1) Chromium present in stainless steel, (2) nickel contained in stainless steel and other alloys, (3) chromium, nickel, and copper contained in stainless steels and solid copper based metals, such as brass and bronze, from section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA). The denial cited a lack of information concerning whether certain forms of brass, bronze, and stainless steel corrode under various processing, use, or disposal conditions. On August 13, 1993, EPA received a request for a 60-day extension of the comment period from the Industrial Fasteners Institute and the Forging Industry Association. In response, EPA is extending the comment period until November 1, 1993.

#### List of Subjects in 40 CFR Part 372

Chemicals, Community-right-to-know, Environmental protection, Reporting and recordkeeping requirements, Toxic chemicals.

Dated: August 27, 1993.

**Mark Greenwood,**

*Director, Office of Pollution Prevention and Toxics.*

[FR Doc. 93-21405 Filed 9-1-93; 8:45 am]

BILLING CODE 6560-50-F

## GENERAL SERVICES ADMINISTRATION

### 41 CFR Part 105-57

### Collection of Debts by Federal Tax Refund Offset

**AGENCY:** General Services Administration.

**ACTION:** Proposed rule.

**SUMMARY:** The General Services Administration (GSA) proposes to amend 41 CFR chapter 105 by adding Part 105-57, Collection of Debts by Federal Tax Refund Offset. The proposed regulation establishes procedures for GSA to refer past due legally enforceable debts to the Internal Revenue Service (IRS) for offset against income tax refunds of taxpayers owing debts to GSA. The proposed regulation is needed because GSA is required to participate in the tax refund offset program by the Cash Management Improvement Act Amendments of 1992, Public Law 102-589.

**DATES:** All comments must be in writing and must be received on or before October 4, 1993.

**ADDRESSES:** Written comments should be sent to LeRoy Boucher, Director, Office of Finance (BC), General Services Administration, 18th and F Streets, NW., Washington, DC 20405.

**FOR FURTHER INFORMATION CONTACT:** Bernie Kanzler, Office of Finance, Financial Information Control Division (BCD) (202-501-2923).

**SUPPLEMENTARY INFORMATION:** GSA has determined that this rule is not a major rule for the purposes of Executive Order 12291 of February 17, 1981, because it is not likely to result in an annual effect on the economy of $100 million or more; a major increase in cost to consumers, individual industries, Federal, state, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. Therefore, a Regulatory Impact Analysis has not been prepared. GSA has based all administrative decisions underlying this rule on adequate information concerning the need for, and the consequence of, this rule; has determined that the potential benefits to society from this rule outweigh the potential costs and has maximized the net benefits; and has chosen the alternative approach involving the least net cost to society.

#### Regulatory Flexibility Act

The General Services Administration has determined that this rule will not have a significant economic impact on a substantial number of small entities under the Regulatory Flexibility Act, 5 U.S.C. 601 *et seq.*).

#### List of Subjects in 41 CFR Part 105-57

Claims, Income taxes.

For the reasons set out in the preamble, GSA proposes to amend 41 CFR chapter 105 as follows:

### PART 105-57—COLLECTION OF DEBTS BY TAX REFUND OFFSET

1. Part 105-57 is added to read as follows:

### PART 105-57—COLLECTION OF DEBTS BY TAX REFUND OFFSET

Sec.



**Authority:** 31 U.S.C. 3720A, Pub. L. 98-369.

#### § 105-57.001 Purpose.

This part establishes procedures for the General Services Administration (GSA) to refer past due debts to the Internal Revenue Service (IRS) for offset