DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 331

[Docket No. 80N-0395]

Hypophosphatemia and Hyperphosphatemia Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would amend the professional labeling section of the monograph for over-the-counter (OTC) antacid drug products to include additional warnings for the professional labeling of aluminum-containing antacid drug products and a hyperphosphatemia claim for products containing aluminum carbonate, and that would establish that drug products labeled for OTC use in treating hypophosphatemia (abnormally low plasma level of phosphate in the blood) or hyperphosphatemia (abnormally high plasma level of phosphate in the blood) are not generally recognized as safe and effective and are misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. 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 May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. 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 (21 CFR 330.10). Written comments on the agency's economic impact determination by May 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 9, 1980 (45 FR 81154) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that would classify OTC hypophosphatemia and hyperphosphatemia drug products as not generally recognized as safe and effective and as being misbranded and would declare these products 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)). The notice was based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by March 9, 1981. Reply comments in response to comments filed in the initial comment period could be submitted by April 8, 1981.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, two pharmaceutical manufacturers, one State government, one health professional organization, and two health professionals submitted comments. In response to the comments submitted, one reply comment was received from a health professional organization. These comments are also on public display in the Dockets Management Branch.

In this proposed rule, FDA states for the first time its position on OTC hypophosphatemia and hyperphosphatemia drug products. Final agency action on this matter will occur with the publication at a future date of a final rule relating to OTC hypophosphatemia and hyperphosphatemia drug products.

This proposed rule would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations by adding to Subpart E of Part 310 new §§ 310.541 and 310.542, and to Subpart D of Part 331 new § 331.31(a) (3) and (4). This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC hypophosphatemia and hyperphosphatemia drug products, based on the comments received and the agency's independent evaluation of the Panel's report. As discussed in the final rule revising the procedural regulations for reviewing and classifying OTC drugs, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Category II and III). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) This document retains the concepts of Category I, II, and III at the proposed rule stage.

The agency recognizes that the Panel considered two ingredients, aluminum phosphate gel and aluminum carbonate gel, for use in hypophosphatemia and hyperphosphatemia, respectively. However, in the final monograph for OTC antacid drug products these compounds are designated as aluminum phosphate and aluminum carbonate. Therefore, throughout this document these ingredients will be referred to by the names used in the antacid final monograph.

The agency advises that the effective date of the final rule will be 12 months after the date of publication in the **Federal Register**. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

1. One comment requested that the agency eliminate all aluminum-containing drug products from the OTC market because recent experimental and clinical data implicate aluminum as the causative agent in some presenile and senile dementia of the Alzheimer's type. The comment pointed out numerous studies which indicate that aluminum plays a role in Alzheimer's disease, an organic brain syndrome (Ref. 1). In several of the studies, aluminum was observed in the tangled neurofilaments of Alzheimer's patients. Other studies suggested that aluminum accumulations in the brain have been correlated with

the oral ingestion of aluminum-containing antacids. The comment argued that these clinical findings are collaborated by animal data in which encephalopathies have been induced in rabbits and rats given toxic doses of aluminum. The comment also pointed out that significant elevations of aluminum have been reported in the parathyroid glands of patients taking aluminum-containing drugs as concurrent therapy during dialysis and speculated that parathyroid function may be affected by these elevations. The comment concluded by suggesting that more research is needed to define the safe use of aluminum salts in chronic therapy for hyperphosphatemia, and suggesting that physicians should be advised to monitor the renal function of those patients taking chronic dosages of aluminum-containing antacids.

A second comment submitted several literature reports regarding the role of aluminum-containing antacids in clacium and fluoride metabolism in man (Ref. 2). The comment noted that urine and stool excretion of calcium apparently increased with small doses of aluminum-containing antacids and concluded that long-term use of such products may lead to substantial clacium loss. The comment also stated that the data demonstrate that aluminum-containing antacids inhibit the intestinal absorption of fluoride.

The agency has evaluated the data submitted by the comments as well as available data reported in the literature in determining the toxicity of aluminum-containing drug products. There is some evidence that ingestion of large amounts of aluminum-containing products for prolonged periods may lead to adverse effects, but there is also considerable speculation in the literature with little supporting data.

Aluminum and Alzheimer's disease. Crapper and colleagues (Refs. 3 through 8) have been the major proponents of a role for aluminum as a causative factor of Alzheimer's disease. They have reported elevated aluminum levels in the brains of persons with Alzheimer's disease. They hypothesized that aluminum may interfere with the transcription of genetic information and may lead to altered protein synthesis within the neuron (Ref. 8). Trapp et al. (Ref. 9) have also reported a higher concentration of brain aluminum contents in a small number of persons with Alzheimer's disease although the difference in aluminum levels between Alzheimer's and control patients was considerably lower than that reported by Crapper. Perl and Brody (Ref. 10) studied the aluminum content within individual neurons of brain tissue from three cases of Alzheimer's disease and three nondemented controls. They found that aluminum is frequently present in the nuclei of neurons with neurofibrillary tangles both in the presence and absence of Alzheimer's disease, although neurons with neurofibrillary tangles were found more often in the Alzheimer patients. McDermott et al. (Ref. 11) measured brain aluminum levels in 10 patients with Alzheimer's disease and in 9 control patients. Aluminum concentrations in individual samples were highly variable, and no significant differences were observed between the two groups. There was also no correlation between mean aluminum concentrations and the degree of neurofibrillary degeneration in each brain. Markesbery et al. (Ref. 12) examined 74 specimens of tissue from 12 Alzheimer's patients and 166 specimens from 28 nondemented individuals. Their data showed no significant difference in aluminum content of Alzheimer's patients and normal controls. No correlation between neurofibrillary tangle formations and aluminum content was established.

Aluminum can produce some of the histopathlogical and clinical features of Alzheimer's disease in certain animal species. Petit, Biederman, and McMullen (Ref. 13) have demonstrated that an infusion of aluminum tartrate into the lateral ventricles of rabbits decreased learning and retention of an avoidance task compared to saline-infused controls. Crapper and Dalton (Refs. 4 and 5) reported that subarachnoid injection of aluminum chloride into cats induced neurofibrillary degeneration and impaired the acquisition and short-term retention of a conditioned avoidance response. The relationship of changes induced in these animals to the human disease is not at all clear, particularly in view of the unphysiological route of administration of the aluminum in these studies. On the other hand, Crapper and De Boni (Ref. 14) have noted that not all species are as affected by such infusions as the cat and rabbit. Aluminum concentrations 4 to 10 times those employed in cats did not induce a progressive encephalopathy or neurofibrillary degeneration in two strains of rats.

Recently, Crapper and De Boni stated that the presence of increased amounts of aluminum in the brain of Alzheimer patients may simply indicate the absorption of aluminum by a deteriorating system. They state that the cause of Alzheimer's disease is unknown and there is no evidence to support the possibility that aluminum initiates the Alzheimer process (Ref. 15).

In an editorial on Alzheimer's disease in the British Medical Journal (Ref. 16), it was stated that "Despite the plethora of hypotheses, however, objective analysis of all the data—immunological, genetic, virological, pathological, and biochemical—shows that we still have no idea of the aetiology of Alzheimer's disease."

Aluminum and the parathyroid glands. Although the comment suggests that aluminum may have an effect on parathyroid function, the agency has reviewed the available literature and found no data to support this hypothesis (Refs. 17 through 22). Some studies in rats suggest that elevated parathyroid hormone levels may increase the absorption of aluminum from the gastrointestinal tract (Ref. 17). There is little evidence, however, that this is of clinical importance.

Aluminum and phosphate/calcium/fluoride metabolism. Several studies have been conducted which imply that aluminum may detrimentally affect phosphate, calcium, and flouride balance. It is known that aluminum forms insoluble complexes with phosphate in the gastrointestinal tract and decreases phosphate absorption. Prolonged use of aluminum-containing antacids by normophosphatemic patients may result in hypophosphatemia which may lead to adverse reactions. Studies by Lotz, Zisman, and Bartter (Ref. 23); Cooke, Teitelbaum, and Avioli (Ref. 24); and Spencer et al. (Refs. 25 and 26) indicate that an increase in calcium excretion may occur with the ingestion of aluminum antacids. These reports are contradicted in a report by Cann, Prussin, and Gordan (Ref. 17) who report that the calcium balance is unchanged. The precise results of any calcium loss related to aluminum ingestion have not been defined.

Spencer et al. (Refs 27 and 28) have conducted studies that apparently show that aluminum forms insoluble complexes with fluoride ions in the gastrointestinal tract, thereby decreasing fluoride absorption. Although the authors have suggested that this decrease in fluoride absorption may contribute to skeletal demineralization, the suggestion is speculative because the fasting plasma fluoride levels did not change and because the role of normal dietary fluoride in maintaining skeletal bone has not been defined. Although there is evidence that oral aluminum antacids can lead to decreased fluoride absorption, the physiological

significance of this finding in adults is unclear.

Aluminum and renal dialysis. Evidence of neurotoxicity associated with aluminum is strongest for encephalopathy that occurs in renal failure patients undergoing dialysis (Refs. 29 through 42). Although aluminum has not been proven to be a causative factor, there is considerable indirect evidence that it has a role in development of the syndrome. The evidence appears to be stronger that high dialysate aluminum levels have contributed to the development of dialysis encephalopathy. It is also considered likely that high doses of oral aluminum compounds may contribute to total body aluminum. Studies have also been reviewed that indicate that bone aluminum levels are significantly elevated in chronic renal failure patients (Refs. 19, 20, 35, and 43 through 46). The level appears to be highest in patients on dialysis, related to the duration of dialysis, and has been correlated with the incidence of osteomalacic renal osteodystrophy in these patients.

In conclusion, the agency believes that a role for aluminum in the pathogenesis of Alzheimer's disease cannot be ruled out, but the evidence supporting such a rule is very weak. No data were found to indicate that parathyroid function is affected by aluminum. There are conflicting reports on the effect of aluminum antacids on calcium balance, but there is little evidence to support an etiologic role for aluminum antacids in osteoporosis. There is evidence that oral aluminum compounds can lead to reduced fluoride absorption, but the significance of this finding in adults is unclear at this time. In view of these findings, the agency does not believe the availability of OTC aluminum-containing antacids presents a significant hazard and thus will not require that they be removed from the OTC market. However, because of the potential role of aluminum in the development of dialysis encephalopathy syndrome, osteomalacic renal osteodystrophy, and hypophosphatemia, the agency believes it is appropriate to provide additional information in the professional labeling section of the antacid monograph (21 CFR 331.31) for aluminum-containing antacids as follows:

(1) Evidence suggests that elevated tissue aluminum levels have a role in development of the dialysis encephalopathy syndrome. A number of cases have been associated with elevated aluminum levels in the dialysate water. There is also evidence that small amounts of ingested aluminum are absorbed from the gastrointestinal tract, and it is likely that renal excretion of absorbed aluminum is impaired in renal failure. Prolonged use of aluminum-containing antacids in such patients may contribute to increased tissue levels of aluminum.

(2) Aluminum forms insoluble complexes with phosphate in the gastrointestinal tract, thus decreasing phosphate absorption. Prolonged use of aluminum-containing antacids by normophosphatemic patients may result in hypophosphatemia if phosphate intake is not adequate. In its more severe forms, hypophosphatemia can lead to anorexia, malaise, muscle weakness, and osteomalacia.

References

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(2) Comment No. C0005, Docket No. 80N–0395, Dockets Management Branch.

(3) De Boni, U., and D.R. Crapper, "Senile Dementia and Alzheimer's Disease: A Current View," *Life Sciences*, 27:1–4, 1980.

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(6) Crapper, D.R., S.S. Krishnan, and S. Quittkat, "Aluminum Neurofibrillary Degeneration and Alzheimer's Disease," *Brain*, 99:67–80, 1976.

(7) De Boni, U., and D.R. Crapper, "Paired Helical Filaments of the Alzheimer Type in Cultured Neurones," *Nature*, 271:566–568, 1978.

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2. One comment disagreed with the Panel's recommendation to include in the OTC labeling of aluminum-containing antacids a warning advising consumers against the use of such products if they have kidney disease except under the advice and supervision of a physician. The comment noted that the Panel cited only one report as evidence supporting this proposed warning (Ref. 1). Although the report suggests that the oral ingestion of aluminum may play a role in the development of dialysis encephalopathy in patients with severe kidney disease, the comment argued that the cause of dialysis encephalopathy in patients with severe kidney disease is complex and that there is disagreement about the toxicity or lack of toxicity of aluminum. In support of its argument, the comment cited a survey conducted by the European Dialysis and Transplant Association (Ref. 2), which showed no correlation between the ingestion of aluminum hydroxide and dialysis encephalopathy. The comment concluded that, although a warning concerning the risk potential in dialysis patients may be appropriate for professional labeling, such a warning was unwarranted on the OTC labeling of aluminum-containing antacid products. A second comment disagreed and cited a number of references in support of its opinion that there is a causative relationship between orally consumed aluminum-containing drugs and dialysis encephalopathy. (Ref. 3).

The agency has thoroughly reviewed all of the available data concerning aluminum toxicity. (See comment 1 above.) In view of the evidence available at this time, the agency does not believe that the kidney-disease warning recommended by the Panel is warranted on the OTC labeling of aluminum-containing antacid products. No data could be found on the effects of mild or moderate impairment of renal function on the absorption, urinary excretion, or overall balance of oral aluminum. While there is evidence that ingestion of large amounts of aluminum-containing products for prolonged periods may lead to adverse effects, the labeling for OTC aluminum-containing antacids already includes a warning advising against the use of these products for more than 2 weeks. In addition, the strongest evidence for toxicity of aluminum is the encephalopathy that occurs in renal failure patients undergoing dialysis. While the evidence appears to be stronger that high aluminum levels of the dialysate have contributed to the development of dialysis encephalopathy, oral ingestion of aluminum compounds may contribute to total body aluminum. However, because there are no data on the effects of mild or moderate impairment of renal function on the absorption, urinary excretion, or overall balance of oral aluminum, and because persons at highest risk are those with severe renal failure who are generally under the care of a physician, the agency believes it is more prudent to inform the health professional of the potential risks involved rather than to require the kidney-disease warning recommended by the Panel. (See comment 1 above.)

References

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(3) Comment No. C0006, Docket No. 80N–0395, Dockets Management Branch.

3. One comment was concerned that the commercial availability of aluminum phosphate may be interrupted if the Panel's recommendation to eliminate the drug as an OTC antacid product is adopted. It was the comment's understanding that during the change from OTC to prescription status aluminum phosphate would be unavailable to physicians for use by kidney transplant patients who depend on the drug for postoperative management. A second comment, from a manufacutuer of aluminum phosphate, advised the agency of its intent to change the claims on its product from antiacid to hypophosphatemia and to switch the product from OTC to prescription status within the time period established for the implementation of the final monograph.

The agency appreciates the comment's concern regarding the continued availability of aluminum phosphate; however, it is unlikely that the marketplace will be interrupted in switching the product from OTC to prescription status. As discussed below, the agency believes that claims for the treatment of hypophosphatemia should not be permitted in the labeling of OTC drug products. Between publication of this tentative final regulation and the final regulation on hypophosphatemia and hyperphosphatemia drug products, manufacturers will have sufficient time to submit and have approved a new drug application for the prescription use of aluminum phosphate in treating hypophosphatemia. If a new drug application (NDA) is approved before the regulation becomes effective, the product may be switched to prescription status at that time. As noted above, the manufacturer of one aluminum phosphate product has advised the agency of its intention to change the marketing status of its product from OTC to prescription within the specified time period.

4. One comment suggested that the Panel's recommended regulation in § 310.542, which describes hyperphosphatemia and sets conditions that restrict the marketing of products containing aluminum carbonate labeled to treat hyperphosphatemia, would not serve any useful purpose because the marketing of OTC drug products containing aluminum carbonate would be regulated by professional labeling appearing in the monograph for OTC

antacid drug products. The comment added that a petition had been submitted to amend the professional labeling for antacid drug products (21 CFR 331.31) to include the use of aluminum carbonate for the treatment of hyperphosphatemia, and that this amendment will ensure that this indication will be included only in the professional labeling of antacid drug products containing aluminum carbonate.

The Panel recognized in its report (45 FR 81157) that aluminum carbonate can be marketed OTC as an antacid drug product and recommended that any labeling claims for hyperphosphatemia be limited to professional labeling only. The citizen petition (Docket No. 81P-0091/CP) requesting that the professional labeling of the monograph for OTC antacid drug products (21 CFR 331.31) be amended to include the hyperphosphatemia indication for aluminum carbonate was responded to by the agency on October 23, 1981 (Ref. 1). The agency stated that aluminum carbonate is safe and effective for the treatment, control, and management of hyperphosphatemia under medical supervision and that information distributed to medical professionals may include this indication. Because aluminum carbonate may be marketed OTC as an antacid without an NDA, the agency believes that the hyperphosphatemia claim may be considered as professional labeling for this ingredient. Therefore, the agency is proposing in this document to amend the professional labeling section of the antacid monograph (§ 331.31) to include the hyperphosphatemia claim. However, proposed § 310.542 states that the hyperphosphatemia claim is not acceptable for OTC labeling and that any drug product promoting this claim for OTC use is regarded as a new drug.

Reference

(1) Letter from W. F. Randolph, FDA, to J. N. Bathish, Wyeth Laboratories, Inc., October 23, 1981, Item Code PAV, Docket No. 81P-0091/CP, Dockets Management Branch.

II. The Agency's Tentative Adoption of the Panel's Report

FDA has considered the comments and other relevant data and information available and concurs with the Panel that, because the conditions of hypophosphatemia and hyperphosphatemia are not amenable to self-treatment, claims for the treatment of hypophosphatemia or hyperphosphatemia should not be permitted in the labeling of OTC drug products. However, the agency only concurs in part with the Panel's recommended rule that manufacturers wishing to make such claims for their products need to proceed through the new drug route. As discussed in comment number 4 above, the agency believes it is reasonable for hyperphosphatemia claims for aluminum carbonate to be included in the professional labeling section of the monograph for OTC antacid drug products because aluminum carbonate can be marketed OTC as a single ingredient antacid product.

However, a similar approach is not viable for aluminum phosphate. Although aluminum phosphate historically has been promoted as an OTC antacid, the Panel expressed concern that products containing this ingredient would not meet the acid neutralizing requirements of the antacid monograph (21 CFR Part 331, Subpart C). In fact, the manufacturer of one such product pointed out in its submission to the Panel that its product would not meet the acid neutralizing requirements of the antacid monograph (Ref. 1). The agency conducted the acid neutralizing capacity test on the manufacturer's aluminum phosphate product and found that the labeled minimum antacid dose of 15 milliliters (mL) neutralized only 4.38 milliequivalents (mEq) of acid, while a stable pH of 3.5 could not be established for the maximum dose of 30 mL (Ref. 2). Therefore, aluminum phosphate does not meet the acid neutralizing requirements of the antacid monograph and cannot be marketed as a single ingredient antacid drug product. Because the available data indicate that aluminum phosphate cannot be marketed OTC as a single ingredient antacid product, the professional labeling approach is not an appropriate mechanism with respect to this ingredient and an approved NDA would be required for marketing of the product.

The Panel recommended that if aluminum phosphate does not conform to the acid neutralizing requirement of the antacid monograph that it be removed from the list of antacid ingredients generally recognized as safe and effective (§ 331.11). Although aluminum phosphate as a single ingredient does not meet the requirements of the antacid monograph, it could potentially meet the requirements of that portion of § 331.10(a) that each ingredient of a combination product be included at a level that contributes at least 25 percent of the total acid neutralizing capacity of a combination antacid product, calculated on the basis of the procedures in § 331.21. Because aluminum phosphate does have some acid neutralizing capacity, it could be utilized as one component of a combination antacid drug product. Therefore, the agency will not adopt the Panel's recommendation to remove aluminum phosphate from the antacid monograph, but is proposing to amend the antacid monograph to clarify that aluminum phosphate is acceptable for use only in combination.

The agency is revising § 310.541(b) and § 310.542(b) to clarify that a product covered by the regulation is a new drug for which an approved NDA is required for marketing, and in the absence of an approved NDA the product would also be misbranded under section 502 of the act.

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 hypophosphatemia and hyperphosphatemia drug products, is a major rule.

For purposes of the Regulatory Flexibility Act, the economic assessment concluded that, while the average economic impact of the overall OTC drug review on small entities will not be significant, the possibility of larger-than-average impacts on some small firms in some years might exist. Therefore, the assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose a significant impact on a substantial number of small entities. The analysis identified the possibilities of reducing burdens on small firms through the use of (a) relaxed safety and efficacy standards or (b) labels acknowledging unproven safety or efficacy. However, the analysis concluded that there is no legal basis for any preferential waiver, exemption, or tiering strategy for small firms compatible with the public health requirements of the Federal Food, Drug, and Cosmetic Act. Nevertheless, to avoid overlooking any problems or feasible possibilities of relief peculiar to this group of products, the agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have

on OTC hypophosphatemia and hyperphosphatemia drug products. Comments regarding the economic impact of this rulemaking should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on hypophosphatemia and hypophosphatemia drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments 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 that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

References

(1) OTC Volume No. 170043, Docket No. 80N–0395, Dockets Management Branch.

(2) Memorandum from Director, Division of Drug Chemistry (HFN–420) to Director, Division of OTC Drug Evaluation (HFN–510), FDA, December 28, 1982, OTC Volume 17HTFM, Docket No. 80N–0395, Dockets Management Branch.

List of Subjects

21 CFR Part 310

New drugs.

21 CFR Part 331

OTC drugs, Antacids.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended, by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Parts 310 and 331 to read as follows:

PART 310—NEW DRUGS

1. Part 310 is amended by adding new §§ 310.541 and 310.542, to read as follows:

§ 310.541 Over-the-counter (OTC) drug products containing active ingredients offered for use in the treatment of hypophosphatemia.

(a) Hypophosphatemia is a condition in which an abnormally low plasma level of phosphate occurs in the blood. This condition is not amenable to self-diagnosis or self-treatment. Treatment of this condition should be restricted to the supervision of a physician. For this reason, any drug product containing ingredients offered for OTC use in the treatment of hypophosphatemia cannot be considered generally recognized as safe and effective.

(b) Any drug product that is labeled, represented, or promoted for OTC use in the treatment of hypophosphatemia is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) A completed and signed "Notice of Claimed Investigational Exemption For a New Drug" (Form FDA–1571) (OMB Approval No. 0910–0014), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for use in the treatment of hypophosphatemia is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any such drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

§ 310.542 Over-the-counter (OTC) drug products containing active ingredients offered for use in the treatment of hyperphosphatemia.

(a) Hyperphosphatemia is a condition in which an abnormally high plasma level of phosphate occurs in the blood. This condition is not amenable to self-diagnosis or self-treatment. Treatment of this condition should be restricted to the supervision of a physician. For this reason, any drug product containing ingredients offered for OTC use in the treatment of hyperphosphatemia cannot be considered generally recognized as safe and effective.

(b) Any drug product that is labeled, represented, or promoted for OTC use in the treatment of hyperphosphatemia is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) A completed and signed "Notice of Claimed Investigational Exemption For a New Drug" (Form FDA–1571) (OMB Approval No. 0910–0014), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for use in the treatment of hyperphosphatemia is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any such drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

PART 331—ANTACID PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

2. Part 331 is amended by revising § 331.11(a)(4) to read as follows:

§ 331.11 Listing of specific antacid ingredients.

(a) * * *

(4) Aluminum phosphate when used as part of an antacid combination product and contributing at least 25 percent of the total acid neutralizing capacity. Maximum daily dosage limit is 8 grams.

3. Part 331 is amended in § 331.31 by adding new paragraphs (a)(3) and (4) to read as follows:

§ 331.31 Professional labeling.

(a) * * *

(3) *For products containing aluminum identified in § 331.11(a)—Warnings.* (i) Evidence suggests that elevated tissue aluminum levels have a role in development of the dialysis encephalopathy syndrome. A number of cases have been associated with elevated aluminum levels in the dialysate water. There is also evidence that small amounts of ingested aluminum are absorbed from the gastrointestinal tract, and it is likely that renal excretion of absorbed aluminum is impaired in renal failure. Prolonged use of aluminum-containing antacids in such patients may contribute to increased tissue levels of aluminum.

(ii) Aluminum forms insoluble complexes with phosphate in the gastrointestinal tract, thus decreasing phosphate absorption. Prolonged use of aluminum-containing antacids by

normophosphatemic patients may result in hypophosphatemia if phosphate intake is not adequate. In its more severe forms, hypophosphatemia can lead to anorexia, malaise, muscle weakness, and osteomalacia.

(4)— *For products containing aluminum carbonate identified in § 331.11(a)(1)—Indication.* "For the treatment, control, or management of hyperphosphatemia, or for use with a low phosphate diet to prevent formation of phosphate urinary stones, through the reduction of phosphates in the serum and urine."

* * * * *

Interested persons may, on or before May 15, 1985, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on before May 15, 1985. 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 accompained 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 oral hearing will be announced in the **Federal Register.**

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. 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 47730).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 addressed to the Dockets Management Branch (HFA–305) (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 rule, the agency will ordinarily consider only data submitted prior to the closing of the administrative record in March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule is published in the **Federal Register** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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