DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N-0395]

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

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This notice proposes that hypophosphatemia and hyperphosphatemia drug products be classified in Category II as not being generally recognized as safe and effective or as being misbranded for over-the-counter (OTC) use. Hypophosphatemia and hyperphosphatemia drug products are medications which are intended, respectively, to increase or decrease phosphate levels in the blood. This notice, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by March 9, 1981. Reply comments by April 8, 1981.

ADDRESS: Written comments to the Dockets Management Branch (HFA—305), Food and Drug Administration, Rm. 4–62, 5600 Fisher Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on September 30, 1978 a report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner of Food and Drugs issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the mongraph because the Panel determined that the available data are insufficient to classify such conditions under either (1) and (2) above; and (4) the conclusions and recommendations of the Panel. The Panel recommended that OTC hypophosphatemia and hyperphosphatemia drug products be classified in Category II. Thus, no monograph is included in this document and FDA is issuing the Panel's recommendations as a formal notice to propose classifying OTC hypophosphatemia and hyperphosphatemia drug products in Category II. The agency wishes to obtain public comment before it makes any decision on the Panel's recommendations.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep on the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. Should FDA accept the Panel's recommendation that the ingredients in OTC hypophosphatemia and hyperphosphatemia drug products be classified as Category II, tentative final regulations stating that such products are new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) will be proposed for inclusion in Part 310, Subpart E (21 CFR 310.541 and 310.542). FDA is including the proposed regulations in this notice in order to obtain full public comment at this time. After FDA has carefully reviewed the comments submitted in response to this notice, the agency will issue tentative final orders on OTC hypophosphatemia and hyperphosphatemia drug products.

Should FDA accept the Panel's recommendations, the agency would classify aluminum phosphate gel as Category II for the treatment of hyperphosphatemia (an abnormally low plasma phosphate level in the blood) and aluminum carbonate gel as Category II for the treatment of hypophosphatemia (an abnormally high plasma phosphate level in the blood). Moreover, if the agency confirms the Panel's contention that aluminum phosphate gel does not meet the acid neutralization requirements of the antacid monograph (21 CFR 331. 10), the agency will propose to amend the antacid monograph (21 CFR 331) to remove aluminum phosphate as a Category I active ingredient. Aluminum phosphate gel would then be eliminated from the OTC drug market effective 6 months after the date of publication of a final order in the **Federal Register,** regardless of whether further testing is undertaken to justify its future use.

The Panel based its recommendation on safety considerations. Aluminum phosphate gel has the potential to produce aluminum toxicity in patients with kidney disease and the drug is indicated primarily for use in such patients. Further, aluminum phosphate gel is recommended for hypophosphatemia, a condition which must be diagnosed and treated by a physician. (See part D. paragraph 1. c. below—Evaluation.)

Aluminum carbonate gel, unlike aluminum phosphate gel, is not used primarily by patients with kidney disease and therefore presents little possibility of aluminum toxicity. Hyperphosphatemia, like hypophosphatemia, is not self-diagnosable or self-treatable. For that reason, if FDA accepts the Panel's recommendations, any OTC drug product containing aluminim carbonate gel which claims to relieve the condition of hyperphosphatemia would be considered misbranded. Such a claim would have to be removed from the product's labeling effective 6 months after the date of publication of a final order in the **Federal Register,**. Aluminum carbonate gel may remain on the OTC drug market as an antacid. If FDA accepts the Panel's recommendations, the agency would amend the antacid monograph to include professional labeling for the use of aluminum carbonate gel in treating hyperphosphatemia.

The antacid monograph (21 CFR 331) does not require that the labeling of aluminum-containing antacids include a warning against the use of such products in the presence of kidney disease except under the advice and supervision of a physican. The Advisory Review Panel on Miscellaneous Internal Drug Products has expressed a concern about aluminum encephalopathy in individuals with impaired kidney function. In its review of this report the agency will evaluate the data on which the Panel based its conclusion as well as other data which become available. Should the Panel's concern be substantiated, the agency will publish a proposal to amend the antacid monograph to include such a warning in the labeling of all aluminum-containing antacid drug products or take other action if necessary. The agency invites comment on whether such a warning should be required.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the Panel and FDA

have held as confidential all information concerning OTC hypophosphatemia and hyperphosphatemia drug products submitted for consideration by the Advisory Review Panel. All this information will be put on public display at the Dockets Management Branch, Food and Drug Administration, after January 8, 1971, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register**, of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register**, of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register**, of November 16, 1973 (38 FR 31696). In the **Federal Register**, of August 27, 1975 (40 FR 38179), an additional notice supplemented the initial notice with a detailed list of ingredients contained in OTC miscellaneous internal drug products.

The Commissioner appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of the ingredients in those products:

John W. Norcross, M.D., Chairman
Ruth Eleanor Brown, R. Ph. (resigned May 1976)
Elizabeth C. Giblin, Ed. D.
Richard D. Harshfield, M.D.
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O.
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)
Diana F. Rodriguez-Calvert, Pharm. D. (appointed July 1976)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D.; Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator; Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer; Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph.

In order to expand its scientific base, the Panel called upon Ralph B. D'Agostino, Ph. D., as a consultant for advice in areas which required expertise in statistics.

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs. Because of the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for hypophosphatemia and hyperphosphatemia drug products in this document. The review of all other categories of miscellaneous internal drug products will be contined by the Panel, and its findings will be published periodically in future issues of the **Federal Register**.

The Panel was first convened on January 13, 1975 in an organizational meeting. Meetings at which hypophosphatemia and hyperphosphatemia drug products were discussed were held on the following dates: June 22 and 23 and November 16 and 17, 1975; February 8 and 9 and May 9 and 10, 1976; October 15, 16, and 17, 1977; June 23, 24, and 25, August 4, 5, and 6, and September 29 and 30, 1978.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

No person requested an opportunity to appear before the Panel to express his or her views on hypophosphatemia and hyperphosphatemia drug products.

The Panel has thoroughly reviewed the literature and the two data submissions and has considered all pertinent information submitted through September 30, 1978 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considerd OTC hypophosphatemia and hyperphosphatemia drug products with respect to the following three categories:

Category I. Conditions under which OTC hypophosphatemia and hyperphosphatemia drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC hypophosphatemia and hyperphosphatemia drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

A. *Submission of Data and Information.*

Pursuant to the notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on OTC miscellaneous internal drug products, the following firm made submissions related to products used for the treatment of hypophosphatemia and hyperphosphatemia.

1. *Submissions by firms.*

Firms and marketed products

a. *Drug products for the treatment of hypophosphatemia.*
Wyeth Laboratories, Inc., Philadelphia, PA 19101. Phosphaljel suspension.

b. *Drug products for the treatement of hyperphosphatemia.*
Wyeth Laboratories, Inc., Philadelphia, PA 19101. Basaljel capsules, Basaljel swallow tablets, Basaljel suspension, Basaljel suspension, extra strength.

2. *Classification of ingredients.*

a. The active ingredient in hypophosphatemia drug products is aluminum phosphate gel.

b. The active ingredient in hyperphosphatemia drug products is aluminum carbonate gel.

B. *Referenced OTC Volumes.*

The "OTC Volumes" cited throughout this document include 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). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on display after January 8, 1981, in the Dockets Management Branch, (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

C. *Definition of Terms.*

For the purpose of this document, the Panel agreed on the following definitions:

1. *Encephalopathy.* A toxic degeneration of the brain.

2. Hypophosphatemia. A condition in which an abnormally low plasma level of phosphate occurs in the blood.

3. *Hyperphosphatemia.* A condition in which an abnormally high plasma level of phosphate occurs in the blood.

D. *Category II Conditions for Hypophosphatemia Drug Products.*

The following are Category II conditions under which drug products used in the treatment of hypophosphatemia are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredient—aluminum phosphate gel.* The Panel concludes that aluminum phosphate gel is not considered safe for OTC use for the treatment of hypophosphatemia but is safe and effective in the treatment of hypophosphatemia under the supervision of a physician.

a. *Safety.* Aluminum phosphate gel was previously reviewed by the Advisory Review Panel on OTC Antacid Drug Products for its antacid action; and, as an aluminum salt, it was found to be "* * * safe in amounts usually taken orally in antacid products." (See the **Federal Register** of April 5, 1973 (38 FR 8714)). That Panel concluded that aluminum phosphate gel is safe in a daily dose of 8 grams (g) per day, and FDA concurred with that Panel in the Antacid Final Monograph published in the **Federal Register** of June 4, 1974 (39 FR 19862).

Since the publication of the Antacid Final Monograph, information has been reported which strongly suggests that ingested aluminum is absorbed, resulting in increased blood and brain levels of aluminum (Ref. *1*). Experimental evidence suggests that hyperparathyroidism, (i.e., excessive secretion of parathyroid hormone leading to the decalification of bones) such as found in patients with severe kidney disease, among other conditions, may further increase the ability of the body to absorb aluminum and cause increased deposition in the brain which may lead to encephalopathy.

The primary use of aluminum phosphate gel is in the treatment of hyperparathyroid states which lead to serum phosphate depletion (hypophosphatemia). These conditions require supervision by a physician and are not amenable to self-diagnosis or self-treatment. The Panel, therefore, concludes that due to the potential for aluminum encephalopathy, aluminum phosphate gel is not safe for OTC use in the treatment of hypophosphatemia.

b. *Effectiveness.* Aluminum phosphate gel is frequently used as part of the standard regimen following kidney transplants. These patients usually develop secondary hyperparathyroidism which, along with other factors, causes phosphate depletion in the blood (hypophosphatemia) (Refs. *2* and *3*). Antacids are generally used in kidney transplant patients to counteract the potential gastric effects of the required steriod therapy. Most of the available nonabsorbable antacids combine with existing phosphate in the intestinal tract and thereby prevent its absorption, causing further phosphate depletion and worsening of the hypophosphatemia.

The phosphate depletion which occurs following many kidney transplants leads to the more serious complication of hypercalcemia (i.e., decreased excretion of calcium). In fact, hypophosphatemia is believed to be a significant cause of hypercalcemia in patients with hyperparathyroidism (Ref. *3*). Aluminum phosphate gel has been used extensively (Refs. *2, 3,* and *4*) as a source of phosphate supplementation and for its mild antacid action. Further, it can often effectively improve hypercalcemia. In one study, 9 of 17 patients developed hypercalcemia following kidney transplant; 8 of these responded favorably to the administration of aluminum phosphate gel (Ref. *4*).

The Panel concludes that aluminum phosphate gel is effective in the treatment of hypophosphatemia but its safe use requires medical supervision.

c. *Evaluation.* The Panel recognizes that aluminum phosphate gel is used effectively to treat hypophosphatemia. Because many patients with hypophosphatemia have a kidney problem, which may predispose them to aluminum toxicity, and as such conditions are not amenable to self-diagnosis or self-treatment, the Panel recommends that aluminum phosphate gel for the treatment of hypophosphatemia be available only under the supervision of a physician.

The Panel is aware that for many years aluminum phosphate gel has been marketed as an OTC antacid. In establishing the OTC antacid monograph (21 CFR Part 331) a requirement was included that in order for any product to bear an antacid claim, it must meet certain in vitro tests contained in the regulations (21 CFR 331.10). Information submitted to the Panel (Ref. *2*) indicates that aluminum phosphate gel does not fully meet the numerical criteria (pH and time) of the acid neutralization test and, therefore, is not acceptable as an antacid. If FDA confirms this, the Panel believes that the antacid monograph (21 CFR 331) would have to be amended to delete aluminum phosphate as a Category I active ingredient.

No other information was submitted, and the Panel is not aware of any other OTC indication for this ingredient. Promulgation of the proposed regulation in § 310.541 will result in aluminum phosphate gel being eliminated from the OTC drug market for use in the treatment of hypophosphatemia 6 months after the date of publication of the final monograph in the **Federal Register.** However, the Panel recommends that aluminum phosphate gel be available on prescription for the treatment of phosphate depletion conditions under the supervision of a physician. The Panel strongly recommends that a warning statement regarding its potential for aluminum toxicity in kidney disease be included in the prescription labeling.

2. *Category II labeling.* The Panel concludes that the following labeling claims will result in the misbranding of hypophosphatemia drug products for OTC use: phrases which represent or imply that the product is useful in the treatment, control, or management of hypophosphatemia, or in the reduction of fecal excretion of phosphates.

References

(1) Mayor, G. H., J. A. Keiser, and P. K. Ku, "Aluminum Absorption and Distribution: Effect of Parathyroid Hormone," *Science,* 197:1187–1189, 1977.

(2) OTC Volume 170043.

(3) Schwartz, G. H., et al., "Hypercalcemia After Renal Transplant," *American Journal of Medicine,* 49:42–51, 1970.

(4) Alfrey, A. C., et al., "Resolution of Hyperparathyroidism, Renal Osteodystrophy and Metastatic Calcification After Renal Homotransplantation," *New England Journal of Medicine,* 279:1349–1356, 1968.

E. *Category II Conditions for Hyperphosphatemia Drug Products.*

The following are Category II conditions under which drug products used in the treatment of hyperphosphatemia are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredient—aluminum carbonate gel.* The Panel concludes that aluminum carbonate gel is not considered safe for OTC use for the treatment of hyperphosphatemia but is safe and effective as an adjunct to dietary control in the treatment of hyperphosphatemia under the supervision of a physician.

a. *Safety.* The Advisory Review Panel on OTC Antacid Drug Products found aluminum salts to be "* * * safe in amounts usually taken in antacid

products" (38 FR 8717), but no dosage was established specifically for aluminum carbonate gel. The Advisory Review Panel on OTC Miscellaneous Internal Drug Products considers aluminum carbonate gel to be safe at a dose up to the equivalent of 12 g of aluminum hydroxide daily in divided doses (after meals and at bedtime) (Ref. *1*) when used under the direction of a physician for the treatment of hyperphosphatemia.

Use of aluminum carbonate gel may cause temporary constipation; and excessive or uncontrolled use may result in hypophosphatemia with symptoms of weakness, dizziness, and anorexia (Ref. *2*).

Since the June 4, 1974 publication of the Antacid Final Monograph in the **Federal Register**, information has been reported (Ref. *3*) which strongly suggests that ingested aluminum is absorbed, resulting in increased blood and brain levels of aluminum. Experimental evidence suggests that hyperparathyroidism, such as found in patients with severe kidney disease, among other conditions, may further increase the ability of the body to absorb aluminum and cause increased deposition in the brain which may lead to encephalopathy. OTC labeling for this product, when used as an antacid, should contain an appropriate warning which should read as follows: "If you have kidney disease, do not use this product except under the supervision of a physician."

In addition to its antacid action, aluminum carbonate gel is also used in the treatment of hyperphosphatemia, which is not amenable to self-diagnosis or self-treatment. The Panel, therefore, concludes that due to the potential for aluminum encephalopathy, aluminum carbonate gel is not safe for OTC use in the treatment of hyperphosphatemia.

b. *Effectiveness.* Aluminum carbonate, when taken orally, ionizes and combines with phosphate present from normal ingestion to form relatively insoluble aluminum phosphate complexes, thereby reducing the amount of phosphate absorbed into te bloodstream and excreted in the urine (Refs. *4* and *5*). Such a reduction may be necessary in the treatment of conditions such as uremic osteodystrophy, hypoparathyroidism, and phosphate kidney stone formation. These conditions are not amenable to self-diagnosis or self-treatment. Treatment of elevated serum phosphate or reduction of urinary phosphate excretion requires the supervision of a physician. The Panel concludes that aluminum carbonate gel is effective in the treatment of hyperphosphatemia but recommends that the conditions for such use be restricted to professional labeling.

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products, emphasizes that the availability of aluminum carbonate gel need not be restricted to prescription-only status as long as the consumer labeling of products containing aluminum carbonate gel makes no claims regarding the safety and effectiveness of its use in the treatment of hyperphosphatemia.

c. *Evaluation.* The Panel understands that products containing this ingredient can be properly labeled as an antacid in compliance with the Antacid Monograph (21 CFR 331). Because hyperhosphatemia is not amenable to self-diagnosis or self-treatment, the Panel recommends that any claims for the use of aluminum carbonate gel for this condition be restricted to professional labeling only. The Panel considers claims such as "For the ["treatment," "control," or "management"] of hyperphosphatemia" to be appropriate for such professional labeling.

2. *Category II labeling.* The Panel concludes that the following labeling claims will result in the misbranding of hyperphosphatemia drug products for OTC use: phrases which represent or imply that the product is useful in the treatment, control, or management of hyperhosphatemia, 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.

References

(1) OTC Volume 170005.

(2) Lietman, M. A., et al., "Erythrocyte Adenosine Triphosphate Depletion During Hypophosphatemia in a Uremic Subject," *New England Journal of Medicine*, 280:240–244, 1969.

(3) Mayor, G. H., J. A. Kaiser, and P. K. Ku, "Aluminum Absorption and Distribution: Effect of Parathyroid Hormone," *Science*, 197:1187–1189, 1977.

(4) Shore, E., and A. C. Carter, "Aluminum Gels in the Management of Renal Phosphatic Calculi," *Journal of the American Medical Association*, 144:1549–1556, 1950.

(5) Rubini, M. E., et al., "Renal Osteodystrophy," *Archives of Internal Medicine*, 124:663–639, 1969.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) that 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.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 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 authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new §§ 310.541 and 310.542, to read as follows:

§ 310.541 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 OTC drug product containing ingredients offered for use in the treatment of hypophosphatemia cannot be considered generally recognized as safe and effective.

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

(c) A completed and signed "Notice of Claimed Investigational Exemption For a New Drug" (Form FD–1571), 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 introduced in interstate commerce that is not in compliance with this section is subject to regulatory action.

§ 310.542 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 OTC drug product containing ingredients offered for use in the treatment of hyperphosphatemia cannot be considered generally recognized as safe and effective.

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

(c) A completed and signed "Notice of Claimed Investigational Exemption For a New Drug" (Form FD–1571), 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 introduced in interstate commerce that is not in compliance with this section is subject to regulatory action.

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this Proposal on or before March 9, 1981. Comments should be addressed to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to any comments may also be submitted on or before April 8, 1981. Comments may be seen in the above office between 9 a.m. and 4 p.m. Monday through Friday.

In accordance with Executive Order 12044, as amended by Executive Order 12221, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of this regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: November 26, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80–37893 Filed 12–8–80; 8:45 am]

BILLING CODE 4110–03–M