DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 331

[Docket No. 80N-0395]

RIN 0905-AA06

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any drug product labeled for over-the-counter (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) is not generally recognized as safe and effective and is misbranded. This final rule also amends the monograph for OTC antacid drug products to revise the ingredient listing for aluminum phosphate to state that this ingredient is for use only in combination with other OTC antacid ingredients, to include professional labeling for a hyperphosphatemia claim for products containing aluminum carbonate, and to include professional labeling for additional warnings for aluminum-containing antacid drug products. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final rule, and all new data and information on hypophosphatemia and hyperphosphatemia drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATES: The effective date for §§ 310.541 and 310.542 is November 12, 1990, and the effective date for §§ 331.11 and 331.80 is May 13, 1991.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

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 (1) would classify OTC hypophosphatemia and hyperphosphatemia drug products as not generally recognized as safe and effective and as being misbranded and (2) 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 (Miscellaneous Internal Panel), 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 display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final rule, for OTC hypophosphatemia and hyperphosphatemia drug products was published in the **Federal Register** of January 15, 1985 (50 FR 2160). Interested persons were invited to file by May 15, 1985, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986. Final agency action occurs with the publication of this final rule on OTC hypophosphatemia and hyperphosphatemia drug products.

As discussed in the advance notice of proposed rulemaking for OTC hypophosphatemia and hyperphosphatemia drug products (45 FR 81154), the agency stated that conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of a final order in the **Federal Register.** However, in the proposed rule (50 FR 2160), the agency advised that the effective date of the final rule would be 12 months after the date of publication in the **Federal Register.** The agency's intent in the proposed rule was that the 12-month effective date was applicable to the "monograph" conditions in the document. In this final rule, OTC hypophosphatemia and hyperphosphatemia drug products are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In this same document, the monograph for OTC antacid drug products is being amended to include (1) a revision in the aluminum phosphate ingredient listing, (2) a professional labeling claim, and (3) professional labeling warnings (monograph conditions). Because of the nonmonograph and monograph conditions included in this document, the agency is establishing dual effective dates of 6 and 12 months, respectively. The nonmonograph conditions (§§ 310.541 and 310.542) will be effective 6 months after the date of publication of the final rule in the **Federal Register.** This 6-month effective date is consistent with other final rules promulgated by the agency establishing that certain drugs are not generally recognized as safe and effective for OTC use (see, e.g., 21 CFR 310.519 and 310.529). On or after November 12, 1990, no OTC drug products for hypophosphatemia or hyperphosphatemia may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the effective date of this final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

The amendment to the monograph for OTC antacid drug products in this final rule (§§ 331.11 and 331.80) will be effective 12 months after the date of publication in the **Federal Register.** Therefore, on or after May 13, 1991, no OTC drug products that are subject to the monograph for OTC antacid drug products and that contain a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with

the monograph at the earliest possible date.

The agency recognizes that the Panel considered the ingredients aluminum phosphate gel and aluminum carbonate gel for use in hypophosphatemia and hyperphosphatemia, respectively. In the final monograph for OTC antacid drug products (21 CFR 331.11), these ingredients are named aluminum phosphate and aluminum carbonate. In accordance with the USAN and USP Dictionary of Drug Names (Ref. 1) and The United States Pharmacopeia XXII/ National Formulary XVII (U.S.P. XXII/ N.F. XVII) (Ref. 2), these ingredients are currently designated as aluminum phosphate gel and basic aluminum carbonate gel. Therefore, in responding to comments throughout this document, these ingredients will be referred to by their current compendial names.

In response to the proposed rule on OTC hypophosphatemia and hyperphosphatemia drug products, one drug manufacturer, one drug manufacturers' association, one professional association, and eight individuals submitted comments. No requests for oral hearing before the Commissioner were received. Copies of the comments received are on public display in the Dockets Management Branch (address above). Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final rule, the agency has considered all comments and changes in the procedural regulations.

References

(1) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 32–33, 1989

(2) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 50–54, 1989.

I. The Agency's Conclusions on the Comments

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464), and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. One comment stated that FDA cannot legally prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn and thus prohibit alternative OTC labeling terminology to described such indications which is truthful, not misleading, intelligible to the consumer. The comment noted that its views were presented to FDA in connection with the September 29, 1982 hearing on the "Exclusivity Policy."

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear a boxed are nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). However, the above provisions are not applicable to the final rule for OTC hypophosphatemia and hyperphosphatemia drug products because there are no drug products that are generally recognized as safe and effective for OTC use for these indications.

3. Two comments objected to the characterization of the statement in the professional labeling in proposed § 331.31(a)(3) as "Warning(s)" and requested that they be changed to "Cautions." The comments contended that the proposed statements are more accurately characterized as "caution(s)" because, rather than precluding use, they provide information about potential problems. If the agency were to insist on the need for a warning in the professional labeling of OTC antacid drug products containing aluminum, one comment recommended that the "warning" be changed to a "caution" because its primary purpose is to alert the physician to a potential problem.

The "warning" statements referred to by the comments in proposed § 331.31(a)(3) are not intended for the OTC labeling of aluminum-containing antacids directed to the lay consumer, but are intended for "professional labeling" to be distributed to physicians. However, the agency considers its general policy concerning the use of the signal words "caution" or "warning" in OTC drug labeling to be equally appropriate for professional labeling of OTC drugs.

Section 502(f)(2) of the act (21 U.S.C. 352(f)(2)) states, in part, that unless exempted by regulation, the labeling for a drug must bear " * * * such adequate warnings * * * as are necessary for the protection of users." Section 330.10(a)(4)(v) of the OTC drug regulations (21 CFR 330.10(a)(4)(v)) provides that labeling of OTC drug products should include " * * * warnings against unsafe use, side effects, and adverse reactions * * *."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information.

For OTC drug labeling, FDA has concluded that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling. In order to maintain uniformity in labeling, the agency is using this same approach for the professional labeling included in OTC drug monographs.

4. One comment considered the use of the term "magaldrate" in the labeling of

OTC antacids as "mislabeling." The comment stated that one pharmacist had incorrectly recommended a magaldrate-containing antacid as a non-aluminum-containing antacid, while a second pharmacist recognized the presence of aluminum in the antacid product. The comment questioned "why the manufacturer is allowed to use a 'made up' name to conceal the presence" of aluminum in a product.

Under section 502(e)(1) of the act (21 U.S.C. 352(e)(1)), a drug is considered misbranded if its label does not bear the established name of the drug, if one exists. The established name of a drug is defined in section 502(e)(3) of the act (21 U.S.C. 352(e)(3)), as follows: " * * * (A) the applicable official name designated pursuant to section 508, or (B) if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient * * *." The agency has further clarified this definition in 21 CFR 299.4(b) as follows: " * * * (1) an official name designated pursuant to section 508 of the act; (2) if no such official name has been designated for the drug and the drug is an article recognized in an official compendium, then the official title thereof in such compendium; and (3) if neither paragraphs (b) (1) or (2) of this section applies, then the common or usual name of the drug."

The agency recognizes the skill and experience of the United States Adopted Names Council (USAN) in deriving names for drugs. (See 21 CFR 299.4(c).) USAN chose the name "magaldrate" to represent this drug based on its guiding principles for coining adopted names for drugs (Ref. 1). These principles include, among others, suitability, simplicity, and established usage. The name "magaldrate" has appeared in an official compendium in the United States for 20 years. "Magaldrate" was included in the National Formulary XIII in 1970 (Ref. 2) and later in the United States Pharmacopeia XIX in 1975 (Ref. 3). These official compendia have been published in one volume, the United States Pharmacopeia/National Formulary (U.S.P/N.F.), since 1980, and the name "magaldrate" has been used in each edition (Refs. 4, 5, and 6).

The monograph for OTC antacid drug products has listed "magaldrate" as an active ingredient since its publication in the Federal Register of June 4, 1974 (39 FR 19862), and "magaldrate" is currently listed as a specific active ingredient in § 331.11(g)(2) of the OTC antacid monograph (21 CFR 331.11(g)(2)). The agency regrets that the individual who submitted the comment was mislead by one pharmacist and is confident that this represents an isolated incident. The vast majority of pharmacists in the United States are familiar with the chemical composition of specific ingredients in OTC drug products. Also, reference books are readily available to answer questions about a drug ingredient.

References

(1) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 640–645, 1989.
(2) "National Formulary XIII," American Pharmaceutical Association, Washington, pp. 396–397, 1970.
(3) "The United States Pharmacopeia—XIX," United States Pharmacopeial Convention, Rockville, MD, p. 290, 1975.
(4) "The United States Pharmacopeia XX—The National Formulary XV," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 456–457, 1980.
(5) "The United States Pharmacopeia XXI—The National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 607–608, 1985.
(6) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 785–786, 1989.

5. One comment requested that the professional labeling indication in proposed § 331.31(a)(4), which states "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," be extended to products containing aluminum hydroxide in addition to products containing aluminum carbonate (50 FR 2160 at 2166). Pointing out that reactive aluminum hydroxide gels usually contain carbonate, the comment stated that aluminum carbonate, as such, does not exist, and that conventional pharmaceutical aluminum carbonate is, in fact, a mixture of aluminum hydroxide and bicarbonate and/or carbonate species that form the hydroxy carbonate species called "basic aluminum carbonates." Noting that the British Pharmacopeia defines aluminum hydroxide gel as containing * * * varying quantities of basic aluminum carbonate and that the U.S.P. states that aluminum hydroxide gel * * * may contain varying quantities of basic aluminum carbonate and bicarbonate (Ref. 1), the comment stated that aluminum hydroxide U.S.P. and basic aluminum carbonate are essentially identical and should be recognized as such with respect to the professional labeling for phosphate binding. The submission also included an in vitro study of the relative phosphate binding capacities of commercially-available aluminum hydroxide gels and basic aluminum carbonate gels and published information on the in vivo phosphate binding ability of a range of aluminum salts (Ref. 1).

The Miscellaneous Internal Panel reviewed ingredients used in the OTC treatment of hyperphosphatemia in its report published in the Federal Register of December 9, 1980 (45 FR 81154). Only one ingredient, basic aluminum carbonate gel, was submitted for the Panel's review, and the Panel did not identify any other ingredients through its review of the literature. The Panel concluded that, although hyperphosphatemia was not amenable to OTC treatment, basic aluminum carbonate gel is safe and effective in the treatment of hyperphosphatemia under the supervision of a physician (45 FR 81154 at 81156 and 81157). Although the Panel concluded that basic aluminum carbonate gel was safe " * * * at a dose up to the equivalent of 12 g of aluminum hydroxide daily * * *," the Panel did not suggest that the professional labeling indication for hyperphosphatemia be extended to aluminum hydroxide.

The current edition of the United States Pharmacopeia/National Formulary (U.S.P. XXII/N.F. XVII), effective on January 1, 1990, defines basic aluminum carbonate gel in terms of its aluminum hydroxide equivalent content and defines aluminum hydroxide gel as containing amorphous aluminum hydroxide in which there is a partial substitution of carbonate for hydroxide (Ref. 2). The agency acknowledges that these two drugs are chemically similar. However, the comment did not submit sufficient data for the agency to determine if aluminum hydroxide is generally recognized as safe and effective for the professional labeling indication of hyperphosphatemia.

The agency believes that the most important consideration in selecting an ingredient to be used for the treatment of hyperphosphatemia is the phosphate binding capacity of the ingredient. As discussed by the Panel in its report (45 FR 81154 at 81157), some aluminum-containing compounds, when taken orally, combine with phosphate present from normal ingestion to form relatively insoluble aluminum phosphate complexes. These phosphate binding aluminum-containing compounds reduce

the amount of phosphate absorbed into the bloodstream and excreted in the urine. The in vivo and in vitro data ...mitted by the comment, though ...ited, indicate that aluminum ...droxide possesses the property of phosphate binding. In the submitted clinical study, 19 patients who were maintained by hemodialysis received 2 formulations of aluminum phosphate binders, aluminum hydroxide suspension and dried basic aluminum carbonate gel in the form of capsules (Ref. 3). In this 30-week study, patients received no treatment (i.e., no drug or placebo) for weeks 1 to 4, either aluminum hydroxide or basic aluminum carbonate gel for weeks 5 to 13, placebo for weeks 14 to 18, and either basic aluminum carbonate gel or aluminum hydroxide for weeks 19 to 27 (i.e., patients were crossed over to the phosphate binder that was not given during weeks 5 to 13), and no treatment for weeks 28 to 30. Of the 19 patients, 5 did not complete the last phase of the study (weeks 28 to 30), and 1 patient failed to complete half of the study. The results showed that aluminum hydroxide was statistically the same as basic aluminum carbonate gel in lowering plasma phosphate at one dose, equivalent to 170 milligrams of aluminum. However, the in vitro data, although also limited, show that basic ...minum carbonate gel has ...sistently higher phosphate binding ...pacity than aluminum hydroxide when compared per milligram of aluminum hydroxide. The agency does not consider these data as sufficient to establish general recognition of effectiveness to support a professional labeling indication for aluminum hydroxide for this use. If, in the future, additional data are submitted in support of the use aluminum hydroxide for the professional labeling indication for the treatment of hyperphosphatemia, the agency will consider this issue further. Interested parties should meet with the agency to ascertain what additional data are needed.

References

(1) Comment No. C00016, Docket No. 80N–0395, Dockets Management Branch.

(2) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 50–52, 1989.

(3) Johnson, W.J., and P.C. O'Brien, "Effectiveness of Intestinal Phosphate Binders in Patients Maintained by Hemodialysis," *Nephron*, 21:123–130, 1978.

6. Two comments objected to the ...rnings proposed for the professional ...eling of OTC aluminum-containing antacid drug products and requested that neither warning be included in the antacid monograph. The warnings proposed for inclusion in § 331.31(a)(3) of the antacid monograph were as follows:

(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.

Referring to the warning in paragraph (i) above, the comments stated that the warning relates to individuals with impaired renal function and those receiving kidney dialysis treatment who are maintained under the close supervision of a specialist in renal disease. Because of this supervision, one comment argued that it would be "highly improbable" that such patients would be exposed to medications which might exacerbate their condition. The comment added that inclusion of an 80-word warning in the professional labeling of aluminum-containing antacid drug products is irrelevant, unnecessary, and excessive. The other comment stated that this warning has no bearing on the promotion of the product to the health-care professional for general antacid uses.

Regarding the proposed warning in paragraph (ii) above, the comments stated that this warning is relevant only in situations where dietary phosphate is not adequate in normophosphatemic patients. The comment stated that dietary phosphate deficiency in man essentially does not occur given that "phosphate is available in all foods consisting of plant and animal cells as well as all dairy products." One of the comments noted that the possibility of the occurrence of disturbances in mineral metabolism in patients with normal renal function is highly unlikely even where there is abuse of the aluminum-containing antacids by very prolonged use of high doses. The comment mentioned that a literature search covering 1966 to 1984 produced only 16 such cases (Ref. 1). The comments concluded that the warning is unnecessary and should not be required in the professional labeling of OTC aluminum-containing antacid drug products.

One of the comments also recommended that if the agency concludes that warnings are necessary for the professional labeling of OTC aluminum-containing antacid drug products, the wording should be revised as follows:

For products indicated only for antacid use. Prolonged use of aluminum-containing antacids in patients *with renal disease* may contribute to increased tissue levels of aluminum.

For products indicated for use in hyperphosphatemia. Evidence suggests that elevated tissue aluminum levels have a role in the development of the dialysis encephalopathy syndrome. A number of cases have been associated with elevated aluminum levels in the dialysate water. There is *some* evidence that small amounts of ingested aluminum *may* be absorbed from the gastrointestinal tract and it is *possible* that renal excretion of absorbed aluminum is impaired in renal disease.

In the notice of proposed rulemaking on hypophosphatemia and hyperphosphatemia drug products, published in the **Federal Register** of January 15, 1985 (50 FR 2160), the agency reviewed all the available data on the involvement of aluminum as an etiological factor in various conditions and concluded that it would be appropriate to provide additional information in the professionsl labeling section of the antacid monograph for aluminum-containing antacid drug products. Accordingly, the agency proposed that the two warnings in paragraphs (i) and (ii) above be added to § 331.31(a) of the antacid monograph.

The comments submitted no new data establishing that these warnings are not needed. The agency does not agree with the comments that the warnings proposed for the professional labeling of aluminum-containing antacid drug products are unnecessary and irrelevant. The agency acknowledges that specialists may have knowledge of information concerning the safe and effective use of a product. However, the agency does not agree that such knowledge makes the inclusion of this information in the labeling unnecessary. The agency believes that these warnings in the professional labeling of OTC drug products provide physicians, including physicians who are not specialists in the treatment of renal disease, with the kind of information that is presented in the package inserts of prescription drug products. In addition, the agency

believes that the comments recognize the validity of the concerns raised by this warning information, which is intended to be informative to physicians who are treating patients with any of the aluminum-containing antacid drug products. The agency finds that the alternative warnings submitted by one comment are inadequate because they do not include any reference to the effect of aluminum on normophosphatemic patients and because the suggested revisions weaken the intent of the statement in (i) by changing key words, e.g., "may be absorbed" instead of "are absorbed." For the above reasons, the agency disagrees with the comments and is amending proposed § 331.31(a) to add the information proposed in § 331.31(a)(3)(ii). In addition, another comment submitted a number of references from the scientific literature that have led the agency to expand and revise the information contained in proposed § 331.31(a)(3)(i). (See discussion of the revised warning in comment 7 below.)

Reference

(1) Comment No. C00018, Docket No. 80N–0395, Dockets Management Branch.

7. One comment contended that the professional labeling warnings proposed in § 331.31(a)(3) for aluminum-containing antacids are inadequate because they do not discuss the direct toxicity of aluminum to bone tissue. Stating that the proposed professional warnings fail to discuss the large body of evidence which indicates that orally administered aluminum can accumulate in bone tissue and be harmful to the growth of bone, the comment included references from the scientific literature in support of this position (Ref. 1) and requested that the warnings be expanded to describe the toxic effects of aluminum to bone tissue.

The agency has reviewed all the available data on the relationship between aluminum-containing antacids and bone toxicity and concurs with the comment that the body of evidence presented supports expansion of the professional labeling warnings for aluminum-containing antacids in § 331.31(a)(3) of the antacid monograph. When the agency last evaluated this issue prior to publishing the proposed antacid monograph amendment to add professional labeling warnings for OTC aluminum-containing antacids (50 FR 2160 at 2165), the relationship of aluminum to bone disease was not established. There was even some doubt about the relationship of aluminum to encephalopathy (a toxic degeneration of the brain) at that time. Subsequently it has become clear that both encephalopathy and osteomalacia (softening of the bones) can be caused by long-term use of aluminum in renal dialysis patients. Therefore, in this amendment to the antacid monograph, the agency has reconsidered the proposed warnings and included information about the direct toxic effects of aluminum on bone mineralization in these patients.

Long-term use of aluminum-containing antacids contributes to dialysis osteomalacia (Refs. 2 through 10). Although only a small fraction of ingested aluminum is absorbed, that amount must be removed by functioning kidneys, bile secretion, or dialysis, or else it will accumulate. Dialysis does not remove aluminum well because the aluminum is bound to albumin and transferrin, which do not cross dialysis membranes (Ref. 11). When aluminum accumulates, it tends to be deposited in bone (Refs. 12 through 15) at the mineralization front, blocking mineralization of newly formed bone, increasing calcium loss from bone into serum, and producing osteomalacia (Refs. 16 through 20). The agency recognizes that renal osteodystrophy (defective bone formation) is very complicated and results not only from aluminum excess but also from hyperparathyroidism, acidosis, and abnormal metabolism of vitamin D, calcium, and phosphorus. These factors have little to do with aluminum excess (Refs. 21 and 22), and removal of aluminum will not correct any of these other factors. Nevertheless, the agency believes that the role of aluminum is significant and that attempts should be made to reduce its contribution to renal osteodystrophy.

In addition, the agency points out that the dialysis encephalopathy that was due to aluminum (as discussed above) resulted from two factors: (1) Oral aluminum-containing antacids taken as phosphate binders and (2) aluminum-containing dialysis fluids. Removal of aluminum from dialysis fluids has reduced the encephalopathy that was seen in association with dialysis.

For the above reasons, the agency is expanding and revising the warning in proposed § 331.31(a)(3)(i) to read as follows:

> Prolonged use of aluminum-containing antacids in patients with renal failure may result in or worsen dialysis osteomalacia. Elevated tissue aluminum levels contribute to the development of the dialysis encephalopathy and osteomalacia syndromes. Small amounts of aluminum are absorbed from the gastrointestinal tract and renal excretion of aluminum is impaired in renal failure. Aluminum is not well removed by dialysis because it is bound to albumin and transferrin, which do not cross dialysis membranes. As a result, aluminum is deposited in bone, and dialysis osteomalacia may develop when large amounts of aluminum are ingested orally by patients with impaired renal function.

References

(1) Comment No. C00017, Docket No. 80N–0395, Dockets Management Branch.

(2) "Toxicologic Consequences of Oral Aluminum," *Nutrition Reviews*, 45:72–74, 1987.

(3) Milliner, D.S., et al., "Plasma Aluminum Levels in Pediatric Dialysis Patients: Comparison of Hemodialysis and Continuous Peritoneal Dialysis," *Mayo Clinic Proceedings*, 62:269–274, 1987.

(4) Hodsman, A.B., et al., "Do Serum Aluminum Levels Reflect Underlying Skeletal Aluminum Accumulation and Bone Histology Before or After Chelation by Deferoxamine?" *Journal of Laboratory and Clinical Medicine*, 16:674–681, 1985.

(5) Winney, R.J., J.F. Cowie, and J.S. Robson, "What is the Value of Plasma/Serum Aluminum in Patients With Chronic Renal Failure?" *Clinical Nephrology*, 24:S2–S8, 1985.

(6) Andreoli, S.P., J.A. Smith, and J.M. Bergstein, "Aluminum Bone Disease in Children: Radiographic Features from Diagnosis to Resolution," *Radiology*, 156:663–667, 1985.

(7) Recker, R.R., et al., "Evidence for Aluminum Absorption from the Gastrointestinal Tract and Bone Deposition by Aluminum Carbonate Ingestion with Normal Renal Function," *Journal of Laboratory and Clinical Medicine*, 90:810–815, 1977.

(8) Kaehny, W.D., A.P. Hegg, and A.C. Alfrey, "Gastrointestinal Absorption of Aluminum from Aluminum-Containing Antacids," *New England Journal of Medicine*, 296:1389–1390, 1977.

(9) McCarthy, J.T., et al., "Interpretation of Serum Aluminum Values in Dialysis Patients," *American Journal of Clinical Pathology*, 86:629–636, 1986.

(10) Monteagudo, F.S.E., M.J.D. Cassidy, and P.I. Folb, "Recent Developments in Aluminum Toxicology," *Medical Toxicology*, 4:1–16, 1989.

(11) Alfrey, A.C., "Aluminum Metabolism," *Kidney International*, 29 (Supplement 18): S–8–S–11, 1986.

(12) Kriegshauser, J.S., et al., "Aluminum Toxicity in Patients Undergoing Dialysis: Radiographic Findings and Prediction of Bone Biopsy Results," *Radiology*, 164:399–403, 1987.

(13) Ihle, B.U., G.J. Becker, and P.S. Kincaid-Smith, "Clinical and Biochemical Features of Aluminum-Related Bone Disease," *Kidney International*, 29 (Supplement 18): S–80–S–86, 1986.

(14) Andress, D.L., et al., "Early Deposition of Aluminum in Bone in Diabetic Patients on Hemodialysis," *New England Journal of Medicine*, 316:292–296, 1987.

(15) Chazan, J.A., "Aluminum in Bone in Diabetic Patients," *New England Journal of Medicine*, 317:366–367, 1987.

(16) O'Connor, M., et al., "Aluminum-Related Bone Disease: Correlation Between Symptoms, Osteoid Volume, and Aluminum Staining," *American Journal of Clinical Pathology*, 86:168–174, 1986.
(17) Andress, D.L., et al., "Osteomalacia and Aplastic Bone Disease in Aluminum-Related Osteodystrophy," *Journal of Clinical Endocrinology and Metabolism*, 65:11–16, 1987.
(18) Cournot-Witmer, G., et al., "Effect of Aluminum on Bone and Cell Localization," *Kidney International*, 29 (Supplement 18): S–37–S–40, 1986.
(19) Posner, A.S., N.C. Blumenthal, and A.L. Boskey, "Model of Aluminum-Induced Osteomalacia: Inhibition of Apatite Formation and Growth," *Kidney International*, 29 (Supplement 18): S–17–S–19, 1986.
(20) Dustan, C.R., et al., "Clinical Investigations: Effect of Aluminum and Parathyroid Hormone on Osteoblasts and Bone Mineralization in Chronic Renal Failure," *Calcified Tissue International*, 36:133–138, 1984.
(21) Slatopolsky, E., "The Interaction of Parathyroid Hormone and Aluminum in Renal Osteodystrophy," *Kidney International*, 31:842–854, 1987.
(22) Piraino, B.M., et al., "Spontaneous Hypercalcemia in Patients Undergoing Dialysis: Etiologic and Therapeutic Considerations," *American Journal of Medicine*, 80:607–615, 1986.

8. One comment requested that the agency accept the recommendation of the Miscellaneous Internal Panel that a warning be added to the labeling of OTC aluminum-containing antacid drug products to discourage their use, without the supervision of a physician, by patients with kidney disease (45 FR 81154 at 81157). The comment maintained that current medical literature indicates: (1) That children with renal failure are the most susceptible victims of aluminum intoxication from the use of OTC antacids and (2) that some adult patients suffering from aluminum intoxication have also benefited from restriction of aluminum-containing antacids. The comment cited clinical reports to support this position (Ref. 1). In addition, the comment stated that the agency's decision in the tentative final monograph (50 FR 2160 at 2163) against requiring such a warning is inconsistent with the comparable warning currently required in 21 CFR 331.30(c)(4) for magnesium-containing antacids, which states for products containing more than 50 milliequivalents (mEq) of magnesium in the recommended daily dosage: "Do not use this product except under the advice and supervision of a physician if you have kidney disease." The comment argued that the lack of a warning on OTC aluminum-containing antacids against their use by patients with kidney disease denies potential users of important information in their own health care or in the care they provide to a young child with kidney disease. The comment contended that the proposed professional labeling warnings will not be sufficient to get adequate information into the hands of individual users of OTC aluminum-containing antacids because these products are usually sold without a physician's supervision. Therefore, the comment requested that the agency add an appropriate statement to the labeling of OTC aluminum-containing antacids warning against use of these products by patients with kidney disease, without the supervision of a physician.

The Advisory Review Panel on OTC Antacid Drug Products in its report (38 FR 8714 at 8719) recommended that a warning was needed on OTC products to advise patients with kidney disease not to use magnesium-containing antacids that contain more than 50 mEq of magnesium in the recommended daily dose even when such use would not exceed the recommended 2-week limitation period. That Panel did not recommend a similar warning for OTC aluminum-containing antacids. The agency has considered the submitted information and all other available information and concludes that there is no evidence that short term (less than 2 weeks), intermittent use of antacids for OTC indications of heartburn, sour stomach, and/or acid indigestion produces aluminum intoxication in either adults or children. Therefore, on the basis of present safety evidence concerning aluminum-containing antacids, the 2-week limitation on use without a doctor's supervision, the intermittent nature of use (which is primarily by adults), and the warnings in the professional labeling section of the monograph which provide adequate information for health professionals to alert patients who will use these products for long periods of time, the agency concludes that a separate OTC warning is not indicated at this time.

Reference

(1) Comment No. C00017, Docket No. 80N–0395, Dockets Management Branch.

II. Summary of Significant Changes From the Proposed Rule

FDA has considered the comments and other relevant information and concludes that it will adopt the proposed rule (January 15, 1985; 50 FR 2160) with the changes described in FDA's responses to the comments above and with other changes described in the summary below.

1. The ingredient names aluminum carbonate and aluminum phosphate in 21 CFR 331.11(a) (1) and (4), respectively, are being changed to basic aluminum carbonate gel and aluminum phosphate gel, respectively, to be in accord with current names in the USAN and the USP Dictionary of Drug Names and the U.S.P. XXII/N.F. XVII.

2. The professional labeling warning concerning the effects of aluminum-containing antacids on patients with renal failure has been revised and expanded to address the direct toxic effects of aluminum on bone mineralization in these patients. (See comment 7 above.)

3. In the **Federal Register** of November 16, 1988 (53 FR 46190 at 46191), the agency proposed to redesignate the professional labeling section of the antacid monograph from § 331.31 to § 331.80 in accordance with the format of other recently published tentative final and final monographs. In this final rule, the redesignation of § 331.31 to § 331.80 is made final. Additionally, to conform with the format of other recently published tentative final and final monographs, the agency has reversed the order of the indication and warning statements in the professional labeling section. Therefore, the indications statement now appears as § 331.80(a)(3) and the warning statements now appear as § 331.80(a)(4) (i) and (ii).

III. The Agency's Final Conclusions on OTC Hypophosphatemia and Hyperphosphatemia Drug Products

The agency has determined that no OTC drug product has been found to be generally recognized as safe and effective and not misbranded for use in the treatment of hypophosphatemia or hyperphosphatemia. Therefore, all such drug products, including those containing the ingredients aluminum phosphate gel and basic aluminum carbonate gel, which were reviewed by the Panel, are considered nonmonograph and misbranded under section 502 of the act (21 U.S.C. 352) and are new drugs under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) is required for marketing. As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in a citizen petition to establish a monograph for OTC drug products for the treatment of hypophosphatemia or hyperphosphatemia. (See 21 CFR 10.30.)

Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

Although the agency has determined that OTC use of drug products for hypophosphatemia and hyperphosphatemia is not appropriate because such conditions are not amenable to self-diagnosis or self-treatment and treatment of these conditions should be restricted to the supervision of a physician, the agency acknowledges that cetain OTC antacid drug products are used to treat these conditions. Accordingly, the agency is amending the monograph for OTC antacid drug products to include professional labeling for the use of basic aluminum carbonate gel-containing antacid drug products in the treatment of hyperphosphatemia and professional labeling warnings addressing the effects of long-term use of aluminum-containing antacids for professional indications. This final rule also amends the ingredient listing for aluminum phosphate gel to state that this ingredient is for use only in combination with other OTC antacid ingredients.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 2160 at 2166). The agency has examined the economic consequences of this final rule 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 final rule for OTC hypophosphatemia and hyperphosphatemia drug products, is a major rule.

The economic assessment 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 hypophosphatemia and hyperphosphatemia drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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.

List of Subjects in 21 CFR

Part 310: Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Part 331: Antacid drug products, Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended as follows:

PART 310—NEW DRUGS

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Sections 310.541 and 310.542 are added to subpart E 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 (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use in the treatment of hypophosphatemia is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in Part 312 of his chapter.

(d) After November 12, 1990, any such OTC 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 in 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 (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) 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 must comply with the requirements and procedures governing use of investigational new drugs set forth in part 312 of this chapter.

(d) After November 12, 1990, any such OTC 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

3. The authority citation for 21 CFR part 331 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

4. Section 331.11 is amended by revising paragraphs (a) (1) and (4) to read as follows:

§ 331.11 Listing of specific active ingredients.

(a) * * *

(1) Basic aluminum carbonate gel.

* * * * *

(4) Aluminum phosphate gel 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.

* * * * *

5. Section 331.31 is redesignated as § 331.80 and new paragraphs (a) (3) and (4) are added to read as follows:

§ 331.80 Professional labeling.

(a) * * *

(3) *For products containing basic aluminum carbonate gel 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."

(4) *For products containing aluminum identified in § 331.11(a)—Warnings.* (i) Prolonged use of aluminum-containing antacids in patients with renal failure may result in or worsen dialysis osteomalacia. Elevated tissue aluminum levels contribute to the development of the dialysis encephalopathy and osteomalacia syndromes. Small amounts of aluminum are absorbed from the gastrointestinal tract and renal excretion of aluminum is impaired in renal failure. Aluminum is not well removed by dialysis because it is bound to albumin and transferrin, which do not cross dialysis membranes. As a result, aluminum is deposited in bone, and dialysis osteomalacia may develop when large amounts of aluminum are ingested orally by patients with impaired renal function.

(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.

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Dated: March 27, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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