DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 79N–0379]

RIN 0905–AA06

Exocrine Pancreatic Insufficiency 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 over-the-counter (OTC) exocrine pancreatic insufficiency drug products (drug products used to treat pancreatic enzyme deficiency) are not generally recognized as safe and effective and are misbranded. FDA is issuing this final rule after considering public comments on the agency's notice of proposed rulemaking and all new information on OTC exocrine pancreatic insufficiency drug products that has come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: October 24, 1995.

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

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of December 21, 1979 (44 FR 75666), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC exocrine pancreatic insufficiency drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by April 21, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by May 21, 1980.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were placed on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information. Only five comments were submitted in response to the publication of the advance notice of proposed rulemaking.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC exocrine pancreatic insufficiency drug products was published in the **Federal Register** of November 8, 1985 (50 FR 46594). That proposal constituted FDA's tentative adoption of the Panel's conclusions and recommendations on OTC exocrine pancreatic insufficiency drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report and information available at that time. In that document, the agency accepted the Panel's recommendation that exocrine pancreatic insufficiency drug products be available as OTC drug products and proposed the conditions under which these drug products would be generally recognized as safe and effective and not misbranded. Interested persons were invited to file by January 7, 1986, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs (the Commissioner) regarding the proposal, and by March 10, 1986, to file comments on the agency's economic impact determination. New data could have been submitted until November 10, 1986, and comments on the new data until January 8, 1987.

New information submitted in response to the tentative final monograph caused the agency to reconsider the approach proposed in that document. In vivo and in vitro studies of various commercial pancreatic enzyme preparations had demonstrated variations in lipase activity and release rates among the products. These variations in pancreatic extract drug products occurred both among various dosage forms and among products from different manufacturers of the same dosage form. In addition, problems had been reported with pancreatic extract products manufactured as tablets with enteric coatings and as encapsulated enteric-coated microspheres. As a result of the wide range of enzyme activity in these products, the variety of dosage forms marketed, and the apparent uneven quality of the enteric coatings among pancreatic extract drug products, instances of underdosing and overdosing with pancreatic extract products have occurred. The agency determined that preclearance of each product in order to standardize enzyme bioactivity was necessary to avoid serious safety problems resulting from too little or too much enzyme supplementation. The agency tentatively concluded that an OTC drug monograph would not be sufficient to adequately regulate these drug products. The agency discussed these problems in the **Federal Register** of July 15, 1991 (56 FR 32282 at 32286 and 32287).

In that notice, FDA proposed to classify OTC drug products to treat exocrine pancreatic insufficiency as not generally recognized as safe and effective, as being misbranded, and as 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)). FDA proposed to amend part 310, subpart E by adding new § 310.543 (21 CFR 310.543) for OTC exocrine pancreatic insufficiency drug products. The agency also withdrew its proposed rule (part 357, subpart E) issued on November 8, 1985. Interested persons were invited to file by November 12, 1991, written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner, and to file comments on the agency's economic impact determination by November 12, 1991. Final agency action occurs with the publication of this final rule on OTC exocrine pancreatic insufficiency drug products.

In the **Federal Register** of March 11, 1992 (57 FR 8586), the agency reopened the administrative record and announced that a workshop would be held on April 23, 1992, to discuss testing procedures that will be required as part of new drug applications (NDA's) for all exocrine pancreatic insufficiency drug products. Relevant data and notice of participation were to be submitted by April 10, 1992. The administrative record remained open until July 23, 1992, to receive comments regarding matters raised at the workshop.

In response to the announcement of the workshop, eight notices of participation and three comments were submitted. Copies of the comments, notices received, and information coming to the agency's attention after the workshop are also on public display in the Dockets Management Branch (address above). At the conclusion of the workshop, manufacturers were encouraged to arrange pre-NDA meetings with agency personnel so that NDA submissions could proceed as quickly as possible (Ref. 1).

This final rule amends part 310 to include drug products containing ingredients for the treatment of exocrine pancreatic insufficiency by adding new

§ 310.543 to subpart E. The inclusion of OTC exocrine pancreatic insufficiency drug products in part 310 follows FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, 310.526, 310.532, 310.533, 310.534, and 310.546.) It is the agency's intent that exocrine pancreatic insufficiency drug products be marketed by prescription only. However, if, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC exocrine pancreatic insufficiency drug product, the agency will promulgate an appropriate regulation at that time.

FDA no longer uses 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 rule stage. In place of Category I, the term "monograph conditions" is used; in place of Category II or III, the term "nonmonograph conditions" is used.

In the proposed rule for OTC exocrine pancreatic insufficiency drug products (56 FR 32282 at 32283), the agency advised that the final rule for these drug products would be effective 6 months after the date of its publication in the **Federal Register**. Therefore, on or after October 24, 1995, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application. The agency is unaware of any OTC exocrine pancreatic insufficiency drug products that are the subject of an approved application. Any such drug product in interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

In response to the proposed rule on OTC exocrine pancreatic insufficiency drug products, five drug manufacturers, one foundation, and three individuals submitted comments. Copies of the comments received and any additional information that has come to the agency's attention since publication of the proposed rule are on public display in the Dockets Management Branch (address above).

Reference

(1) Comment No. MM1, Docket No. 79N–0379, Dockets Management Branch.

II. The Agency's Conclusions on the Comments

1. Six comments (including the Cystic Fibrosis Foundation and the American Academy of Pediatrics) agreed with the agency's proposal that exocrine pancreatic insufficiency drug products should not be marketed OTC. Three comments opposed the proposal. Two of those comments stated that increased costs to consumers would include a physician's fee and a higher markup when sold by prescription. The third comment indicated that these products are currently reasonably priced as nonprescription drugs.

The agency appreciates the support of the six agreeing comments and is finalizing its proposal that all exocrine pancreatic insufficiency drug products should be available only by a doctor's prescription. The agency stated in the proposed rule that continuous physician monitoring of patients appears to be one of several important factors in the increased survival rates for exocrine pancreatic insufficiency patients (56 FR 32282 at 32285). Accordingly, such collateral measures necessary to the use of these drug products require that they be available by prescription only, as required by section 503(b)(1)(B) of the act (21 U.S.C. 353(b)(1)(B)). The agency acknowledges the cost concerns raised by the three opposing comments. However, as stated in the proposed rule (56 FR 32282 at 32285), financial considerations are not among the statutory criteria for determining whether a drug product should be restricted to prescription status.

2. Two comments disagreed with the agency's proposal that NDA approval be required for continued marketing of all exocrine pancreatic insufficiency drug products. One comment stated that the proposal is inconsistent with the Panel's and the agency's previous conclusion that these products have been safely used to treat exocrine pancreatic insufficiency for many years (50 FR 46594 at 46597). The comment contended that the July 15, 1991, proposal did not contain any new evidence showing that the initial conclusion was erroneous. The comment stated that the agency's concerns are based on a perceived inability of patients to treat themselves and mentioned that this problem could be remedied by requiring these products to be available by prescription, without the need for an NDA for continued safe and effective use. The comment contended that an NDA requirement would have a devastating effect on patients who require these products for survival, e.g., cystic fibrosis patients. The comment surmised that most manufacturers would withdraw their exocrine pancreatic insufficiency drug products from the market if an NDA were required, primarily because of NDA-associated costs. The comment added that manufacturers would wait until another manufacturer's application was approved so they could submit an abbreviated NDA. A third comment made a number of suggestions for the bioactivity testing requirements, urged that certain products that had been extensively used and studied be granted approval on the basis of published reports and in vitro data, and contended that placebo-controlled safety and effectiveness studies in cystic fibrosis patients are unethical.

The agency disagrees with the first two comments. The agency's position on exocrine pancreatic insufficiency drug products changed between 1985 and 1991. Based on variations in formulations and dosage forms, e.g., encapsulated microsphere dosage forms, in use in 1991, the agency determined that final formulation effectiveness testing and information on the product's formulation, manufacture, and quality control procedures are necessary to ensure that a company has the ability to manufacture a proper, bioactive formulation (56 FR 32282 at 32283). Because there are no approved NDA's for any exocrine pancreatic insufficiency drug products, the agency has no information on the bioactivity of these products. The agency notes that even if all products were available only by prescription, variances in bioactivity of final formulations could pose safety concerns. Additional information (which an NDA would contain) is needed to assure safe and effective use of these products. Bioactivity must be shown to correlate with the stated potency of each proposed product, particularly for newer formulations that include microspheres and high potency levels of the pancreatic enzymes.

The agency is not persuaded by the comment's suggestion that manufacturers would not submit applications for pancreatic enzyme products and would wait until abbreviated NDA's were possible. The agency acknowledges that a number of manufacturers are currently seeking NDA approval for their currently marketed exocrine pancreatic insufficiency drug products.

The agency has received a number of reports of occurrences of stricture of the colon in cystic fibrosis patients who had taken higher potency pancreatic enzymes in delayed release microtablets and microspheres for varying numbers of months prior to corrective surgery

(Refs. 1 through 8). The agency is concerned that there may be a relationship between the use of these formulations and stricture of the colon. The agency needs to evaluate manufacturing information for these formulations, which would be included in an NDA.

The third comment's suggested bioactivity testing requirements, support for approval of certain products, and opposition to placebo-controlled studies are outside the scope of this document. The agency notes, however, that it is widely believed that demonstration of the fat digestive actions of various preparations can be done in ethical human studies. Inquiries relating to these subjects should be directed to the Division of Gastrointestinal and Coagulation Drug Products (HFD–180), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–0479.

References

(1) Cystic Fibrosis Foundation Results of a Survey of 114 Cystic Fibrosis Care Centers in United States, Patient Registry 1992 Annual Data Report, Bethesda, MD, October 1993, in OTC Vol. 17BFR, Docket No. 79N–0379, Dockets Management Branch.

(2) Smyth, R. L. et al., "Strictures of Ascending Colon in Cystic Fibrosis and High-Strength Pancreatic Enzymes," Lancet, 343:85–86, 1994.

(3) Oades, P. J. et al., "Letter to the Editor," Lancet, 343:109, 1994.

(4) Campbell, C. A., J. Forrest, and C. Musgrove, "Letter to the Editor," Lancet, 343:109, 1994.

(5) Briars, G. L. et al., "Letter to the Editor," Lancet, 343:600, 1994.

(6) Mahony, M. J., and M. Corcoran, "Letter to the Editor," Lancet, 343:599–600, 1994.

(7) Knabe, N. et al., "Letter to the Editor," Lancet, 343:1230, 1994.

(8) Taylor, C. J., "Colonic Strictures in Cystic Fibrosis," Lancet, 343:615–616, 1994.

3. As an alternative to the NDA process, one comment recommended that a uniform convention be developed for labeling exocrine pancreatic insufficiency drug products to clearly describe product potency. The comment urged that labels include the expiration date and rate of loss of potency, and indicate that proprietary agents are not generally equivalent.

The agency disagrees with the comment's alternative to the NDA process. Uniform labeling to describe product potency is important; however, that alone will not ensure safety and effectiveness of these products. The comment's labeling suggestions will be considered, based on data considered in applications, as NDA's for these products are approved. These issues are outside of the scope of this rulemaking.

4. One comment urged the agency not to issue a final rule for OTC exocrine pancreatic insufficiency drug products until NDA's for these products have been approved. Alternatively, the comment asked that the agency withdraw its proposal and request that NDA's be submitted for exocrine pancreatic insufficiency drug products. The comment contended that the latter action would be similar to the agency's action in 1978 regarding potassium iodide. The comment stated that either approach would guarantee the availability of these products to patients who are benefitting from them.

The agency disagrees with both of the comment's suggestions. In the **Federal Register** of December 15, 1978 (43 FR 58798), the agency published a notice requesting submission of NDA's for potassium iodide in oral dosage forms for use as a thyroid-blocking agent in a radiation emergency. The Commissioner concluded that potassium iodide was safe and effective under certain specified conditions of use. However, the Commissioner did not conclude that potassium iodide was generally recognized as safe and effective (43 FR 58798 at 58799). Therefore, potassium iodide was regarded as a new drug requiring an approved NDA as a condition of marketing.

Exocrine pancreatic insufficiency drug products are a similar situation. These products are safe and effective under specified conditions of use, but their bioactivity raises both safety and effectiveness concerns that require agency preclearance under NDA's. The agency sees no reason to withdraw its proposal because the final rule resulting from that proposal requires that an NDA be submitted for any exocrine pancreatic insufficiency drug product marketed OTC. Manufacturers have known since 1991 that an approved NDA would be needed for continued marketing of their product(s) on an OTC basis. While this final rule affects availability of these products when marketed OTC, it does not affect products marketed on a prescription basis. The agency intends that exocrine pancreatic insufficiency drug products marketed by prescription also have an approved NDA. All manufacturers of prescription exocrine pancreatic insufficiency drug products will need to have an NDA for their product(s). The agency will address this subject further in a future issue of the **Federal Register**.

III. The Agency's Final Conclusions on OTC Exocrine Pancreatic Insufficiency Drug Products

A number of pancreatic enzyme drug products are currently marketed OTC, and other products are marketed by prescription. Some of the prescription products are encapsulated enteric coated microsphere dosage forms. None of these pancreatic enzyme drug products have approved applications, i.e, none have been precleared for marketing by FDA. Some products are produced by different manufacturers and contain the same active ingredient(s); however, these products have shown significant differences in bioavailability. The agency finds that these differences raise a potential for serious risk to patients using these products.

Based on all available evidence, the agency has determined that the bioavailability of pancreatic enzymes is dependent on the process used to manufacture the drug products. Information on this process is not addressed by an OTC drug monograph. Therefore, the agency has determined that the safe and effective use of these enzymes for treating exocrine pancreatic insufficiency cannot be regulated adequately by an OTC drug monograph. In this final rule, the agency is declaring that all exocrine pancreatic insufficiency drug products (whether currently marketed on an OTC or prescription basis) are new drugs for which approved applications will be required for marketing.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991, and included in § 310.545(a)(9) the ingredient hemicellulase, which had been previously considered under this rulemaking for OTC exocrine pancreatic insufficiency drug products. In order to avoid duplication in listing OTC exocrine pancreatic insufficiency active ingredients in more than one regulation, and for ease in locating these ingredients in the Code of Federal Regulations, the agency is listing all of these ingredients in a single regulation in new § 310.543 entitled "Drug products containing active ingredients offered over-the-counter (OTC) for human use in exocrine pancreatic insufficiency." Accordingly, the ingredient hemicellulase, currently listed in § 310.545(a)(9) is now being listed in § 310.543(d), and § 310.545(a)(9) is being removed and reserved. The ingredients pancreatin and pancrelipase, covered by this final rule, are being listed in § 310.543(e).

IV. Analysis of Impacts

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12291 was discussed in the proposed rule (56 FR 32282 at 32289). Comments received were discussed in part II of this final rule. Executive Order 12291 has been superseded by Executive Order 12866.

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and, so, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This final rule will result in the removal of all drug products containing the ingredients pancreatin and pancrelipase from the OTC marketplace. However, only a limited number of OTC drug products are marketed in this manner and are affected by this final rule. Accordingly, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

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.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 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, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379(e); 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. New § 310.543 is added to subpart E to read as follows:

§ 310.543 Drug products containing active ingredients offered over-the-counter (OTC) for human use in exocrine pancreatic insufficiency.

(a) Hemicellulase, pancreatin, and pancrelipase have been present as ingredients in exocrine pancreatic insufficiency drug products. Pancreatin and pancrelipase are composed of enzymes: amylase, trypsin (protease), and lipase. Significant differences have been shown in the bioavailability of marketed exocrine pancreatic insufficiency drug products produced by different manufacturers. These differences raise a potential for serious risk to patients using these drug products. The bioavailability of pancreatic enzymes is dependent on the process used to manufacture the drug products. Information on this process is not included in an OTC drug monograph. Therefore, the safe and effective use of these enzymes for treating exocrine pancreatic insufficiency cannot be regulated adequately by an OTC drug monograph. Information on the product's formulation, manufacture, quality control procedures, and final formulation effectiveness testing are necessary in an approved application to ensure that a company has the ability to manufacture a proper bioactive formulation. In addition, continuous physician monitoring of patients who take these drug products is a collateral measure necessary to the safe and effective use of these enzymes, causing such products to be available by prescription only.

(b) Any drug product that is labeled, represented, or promoted for OTC use in the treatment of exocrine pancreatic insufficiency 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 exocrine pancreatic insufficiency 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 this chapter.

(d) After May 7, 1991, any such OTC drug product that contains hemicellulase initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(e) After October 24, 1995, any such OTC drug product that contains pancreatin or pancrelipase initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

§ 310.545 [Amended]

3. Section 310.545 *Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses* is amended by removing and reserving paragraph (a)(9), and by revising paragraph (d)(1) to read as follows:

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

(d) * * *

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

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Dated: April 13, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

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