

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 81N-0022]

RIN 0905-AA06

Weight Control Drug Products for Over-the-Counter Human Use; Certain Active Ingredients**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that certain active ingredients in over-the-counter (OTC) weight control drug products are not generally recognized as safe and effective or are misbranded. FDA is issuing this final rule after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and public comments on the agency's advance notice of proposed rulemaking that was based on those recommendations. No substantive comments and no new data or information were submitted to FDA under 21 CFR 330.10(a)(6)(iv) opposing nonmonograph status for these ingredients. FDA has determined that these ingredients would result in an OTC weight control drug product not being generally recognized as safe and effective or would result in its misbranding. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: February 8, 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 February 26, 1982 (47 FR 8466), 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 weight control drug products, together with 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 this drug class. The Miscellaneous Internal Panel classified a total of 113 OTC weight control drug product ingredients. Two ingredients

were classified in Category I (safe and effective for OTC use): Phenylpropanolamine hydrochloride and benzocaine. One hundred ingredients were classified in Category II (not safe and effective for OTC use), and 11 ingredients were classified in Category III (insufficient data to classify in Category I or Category II, more studies are needed). The ingredients classified in Category II included all of the ingredients listed in the call-for-data notice published in the Federal Register of August 27, 1975 (40 FR 38179) for which the Panel was not able to locate, and was not aware of, any significant body of data demonstrating the safety and effectiveness of use for weight control (47 FR 8466 at 8471). Of the 11 ingredients that the Panel classified in Category III, no data were submitted on 6 ingredients: Carrageenan, chondrus, guar gum, karaya gum, sea kelp, and psyllium, all of which are hydrophilic colloids. The Panel received safety and effectiveness data on the other 5 ingredients: Alginate acid, carboxymethylcellulose sodium, methylcellulose, sodium bicarbonate (in combination with bulking agents), and xanthan gum. Although the effectiveness data were insufficient, the Panel classified these 5 ingredients in Category III. The Panel stated that these ingredients may act as bulking agents and possibly could be shown effective for weight control use. The Panel did not question the safety of bulking agents because "they have been in use for years as food additives and some have had medicinal use." (47 FR 8477).

Interested persons were invited to submit comments on the Panel's recommendations by May 27, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by June 28, 1982. In a notice published in the Federal Register of April 23, 1982 (47 FR 17576), the agency advised that it had extended the comment period until July 26, 1982, and the reply comment period until August 27, 1982.

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. In response to the advance notice of proposed rulemaking, 6 drug manufacturers, 1 drug manufacturers' association, 1 clinical consulting firm, 6 professional associations, 8 physicians, 1 nutritionist, 1 health department, 2 Congressmen, 1 consumer organization, and 10 individuals submitted comments. No

comments or data were submitted on OTC weight control drug products containing any ingredient that the Panel had classified as nonmonograph (Category II or Category III). Copies of the comments received are on public display in the Dockets Management Branch.

Under the OTC drug review administrative procedures (21 CFR 330.10(a)(7)(ii)), the Commissioner may publish a separate tentative order covering active ingredients that have been reviewed and may propose that these ingredients be excluded from an OTC drug monograph on the basis of the Commissioner's determination that they would result in a drug product not being generally recognized as safe and effective or would result in misbranding. This order may include active ingredients for which no substantial comments were received in opposition to the advisory panel's proposed classification and for which no new data and information were received pursuant to § 330.10(a)(6)(iv) (21 CFR 330.10(a)(6)(iv)).

In the Federal Register of October 30, 1980 (55 FR 45788), FDA published, under § 330.10(a)(7)(ii), a proposed rulemaking encompassing the 111 active ingredients classified as Category II and Category III in the advance notice of proposed rulemaking. No significant comments or new data have been submitted to upgrade the status of these 111 active ingredients. Comments and new data were received on the two proposed Category I ingredients, phenylpropanolamine hydrochloride and benzocaine. Comments were also received on the labeling proposed for this class of OTC drug products.

The Commissioner is issuing a separate final rule on the 111 Category II and III ingredients prior to completing the rulemaking on the Category I ingredients. The Commissioner has determined that these 111 ingredients are not generally recognized as safe and effective. Therefore, any OTC weight control drug product containing any of these active ingredients may not continue to be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. FDA has completed action on these ingredients before finalizing the rest of the monograph in order to expedite removal from the market of products that lack adequate evidence of effectiveness.

FDA advises that the active ingredients listed in this final rule will not be included in the tentative final monograph for OTC weight control drug

products because they have not been shown to be generally recognized as safe and effective for weight control use. The agency is amending 21 CFR part 310 to list all of the active ingredients covered by this final rule by adding to subpart E, new § 310.545(a)(20) (21 CFR 310.545(a)(20)). The agency further advises that these active ingredients for OTC weight control use should be eliminated from OTC drug products by February 8, 1991, regardless of whether further testing is undertaken to justify future use. Therefore, on or after February 8, 1991, no OTC drug product containing any active ingredient listed in § 310.545(a)(20), either labeled or intended as an active ingredient for weight control use, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product containing any active ingredient 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. Manufacturers are urged to comply voluntarily with this final rule at the earliest possible date.

The agency points out that publication of this final rule does not preclude a manufacturer's testing an ingredient. New, relevant data can be submitted to the agency at a later date as the subject of an application that may provide for prescription or OTC marketing status. (See 21 CFR part 314.) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in an appropriate citizen petition to amend or establish a monograph, as appropriate. (See 21 CFR 10.30.) However, marketing of products containing these active ingredients may not begin or continue while the data are being evaluated by the agency.

In response to the proposed rule on OTC weight control Category II and III ingredients, three drug manufacturers, one trade association, the Attorney General of Iowa, and six individuals submitted comments. 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.

I. The Agency's Conclusions on the Comments

A. General Comments

1. Two comments expressed support for the agency's proposal to prohibit the continued marketing of certain OTC weight control drug products that contain active ingredients that are not generally recognized as safe and effective or are misbranded. One comment stated that if sufficient evidence is not available to demonstrate that an ingredient is both safe and effective, it should be prohibited from use. The other comment estimated that ineffective weight loss products cost consumers billions of dollars per year. The comment added that while a certain amount of risk is inherent in taking any drug product, taking such risk is clearly unwarranted and unnecessary where the products have not been shown to be effective for their intended use. The comment asserted that under the Federal Food, Drug, and Cosmetic Act (the act) all drugs, including weight control drugs, either must be generally recognized by experts as safe and effective for their intended use or they must be the subject of a new drug application approved by the FDA. The comment contended that continued marketing of Category II and III OTC weight loss products is inconsistent with this statutory mandate.

The comment contended that consumers taking questionable diet products are often subjected to serious health risks. The comment mentioned an instance where a consumer suffered an epileptic seizure because a fiber-based diet pill absorbed the medication meant to control seizures (Ref. 1). The comment discussed another instance where a person was hospitalized due to complications resulting from taking a diet pill and following a diet program that has not been shown to be safe or effective. Lastly, the comment noted the agency's discussion of the serious safety hazard that guar gum used in diet products can pose, and stated that many individuals had been hospitalized and at least one person had died from complications resulting from esophageal obstruction caused by consumption of guar gum diet products (Ref. 1).

Reference

(1) Comment No. C00042, Docket No. 81N-0022, Dockets Management Branch.

2. One comment questioned whether the proposed rule applied to foods for special dietary use, as defined in 21 CFR part 105. The comment particularly referred to products known as formulated meal replacements, which supply nutrients and micronutrients and

are intended to replace normal meals. The comment stated that a number of vitamins and minerals are classified in Category II as active ingredients for weight control. According to the comment, however, it would be reasonable to combine a weight control active ingredient with such nutritional supplements in order to replace essential vitamins and minerals missing from the reduced calorie diets normally followed by individuals attempting to lose weight. The comment added that a number of these vitamins and minerals are generally recognized by FDA as safe for use as nutritional supplements.

Part 105 of the regulations covers foods for special dietary use. The term "special dietary use" is defined in § 105.3(a)(1). Other sections set out labeling and other requirements that such products must meet.

The scope of this document, however, is limited to drug products intended for weight control use. It does not apply to foods for special dietary use as covered by 21 CFR part 105. Some foods regulated under part 105 are also Category II and III active ingredients in this final rule. When products containing such ingredients are labeled for drug use such as for appetite control, they will be regulated as drugs under § 310.545(a)(20). These same products when labeled as foods for special dietary use will be subject to part 105.

The agency recognizes that it may be difficult for a person on a diet to achieve the recommended dietary intake of essential nutrients, particularly vitamins and minerals, while using an OTC weight control drug product. The United States Department of Agriculture (Ref. 1) has stated that it is hard for a person to get the recommended levels of essential nutrients in diets of fewer than 1,800 calories, and this is particularly true of vitamins and minerals, which are present only in low concentrations in most foods. The same view has been expressed for diets ranging from 1,000 to 1,600 calories per day (Refs. 2 through 5). A publication from the National Academy of Sciences, in cautioning about the difficulty of designing a nutritionally-adequate 1,000 calorie diet, states that such a diet " * * * would have to supply most nutrients in at least double the allowance per thousand calories, an objective that is difficult to maintain without supplementation," (Ref. 5). The agency agrees with the comment that it would be reasonable to allow such nutrients to be combined with an active weight control drug. Such combination products will be discussed further in the notice of proposed rulemaking for Category I weight control

drug products in a future issue of the Federal Register.

References

- (1) "Ideas for Better Eating," U.S. Department of Agriculture, p. 11, January 1981.
- (2) Lasagna, L., "One-A-Day, Plus C," The Sciences, 21:35, 1981.
- (3) Olson, R.E., "Letter to the Editor-Reply," Nutrition Reviews, 40:160, 1982.
- (4) Blonz, E.R., and J.S. Stern, "Obesity and Fad Diets," in "Contemporary Issues in Clinical Nutrition: Controversies in Nutrition," Vol. 2, edited by L. Ellenbogen, Churchill Livingstone, New York, p. 120, 1981.
- (5) "Recommended Dietary Allowances," 9th Ed., National Academy of Sciences, Washington, p. 13, 1980.

3. Five comments stated that the entire OTC weight control drug products rulemaking was unconstitutional under the ninth amendment of the Constitution. The comments contended that FDA has no authority to regulate the purchase, sale, manufacture, or labeling of any or all Category I, II, or III OTC weight control ingredients and that consumers have the right of freedom of choice and a "health care" right to purchase any Category I, II, or III OTC weight control ingredient.

FDA's statutory mandate includes protection and promotion of the public health by ensuring that drugs are not only safe but also effective for their intended use. The Commissioner's Decision on the Status of Laetrile, published in the Federal Register of August 5, 1977 (42 FR 39768), expresses the agency's position on freedom of choice with respect to ensuring that drugs are not only safe, but also effective. That statement reads in part as follows:

In passing the 1962 Amendments to the act—the amendments that require that a drug be proved effective before it may be marketed—Congress indicated its conclusions that the absolute freedom to choose an ineffective drug was properly surrendered in exchange for the freedom from the danger to each person's health and well-being from the sale and use of worthless drugs * * *. To the extent that any freedom has been surrendered by the passage of the legislation which bans from the marketplace drugs that have not been proven to be effective, that surrender was a rational decision which has resulted in the achievement of a greater freedom from the dangers to health and welfare represented by such drugs.

It is settled law that there is no constitutional right to privacy allowing a person specific drugs regardless of FDA's determination as to their safety and effectiveness. While a patient may have a protected right not to seek treatment, the selection of a particular treatment or medication is well within

the recognized area of governmental interest in protecting the public health. *Rutherford v. U.S.*, 618 F.2d 455, 456-457 (10th Cir.), cert. denied, 449 U.S. 937 (1980). The drug premarketing review provisions of the act and FDA's implementing programs, including the OTC drug review, are a legitimate exercise of congressional authority limiting a person's choice of drugs. FDA's OTC drug review has been discussed and tacitly approved in numerous court decisions. See *Cutler v. Hayes*, 818 F.2d 879, 895 (DC Cir. 1987), for discussion of the Supreme Court's implicit approval of the OTC drug review in *Weinberger v. Bentex Pharmaceuticals*, 412 U.S. 645 (1973). The review was also implicitly approved in *Cutler v. Kennedy*, 475 F. Supp 844, 845 (D.D.C. 1979) and *Cutler v. Hayes*, 549 F. Supp. 1341, 1344 (D.D.C. 1982).

OTC weight control drug products that are subject to this rulemaking, and that are not the subject of an approved new drug application (NDA), will have to comply with the final rule. In the absence of data demonstrating that the ingredients present in OTC weight control drug products are generally recognized as safe and effective, these ingredients cannot be included in an OTC drug monograph. After the effective date of the final regulation, any such OTC weight control drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this regulation will be subject to regulatory action.

4. One comment disagreed with the agency's policy that the proposed rulemaking "does not constitute a reopening of the administrative record or an opportunity to submit any new data to the OTC weight control rulemaking." (See 55 FR 45788 at 45789.) The comment argued that this approach is contrary to the FDA's rulemaking regulations and the Administrative Procedures Act. The comment argued that FDA's procedure has denied the public the opportunity to submit information and substantive comments for inclusion in the administrative record because the proposed rule announces a new rulemaking, separate from the rulemaking indicated in 1982. The comment contended that because the administrative record had been closed for over 8 years, it should now be reopened so that relevant information and data can be considered by FDA before the final rule is issued. Specifically, the comment wanted the administrative record to be reopened so that additional data regarding the safety and effectiveness of guar gum could be considered before the final rule is

issued. The comment indicated that FDA should consider this request to be a petition to reopen the administrative record.

FDA administrative procedures for classifying OTC drugs and for establishing monographs in 21 CFR 330.10(a)(7)(ii) provide that the Commissioner may publish a separate tentative order covering active ingredients that have been reviewed and may propose that these ingredients be excluded from an OTC drug monograph on the basis of the Commissioner's determination that they would result in a drug not being generally recognized as safe and effective or would result in misbranding. This order may include active ingredients for which no substantial comments in opposition to the advisory panel's proposed classification and for which no new data and information were received pursuant to 21 CFR 330.10(a)(8)(iv). As noted in the proposal, no substantive comments or new data were submitted to support reclassification of any of these 111 Category II and Category III OTC weight control ingredients to monograph status (55 FR 45788). Thus, the agency precisely followed its administrative procedures in issuing the notice of proposed rulemaking on October 30, 1990 stating that these ingredients are proposed for nonmonograph status.

Regarding the specific ingredient guar gum mentioned in the comment, the agency specifically discussed both the safety and effectiveness of this ingredient in the notice of proposed rulemaking (55 FR 45788 at 45790 to 45792). The agency mentioned a number of safety problems and health risks associated with the OTC use of guar gum-containing weight control drug products. Further, the agency stated that available effectiveness data were inadequate to support effectiveness of guar gum for this use. In the absence of data establishing general recognition of safety and effectiveness, the agency has concluded that guar gum-containing weight control drug products are not appropriate for OTC use and should not continue to be marketed.

The administrative procedures in 21 CFR 330.10(a)(7)(v) for classifying OTC drugs and for establishing monographs address the question of new data and information submitted after the times provided in other parts of the regulations but prior to the establishment of a final monograph. These procedures provide that such data and information will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final monograph has been

published in the *Federal Register* unless the Commissioner finds that good cause has been shown that warrants earlier consideration. At this time, the Commissioner does not find that good cause has been shown to warrant earlier consideration or to allow guar gum to remain under consideration in the ongoing rulemaking for OTC weight control drug products. Because this rulemaking is not likely to be finalized in the near future, any manufacturer interested in the continued marketing of guar gum for weight control use should proceed under the new drug procedures in 21 CFR parts 312 and 314.

The agency points out that publication of a final rule under this current proceeding does not preclude a manufacturer from testing any ingredient covered by the final rule. New, relevant data can be submitted to the agency at a later date as the subject of an NDA that may provide for prescription or OTC marketing status. (See 21 CFR part 314.) As an alternative, if a manufacturer believes it has adequate data establishing general recognition of safety and effectiveness for any of these ingredients, such data may be submitted to the agency in an appropriate citizen petition to amend or establish a monograph, as appropriate. (See 21 CFR 10.30.) However, products containing such ingredients may not continue to be marketed while the agency evaluates any new, relevant data provided. Accordingly, the agency is not denying manufacturers an opportunity to submit information, but rather it is following the act and its regulations to ensure the safety and effectiveness of OTC drug products in the marketplace.

5. One comment contended the FDA should provide the public with detailed information regarding the requirements for studies necessary to support future petitions to modify the monograph to add Category I ingredients. The comment argued that current guidelines in this regard are vague and do not provide sufficient guidance, that such studies are costly to the manufacturers, and the public should be advised of the agency's requirements before manufacturers incur the expense of conducting such studies.

The Miscellaneous Internal Panel provided fairly extensive testing guidelines in its report (47 FR 8466 at 8480 to 8483). However, the agency is not addressing specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III ingredients, published in the *Federal Register* of September 29, 1981 (46 FR 47730), the

agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. In the same issue of the *Federal Register* (46 FR 47740), the agency published a policy statement concerning the submission and review of protocols to evaluate an ingredient or condition in the OTC drug review. The agency will meet with manufacturers, at their request, to discuss protocols and other testing issues involving conditions that industry is interested in upgrading and to advise industry on the adequacy of proposed testing protocols.

6. One comment stated that the proposed rule is likely to cause a major increase in costs to consumers who wish to lose weight. The comment contended that increased costs to consumers would result from the agency's initial determination that all OTC drug ingredients, other than non-time-released phenylpropranolamine hydrochloride and benzocaine, would be banned unless an approved NDA is obtained under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314. The comment estimated the cost of the agency's drug approval process as between \$50 million and \$150 million and contended that these costs of regulatory approval will be passed on to the consumer, resulting in major price increases. The comment argued that the proposed rule is likely to have a severe adverse effect on competition and innovation because small companies are not capable of funding the new drug approval process. The comment contended that competition would be limited to the few existing major drug companies. The comment disagreed with the agency's position that the proposed rule is not a major rule under Executive Order 12291 and that it would not have a significant impact on small business. The comment concluded that the proposed rule would create an insurmountable barrier to small businesses seeking access to the OTC weight loss drug market and, therefore, the agency needs to reevaluate the impact of its proposed rule.

The agency does not agree with the comment. In the *Federal Register* of February 8, 1983 (48 FR 5806), FDA announced the availability of an assessment of the economic impacts of the OTC drug review process. The assessment was prepared to determine whether the economic effects of the OTC drug review process, as a whole, are sufficient to warrant a Regulatory Impact Analysis (as specified in Executive Order 12291) or a Regulatory

Flexibility Analysis (as required by the Regulatory Flexibility Act, Pub. L. 96-354). The assessment evaluates the economic effects (costs) of any required labeling, reformulation, and/or testing of OTC drug products as a direct result of the OTC drug review process. The assessment also examines the economic impact of the establishment of a monograph for any particular therapeutic class of OTC drugs. The assessment demonstrates that the review process in its entirety will not have a "major impact" as defined in Executive Order 12291 and probably will not have a "significant economic impact on a substantial number of small entities," as defined in the Regulatory Flexibility Act.

Regarding this specific rule for OTC weight control drug products, the agency has determined that this rule will actually result in savings for consumers who are now spending billions of dollars a year for OTC weight control drug products containing certain ingredients that have not been proven to be safe and/or effective. Although a large number of ingredients are covered by this final rule, the agency estimates that the market impact by sales volume of the products affected by this final rule is quite small. Most of the major selling OTC weight control drug products contain the ingredients phenylpropranolamine hydrochloride or benzocaine. These ingredients are not affected by this final rule. For example, of 27 products listed in an "appetite suppressant product table" in the latest edition of the Handbook of Nonprescription Drugs (Ref. 1), all contain either phenylpropranolamine hydrochloride or benzocaine. In the same table, only five products are listed as "bulk producers" weight control products. Three of these products are marketed primarily as laxatives, not as weight control products, and may remain on the market after this final rule becomes effective. The other 2 products contain ingredients that the Panel placed in Category III, for which no additional data have been submitted. Finally, the agency believes that many of the 111 ingredients covered by this final rule, for which the Panel was not able to locate nor was aware of any significant body of data demonstrating use for weight control (39 FR 8466 at 8471), are not currently marketed as OTC weight control active ingredients. Nonetheless, a regulation is still needed to prevent their future marketing for this use and to complete the rulemaking for those ingredients.

Companies that market products containing ingredients, affected by this

final rule may (1) obtain a new drug application, (2) submit a citizen petition with supporting data to include the ingredient in the OTC weight control drug products monograph, or (3) reformulate to use alternative ingredients being considered as being generally recognized as safe and effective, without incurring additional expense of clinical testing for those ingredients. The agency does not agree with the comment that this rule would create an insurmountable barrier to small businesses because virtually all companies affected by this final rule can reformulate their products. Some products may need stability data (if none exists) or new labeling. These should be one-time expenses. In some instances, companies might be able to revise their labeling to delete claims promoting their products as effective for weight control and continue to market the products as nutritional supplements.

Many companies that market ingredients affected by this rulemaking are small companies that are not manufacturers, but rather are distributors that have their products manufactured for them by other companies that produce custom products on order. Thus, the actual reformulation will be handled by the manufacturer, not the distributor.

In its 1983 assessment, FDA states that the outcome of the OTC drug review will produce social benefits to the extent that unsafe and ineffective OTC drug ingredients are removed from the market. Private costs to manufacturers associated with any loss of markets for products using withdrawn ingredients that are not generally recognized as safe and effective, do not translate into social costs. Rather, they indicate the social benefits of the OTC drug review by reallocating consumer expenditures and industry resources away from socially counterproductive OTC drugs. The assessment also contains a detailed discussion of testing costs. The agency has reevaluated the impacts of this proposed rule for OTC weight control drug products in light of the assessment of the economic impacts of the entire OTC drug review process that was prepared in 1983. The agency concludes that the basic principles of that assessment are still applicable today. The agency also concludes that the final rule in the current proceeding is not a major rule under Executive Order 12291 and will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act. Accordingly, the rulemaking to remove these drugs from the marketplace will

not be delayed to allow interested persons another opportunity to submit data for the FDA to review. Such an approach would only result in further delay and continued marketing of potentially unsafe and ineffective drugs at the expense of consumers. (See discussion regarding the agency's formal determination of economic impact in section II.)

Reference

(1) "Handbook of Nonprescription Drugs," 9th Ed., The American Pharmaceutical Association, Washington, pp. 578-580, 1990.

7. One comment requested clarification that this rulemaking does not affect the use of saccharin and other listed ingredients as inactive or "formulation" ingredients in OTC weight control drug products, or in drugs generally.

This final rule affects the use of the listed ingredients only as active ingredients for the specific indication of weight control. The agency recognizes that some of the ingredients included in this final rule have valid uses as inactive ingredients. Examples include the use of dextrose, fructose, saccharin, and sucrose for sweetening. It is possible that one or more of these ingredients could be present for this purpose in an OTC weight control drug product containing a monograph ingredient. This final rule does not affect such use. However, any inactive ingredient present in a product should have an appropriate purpose and be safe and suitable for use in the product in accord with 21 CFR 330.1(e).

B. Comments On Guar Gum

8. Two comments objected to the agency's determination that guar gum is unsafe and ineffective (55 FR 45788 at 45790). One comment contended that the agency did not have sufficient data to justify the reclassification of guar gum from Category III to Category II. The comment argued that the vast majority of the data discussed in the proposed rule related to a specific product. This particular product contained high levels of guar gum (another comment stated these levels were 80 to 90 percent) and was manufactured in a manner that contributed to the problem of esophageal obstruction. The comment added that FDA is aware that guar gum is safe when consumed in certain amounts.

Another comment asserted that while guar gum may be unsafe at high concentrations, it has been used safely as a food ingredient at levels of 10 percent or less. The comment requested FDA to approve the use of 10 percent or less guar gum in dietary food products

that contain at least 50 percent of food grade, natural, nonswellable, cellulose fibers. Another comment described personal experience in manufacturing guar gum tablets. The comment stated that there are various grades of guar gum powder from which to choose, and each grade of guar gum appears to have different rates of gelling. The comment stated that the guar gum product that caused the esophageal obstruction problems discussed in the agency's proposal was manufactured by at least four different companies. The comment suggested that before FDA condemns guar gum as unsafe, it should try to determine if the esophageal obstruction was caused by a particular manufacturer's version of this guar gum product. The comment argued that it would be unfair to condemn guar gum because of one or two irresponsible manufacturers/distributors. The comment also mentioned that the vast majority of guar gum tablets sold over the years were manufactured by "food supplement" manufacturers without the regulatory oversight afforded to "drug manufacturers." The comment mentioned several studies that support the safety and effectiveness of guar gum (Refs. 1, 2, and 3) and stated that the medical literature is replete with studies conducted with guar gum, with minimal side effects (bloating, transient diarrhea, and flatulence) being reported.

The request for FDA to approve use of 10 percent or less guar gum in dietary food products that contain at least 50 percent of food grade, natural, nonswellable, cellulose fibers is outside the scope of the current rulemaking. The agency notes that guar gum is listed in 21 CFR 184.1339 as a direct food substance affirmed as generally recognized as safe. Various uses at low levels (with a maximum usage level of 2 percent permitted) are allowed in food products. As discussed in comment 2 above, these food uses of guar gum are not affected by this rulemaking.

The agency agrees with the comment that there may be methods of formulation and manufacture of tablets containing high concentrations of guar gum as an active weight control drug ingredient that could result in a safe product having little or no risk of esophageal obstruction. For some of the very reasons mentioned by one comment, however, the agency considers the method of manufacture and exact details of formulation, as well as dissolution and gelling data, to be critical in determining the safety and effectiveness of each product. Accordingly, the agency has determined that individual product testing and

approval under the new drug approval procedures, rather than an OTC drug monograph, are necessary to ensure the safety of such products. For this reason, the agency is not addressing the safety and efficacy data provided by the comment, but rather is deferring any further evaluation until such data are submitted as part of an NDA.

References

(1) Uncited studies by Mendeloff, A. I., and M. McIver, Comment No. C44, Docket No. 81N-0022, Dockets Management Branch.

(2) Krotkiewski, M., "Use of Various Fibres in Different Weight Reduction Programs," draft of unpublished study, Exhibit No. 1 in Comment No. C44, Docket No. 81N-0022, Dockets Management Branch.

(3) Evans, E., and D.S. Miller, "Bulking Agents in The Treatment of Obesity," *Nutrition and Metabolism*, 18:199-203, 1975.

II. The Agency's Final Conclusions on Certain OTC Weight Control Category II and III Active Ingredients

The agency has determined that no substantive comments or adequate additional data have been submitted to the OTC drug review to support any of the ingredients listed below as being generally recognized as safe and effective for use in OTC weight control drug products. Based on the agency's procedural regulations (21 CFR 330.10(a)(7)(ii)), the agency has determined that the following ingredients are not generally recognized as safe and effective and are misbranded when present in OTC weight control drug products:

Alcohol
Alfalfa
Alginate
Alginic acid
Anise oil
Arginine
Ascorbic acid¹
Bearberry²
Biotin
Bone marrow, red³
Buchu
Buchu, potassium extract
Caffeine
Caffeine citrate
Calcium
Calcium carbonate
Calcium caseinate
Calcium lactate

¹ The Panel designated this ingredient "ascorbic acid (vitamin C)." However, "ascorbic acid" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

² The Panel designated this ingredient "uva ursi." However, "bearberry" is the official name for this ingredient in the Center for Drug Evaluation and Research dictionary of drug names.

³ The Panel designated this ingredient "bone marrow-red-glycerin extract." However, "bone marrow, red" is the official name for this ingredient in the Center for Drug Evaluation and Research dictionary of drug names.

Calcium pantothenate⁴
Carboxymethylcellulose sodium
Carrageenan
Cholecalciferol⁵
Choline
Chondrus
Citric acid
Cnicus benedictus
Copper
Copper gluconate
Corn oil
Corn syrup
Corn silk, potassium extract
Cupric sulfate
Cyanocobalamin (vitamin B₁₂)
Cystine
Dextrose
Docusate sodium⁶
Ergocalciferol⁷
Ferric ammonium citrate
Ferric pyrophosphate
Ferrous fumarate
Ferrous gluconate
Ferrous sulfate (iron)
Flax seed
Folic acid
Fructose
Guar gum
Histidine
Hydrastis canadensis
Inositol
Iodine
Isoleucine
Juniper, potassium extract
Karaya gum
Kelp⁸
Lactose
Lecithin
Leucine
Liver concentrate
Lysine⁹
Lysine hydrochloride¹⁰

⁴ The Panel designated this ingredient "calcium pantothenate (D-calcium pantothenate)." However, "calcium pantothenate" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

⁵ The Panel designated this ingredient "vitamin D₂." However, "cholecalciferol" is the official name for this ingredient in the "United States Pharmacopoeia XXII—National Formulary XVII," 1990.

⁶ The Panel designated this ingredient "dioctyl sodium sulfosuccinate." However, "docusate sodium" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

⁷ The Panel designated this ingredient "vitamin D₂." However, "ergocalciferol" is the official name for this ingredient in the "United States Pharmacopoeia XXII—National Formulary XVII," 1990.

⁸ The Panel designated this ingredient "sea kelp." However, "kelp" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

⁹ The Panel designated this ingredient "L-lysine." However, "lysine" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

¹⁰ The Panel designated this ingredient "L-lysine monohydrochloride." However, "lysine hydrochloride" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

Magnesium
Magnesium oxide
Malt
Maltodextrin
Manganese citrate
Mannitol
Methionine
Methylcellulose
Mono- and di-glycerides¹¹
Niacinamide
Organic vegetables
Pancreatin¹²
Pantothenic acid
Papain
Papaya enzymes
Pepsin
Phenacetin¹³
Phenylalanine
Phosphorus
Phytolacca¹⁴
Pineapple enzymes
Plantago seed¹⁵
Potassium fumarate
Pyridoxine hydrochloride (vitamin B₆)
Riboflavin
Rice polishings
Saccharin
Sea minerals
Sesame seed
Sodium
Sodium bicarbonate
Sodium caseinate
Sodium chloride (salt)
Soybean protein¹⁶
Soy meal
Sucrose
Thiamine hydrochloride (vitamin B₁)
Thiamine mononitrate (vitamin B₁ mononitrate)
Threonine
Tricalcium phosphate
Tryptophan
Tyrosine
Uva ursi, potassium extract
Valine
Vegetable
Vitamin A

¹¹ The Panel designated these ingredients "glycerides (mono and di)." However, "mono- and di-glycerides" is the official name for this ingredient in the "United States Pharmacopoeia XXII—National Formulary XVII," 1990.

¹² The Panel designated this ingredient "pancreatin enzymes." However, "pancreatin" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

¹³ In the Federal Register of October 5, 1983 (48 CFR 45406), the agency stated that effective November 4, 1983, products containing phenacetin are considered new drugs for which an approved NDA is required for marketing. This action was taken because of phenacetin's high potential for misuse and its unfavorable benefit-to-risk ratio with chronic use.

¹⁴ The Panel designated this ingredient "phytolacca berry juice." However "phytolacca" is the official name for this ingredient in the Center for Drug Evaluation and Research dictionary of drug names.

¹⁵ The Panel designated this ingredient "pyllium." However, "plantago seed" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

¹⁶ The Panel designated this ingredient "soy bean protein." However, "soybean protein" is the official name for this ingredient in the Center for Drug Evaluation and Research dictionary of drug names.

Vitamin A acetate
 Vitamin A palmitate
 Vitamin E
 Wheat germ
 Xanthan gum
 Yeast

The agency is amending 21 CFR 310.545 by adding new paragraph (a)(20) and by revising paragraph (d) to establish that certain active ingredients in OTC weight control drug products are not generally recognized as safe and effective. Any drug product containing any of these active ingredients and labeled for OTC weight control use will be considered nonmonograph and misbranded under section 502 of the act (21 U.S.C. 352) and a new drug 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 21 CFR part 314 of the regulations 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 amend the OTC weight control drug products monograph, after it is finalized, to include any of the above active ingredients in OTC weight control drug products. (See 21 CFR 10.30.) Products containing such ingredients may not be marketed while the agency is evaluating the petition.

Any OTC drug product containing any of the above ingredients either labeled or intended as an OTC weight control active ingredient that is initially introduced or initially delivered for introduction into interstate commerce after February 8, 1991, and that is not the subject of an approved application will be in violation of sections 502 and 505 of the act (21 U.S.C. 352 and 355) and, therefore, subject to regulatory action. Further, any OTC drug product containing an ingredient subject to this rulemaking that is repackaged or relabeled after February 8, 1991, must be in compliance with the rule 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 rule at the earliest possible date.

One comment was received in response to the agency's request for specific comment on the economic impact of this rulemaking (55 FR 45788 at 45792). The issues raised by this comment are discussed in comment 6 above. There currently are two other ingredients being considered for monograph status that manufacturers can use to reformulate affected products. As a result of this final rule, manufacturers may need to reformulate

some products prior to promulgation of the applicable final monograph. However, there will be no additional costs because reformulation would be required, in any event, when the final monograph is published.

Early finalization of the nonmonograph status of the ingredients listed in this notice will benefit both consumers and manufacturers. Consumers will benefit from the early removal from the marketplace of ingredients for which safety and effectiveness have not been established. This will result in a direct economic savings to consumers. Most manufacturers will benefit from being able to use alternative ingredients that have been recommended by the Panel as being generally recognized as safe and effective, without incurring additional expense of clinical testing for these ingredients. Based on the above, 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.

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 in part 310 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, 512-518, 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. Section 310.545 is amended by adding new paragraph (a)(20) and by revising paragraph (d) to read as follows:

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

(a) * * *

(20) Weight control drug products.

Alcohol
 Alfalfa
 Alginic acid
 Anise oil
 Arginine
 Ascorbic acid
 Bearberry
 Biotin
 Bone marrow, red
 Buchu
 Buchu, potassium extract
 Caffeine
 Caffeine citrate
 Calcium
 Calcium carbonate
 Calcium caseinate
 Calcium lactate
 Calcium pantothenate
 Carboxymethylcellulose sodium
 Carrageenan
 Cholecalciferol
 Choline
 Chondrus
 Citric acid
 Cnicus benedictus
 Copper
 Copper gluconate
 Corn oil
 Corn syrup
 Corn silk, potassium extract
 Cupric sulfate
 Cyanocobalamin (vitamin B₁₂)
 Cystine
 Dextrose
 Docusate sodium
 Ergocalciferol
 Ferric ammonium citrate
 Ferric pyrophosphate
 Ferrous fumarate
 Ferrous gluconate
 Ferrous sulfate (iron)
 Flax seed
 Folic acid
 Fructose
 Guar gum
 Histidine
 Hydrastis canadensis
 Inositol
 Iodine
 Isoleucine
 Juniper, potassium extract
 Karaya gum
 Kelp
 Lactose
 Lecithin
 Leucine
 Liver concentrate
 Lysine
 Lysine hydrochloride
 Magnesium
 Magnesium oxide
 Malt
 Maltodextrin
 Manganese citrate
 Mannitol
 Methionine
 Methylcellulose
 Mono- and di-glycerides
 Niacinamide
 Organic vegetables
 Pancreatin
 Pantothenic acid
 Papain
 Papaya enzymes

Pepsin
Phenacetin
Phenylalanine
Phosphorus
Phytolacca
Pineapple enzymes
Plantago seed
Potassium citrate
Pyridoxine hydrochloride (vitamin B₆)
Riboflavin
Rice polishings
Saccharin
Sea minerals
Sesame seed
Sodium
Sodium bicarbonate
Sodium caseinate
Sodium chloride (salt)
Soybean protein
Soy meal

Sucrose
Thiamine hydrochloride (vitamin B₁)
Thiamine mononitrate (vitamin B₁
mononitrate)
Threonine
Tricalcium phosphate
Tryptophan
Tyrosine
Uva ursi, potassium extract
Valine
Vegetable
Vitamin A
Vitamin A acetate
Vitamin A palmitate
Vitamin E
Wheat germ
Xanthan gum
Yeast
* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) and (d)(2) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(19) of this section; and

(2) February 8, 1991, for products subject to paragraph (a)(20) of this section.

Dated: April 18, 1991.
David A. Kessler,
Commissioner of Food and Drugs.
[FR Doc. 91-18756 Filed 8-7-91; 8:45 am]
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