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**Department of
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Services**

Food and Drug Administration

**21 CFR Part 357
Weight Control Drug Products for Over-
the-Counter Human Use; Proposed Rule**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0022]

RIN 0905-AA06

Weight Control Drug Products for Over-the-Counter Human Use; Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking stating that certain ingredients in over-the-counter (OTC) weight control drug products are not generally recognized as safe and effective and are misbranded (nonmonograph status). FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and the public comments on an advance notice of proposed rulemaking that was based on those recommendations. Based on the absence of substantive comments in opposition to the Panel's proposed nonmonograph status for these ingredients as well as the failure of interested parties to submit new data or information to FDA pursuant to 21 CFR 330.10(a)(6)(iv), FDA has determined that the presence of these ingredients in an OTC weight control drug product would result in that drug product not being generally recognized as safe and effective or would result in misbranding. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposal before the Commissioner of Food and Drugs by December 31, 1990. Written comments on the agency's economic impact determination by December 31, 1990.

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

FOR FURTHER INFORMATION CONTACT: William F. 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) (see table I below). Eleven ingredients were classified in Category III (insufficient data to classify in Category I or Category II, more studies are needed) (see table II below). 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 hydrophilic colloids. The Panel received safety and effectiveness data on the 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 all of these hydrophilic colloids in Category III, stating that these ingredients may act as bulking agents and should be provided an opportunity to demonstrate their effectiveness for weight control use (47 FR 8477). 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."

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 (address above), 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 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.

This proposed rulemaking encompasses all ingredients classified as Category II and Category III in the advance notice of proposed rulemaking for OTC weight control drug products. No significant comments or new data have been submitted to upgrade the status of these ingredients. 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 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)).

As mentioned, 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. Comments and new data were received on the proposed Category I ingredients, phenylpropanolamine hydrochloride and benzocaine, and on the labeling proposed for this class of OTC drug

products. Before issuing a tentative final monograph on OTC weight control drug products that addresses proposed Category I ingredients and labeling issues, the Commissioner is issuing a separate notice proposing that these 111 Category II and III ingredients be found not generally recognized as safe and effective. Any OTC weight control drug product containing any of these 111 ingredients would not be allowed to continue to be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. FDA has elected to act on these 111 ingredients in advance of finalization of other monograph conditions in order to expedite completion of the OTC weight control drug product review. Manufacturers are encouraged to comply voluntarily at the earliest possible date.

This proposal does not constitute a reopening of the administrative record or an opportunity to submit any new data to the OTC weight control rulemaking. Should an interested person submit a comment indicating that substantive comments or new data were previously submitted to the administrative record, the agency will review the record for the OTC weight control drug product rulemaking and make a determination whether the affected ingredient shall continue to be evaluated under this rulemaking or be included in the final rule that will issue pursuant to this proposed rule.

FDA advises that the active ingredients discussed in this document (see tables I and II below) will not be included in the tentative final monograph on OTC weight control drug products, to be published in a future issue of the *Federal Register*, because they have not been shown to be generally recognized as safe and effective for their intended use. The agency further advises that these ingredients should be eliminated from OTC weight control drug products 6 months after the date of publication in the *Federal Register* of a final rule regarding their status, regardless of whether further testing is undertaken to justify future use. The OTC drug review administrative procedures provide that any new data and information submitted after the administrative record has closed following publication of a tentative final monograph (notice of proposed rulemaking), but prior to the establishment of a final monograph, 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. (See 21 CFR 330.10(a)(7)(v).)

The agency points out that publication of a final rule under this proceeding 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 a new drug application (NDA) 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.)

I. OTC Weight Control Drug Category II and III Ingredients

Based on the criteria discussed above, FDA is proposing that the following ingredients are not generally recognized as safe and effective and are misbranded when labeled for use in OTC weight control drug products:

TABLE I.—Ingredients Classified by the Panel as Category II Weight Control Active Ingredients

Alcohol
Alfalfa
Anise oil
Arginine
Ascorbic acid¹
Bearberry¹
Biotin
Bone marrow, red²
Buchu
Buchu, potassium extract
Caffeine
Caffeine citrate
Calcium
Calcium carbonate
Calcium caseinate
Calcium lactate
Calcium pantothenate⁴
Cholecalciferol⁵
Choline
Citric acid
Cnicus benedictus
Copper
Copper gluconate
Corn oil
Corn syrup
Corn silk, potassium extract
Cupric sulfate
Cyanocobalamin (vitamin B₁₂)
Cystine
Dextrose
Docosate sodium⁶
Ergocalciferol⁷
Ferric ammonium citrate
Ferric pyrophosphate
Ferrous fumarate

TABLE I.—Ingredients Classified by the Panel as Category II Weight Control Active Ingredients—Continued

Ferrous gluconate
Ferrous sulfate (iron)
Flax seed
Folic acid
Fructose
Histidine
Hydrastic canadensis
Inositol
Iodine
Isoleucine
Juniper, potassium extract
Lactose
Lecithin
Leucine
Liver concentrate
Lysine⁸
Lysine hydrochloride⁹
Magnesium
Magnesium oxide
Malt
Maltodextrin
Manganese citrate
Mannitol
Methionine
Mono- and di-glycerides¹⁰
Niacinamide
Organic vegetables
Pancreatin¹¹
Pantothenic acid
Papain
Papaya enzymes
Pepsin
Phenacetin
Phenylalanine
Phosphorus
Phytolacca¹²
Pineapple enzymes
Potassium citrate
Pyridoxine hydrochloride (vitamin B₆)
Riboflavin
Rice polishings
Saccharin
Sea minerals
Sesame seed
Sodium
Sodium caseinate
Sodium chloride (salt)
Soybean protein¹³
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
Yeast

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

³ 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.

⁴ 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.

⁵ 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."

⁶ The Panel designated this ingredient "vitamin D." However, "cholecalciferol" is the official name for this ingredient in the "United States Pharmacopeia XXII—National Formulary XVII," 1990.

⁷ The Panel designated this ingredient "dioctyl sodium sulfosuccinate." However, "docosate sodium" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

⁸ The Panel designated this ingredient "vitamin D₂." However, "ergocalciferol" is the official name for this ingredient in the "United States Pharmacopeia XXII—National Formulary XVII," 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."

¹¹ The Panel designated these ingredients "glycerides (mono and di)." However, "mono- and diglycerides" is the official name for this ingredient in the "United States Pharmacopeia 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 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.

¹⁴ 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.

TABLE II—Ingredient Classified by the Panel as Category III Weight Control Active Ingredients

Alginate acid
Carboxymethylcellulose sodium
Carrageenan
Chondrus
Guar gum
Karaya gum
Kelp¹⁴
Methylcellulose
Plantago seed¹⁵
Sodium bicarbonate
Xanthan gum

¹⁵ 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."

¹⁶ The Panel designated this ingredient "psyllium." However, "plantago seed" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

As noted above, no data were submitted to the Panel on the ingredient guar gum. Since the Panel's report was published in 1982, FDA's spontaneous reporting system has received 17 reports of esophageal obstruction (16 between June 1988 and August 1989) resulting from the use of an OTC weight control

drug product containing guar gum (Ref. 1). The product contained 500 milligrams (mg) guar gum per tablet, with directions to start with 4 tablets 30 minutes before each meal on the first day and to increase up to 10 tablets 30 minutes before each meal on the 15th day and thereafter. This dosage regimen eventually results in a maximum dose of 15 grams (g) of guar gum per day. Ten of the cases of esophageal obstruction required hospitalization, and one person eventually died as an indirect result of the obstruction, developing massive pulmonary emboli one week after open chest surgery to repair an esophageal tear sustained during removal of the guar gum obstruction.

This potential for esophageal obstruction represents a serious hazard for an OTC drug, and the 17 cases are presumed to represent a substantial underreporting. OTC drugs of this type, i.e., those without approved applications, are not subject to mandatory reporting requirements, and reports such as the above 17, which were voluntarily submitted by health professionals, normally account for only about 10 percent of all reports in the agency's spontaneous reporting system.

There has also been a report in the literature of an esophageal obstruction resulting from another guar gum product, this one composed of guar gum and grapefruit fiber (Ref. 2). In that case, a middle-aged man was unable to eat or drink for 12 hours after taking one weight control tablet composed of an unspecified amount of guar gum and grapefruit fiber. Endoscopy revealed a soft, fibrous mass impacted in the esophagus; it was broken apart by the endoscope. The agency is also aware of a report in which a 63-year-old diabetic suffered an esophageal obstruction after taking an OTC product containing guar gum. The obstruction required removal with biopsy tongs (Ref. 3). In another report, 59-year-old male suffered esophageal obstruction, requiring esophagoscopy to remove the obstruction, after taking a product containing guar gum (Ref. 4).

The agency is also aware that the United Kingdom has banned (effective June 13, 1989) the sale of "slimming pills" containing more than 15 percent guar gum (Ref. 5). That action was taken by the Ministry of Agriculture, Fisheries and Food on the recommendation of the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) and the Food Advisory Committee. The two committees advised that these products pose a health risk because the gum tends to swell rapidly when swallowed

and can lodge in the throat. The COT has also advised that the restrictions on substances used in the slimming products should also be extended to cover the sale of all formulations containing dehydrated products which could swell and create a blockage in the throat. The United Kingdom Ministry of Agriculture, Fisheries and Food is currently considering that recommendation.

In the consumer information provided with the guar gum weight control drug product involved in the adverse drug reactions reported to FDA, the manufacturer cites three references in the literature in support of the effectiveness of guar gum as a weight control drug product ingredient (Refs. 6, 7, and 8). These references were not reviewed by the Miscellaneous Internal Panel. The agency has reviewed the references and finds that they are inadequate to support the effectiveness of guar gum as an ingredient in OTC weight control drug products.

The first publication (Ref. 6) reports on two studies. One study involved nine obese female subjects recruited from an outpatient obesity clinic. The subjects were studied primarily to examine the acute effects of a single dose of guar gum on post-prandial glucose levels and insulin, by they were also studied for long-term effects, including weight loss, for a period of 8 weeks, taking 10 g guar gum twice daily. All subjects received the experimental therapy; there was no concurrent control group. The subjects were asked explicitly not to alter their normal diet or energy intake during the trial period. The subjects were reported to have lost an average of 4.3 kilograms (kg) after 8 weeks (said to be a statistically significant change), but in the absence of a control group, the agency does not consider this result to be persuasive evidence of effectiveness. The investigator's direction to the subjects not to alter their normal dietary habits does not alter the fact that these were obese subjects who were aware that the study was examining cholesterol and obesity. The agency believes that these circumstances would make the subject more conscious of their diet than they were prior to their entry into this study and that this awareness might well have led them to alter their eating patterns. The study does not rule out the possibility that guar gum can contribute to weight loss, but in the absence of a concurrent control, or an explicit historical control, the study is not considered to be an adequate and well-controlled study. Additionally, the number of subjects in this study is too small to provide sufficient information

to support the effectiveness of this ingredient.

The second study involved 21 subjects (12 males and 9 females), also recruited from an outpatient obesity clinic. The subjects were given either 10 g of wheat bran or 10 g of guar gum twice daily for a week and then switched to the other therapy. This procedure was repeated a total of 10 times for the patients who completed the study. Body weight was measured each week before treatment, and hunger ratings were also examined. The author's description of the study, with respect to the number of subjects completing the study and the fate of individual subjects, is not well described. It appears that only 7 of the 21 entered subjects completed all 10 weeks of the study. In those subjects, there was a mean weight loss of 7 kg. The fate of the other 14 subjects is not clear; however, a table in the publication provides information on 9 subjects who the author describes as having completed the 10-week study. In this table, the average weight loss each week is presented according to whether the subjects were on guar gum or wheat bran. The mean weekly weight loss of 0.94 kg on guar gum was not significantly different from the weight loss of 0.64 kg on wheat bran ($p < 0.1$). How the 9 subjects in this analysis differ from the 7 subjects in the other analysis is not clear from the information provided. Even if one ignores potential carryover effects and the impossibility of determining which subjects were included in the results and why, the two treatments were not significantly different. Although the results of this study do not rule out a possible effect of guar gum, the study does not support an effect of guar gum on weight control because no significant difference in weight loss between the groups was found and because the conduct of the study was not described adequately.

The second publication (Ref. 7) involved an open, uncontrolled study in 11 hyperlipidemic subjects (4 men and 7 women) (Ref. 7). The study focused predominantly on blood lipids. The subjects were treated for 8 weeks with guar-containing crispbread—not the product described above, but one that might be considered somewhat related. The subjects had a mean weight loss of 2.4 kg over the 8-week period. As pointed out above, the agency believes that subjects who are conscious of being in a lipid trial might well be more attentive to the proper diet and fat content of their meals, and may lose weight in the absence of any medical treatment. A concurrent control group is essential to evaluate the effectiveness of

such a therapy. Although the agency again recognizes that the study does not rule out the possibility that guar gum-containing products might contribute to weight loss, it does not provide evidence that they do.

The third publication (Ref. 8) appears to be a reasonably well-designed trial of guar gum, 15 g/day, compared with a placebo (wheat flour containing no fiber), and with no treatment. Thirty three middle-aged women were identified as hypercholesterolemic during screening for the prevention of coronary heart disease. Eleven subjects each were randomized to 1 of 3 treatment groups: Guar gum, placebo, or no treatment. One subject dropped out of the guar gum treatment group, and her data were not included in any analyses. Thus, there were 10, 11, and 11 subjects in the guar gum, placebo, and no-treatment groups, respectively. The guar gum was administered as 5 g of granules (equivalent to 3.65 g pure guar gum) three times a day before meals. The placebo treatment, consisting of 5 g of wheat flour with no fiber, was also given three times a day before meals. Baseline measurements of blood lipid profiles, body weight, and blood pressure were taken every 4 weeks for a total of 3 times. Subjects were instructed to decrease their intake of saturated fats, simple carbohydrates, and excessive alcohol. Subjects in the 2 treatment groups appear to have been seen once a month for 4 months; the no-treatment group appears to have been seen only at the end of 4 months.

Individual subjects data were not provided. Mean body weights at baseline were given as 62.9 kg (± 6.6 kg), 66.1 kg (± 13.3 kg), and 63.3 kg (± 9.6 kg), respectively. After 4 months, the guar gum group had a mean weight of 60.4 kg (± 9.5 kg), a 2.5 kg decrease. The decreases seen in the placebo and no-treatment groups were 0.4 and 0.6 kg, with final weights of 65.7 kg (± 17.9 kg) and 62.7 kg (± 13.6 kg), respectively. The authors did not compare treatments. Instead, they did within-treatment comparisons of baseline and month 4 body weight. They concluded that month 4 body weight was significantly lower than baseline only in the guar gum group. However, when guar gum treatment is compared with placebo treatment, there is no significant difference between the two groups (independent sample t-test, $p = .413$).

Although body weight did decrease more in the guar gum group over 4 months than in the other groups, the study does not demonstrate the effectiveness of guar gum as a weight loss agent, as there was no statistically

significant difference between guar gum and either placebo or no treatment. In addition, the study was not specifically designed to study weight loss and was not done solely in obese subjects. Therefore, the results, even if favorable, would not necessarily be applicable to the population of interest. Further, because the study was not intended to study weight loss, this raises the problem of making comparisons with unrelated data and drawing invalid conclusions from the data.

The agency concludes that the results of the three cited studies are not adequate to support the effectiveness of guar gum as an ingredient in OTC weight control drug products. Two of the reports provided data from uncontrolled, poorly-designed studies (Refs. 6 and 7), and the one well-designed study did not show a significant difference in weight loss when the guar gum group was compared with either the control or the no-treatment group (Ref. 8).

Based on the above information, the agency concludes that there are not adequate data to support the effectiveness of guar gum as an ingredient in OTC weight control drug products. Further, there are data indicating a safety hazard of esophageal obstruction from the use of weight control drug products containing this ingredient. Recently, the agency issued a number of regulatory letters (Refs. 9 and 10) to manufacturers of weight control drug products containing guar gum. The agency stated that such products are 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)), and that the products are misbranded in that their labeling is false and misleading by representing and suggesting that there is substantial scientific evidence to establish that the products are safe and effective for use as weight control drugs. Further, these products do not have approved new drug applications filed pursuant to section 505(b) of the act (21 U.S.C. 355(b)). Accordingly, FDA requested the manufacturers to cease distribution of such products. Therefore, FDA concludes that guar gum-containing weight control drug products are not appropriate for OTC use. Accordingly, the agency is reclassifying guar gum for use in OTC weight control drug products from Category III to Category II.

References

- (1) Adverse Drug Reaction Reports, in OTC Volume 17ETFR, Docket No. 81N-0022, Dockets Management Branch.
- (2) Gebhard, R. L., and J. Albrecht, "The Diet Pill That Worked," Letter to the Editor,

The New England Journal of Medicine, 322:702, 1990.

(3) Ranft, K., and W. Imhof, "Bolusobstruktion des Distalen Oesophagus Durch Pflanzliche Quellstoffe (Guarmehl)," *Deutsche Medizinische Wochenschrift*, 108: 1968-1969, 1983.

(4) Sorensen, A. J., and O. R. Rasmussen, "Synkestop Efter Indtagelse af Fiberholding Helsekostprodukt Lej-Guar," *Ugeskrift for Laeger*, 145:171-172, 1983.

(5) News Release, United Kingdom Ministry of Agriculture, Fisheries and Food, "Macgregor Bans Health Risk Slimming Pills," 212/89, May 23, 1989.

(6) Krotkiewski, M., "Effect of Guar Gum on Body-Weight, Hunger Ratings and Metabolism in Obese Subjects," *British Journal of Nutrition*, 52:97-105, 1984.

(7) Jenkins, D. J., et al., "Dietary Fiber and Blood Lipids: Treatment of Hypercholesterolemia with Guar Crispbread," *American Journal of Clinical Nutrition*, 33:575-581, 1980.

(8) Tuomilehto, J., et al., "Effect of Guar Gum on Body Weight and Serum Lipids in Hypercholesterolemic Females," *Acta Medica Scandinavica*, 208:45-48, 1980.

(9) Letter from R. G. Chesmore, FDA, to Health Care Products, Inc., in OTC Volume 17ETFR, Docket No. 81N-0022, Dockets Management Branch.

(10) Letter from D. L. Michels, FDA, to Universal Nutrition Corporation, Nutrition Headquarters, Fat Busters, Inc., in OTC Volume 17ETFR, Docket No. 81N-0022, Dockets Management Branch.

The Panel identified caffeine and caffeine citrate as ingredients having a stimulant effect but no anorectic effect (47 FR 8466 at 8472). The Panel reviewed one study on a combination product containing phenylpropanolamine hydrochloride and caffeine as an anorectic only. Although the study showed a greater weight loss for the combination than when using the phenylpropanolamine alone, the results were not statistically significant because the study was not long enough and did not contain a sufficient number of subjects (47 FR 8476). Based on the Panel's evaluation, the agency is classifying caffeine and caffeine citrate as Category II ingredients for weight control use in this document.

B. The Agency's Tentative Conclusions on Category II and III Ingredients in OTC Weight Control Drug Products

The agency has determined that no substantive comments or additional data have been submitted to the OTC drug review to support any of the ingredients listed above as being generally recognized as safe and effective 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 these ingredients should be found to be not generally recognized

as safe and effective for OTC use before a final monograph for OTC weight control drug products is established.

Accordingly, any drug product containing any of these ingredients and labeled for OTC use as a weight control drug product will be considered nonmonograph and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (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 regulation 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 or establish a monograph for OTC weight control drug products to include any of the above ingredients. (See 21 CFR 10.30.) Any OTC weight control drug product containing any of the above ingredients initially introduced or initially delivered for introduction into interstate commerce after the effective date of final rule that removes these Category II and III ingredients from the market 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 subject to the final rule that is repackaged or relabeled after the effective date of the rule would be required to 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.

The agency has examined the economic consequences of this proposed rulemaking in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354). The agency invited public comment in the advance notice of proposed rulemaking on OTC weight control drug products regarding any impact that this rulemaking would have on OTC weight control drug products (47 FR 8466 at 8489). No comments on economic impacts were received. Moreover, manufacturers of products containing these ingredients have not provided any substantive data to support their continued marketing. Accordingly, the agency concludes that there is no basis for the continued marketing of these ingredients for OTC use in weight control drug products. Further, there are ingredients recommended by the Panel which manufacturers can use to

reformulate affected products. As a result of this proposal, manufacturers may need to reformulate or discontinue marketing some products prior to promulgation of the final monograph on OTC weight control drug products. If reformulation is chosen, there will be no additional costs because reformulation will 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. Manufacturers will benefit from being able to use alternative ingredients that a Panel has recommended be found to be generally recognized as safe and effective without incurring the additional expense of clinical testing for these ingredients. Based on the above, the agency has determined that this proposed rule is not a major rule under Executive Order 12291. Further, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by December 31, 1990. Such comments should be submitted to the Dockets Management Branch (address above) and identified with the docket number found in brackets in the heading of this document. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined 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.

Interested persons may, on or before December 31, 1990, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the Commissioner on the proposed rulemaking. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 31, 1990. Three

copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy.

Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief.

Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

Dated, September 1, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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