DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 81N-0022]

Weight Control Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) weight control drug products are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by May 27, 1982, and reply comments by June 28, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on March 2, 1979 a report on OTC weight control drug products from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed order containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC weight control drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA; however, the agency has reviewed a portion of the Panel's report because the Panel recommended a higher dosage for phenylpropanolamine than had previously been marketed OTC, and recent reports in the medical literature have shown moderate to marked elevations in blood pressure induced by this ingredient. The Panel's findings appear in this document to obtain public comment before the agency reaches a final decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on all matters contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC weight control drug products as a notice of proposed regulation. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which had the status of a proposed rule. Final agency action occurs in the final monograph, which had the status of a final rule.

The agency notes that the Panel placed single doses of 25 to 50 milligrams (mg) and a total daily dose of not more than 150 mg of phenylpropanolamine hydrochloride in Category I. In addition, the Panel recommended that the single and daily doses for any timed-release preparation not exceed those for immediate-release preparations.

The agency is aware of reports of data, made available after the Panel's report was submitted, indicating that phenylpropanolamine doses higher than those currently marketed (but within the higher range recommended as safe by the Panel) cause elevation of blood pressure. Other studies show that currently marketed dosages produce no such effect. The most striking new finding, reported by Horowitz et al., demonstrates the acute effects of phenylpropanolamine from a single timed-release capsule (Ref. *1*). Specifically, in a double-blind trial, single timed-release capsules containing 85 mg and 50 mg of phenylpropanolamine respectively were compared with a placebo in medical students who did not have hypertension or heart disease. Both capsules had been marketed in Australia, the 85-mg capsule as a weight control product, and the 50-mg capsule as a nasal decongestant. The 85-mg product was given to 37 subjects, and a matching placebo was given to 35. In those who received the 85-mg product, mean supine diastolic pressure rose from 70 millimeters (mm) mercury at baseline to a mean peak level of 94 mm mercury. Peak supine diastolic pressures of 100 mm mercury or greater were recorded in 12 of the 37 subjects (32 percent). Peak blood pressure elevations occurred between 1.5 and 3 hours after phenylpropanolamine ingestion. In the placebo group, mean supine diastolic blood pressure rose from 74 mm mercury at baseline to a peak of 77 mm mercury; only one subject receiving a placebo had a peak diastolic blood pressure as high as 100 mm mercury. Side effects were reported by 20 subjects receiving the 85-mg product and 1 subject receiving a placebo. These effects, including dizziness, palpitations and headache, corresponded closely to the increase in blood pressure. The 50-mg product was given to 34 subjects, and a matching placebo to 35. In those who received the 50-mg product, mean supine diastolic blood pressure rose from 78 mm mercury to a peak of 83 mm mercury. In four subjects (11 percent), diastolic blood pressure rose to 100 mm mercury or more (maximum pressure of 110 mm mercury in one subject). There was no change in blood pressure in the placebo group. There were no other adverse reactions in either group.

Whether the significantly greater incidence and severity of hypertension seen with the 85-mg product as compated with the 50-mg product is due only to a higher dosage (85 mg vs. 50 mg phenylpropanolamine) or also to a greater release rate was not studied by the investigators. It should be noted, however, that the Panel recommended a dosage up to 50 mg of phenylpropanolamine in adults for single-dose immediate-release preparations. Eleven percent of the subjects given the 50-mg product in a timed-release capsule developed clinically significant hypertension. It is not likely, however, that the entire dose was released at one time, so that, with an immediate-release preparation of 50 mg, it would be expected that more than 11 percent of subjects would exhibit a clinically significant increase in supine blood pressure.

The authors did not report standing blood pressures. No subjects developed postural hypotension.

In another study (double blind, crossover) by Horowitz et al. (Ref. *2*) in six volunteer medical students with a baseline supine diastolic pressure of about 82 mm mercury, a single capsule of the same timed-released 85-mg product described above caused a mean peak supine diastolic pressure of 100 mm mercury. Levels of greater than 110 mm mercury were noted in two of the six subjects. Adverse effects (malaise, headache, tightness of the chest) were reported in five of six subjects. Blood pressure fell slightly when the placebo was given, and there were no adverse reactions to the placebo. With the 85-mg product, supine pulse rate dropped from 71 at baseline to a low of 55. The authors state that standing blood pressure also rose in the 85-mg product group but to a less marked degree. They did not give the figures for standing blood pressure. In the same article, the authors also report a case of severe hypertension in a patient taking the 85-mg product. A 17-year-old woman had ingested six capsules hoping for an increased anorectic effect. Three hours later she developed severe headache with a supine blood pressure of 200/130 mm mercury. While the patient remained fully conscious and well-oriented, she was hospitalized for bed rest for 48 hours until her blood pressure level returned to 130/70 mm mercury. Frewein, Leonello, and Frewin (Ref. *3*) reported a similar case involving a 21-year-old woman following ingestion of a single 85-mg capsule. Both sets of authors question the safety and further OTC availability of phenylpropanolamine.

King (Ref. *4*) reported two cases of presumed hypertension. In one case, cerebral hemorrhage was observed upon examination 36 hours after ingestion of only two capsules of the 85-mg product. In the other case, one capsule of the 85-mg product resulted in palpitations and neck pain 30 minutes after ingestion. Although the maximum blood pressure level is not known in either case, the author reports that the symptoms resemble those in previously reported cases in which acute hypertensive episodes were documented after taking the 85-mg product.

Peterson and Vasquez (Ref. *5*) reported severe hypertension and cardiac arrhythmias in a 15-year-old woman who had been ingesting, as an anorectic, the labeled dose of three tablets a day of a combination of 25 mg of phenylpropanolamine and 25 mg of caffeine. The hypertension and arrhythmias were reversed with therapy, and the patient remained normotensive and without arrhythmias with no further therapy.

Cuthbert, Greenberg, and Morley (Ref. *6*), in a study on themselves (three men), found that a dose of 50 mg phenylpropanolamine caused a modest rise in supine systolic blood pressure between 18 and 26 mm mercury, but only a very slight rise in diastolic pressure. A dose of 100 mg produced a more pronounced rise in blood pressure, increasing the supine diastolic pressure to 97, 109, and 123 mm mercury respectively in the three subjects. There was no effect on blood pressure of 50 mg phenylpropanolamine in a marketed timed-release product containing 50 mg phenylpropanolamine plus belladonna alkaloids equivalent to 0.25 mg or of another marketed product containing 50 mg phenylpropanolamine plus 2.5 mg isopropamide. Following administration of placebo, there was a slight fall in blood pressure.

The agency is aware of an additional study published since completion of the Panel review that examined the safety of the lower dosage limit of phenylpropanolamine recommended by the Panel. Silverman et al. (Ref. *7*) evaluated the effects of a 25-mg phenylpropanolamine dose on 37 healthy normal males at 3 separate study sites. The study subjects were divided into three groups. The first group consisted of 15 subjects, each of whom received a single capsule dose of 25-mg phenylpropanolamine. Supine systolic and diastolic blood pressures and pulse measurements were taken just prior to administration of the drug and at 1, 2, and 3 hours following ingestion. A statistically significant decrease in pulse rates occurred at 2 and 3 hours after administration of the drug, compared to pulse rates prior to administration. Supine systolic and diastolic blood pressures taken after administration of the drug did not differ significantly from those taken before.

In the second group, each of 10 subjects received a single dose of a product containing a combination of 25 mg phenylpropanolamine hydrochloride and 100 mg caffeine. Pulse rates and supine systolic and diastolic blood pressures were measured 30 minutes before administration of the drug and 30, 60, 90, 120, 150, 180, 210, and 240 minutes after. There was no statistically significant difference in pulse rates and supine systolic and diastolic blood pressures taken before and at the eight intervals after administration of the drug.

The third group consisted of 12 subjects who participated in a double-blind crossover study using a single dose of 25-mg of phenylpropanolamine hydrochloride and matching placebo dose containing lactose. The research covered 2 study days. On the morning of each study day, each subject's pulse rate and supine diastolic and systolic blood pressures were determined and each subject then ingested either a drug or placebo capsule. Supine blood pressures and pulse rates were taken at 30, 60, 90, 120, 150, 180, 210 and 240 minutes after ingestion. Following a 48-hour washout period, the subjects were crossed over, using the dosage form they did not take on the first study day. No statistically significant difference between pulse rate and supine blood pressures of subjects taking the drug and subjects taking the placebo capsule was reported at any sample time.

Silverman el al. did not report standing blood pressures for the 37 subjects at any point during the study.

Although the interaction of phenylpropanolamine with monoamine oxidase inhibitors is well known, another interaction has been reported recently by Lee, Beilin, and Vandongen (Ref. *8*). Severe hypertension occurred in a patient taking indomethacin along with an 85-mg dose of phenylpropanolamine, although neither of the drugs was associated with hypertension in the patient when given alone. The authors postulate that the mechanism of action of indomethacin is inhibition of prostaglandin synthesis which will reduce prostaglandin-controlled negative feedback acting on catecholamine release at sympathetic nerve endings. (Phenylpropanolamine is known to release norepinephrine from sympathetic nerve endings. Many nonsteroidal anti-inflammatory agents, including aspirin, are known to inhibit prostaglandin synthesis. Aspirin, of course, is frequently taken with phenylpropanolamine in treatment of the common cold. The authors questioned the continued marketing of phenylpropanolamine in view of the postulated risk of severe hypertension caused by interactions with various commonly used drugs.

In a recent survey Dietz (Ref. *9*) reported on seven patients who experienced acute central nervous system effects. These effects ranged from stimulation of the medullary respiratory center to tremor, restlessness, increased motor activity, agitation, and hallucinations. The author reviewed cases taken from emergency room records over a 6-month period. The patients were all women, ranging in age from 17 to 45 years. Side effects appeared within 1 to 2 hours after ingesting a single 50- or 75-mg dose of phenylpropanolamine. Results of

physical examinations, with the exception of tachypnea and tachycardia, were normal. Several patients complained of nausea and anxiety. All side effects, with the exception of those in one patient, subsided over the course of 2 to 4 hours without treatment. The author stated that physicians should be alerted to the possible side effects from ingesting preparations containing phenylpropanolamine. He concluded that warnings on products containing phenylpropanolamine should include the possible serious central nervous system effects of this agent.

In conclusion, these studies have reported that 11 percent of subjects given a single dose of 50 mg phenylpropanolamine in a timed-release product developed diastolic hypertension (100 mm mercury or more), and a single dose of 85 mg phenylpropanolamine in a timed-release product caused diastolic hypertension, sometimes severe, in 32 to 33 percent of subjects. Cases of significant hypertension, symptomatic and asymptomatic, have been reported by others in subjects and patients taking 25 mg, 50 mg, 85 mg, or 100 mg phenylpropanolamine. The interaction with indomethacin raises the possibility that an interaction might also occur with aspirin and other drugs with similar action. Acute central nervous system effects have also been reported. In addition, the use of weight control products containing phenylpropanolamine by obese persons with hypertension may significantly increase their risk of heart attack, stroke, and kidney failure. In considering the positive association between hypertension and obesity, the increase in risks becomes evident, because obese persons are most likely to use weight control products.

For these reasons, the agency is concerned about the suitable safe dose level of phenylpropanolamine hydrochloride for use in weight control products. Further studies appear necessary to resolve the safety questions raised by the studies discussed above. These studies would be needed to determine the extent to which phenylpropanolamine induces hypertension in normotensive patients or aggravates pre-existing hypertension, and interacts with aspirin and other medications that inhibit prostaglandin synthesis at the dose levels recommended for use by the Panel. Therefore, at this time the agency is specifically requesting comments and information on this issue.

At this time, the agency does not find it necessary to take action to remove from the market products containing phenylpropanolamine at dosage levels which have a marketing history of use in OTC weight control drug products. The daily dosage levels in these marketed products are an immediate-release dose of up to 37.5 mg and a timed-release dose of up to 75 mg phenylpropanolamine, with the total daily dose not to exceed 75 mg in either case.

Until the safety questions described above are resolved, the agency will not allow any increase in the OTC phenylpropanolamine dosages currently permitted, nor will it require any decrease in the currently permitted dosages for immediate-release products.

The agency points out that the OTC drug regulations establish conditions for marketing OTC active ingredients after publication in the **Federal Register** of an advance notice of proposed rulemaking but prior to publication of an applicable final monograph (final rule) (21 CFR 330.13(b)(2)). Under these regulations any OTC drug product containing an active ingredient with a dosage level higher than that in use on December 4, 1975 is regarded as a new drug and is subject to immediate regulatory action, even though a Panel may have recommended that the ingredient and/or dosage be considered Category I, if the agency issues a notice disagreeing with the Panel's recommendation and adopting a different position. The weight control drug products in use on December 4, 1975 had a maximum daily dose level or 75 mg, immediate-release doses of 25 to 37.5 mg, and a timed-release dose of 75 mg of phenylpropanolamine hydrochloride. OTC weight control drug products with a higher single and/or total daily dose of phenylpropanolamine than that available on December 4, 1975 are subject to immediate regulatory action in the absence of an approved new drug application.

Although the studies discussed above show that further testing is needed, the doses used are, with two exceptions (Peterson and Vasquez, Ref. *5*, and Silverman et al., Ref. *7*), above the levels found in currently marketed immediate-release products. Both this Panel and the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products have considered 25-mg single doses to be Category I, based on different, earlier studies. This Panel believed that these earlier studies warranted a Category I classification for single doses as high as 50 mg. Both Panels found that there were few reported side effects from doses up to 50 mg in nasal decongestants in spite of extensive use. Agency regulations currently recommend, in 21 CFR 369.20, that all marketed drug products containing phenylpropanolamine bear or contain a statement warning against use by individuals with high blood pressure, heart disease, diabetes, or thyroid disease. The agency will continue to monitor further studies and information on phenylpropanolamine. If new information shows that any of the existing uses, dosage levels, or dosage forms of phenylpropanolamine pose safety risks requiring immediate action, the agency will provide notice of its determination, and the marketing of these products after that time will require an approved New Drug Application (NDA) or be subject to appropriate regulatory action.

In addition to monitoring further studies and information on all phenylpropanolamine studies, the agency specifically requests information on the dissolution rates of timed-release products. This information an aid the agency in evaluating whether any safety problem is posed by these products that requires action before a final monograph is issued. It is also important to recognize that, under 21 CFR 200.31, timed-release formulations that contain a quantity of an active ingredient that is not generally recognized as safe as a single dose are regarded as new drugs. Therefore, the agency points out that an approved NDA will be necessary at the time of a final monograph to domonstrate that phenylpropanolamine in a timed-release dosage form is properly manufactured and controlled to release the total dose at a safe rate. Any such product without an approved NDA will be subject to regulatory action after the final monograph becomes effective.

At this time the agency has not evaluated the Panel's findings regarding the effectiveness of weight control drug products. However, the agency points out the Panel's finding that "while weight control drug products may assist in reducing an individual's appetite, a significant weight loss can be achieved only if accompanied by a reduction in total daily caloric intake below the energy output." (See part II. paragraph B. below—*General Discussion.*) In order to convey this point to consumers the Panel recommended that all product labeling contain the following statement, under the heading "*Directions*": "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake." (See part III. paragraph A.2. below—Category I labeling.) The agency is concerned that the past promotion of some weight cotrol drug products may

have engendered a misunderstanding among potential consumers that weight loss results directly from the use of the drug product, and, therefore, it is unnecessary to diet in order to lose weight. In order to overcome this possible misunderstanding the agency strongly recommends that manufacturers of OTC weight control drug products voluntarily undertake immediate steps to incorporate the Panel's recommended statement in their labeling.

The agency also points out that the Panel recommends as Category I the combination of phenylpropanolamine hydrochloride and caffeine with labeling that would bear all the warnings and directions specified in proposed §§ 340.50(d) and 357.550(c), as well as a consolidated statement of indications. The agency invites comment on alternate or consolidated labeling of such products. The agency is particularly concerned that the directions for phenylpropanolamine hydrochloride, as proposed in § 357.550(d), specify daily doses for up to 3 months, whereas the warning for caffeine as proposed in § 340.50(c)(2) states, "For occasional use only." FDA will address this difference in labeling in the tentative final monograph.

References

(1) Horowitz J. D. et al., "Hypertensive Responses Induced by Phenylpropanolamine in Anorectic and Decongestant Preparation," *Lancet,* 1:60–61, 1980

(2) Horowitz, J. D. et al., "Hypertension and Postural Hypotension Induced by Phenylpropanolamine (Trimolets)," *Medical Journal Australia,* 1:175–176, 1979.

(3) Frewin, D. B., P. P. Leonello, and M. E. Frewin, "Hypertension After Ingestion of Trimolets," *Medical Journal Australia,* 2:497–498, 1978.

(4) King, J., "Hypertension and Cerebral Hemorrahge After Trimolets Ingestion," *Medical Journal Australia,* 2:258, 1979.

(5) Peterson, R. B., and L. A. Vasquez, "Phenylpropanolamine-Induced Arrhythmias," *Journal of the American Medical Association,* 223:324–325, 1973.

(6) Cuthbert, M. F., M. P. Greenberg, and S. W. Morley, "Cough and Cold Remedies: A Potential Danger to Patients on Monoamine Oxidase Inhibitors," *British Medical Journal,* 1:404–406, 1969.

(7) Silverman, et al., "Lack of Side Effects form Orally Administered Phenylpropanolamine and Phenylpropanolamine with Caffeine: A Controlled three-Phase Study," *Current therapeutic Research,* 28:185–194, 1980.

(8) Lee, K. Y., L. J. Beilin, and R. Vandongen, "Severe Hypertension After Ingestion of an Appetite Suppressant (Phenylpropanolamine) with Indomethacin," *Lancet,* 1:1110–1111, 1979.

(9) Dietz, A. J., "Amphetamine-like Reactions to Phenylpropanolamine ," *Journal of the American Medical Association, 245:601–602, 1981.*

In the preamble to this report, the agency is inviting comment on additional information that has appeared in the medical literature after the Panel adopted its report. The agency is also disagreeing with higher dosage levels recommended by the Panel for phenylpropanolamine hydrochloride and is currently limiting the marketing of products containing phenylpropanolamine to those dosage levels for which there is a marketing history of use in OTC weight control products. Because this represents a maintenance of existing marketing conditions, the agency has determined that there is no regulatory impact of this action at this time.

The agency's full position on OTC weight control drug products will be stated initially when the tentative final monograph is published in **Federal Register** as a notice of proposed regulation. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601–612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC weight control drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing necessary, if any. Comments regarding the impact of this rulemaking on OTC weight control drug products should be accompanied by appropriate documentation.

In accordance with § 330.10a)(2), the Panel and FDA have held as confidential all information concerning OTC weight control drug products submitted for consideration by the Panel. All the submitted information will be put on public display in Dockets Management Branch, Food and Drug Administration, after March 29, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 338 (D.D.C. 1979).The Court in *Culter* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler,* FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into

interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information; on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredients" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the **Federal Register** of August 27, 1975 (40 FR 38179), a notice supplemented the initial notice with a detailed list of ingredients which included weight control active ingredients.

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

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

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

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator. Enrique Fefer, Ph.D., served as the Executive Secretary until July 1976, followed by George W. James, Ph.D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978; Roger Gregorio followed as the liaison for the Offce of New Drug Evaluation. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph.

To expand its medical and scientific base, the Panel called upon the following consultants for advice in areas which required particular expertise:

Ralph B. D'Agostino, Ph.D. (statistics)
Lynn R. Brady, Ph.D. (pharmacognosy)
Arthur E. Schwarting, Ph.D. (pharmacognosy)

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for weight control drug products in this document. The review of other categories of miscellaneous internal drug products will be continued by the Panel, and its findings will be published periodically in the **Federal Register** during the Panel's deliberations.

The Panel was first convened on January 13, 1975, in an organizational meeting. Working meetings were held on the following dates (the dates of those meetings which dealt with the topic of this document are in italics): February 23 and 24, March 23 and 24, April 27 and 28, June 22 and 23, *September 21 and 22,* and November 16 and 17, 1975; *February 8 and 9, March 7 and 8, April 11 and 12, May 9 and 10, July 11 and 12,* and *October 10 and 11,* 1976; February 20 and 21, *April 3 and 4, May 15 and 16, July 9, 10, and 11,* October 15, 16, and 17, and December 2, 3, and 4, 1977; January 28, 29, and 30, March 10, 11, and 12, May 5, 6, and 7, June 23, 24, and 25, *August 4, 5, and 6, September 29, 30, and October 1,* and *November 17, 18, and 19,* 1978; *January 19 and 20,* and *March 2,* 1979.

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

The following individuals were given an opportunity to appear before the Panel to express their views on weight control drug products, either at their own or at the Panel's request:

Stanley L. Altschuler, M.D.
Antony A. Conte, M.D.
Edgar E. Coons, Ph.D.
Devra Lee Davis, Ph.D
Donald J. Flaster, M.D.
Solomon I. Griboff, M.D.
Charles Hamilton, Ph.D.
Saul Heller, M.D.
Bartley G. Hoebel, Ph.D.
Peg Kaplin
Harry R. Kissileff, Ph.D.
Kurt S. Konigsbacher, D.Sc.
James Ramey, M.D.
Marianne Sebok, M.D.
Harold I. Silverman, D.Sc.
Edward L. Steinberg, M.S., O.D.
Charles Winick, Ph.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through March 2, 1979 in arriving at its conclusions and recommendations for OTC weight control drug products.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC weight control drug products are set out in three categories:

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

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

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

The Panel reviewed 111 weight control active ingredients and classified 2 ingredients in Category I, 98

ingredients in Category II, and 11 ingredients in Category III.

I. Submission of Data and Information

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

A. Submissions by Firms

Firm and Marketed Products

Alleghany Pharmaceutical Corp., New York, NY 10017—Hungrex w/P.P.A. tablets, Permathene-12 capsules.
Fox Pharmacal, Inc., Ft. Lauderdale, FL 33309—Odrinex tablets, Super-Odrinex tablets.
Marion Laboratories, Inc., Kansas City, MO 64137—Pretts tablets.
Purex Corp., Carson, CA 90745—Slendron capsules.
Thompson Medical Co., Inc., New York, NY 10022—Appedrine tablets, Slim-Mint gum, Slim-Line candy, Prolamine capsules.

B. Labeled Ingredients Contained in Marketed Products

1. *Ingredients in products submitted to the Panel for review.*

Alginic acid
Benzocaine
Caffeine
d-Calcium pantothenate
Citric acid
Corn syrup
Dextrose
Glycerides (mono- and di-)
Iron (ferrous sulfate, U.S.P.)
Lecithin
Methylcellulose
Niacinamide
Phenylpropanolamine hydrochloride
Riboflavin (vitamin B_2)
Salt (sodium chloride)
Sodium bicarbonate
Sodium carboxymethylcellulose
Sucrose
Thiamine mononitrate (vitamin B_1)
Vegetable oil
Vitamin A
Vitamin A palmitate
Vitamin B_1 (thiamine)
Vitamin B_2 (riboflavin)
Vitamin B_6 (pyridoxine hydrochloride)
Vitamin B_{12} (cyanocobalamin)
Vitamin B_{12} (cobalamin concentrate)
Vitamin C (ascorbic acid)
Vitamin D
Vitamin E (*dl*-alpha-tocopheryl acetate)
Xanthan gum food grade

2. *Other ingredients reviewed by the Panel.* In addition to those ingredients included in the products submitted to the Panel, the following ingredients were listed in the **Federal Register** notice of August 27, 1975 (40 FR 38179):

Alcohol
Alfalfa
Anise oil
Arginine
Biotin
Bone marrow-red-glycerin extract
Buchu
Buchu, potassium extract
Caffeine citrate
Calcium
Calcium carbonate
Calcium caseinate
Calcium lactate
Carrageenan
Choline
Chondrus
Cnicus benedictus
Copper
Copper gluconate
Corn oil
Corn silk, potassium extract
Cupric sulfate
Cystine
Dioctyl sodium sulfosuccinate
Ferric ammonium citrate
Ferric pyrophosphate
Ferrous fumarate
Ferrous gluconate
Flax seed
Folic acid
Fructose
Guar gum
Gum karaya
Histidine
Hydrastis canadensis
Inositol
Iodine
Isoleucine
Juniper, potassium extract
Lactose
Leucine
Liver concentrate
L-lysine
L-lysine monohydrochloride
Magnesium
Magnesium oxide
Malt
Maltodextrin
Manganese citrate
Mannitol
Methionine
Organic vegetables
Pancreatin enzymes
Pantothenic acid
Papain
Papaya enzymes
Pepsin
Phenacetin
Phenylalanine
Phosphorus
Phytolacca berry juice
Pineapple enzymes
Potassium citrate
Psyllium
Rice polishings
Saccharin
Sea kelp
Sea minerals
Sesame seed
Sodium
Sodium caseinate
Soy bean protein
Soy meal
Threonine
Tricalcium phosphate
Tryptophan
Tyrosine
Uva ursi
Uva ursi, potassium extract
Valine
Vitamin A acetate
Vitamin D_2
Wheat germ
Yeast

C. Classification of Ingredients

1. *Active ingredients.*

Alginic acid
Benzocaine
Carrageenan
Carboxymethylcellulose sodium
Chondrus
Guar gum
Karaya gum
Methylcellulose
Phenylpropanollamine hydrochloride
Psyllium
Sea Kelp
Sodium bicarbonate
Xanthan gun

2. *Other ingredients.* The Panel was not able to locate not is it aware of any significant body of data demonstrating the safety and effectiveness of the following OTC ingredients when used for weight control. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be discussed further in this document.

Alcohol
Alfalfa
Anise oil
Arginine
Ascorbic acid (vitamin C)
Biotin
Bone marrow-red-glycerin extract
Buchu
Buchu, potassium extract
Calcium
Calcium carbonate
Calcium caseinate
Calcium lactate
Calcium pantothenate (*D*-calcium pantothenate)
Choline
Citric acid
Conicus benedictus
Copper
Copper gluconate
Corn oil
Corn syrup
Corn silk, potassium extract
Cupric sulfate
Cyanocobalamin (vitamin B_{12})
Cystine
Dextrose
Dioctyl sodium sulfosuccinate
Ferric ammonium citrate
Ferric pyrophoshate
Ferrous fumarate
Ferrous gluconate
Ferrous sulfate (iron)
Flax seed
Folic acid
Fructose
Glycerides (mono-and di-)
Histidine
Hydrastis canadensis
Inositol
Iodine

Isoleucine
Juniper, potassium extract
Lactose
Lecithin
Leucine
Liver concentrate
L-lysine
L-lysine monohydrochloride
Magnesium
Magnesium oxide
Malt
Maltodextrin
Manganese citrate
Mannitol
Methionine
Niacinamide
Organic vegetables
Pancreatin enzymes
Pantothenic acid
Papain
Papaya enzymes
Pepsin
Phenacetin
Phenylalanine
Phosphorus
Phytolacca berry juice
Pineapple enzymes
Potassium citrate
Pyridoxine hydrochloride (vitamin B_6)
Riboflavin
Rice polishings
Saccharin
Sea minerals
Sesame seed
Sodium
Sodium caseinate
Sodium chloride (salt)
Soy bean protein
Soy meal
Sucrose
Thiamine hydrochloride (vitamin B_1)
Thiamine mononitrate (vitamin B_1 mononitrate)
Theronine
Tricalcium phosphate
Tryptophan
Tyrosine
Uva ursi
Ura ursi, potassium extract
Valine
Vegetable
Vitamin A
Vitamin A acetate
Vitamin A palmitate
Vitamin D
Vitamin D_2
Vitamin E
Wheat germ
Yeast

3. *Ingredients having a stimulant effect but no anorectic effect:*

Caffeine
Caffeine citrate

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after March 29, 1982, in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definition of Terms

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

1. *Obesity.* An increase in body weight beyond the limitation of skeletal and physical requirements as the result of an excessive accumulation of fat in the body; that physical state in which body weight in relation to height and body build is more than 10 percent above the ideal desirable weight determined from the Metropolitan Life Insurance Company table of desirable weights (ref. *1*).

2. *Anorectic.* An agent which reduces appetite.

Reference

(*1*) Metropolitan Life Insurance Company, "Desirable Weights for Men and Women," *Statistical Bulletin*, 58:5, 1977.

B. General Discussion

This document refers only to the common type of obesity which occurs in varying degrees in a significant percentage of our population, especially in those who have reached adulthood and who follow sedentary occupations. The condition is more common in females than in males. Obese persons as referred to in this document are otherwise free of known underlying organic causes such as hypothyroidism, hypothalamic disturbances, Frohlich's syndrome or hyperinsulinism.

The common type of obesity is always caused by the intake and absorption of food in excess of that needed by the body for its daily caloric energy output. Whenever the calories derived from food (whether protein, carbohydrate, or fat) are greater than the body needs, over a period of time the excess is stored as fat and obesity results. Childhood training in eating habits, changes in daily energy output, and psychological factors all may play a role in determining whether an individual develops obesity.

Anorectic drugs are sometimes used in an attempt to suppress appetite and thus reduce or control weight. The Panel wishes to stress that, while weight control drug products may assist in reducing an individual's appetite, a significant weight loss can be achieved only if accompanied by a reduction in total daily caloric intake below the energy output.

In this document the Panel evaluates the OTC anorectic drugs as to safety, effectiveness, and adequate labeling. The Panel at the same time, recognizes that effective and sustained weight reduction in large part depends upon the motivation of the person attempting to lose weight, the understanding that caloric reduction for weight loss must be temporary, and the correction of underlying psychological factors which may have originally produced the excessive caloric intake and gain in weight.

The Panel is aware that some weight control drug products now on the market contain a number of vitamins and minerals in addition to their weight control active ingredients. The Panel believes that it is the responsibility of the individual who is taking a weight control drug product to determine the dietary regimen to follow in order to maintain a well-balanced, low-caloric diet; therefore, the addition of vitamins and minerals serves no useful purpose for those following a well balanced diet. The Panel concludes that vitamins and minerals should not be constituents of weight control drug products.

The Panel reviewed timed release weight control drug products and concludes that such products are safe for OTC use when the amount of each safe and effective ingredient does not exceed the amount recommended in the specific ingredient review of non-timed release preparations. (See part III. paragraph A. below—Category I Conditions.) However, the Panel concludes that those timed release preparations which exceed the "per dose" or "daily dose" recommendations for non-timed release preparations, are not generally recognized as safe and effective at this time. The Panel concurs with the existing FDA regulations (21 CFR 200.31 (a) and (b)) which state:

* * * Any such dosage form that contains per dosage unit (for example, capsule or tablet), a quantity of active drug ingredients which is not generally recognized as safe for administration as a single dose under the conditions suggested in its labeling, is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act. (b) The fact that the labeling of this type of drug may claim delayed or prolonged release of all or some of the active ingredients does not affect the new-drug status of such articles. A new-drug application is required in any such case to demonstrate that the drug is in fact safe because it is properly made and controlled to release the total dose at a safe rate. It should be noted particularly that such dosage forms are regarded as new drugs even when the

total daily dosage recommended in the labeling is generally recognized as safe. * * *

C. Combination Policy

The Panel has reviewed FDA's general combination policy on OTC drug products (21 CFR 330.10(a)(4)(iv)) and believes that the policy is rational.

This policy is as follows:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and efffective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel believes that all combination weight control products must conform to each requirement of this general combination policy.

The Panel also believes that if a combination of ingredients is established which is intended to treat separate but concurrent conditions, the labeling of such a combination should inform the consumer that the product is to be used only when the symptoms of both conditions are present.

D. Labeling

The Panel has carefully reviewed the submitted labeling claims for products promoted for the reduction of obesity and has categorized them according to their acceptability into Category I, Category II, or Category III. The Panel is aware that there may be other terms that would be acceptable in expressing the same Category I indications.

Acceptable labeling must include the following: (a) The indication(s) for use, (b) pertinent warnings and contraindications, and (c) the recommended dosage range. The Panel believes that all labeling should be clear, concise, and easily read and understood by most consumers. It has followed this concept in the development of all Category I labeling. The Panel is also concerned about the size and color of the print used in labeling of these and all drug products, and recommends that the industry make the necessary effort to design labeling which can be read easily by consumers.

One of the primary functions of this Panel is to attempt to eliminate confusing labeling claims. Some of the labeling on currently marketed weight control drug products tends to be overly complicated, vague, unsupported by scientific data, and in some cases misleading. Accordingly, such labeling has been placed in Category II.

The indications for use should be simply and clearly stated, the directions for use should provide the user with enough information for safe and effective use of the product, and the label should include the statement that the product is intended only for temporary use in weight control and in conjunction with a reduced caloric intake. The Panel has defined "temporary" as "no more than a 3-month period" for ingestion of any weight control drug product, and this limitation must be clearly stated on the product's label. The Panel believes that a 3-month period should be long enough to establish the necessary change in eating habits. Therefore, the "Directions" should include the statement: "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding 3 months, because that should be enough time to establish new eating habits."

The Panel is also concerned that if two ingredients are indistinguishable with regard to effectiveness, then it is misleading to claim superiority for one of the ingredients. The Panel understands that its function is not to compare various ingredients in order to determine the OTC drug of choice but to determine only safety and effectiveness for active OTC miscellaneous internal ingredients, as well as proper dosage ranges, warnings, and contraindications.

Undocumented, vague, or misleading claims such as "Lose weight starting today * * *. Look your best, feel your best." and colloquial or provincial expressions that do not have meaning to most people must not be used. Statements which recommend phrophylactic use to prevent the onset of obesity shall not appear on the label, as the Panel believes that this might lead to overuse of the medication. In the labeling, effectiveness shall not be related to the taste, odor, consistency, or other physical characteristics of the product except as they may affect the action of the active ingredients. Phrases such as "modern aid," "most powerful diet aid," "strongest diet aid," and "delightful aid," may be vague and misleading and should be avoided unless supported by sound scientific data. Phrases which have no scientific foundation or that are meaningless to the consumer shall not be included in labeling, (e.g., "the modern aid," "delightful aids," and "sicientifically formulated").

The Panel is aware of the current OTC labeling regulation dealing with warning statements (21 CFR 330.1(g)) and recommends that weight control drug product labeling contain a "Warnings" section which contains the following warnings in addition to any drug-specific warnings: "Keep this and all drugs out of the reach of children" and "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." However, the Panel recommends that the latter statement read as follows: "In case of accidental overdose, contact a Poison Control Center, emergency room, or physician immediately for advice." The Panel believes that this revision will be more informative to the consumer. The statement, "Do not give this product to children under 12 years of age," should be included under "Warnings" because the Panel has not been presented with evidence demonstrating the safety of these products for this age group.

Since OTC products can be purchased by anyone, it is the view of the Panel that the public generally does not regard these products as medicines which, if used improperly, can result in injurious or potentially serious consequences. The public needs to be continually alerted to the idea that these products, like all medicines, carry some risk and should be treated with respect. The consumer should also be informed of any possible signs of known toxicity or any symptoms requiring discontinuation of the use of the drug so that appropriate steps may be taken before more severe consequences become apparent.

In addition, the Panel recommends that instructions for the effective use of the product should be displayed prominently on all package labeling.

As previously stated, the Panel recommends that the labeling of combination products intended to treat separate but concurrent conditions should inform the consumer that the product is to be used only when treatment of both conditions is necessary.

The Panel recommends that the label should contain a listing of all ingredients and that it should clearly indicate which are active and which are inactive. Active ingredients should be listed by their established names, and the label should state the quantity of the active ingredient per dosage unit.

III. Weight Control Drug Products

A. Category I Conditions

The following are category I conditions under which weight control drug products are generally recognized as safe and effective and not misbranded.

1. *Category I active ingredients.*

Benzocaine
Phenylpropanolamine hydrochloride

a. *Benzocaine.* The Panel concludes that benzocaine (also known as ethyl aminobenzoate) is generally recognized as safe and effective for OTC weight control in the dose noted below.

(1) *Safety.* Benzocaine is a topical anesthetic of low toxicity. It is relatively insoluble in water and is poorly absorbed (Refs. *1* and *2*). Historically, the use of benzocaine preparations for topical anesthesia, both on the skin and mucous membranes, has been reported many times and has been associated with a high degree of safety. It has been used widely in troches and lozenges containing 1 to 10 mg of benzocaine for the treatment of pharynitis with few side effects. Since benzocaine was introduced in 1903, the medical literature contains a great many case reports and references to its safety and clinical use both as a prescription drug and for OTC use. It is beyond the scope of this Panel to cite a detailed literature survey and case by case report.

Benzocaine, however, is not completely innocous. Allergic sensitivity reactions have infrequently been reported to occur after use as a local anesthetic (Ref. *3*). Methemoglobinemia has been reported rarely after use of benzocaine for diaper rash in an infant (Ref. *4*). The Panel concurs with the findings of the Advisory Review Panel on OTC Topical Analgesic Drug Products (OTC External Analgesic Report), published in the **Federal Register** of December 4, 1979 (44 FR 69768), that there is little or no evidence in controlled, investigative, or epidemiological studies that benzocaine is a potent sensitizer or strong allergen.

The Panel concludes that benzocaine is safe for oral use as an OTC anorectic in a dose of 3 to 15 mg in gum, logenzes, or candy.

(2) *Effectiveness.* One of the factors involved in overeating, and the resulting obesity, is the need to satisfy the sense of taste. Benzocaine is a topical anesthetic of low solubility which acts primarily on the nerve endings (Refs. *1* and *2*). The anesthetic action of benzocaine can be prolonged by keeping the preparations in contact with the mucosa, since its action is entirely within the skin or mucous membranes (Ref. *3*). This action can be obtained through the use of gum, lozenges, or candy containing benzocaine. There appears to be a decreased ability to detect degrees of sweetness by taste perception after chewing gum containing benzocaine (Refs. *5* and *6*).

Studies in weight control with benzocaine in both chewing gum and candy lozenges have demonstrated effective weight loss. Gould (Refs. *7* and *8*) in two studies reported a 1.5 to 2.0 pounds per week weight loss using lozenges containing benzocaine and essential oils in conjunction with dietary guidelines. Plotz (Ref. *9*) reported a satisfactory weight loss (2 pounds per week) in 45 of 50 patients using a benzocaine-methycellulose gum in conjunction with dietary instructions. McClure and Brusch (Ref. *10*) studied 308 patients in a comparative study over a period of 4 to 21 weeks and reported an average weight loss of 3.03 pounds per week over the 4-week period (53 out of the original 62 completed the 4-week trial) and 2.20 pounds per week over the 21-week period (43 out of the same 62 completed the entire study) for those patients using a benzocaine-caffeine-vitamin lozenge as an anorectic in conjunction with dietary restrictions.

In addition to the human studies cited above, work has been performed on rats by Coons (Ref. *11*) demonstrating the effect of a local anesthetic on hunger reduction. Rats were implanted with electrodes into the hypothalamus. The hypothalamus controls the sense of hunger and the taste recognitions of food. With appropriate electrical stimulation it was possible to induce the rats to eat at the desire of the operator. When the rats' tongues were anesthetized with a topical application of a 2 percent tetracaine (a local anesthestic which is structurally similar to benzocaine) solution, the same degree of stimulation that had previously been used did not induce the rats to eat. The Panel considers this study to be an objective demonstration of the effectiveness of a local anesthetic on hunger reduction.

The Panel concludes that benzocaine in the form of gum, lozenges, or candy is an effective OTC drug product for weight control.

(3) *Dosage.* The Panel has determined that a dose of 3 to 15 mg for use in gum, lozenges, or candy just prior to food consumption is generally recognized as safe and effective for weight control.

(4) *Labeling.* The Panel recommends the Category I labeling for weight control ingredients. (See part III. paragraph A.2. below—Category I labeling.)

References

(*1*) Ritchie, J. M., and P. J. Cohen, "Local Anesthetics," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Co., New York, p. 391, 1975.

(*2*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 269, 1977.

(*3*) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 987, 1975.

(*4*) Haggerty, R. J., "Blue Baby Due to Methemoglobinemia," *New England Journal of Medicine,* 267:1303, 1962.

(*5*) Horowitz, S., and R.P. Scalici, "Results of Sensory Panel Tests on Slim-Mint Chewing Gum," contained in OTC Volume 170010.

(*6*) Rosner, L., "To Determine the Effect of Chewing Slim-Mint Gum Upon Taste Perception, Particularly Toward Sweetness," unpublished study, in OTC Volume 170010.

(*7*) Gould, W. L., "On the Use of a Medicament to Reduce the Appetite in the Treatment of Obesity and Other Conditions," *New York State Journal of Medicine,* 47:981–983, 1947.

(*8*) Gould, W. L., "Obesity and Hypertension: The Importance of a Safe Compound to Control Appetite," *North Carolina Medical Journal,* 11:327–334, 1950.

(*9*) Plotz, M., "Obesity," *Medical Times,* 86:860, 1958.

(*10*) McClure, C. W., and C. A. Brush, "Treatment of Oral Syndrome Obesity with Non-traditional Appetite Control Plan," *Journal of the American Medical Woman's Association,* 28:239–248, 1973.

(*11*) Summary Minutes of the 11th meeting of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products held on May 9–10, 1976.

b. *Phenylpropanolamine hydrochloride.* The Panel concludes that phenylpropanolamine hydrochloride is generally recognized as safe and effective when used for OTC weight control in the dosage noted below.

(1) *Safety.* The Advisory Review Panel on OTC Miscellaneous Internal Drug Products agrees with the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (as published in the **Federal Register** of September 9, 1976 (41 FR 38312)) which concluded that phenylpropanolamine and its salts are safe for oral use in adult doses of 25 mg every 4 hours or 50 mg every 8 hours, not to exceed 150 mg in 24 hours (41 FR 38400).

Phenylpropanolamine hydrochloride is a synthetic compound with actions similar to ephedrine; however, it has been reported to have less central nervous system stimulation than ephedrine (Ref. *1*). Since it has both alpha and beta adrenergic effects, ingestion of phenylpropanolamine hydrochloride can be expected to cause vasoconstriction, bronchodilation, and tachycardia. Large doses would be expected to cause anxiety, excitement, insomnia, headache, cardiac arrhythmias, convulsions, and circulatory collapse. The lethal dose of

phenylpropanolamine is considered similar to ephedrine, which approximates 50 milligrams per kilogram (mg/kg) (Ref. *2*).

Ingestion of usually recommended doses of up to 50 mg as a nasal decongestant has resulted in few reported side effects in spite of its extensive use. However, because of its potential for adverse reactions, phenylpropanolamine is contraindicated for persons with hypertension, heart disease, diabetes, and thyroid disease.

In 1976, there were 31 reported cases of acute toxic ingestion (toxic overdosage) of OTC weight control drug products containing phenylpropanolamine hydrochloride by persons ranging in age from 14 months to 30 years. The ingested doses of phenylpropanolamine hydrochloride ranged from 12.5 mg (14-month-old patient) to 1.75 grams (g) (18-year-old patient). Symptoms reported were lethargy, hypertension, nausea, vomiting, dizziness, and tachycardia, and one report of convulsions related to ingestion of 200 mg phenylpropanolamine hydrochloride by a 28-year-old person. No deaths were reported (Ref. *3*).

In spite of extensive use of phenylpropanolamine as an OTC drug and as an ingredient in prescription drug products for many years, there have been no reports implicating its lack of safety in pregnancy or of any carcinogenic properties.

This Panel is concerned that a person might ingest a usual dose of phenylpropanolamine to reduce nasal congestion and another usual dose bearing a different trademark for weight reduction and that the combined dose might have adverse effects. Therefore, the Panel considers it necessary to put a warning statement concerning this possibility on all drug products containing phenylpropanolamine.

The Panel concludes that phenylpropanolamine hydrochloride is of a low order of toxicity when used as directed and that it has an adequate margin of safety for use by the general public without professional supervision.

(2) *Effectiveness.* It has been noted that hypothalamic lesions in animals and humans result in obesity and that in animals such overeating can be checked by amphetamines and similar agents, such as phenylpropanolamine hydrochloride (Ref. *4*). Amphetamines and similar agents have a long history of use as anorectics; however, a mechanism of action has not been proven.

The anorectic effect of phenylpropanolamine has been studied by various investigators for many years. The studies conducted may be criticized as lacking in one or more facets of proper study design and have resulted in confusing or contradictory findings. The Panel has reviewed some of these studies and found them inconclusive. In particular, the Panel is aware of the Fazekas et al. study (Ref. *5*) which has been claimed to demonstrate the ineffectiveness of phenylpropanolamine hydrochloride in weight control. The Panel reviewed this study and analyzed the data. The Panel concludes that accurate interpretation of the data in this study with regard to the effectiveness of phenylpropanolamine hydrochloride in weight control is impossible.

New studies (Refs. *6* through *11*) utilizing placebo-controlled, double-blind procedures involving test subjects on a controlled caloric intake have been performed and have been made available to the Panel. The test subjects approximate the target population who would use weight control drug products. The Panel has reviewed the available literature and considers the recent studies to be more valid in determining the effectiveness of phenylpropanolamine hydrochloride in weight control.

While each of these studies is defective in one of more important facets covered by the Panel's proposed protocol, the Panel believes that the combined evidence of these studies does establish the effectiveness of phenylpropanolamine hydrochloride. (See part III. paragraph D.1. below—Proposed protocol for evaluation of weight control ingredients.) In particular, two of the studies (Refs. *6* and *7*) are adequate to establish the effectiveness of phenylpropanolamine hydrochloride in weight reduction for short time periods (i.e., 4 to 6 weeks). Another study demonstrates statistical superiority of phenylpropanolamine hydrochloride over placebo for up to 16 weeks (Ref. *8*). Four other studies are adequate to establish the effectiveness of the combination of phenylpropanolamine hydrochloride and caffeine for time periods ranging from 4 to 12 weeks (Refs. *9* through *12*). Further, another 8-week, double-blind study without a placebo, comparing phenylpropanolamine hydrochloride to the combination of phenylpropanolamine hydrochloride and caffeine, did not establish a statistically significant difference between these two treatments (Ref. *13*). The sample population, protocol, and weight reductions in this latter study are in agreement with those from other placebo-controlled studies (Refs. *9* through *12*) and, therefore, permit a cross-study comparison of phenylpropanolamine hydrochloride (alone) with a placebo. Such a comparison further indicates the effectiveness of phenylpropanolamine. The Panel considered the above data sufficient to establish the effectiveness of phenylpropanolamine hydrochloride for weight reduction for time periods up to 12 weeks when taken in conjunction with a reduced caloric intake.

(3) *Dosage.* The Panel has determined that a single dose of phenylpropanolamine hydrochloride of 25 to 50 mg and a daily dose of not more than 150 mg given in divided doses 30 minutes before meals is generally recognized as safe and effective for weight control. In addition, for any timed release preparation, the per dose and daily dosage may not exceed those for the non-timed release preparation.

(4) *Labeling.* The Panel recommends the Category I labeling for weight control ingredients. (See part III. paragraph A.2. below—Category I labeling.) In addition, the Panel recommends the following warning statements under the heading "Warnings":

(i) "Do not exceed recommended dosage."

(ii) "If nervousness, dizziness, or sleeplessness occurs, stop taking this medication and consult your physician."

(iii) "If your are being treated for high blood pressure or depression, or have heart disease, diabetes, or thyroid disease, do not take this product except under the supervision of a physician."

(iv) "If you are taking a cough/cold or allergy medication containing any form of phenylpropanolamine, do not take this product."

References

(*1*) Koelle, G. B., "Parasympathomimetic Agents," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 505, 1975.

(*2*) Gosselin, R. E., H. C. Hodge, R. P. Smith, and M. N. Gleason, "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins Co., Baltimore, MD, 1976.

(*3*) Abstract of Poison Control Center case report forms for calendar year 1976—voluntary program. Attached to memo from Mr. Mark Keller to Mr. John Short dated August 9, 1978. See Volume II Panel Administrator's File (17EPAII).

(*4*) OTC Volume 170041 (Section III, Animal Safety Studies).

(*5*) Fazekas, J. F., et al., "Comparative Effectiveness of Phenylpropanolamine and Dextro Amphetamine on Weight Reduction," *Journal of the American Medical Association*, 170:1018–1021, 1959.

(*6*) OTC Volume 170028 (Section D).

(*7*) Hoebel, B. G., D. A. Willard, and I. K. Krauss, "The Effects of Propadrine on Body

Weight in Humans: Study II," contained in OTC Volume 170041 (Section IV and V—A1 and A2).

(*8*) OTC Volume 170050.

(*9*) Sebok, M., "Clinical Evaluation of the Efficacy of Phenylpropanolamine Compared with Placebo in a Double-Blind Six Week Trial," presentation made to the Panel on July 11, 1977. See Volume II Panel Administrator's File (17EPAII).

(*10*) OTC Volume 170060.

(*11*) OTC Volume 170147.

(*12*) Jolly, E. R., "To Assess the Utility of a Phenylpropanolamine-Caffeine Combination Product as an Adjunct in a Therapeutic Program for Uncomplicated Obesity," contained in OTC Volume 170030.

(*13*) OTC Volume 170155.

2. *Category I labeling.* The Panel recommends the following Category I labeling for weight control drug products as being generally recognized as safe and effective and not misbranded, as well as the specific labeling discussed in the individual ingredient statements.

a. *Indications.* The product labeling should contain one or more of the following statements:

(1) "For appetite control to aid weight reduction."

(2) "An aid for effective appetite control to assist weight reduction."

(3) "Helps curb appetite."

(4) "Appetite depressant in the treatment of obesity (excess weight)."

(5) "An aid to diet control in conjunction with a physician's recommended diet."

(6) "An aid in the control of appetite."

(7) "Helps control appetite."

(8) "For use as an aid to diet control."

(9) "Helps you eat less, weigh less."

b. *Directions.* All product labeling must contain the following statement: "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to period not exceeding 3 months, because that should be enough time to establish new eating habits."

c. *Warnings.* All product labeling must contain the following statement: "Do not give this product to children under 12 years of age."

3. *Category I combinations.* A number of submissions to the Panel contain a combination of phenylpropanolamine hydrochloride and caffeine for use as weight control agents. The Panel considered these extensively and concluded that such a combination is safe and effective if labeled as an "Anorectic/Stimulant." In reaching this decision the Panel had to decide whether or not a significant portion of the dieting population becomes fatigued while dieting. Based upon its professional experience the Panel concluded that such a significant patient population does exist and that the combination of phenylpropanolamine hydrochloride and caffeine meets the three criteria of FDA's combination policy. (See part II. paragraph C. above—Combination Policy.)

The Panel also considered the combination of phenylpropanolamine hydrochloride and caffeine as an anorectic only. One submitted study attempted to demonstrate this anorectic action; but, even though the study showed a greater weight loss for the combination than when using the phenylpropanolamine hydrochloride alone, the results were not statistically significant since the study was not long enough and did not contain a sufficient number of subjects (Ref. *1*).

This Category I combination status only applies to phenylpropanolamine hydrochloride and caffeine when labeled as an "Anorectic/Stimulant" and does not apply to a combination of other Category I weight control ingredients and other Category I stimulants. All conditions (e.g., labeling) contained in the final monograph for each ingredient must be met for the marketing of this combination.

Reference

(*1*) OTC Volume 170155.

B. Category II Conditions

The following are Category II conditions under which drug products used for weight control are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients.* The only ingredients which the Panel has classified as Category II are included earlier in this document. (See part I. paragraph C. 2 above—Other ingredients.)

2. *Category II labeling.* The Panel concludes that some labeling claims are either vague, misleading, or unsupported by scientific data. The claims listed below and the related terms, are therefore, classified as Category II labeling for weight control drug products:

a. "Contains one of the most powerful diet aids available without prescription."

b. "Contains one of the strongest diet aids available without prescription."

c. "Encourages water loss with a gentle diuretic."

d. "Easy-to-follow reducing plan built around food you love to eat. You will eat well but less and lose weight without going hungry."

e. "A unique way to help your overweight patient eat less."

f. "The modern aid to appetite control."

g. "Now enjoy a slim, trim figure. Lose pounds. Reduce inches."

h. "Lose weight starting today * * *. Look your best, feel your best."

i. "The delightful aid to appetite control."

j. "Delightfully delicious, scientifically formulated to help you control your appetite quickly, pleasantly."

k. "A most pleasant aid to help you lose weight."

l. "Trim pounds and inches without crash diets or strenuous exercise."

m. "A modern aid to appetite control for people who love to eat."

n. "Get rid of unsightly bulges."

o. "Reduce to the weight and size you want to be."

p. "Lose inches from arms, hips tummy, derriere, waist, thighs, legs."

q. "An effective easy-to-follow diet plan that lets you enjoy eating delicious nutritious foods everday as you lose weight."

r. "Enables the obese individual to lose weight in the most comfortable manner by decreasing the desire for food."

s. "Hunger pains are spared and a low calorie reducing diet may now be more easily tolerated."

t. "You will look better and feel better."

u. "Removes excess body weight."

v. "May be used prophylactically."

C. Category III Conditions

The following are Category III conditions for which the available data are insufficient to permit final classification of weight control drug products at this time. The Panel recommends that a period of 2 years be permitted for the completion of studies which may support the change of Category III conditions to Category I.

1. *Category III active ingredients.* The Panel concludes that the safety of the following ingredients and combination in the recommended doses is unquestioned, except as noted in the individual ingredient evaluations:

Alginic acid
Carrageenan
Carboxymethylcellulose sodium
Chondrus
Guar gum
Karaya gum
Methylcellulose
Psyllium
Sea kelp
Sodium bicarbonate
Xanthan gum

a. *Alginic acid.* The Panel concludes that alginic acid is safe for OTC use in the dose noted below, but data are

insufficient to demonstrate its effectiveness for use in weight control.

(1) *Safety.* Alginic acid has been used by the food industry since the turn of the century. The Advisory Review Panel on OTC Antacid Drug Products concluded (as published in the **Federal Register** of April 5, 1973 (38 FR 8722)) that alginic acid is safe in amounts of 4 g per day for antacid drug products. Alginic acid has also been marketed for many years in a weight control preparation at a dose of 200 mg per tablet with an average daily consumption of 4.8 g (24 tablets) with no apparent adverse effects. The Advisory Review Panel on OTC Miscellaneous Internal Drug Products concludes that alginic acid is safe for OTC use at 4.8 g per day in OTC weight control drug products.

(2) *Effectiveness.* Alginic acid is a hydrophilic colloidal substance and is marketed in combination with sodium bicarbonate. When this combination is ingested, sodium alginate is formed and carbon dioxide is released. The combination of sodium alginate with carbon dioxide creates a bulk-producing foam.

In the data submitted and reviewed by the Panel, no study supported the claim that alginic acid alone was effective in weight control. But one of four double-blind, placebo-controlled studies submitted to the Panel suggest that alginic acid may be of some benefit when used in combination with sodium bicarbonate and carboxymethylcellulose sodium (Ref. *1*). Because of this potential, the Panel recommends that alginic acid in combination with sodium bicarbonate be tested according to the proposed protocol to demonstrate whether or not it is effective for weight control.

(3) *Proposed dosage.* The Panel concludes that alginic acid is safe for OTC use in doses up to 4.8 g per day in divided doses when taken with a full glass of water (8 ounces) with each dose.

(4) *Labeling.* The Panel recommends Category I labeling for weight control ingredients. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following statements be required on products containing the combination of alginic acid and sodium bicarbonate as bulk producers.

(i) *Directions.* "Take a full glass of water (8 ounces) with each dose."

(ii) *Warnings.* "If you are on a sodium-restricted diet, do not use this product except under the supervision of a physician" (only for products containing more than 5 milliequivalents (meq) of sodium in the recommended daily dose).

(5) *Evaluation.* The Panel concludes that alginic acid is safe in the dose recommended above and recognizes that alginic acid in combination with sodium bicarbonate produces bulk in the stomach, but the value of bulk producers in reducing weight by controlling appetite has not been established. the Panel, therefore, recommends that adequate testing of alginic acid in combination with sodium bicarbonate be performed according to the proposed protocol to determine whether or not the combination is effective for weight control. (See part III. paragraph D.1 below—Proposed protocol for evaluation of weight control ingredients.)

Reference

(*1*) Otc Volume 170119 (pp. 28–38).

b. *Carrageenan, chondrus, guar gum, karaya gum, sea kelp, and psyllium.* These ingredients were not submitted to the Panel but were contained in the second **Federal Register** notice dated August 27, 1975 (40 FR 38179). They all are hydrophyllic colloids and, therefore, may act as bulking agents in a way similar to those hydrophyllic colloids submitted and classified in Catagory III, i.e., alginic acid, carboxymethylcellulose sodium, and xanthan gum.

The safety of these ingredients is not questioned since they have been in use for years as food additives and some have had medicinal use.

Carrageenan and chondrus (chondrus crispus) are used as food additives as emulsifiers, stabilizers, or thickeners (21 CFR 172.620 and 21 CFR 182.7255) and have been evaluated and found to be safe by the Advisory Review Panel on Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products as published in the **Federal Register** of March 21, 1975 (40 FR 12917).

Guar gum and karya gum are used as food additives as emulsifiers, stabilizers, thickners, and formulation aids (21 CFR 184.1339 and 21 CFR 184.1349, respectively) and have been evaluated and found to be safe as bulk laxatives by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products as published in the **Federal Register** of March 21, 1975 (40 FR 12917 and 40 FR 12907, respectively).

Kelp is safely used as a food additive as a source of iodine, provided that the maximum daily intake of iodine does not exceed 225 micrograms (ug) for foods labeled without reference to a person's age or physiological state (i.e., pregnancy or lactation) (21 CFR 172.365).

Psyllium has been evaluated and found to be safe as a bulk laxative by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products as published in the **Federal Register** of March 21, 1975 (40 FR 12908).

Although no data were submitted to the Panel for these ingredients, the Panel believes that the same opportunity to demonstrate their effectiveness as weight control ingredients should be provided as is being provided for alginic acid, carboxymethylcellulose sodium, methylcellulose, and xanthan gum, since they are all hydrophyllic colloids. Therefore, the Panel classifies carrageenan, chondrus, guar gum, karay gum, sea kelp, and psyllium as Category III for use in weight control.

c. *Carboxymethylcellulose sodium.* The Panel concludes that carboxymethylcellulose sodium (also known as sodium carboxymethylcellulose) is safe in the dose noted below, but data are insufficient to demonstrate its effectiveness for use in weight control.

(1) *Safety.* The median lethal dose (LD_{50}) of carboxymethylcellulose sodium is 27 grams/kilogram (g/kg) of body weight for white rats and 16 g/kg for guinea pigs. It was nontoxic in doses of 1 g/kg daily when given orally for 6 months to white rats, guinea pigs, and dogs. No pathology was found, and most animals had normal weight gain. However, some experimental animals had greater weight increases than control animals. Doses of 1 g/kg produced no ill effects on fertility or well-being of offspring in three generations of white rats (Ref. *1*).

Carboxymethylcellulose sodium has been used daily as a laxative in humans in doses up to 6 g per day for a year without ill effects (Ref. *2*). It was considered safe in a dose of 200 mg given two to four times daily by the Advisory Review Panel on Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products as published in the **Federal Register** March 21, 1975 (40 FR 12931). This Panel also noted in the **Federal Register** publication of March 21, 1975 (40 FR 12909) that cellulose has been shown to bind digitalis, nitrofurantoin, and salicylate. According to Fingl (Ref. *3*) occasional cases of esophageal obstruction have occurred when this substance is chewed or swallowed without liquid.

The Panel concludes that carboxymethylcellulose sodium is safe when used in the dose noted below.

(2) *Effectiveness.* Carboxymethylcellulose sodium is a hydrophilic semi-synthetic cellulose which, when ingested orally with a full glass of water, forms a soft hydrated bulk creating a feeling of fullness (Ref.

4). Such bulk producers have been considered to act as anorectics by creating a bulky mass in the stomach which slows down the course of the meal and provides time for satiety to take place (Ref.*5*). However, Drenick (Ref. *6*) reported that a methylcellulose mass is almost completely gone from the stomach in 30 minutes and that intestinal peristalsis is increased following this rapid emptying. Some significant reductions in hunger were reported in a series of double-blind placebo-controlled studies involving 263 obese dieting individuals who took a combination of bulk-producing drugs including carboxymethylcellulose sodium for a 2-week period. However, no difference in weight loss was found (Ref. *7*). The Panel concludes that carboxymethylcellulose sodium should be tested according to the proposed protocol to determine whether or not it is effective for weight control.

(3) *Proposed dosage.* The Panel concludes that carboxymethylcellulose sodium is safe for OTC use in doses of up to 2.4 g per day when taken with a full glass of water (8 ounces) with each dose.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used for weight control. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following statements be required on products containing carboxymethylcellulose sodium:

(i) *Directions.* "Take a full glass of water (8 ounces) with each dose."

(ii) *Warnings.* (*a*) "If you are taking digitalis, nitrofurantoin, or salicylates, consult your physician before taking this product."

(*b*) "If you are on a sodium-restricted diet, do not use this product except under the supervision of a physician" (only for products containing more than 5 meq of sodium in the recommended daily dose).

(5) *Evaluation.* The Panel concludes that carboxymethylcellulose sodium is safe in the dose recommended above and recognizes that it does produce bulk in the stomach, but the value of bulk producers in reducing weight by controlling appetite has not been established. The Panel, therefore, recommends that adequate testing of carboxymethylcellulose sodium be performed according to the proposed protocol to determine whether or not it is effective for weight control. (See part III. paragraph D.1. below—Proposed protocol for evaluation of weight control ingredients.)

References

(*1*) Shelanski, H. A., and A. M. Clark, "Physiological Action of Sodium Carboxymethylcellulose on Laboratory Animals and Humans," *Food Research,* 13:29–35, 1948.

(*2*) World Health Organization Technical Report Series 281, "Specifications for the Identity and Purity of Food Additives and Their Toxicological Evaluation: Emulsifiers, Stabilizers, Bleaching and Maturing Agents," World Health Organization, Geneva, Switzerland, 1964.

(*3*) Fingl, E. "Laxatives and Cathartics," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 979, 1975.

(*4*) OTC Volume 170012 (p. 55).

(*5*) Fletcher, D., "Artificial Bulk Producers as Anorectic Agents," *Journal of the American Medical Association,* 230:901, 1974.

(*6*) Drenick, E. J., "Bulk Producers," *Journal of the American Medical Association,* 234:271, 1975.

(*7*) OTC Volume 170119 (pp. 28–38).

d. *Methylcellulose.* The Panel concludes that methylcellulose is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness for use in weight control.

(1) *Safety.* Methylcellulose is a hydrophilic semi-synthetic cellulose derivative which has been found to be nontoxic in animals and man (Ref. *1*). According to Fingl (Ref. *2*), occasional cases of esophageal obstruction have occurred when methylcellulose is chewed or swallowed without liquid.

According to the findings of the Advisory Review Panel on OTC Laxative, Anitdiarrheal, Emetic, and Antiemetic Drug Products (as published in the **Federal Register** of March 21, 1975 (40 FR 12907)), cellulose has been shown to bind digitalis, nitrofurantoin, and salicylate.

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products concludes that methylcellulose is safe in the dose noted below.

(2) *Effectiveness.* According to Fletcher (Ref. *3*), bulk producers work because they absorb up to 50 times their weight in water to form a stable colloid mass. This mass is said to produce satiety by slowing down the course of the meal. However, Drenick (Ref. *4*) found that methylcellulose is almost completely gone from the stomach in 30 minutes and that intestinal peristalsis is increased following the rapid emptying. The action of methylcellulose is similar to that of other bulk-producing agents. Studies indicate that other bulk-producing agents (i.e., the carboxymethylcellulose sodium, alginic acid, and sodium bicarbonate combination) may be effective in providing reduction in appetitie (Ref. *5*).

The Panel concludes that methylcellulose should be tested according to the proposed protocol to determine whether or not it is effective for weight control.

(3) *Proposed dosage.* The Panel concludes that methylcellulose is safe for OTC use in a dose of up to 2.4 g per day in divided doses when taken with a full glass of water (8 ounces) with each dose.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used for weight control. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following statements be required on products containing methylcellulose:

(i) *Directions.* "Take a full glass of water (8 ounces) with each dose."

(ii) *Warnings.* "If you are taking digitalis, nitrofurantoin, or salicylates, consult your physician before taking this product."

(5) *Evaluation.* The Panel concludes that methylcellulose is safe in the dose recommended above and recognizes that it does produce bulk in the stomach, but the value of bulk producers in reducing weight by controlling appetite has not been established. The Panel, therefore, recommends that adequate testing of methylcellulose be performed according to the proposed protocol to determine whether or not it is effective for weight control. (See part III. paragraph D.1. below—Proposed protocol for evaulation of weight control ingredients.)

References

(*1*) World Health Organization, Technical Report Series 539, "Toxicological Evaluation of some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers, and Thickening Agents," World Health Organization, Geneva, Switzerland, 1974.

(*2*) Fingl, E., "Laxatives and Cathartics," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillian Co., New York, p. 979, 1975.

(*3*) Fletcher, D., "Artificial Bulk Producers as Anorectic Agents," *Journal of the American Medical Association,* 230:901, 1974.

(*4*) Drenick, E. J., "Bulk Producers," *Journal of the American Medical Association,* 234:271, 1975.

(*5*) OTC Volume 170119 (pp. 28–38).

e. *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness for use in weight control.

(1) *Safety.* Sodium bicarbonate (baking soda) is an alkalinizing agent which releases carbon dioxide when neutralized by acid. It has a long history of use as an antacid. Sodium bicarbonate was reviewed by the Advisory Review Panel on OTC Antacid Drug Products, and its conclusions were published in the **Federal Register** of April 5, 1973 (38 FR 8714). That Panel reviewed sodium and bicarbonate ions separately and concluded that antacids containing sodium would be safe in a maximum daily dosage of 200 meq of sodium for persons under 60 years of age and 100 meq of sodium for persons 60 years of age or older, and that this dosage would also apply to the bicarbonate ion (38 FR 8718). The agency also concluded that this dosage is safe (21 CFR 331.11(k)(1)). The Advisory Review Panel on OTC Miscellaneous Internal Drug Products agrees with these conclusions and recommends that they apply to weight control drug products containing sodium bicarbonate. This Panel concludes that sodium bicarbonate is safe for OTC use in weight control drug products when used as specified in the dosage section below, and under the labeling restriction noted.

(2) *Effectiveness.* The only data submitted to this Panel for use of sodium bicarbonate in weight control were related to its use as an adjunctive constitutent in combination with other ingredients (alginic acid and carboxymethylcellulose sodium). When wetted, a reaction ensues between the alginic acid and sodium bicarbonate that produces sodium alginate and carbon dioxide. The entrapment of carbon dioxide in the viscous sodium alginate creates a bulk-producing foam. This entrapment is assisted by the emulsifying action of the carboxymethylcellulose sodium in the formulation.

Results of one of four double-blind, placebo-controlled studies submitted to the Panel (Ref. *1*) suggest that, within the limits of subjective appraisal, the combination of carboxymethylcellulose sodium, alginic acid, and sodium bicarbonate (but not the sodium bicarbonate alone) reduces the sensation of hunger to a significant degree when the tablets are taken by obese people trying to reduce their weight. But the studies did not show that the reduced hunger led to a reduction of weight, which the Panel believes should be the measure of a lower caloric intake due to reduced hunger.

The Panel recommends that sodium bicarbonate in combination with alginic acid be tested according to the proposed protocol to determine whether or not it is effective for weight control

(3) *Proposed dosage.* This Panel concludes that sodium bicarbonate is safe for OTC use in doses of up to 16.8 g (200 meq of sodium) for persons under 60 years of age and 8.4 g (100 meq of sodium) for persons aged 60 or older. Since each tablet of the combination in question contains only 1.17 meq of sodium and since the recommended dose is up to 24 tablets per day, this is well within the limits set by the Advisory Review Panel on Antacid Drug Products.

(4) *Labeling.* The Panel recommends Category I labeling for weight control ingredients. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following statements be required on products containing the combination of alginic acid and sodium bicarbonate as bulk producers:

(i) *Directions.* "Take a full glass of water (8 ounces) with each dose."

(ii) *Warning.* "If you are on a sodium-restricted diet, do not use this product except under the supervision of a physician" (only for products containing more than 5 meq of sodium in the recommended daily dose).

(5) *Evaluation.* The Panel concludes that sodium bicarbonate is safe in the dose recommended above and recognizes that sodium bicarbonate in combination with alginic acid produces bulk in the stomach, but the value of bulk producers in reducing weight by controlling appetite has not been established. The Panel, therefore, recommends that adequate testing of sodium bicarbonate in combination with alginic acid be performed according to the proposed protocol to determine whether or not the combination is effective for weight control. (See part III, paragraph D.1. below—Proposed protocol for evaluation of weight control ingredients.)

Reference

(*1*) OTC Volume 170119 (pp. 28–38).

f. *Xanthan gum.* The Panel concludes that xanthan gum is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness for use in weight control.

(1) *Safety.* Xanthan gum is a regulated food additive for use as an emulsifier, stabilizer, or thickener in foods (21 CFR 172.695). Woodward, et al. (Ref. *1*), using doses as high as 1 g/kg body weight in rats and dogs, found no evidence of toxicity and no significant difference in tumor incidence in rats. Doses as high as 0.5 g/kg body weight per day in three generations of rats had no effect on reproductive performance, litter size, or condition. In dogs given a daily intake of up to 1 g/kg body weight for 107 weeks, the incidence of soft stools was dose-related and accompanied by an increase in specific gravity of the urine and an increase in the occurrence of urinary albumin only with the highest doses.

The Panel concludes that xanthan gum is safe in the dose noted below for OTC use in weight control drug products.

(2) *Effectiveness.* Xanthan gum is a hydrophilic colloidal polysaccharide gum containing *d*-glucose, *d*-mannose, and *d*-glucuronic acid as either a potassium or sodium salt. After ingestion it passes through the digestive tract unchanged (Ref. *2*).

Data were submitted to the Panel attempting to demonstrate the effectiveness of xanthan gum for weight control, but the data did not demonstrate statistical superiority of xanthan gum over placebo. However, its action is similar to that of other bulk-producing agents. A combination of carboxymethylcellulose sodium, alginic acid, and sodium bicarbonate was found to be somewhat more effective than placebo in providing subjective reduction of appetite (Ref. *3*).

Since this ingredient seems to have a potential for use in weight control, the Panel recommends that it be tested according to the proposed protocol to determine whether or not it is effective for weight control.

(3) *Proposed dosage.* The Panel concludes that xanthan gum is safe for OTC use in the dosage of 1.1 g taken before each meal with a full glass of water (8 ounces).

(4) *Labeling.* The Panel recommends Category I labeling for weight control ingredients. (See part III, paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following statement be required on products containing xanthan gum under the heading "Directions": "Take a full glass of water (8 ounces) with each dose."

(5) *Evaluation.* The Panel concludes that xanthan gum is safe in the dose recommended above and recognizes that it does produce bulk in the stomach, but the value of bulk producers in reducing weight by controlling appetite has not been established. The Panel, therefore, recommends that adequate testing of xanthan gum be performed according to the proposed protocol to determine whether or not it is effective for weight control. (See part III. paragraph D.1. below—Proposed protocol for evaluation of weight control ingredients.)

References

(*1*) Woodward, G., et al., "Xanthan Gum: Safety Evaluation by 2-year Feeding Studies in Rats and Dogs and a Three Generation Reproduction Study in Rats," *Toxic Applied Pharmacology*. 24:30–36, 1973.

(*2*) OTC Volume 170056.

(*3*) OTC Volume 170119.

2. *Category III labeling.* The Panel concludes that available data are insufficient to permit final classification of the following claim for bulk-producing ingredients:

"Provides bulk to add to low caloric intake and helps to satisfy the feeling of hunger caused by emptiness."

3. *Category III combinations.* The Panel concludes that data are insufficient to demonstrate the effectiveness of the following combinations for use in weight control and, therefore, classifies them as Category III. The Panel recommends that these combinations be tested according to the proposed protocol to determine whether or not they are effective for weight control. (See part III, paragraph D.1. below—Proposed protocol for evaluation of weight control ingredients.)

Alginic acid and sodium bicarbonate.

Alginic acid, sodium bicarbonate, and carboxymethylcellulose sodium.

D. Data Required for Evaluation

1. *Proposed protocol for evaluation of weight control ingredients*—a. *Objective of the study:* To determine the effectiveness of the substance under study in reducing weight. This will be accomplished by use of a randomized placebo-controlled double-blind study incorporating features of both a crossover and parallel sample design. The study will extend over 12 weeks.

b. *Target population.* Persons with obesity which is unrelated to a known disease.

c. *Sample population.* Persons who have no overt evidence of endocrine disorder or other organic disease predisposing to obesity, and who have exogenous obesity resulting in a weight at least 15 percent and not more than 30 percent above desirable weights for height, age, body frame, and sex as determined from the Metropolitan Life Insurance Company table of desirable weights (Ref. *1*).

d. *Study setting.* The study should be conducted by qualified investigators in clinical centers or private practices.

e. *Criteria for admissibility into sample.* The study can include males or females satisfying all of the following criteria:

(1) Must be over 18 years of age.

(2) Must be shown by proper medical evaluation to have no evidence of pregnancy or significant cardiac, renal, hepatic, or endocrine dysfunction.

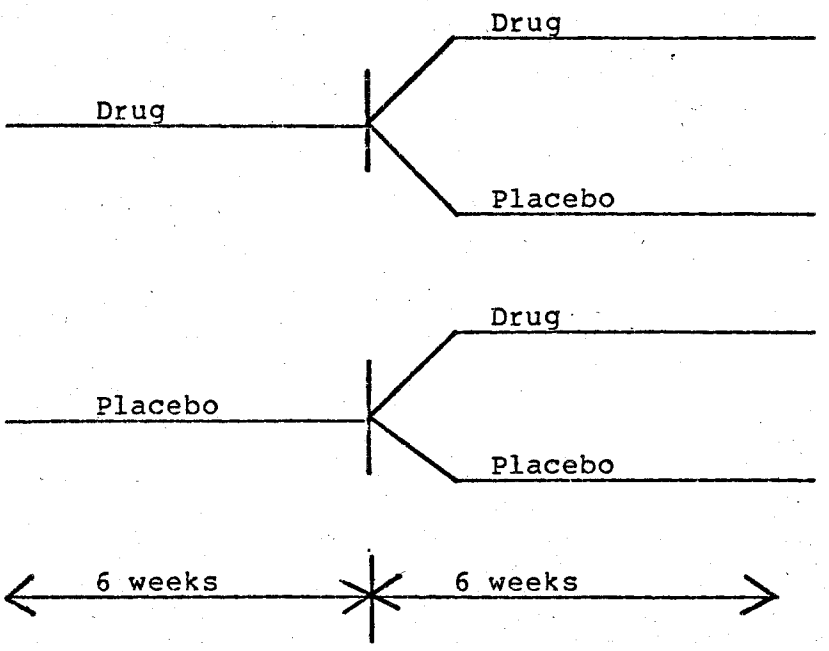
(3) Must not be taking other drugs (including OTC drug products) since these might influence the response to the drug being tested or might cause weight changes independently of the diet. If females are on continual estrogen therapy, or a specific estrogen regimen, such medication may be continued during the study. This is the only exception made for other medication taken during the study.

(4) Must be able to comprehend instructions and adhere to the study protocol.

(5) Must not have lost 10 percent or more weight at any time within the past year by dieting.

f. *Variables to be measured before study.* The subject's pre-study body weight is to be determined from two weighings taken on consecutive days and at the same hour in the morning. The subject is to be weighed (without clothing except for a standard examination gown) by the investigator or an assistant. In addition, information concerning the following variables is to be obtained: age in years, sex, height in inches, subject's usual weight, desirable weight (from the Metropolitan Life Insurance Company's table of desirable weights (Ref. *1*)), percent overweight, usual degree of physical activity, subject's weight pattern over the years, subject's participation in weight reducing programs including diets and medication, estimate of subject's caloric intake for the week before the study, the subject's concept of his or her ideal weight, a subjective evaluation of the subject's usual feeling of hunger (none, slight, moderate, or marked), and an estimate of caffeine intake.

g. *Design of study.* The study design is a randomized placebo-controlled double-blind design incorporating the features of both a crossover and parallel sample design. A diagram of the design is:



One-fourth of the subjects take the drug for 12 consecutive weeks;

One-fourth of the subjects first take the drug for 6 weeks and then take the placebo for 6 weeks;

One-fourth of the subjects first take the placebo for 6 weeks and then take the drug for 6 weeks; and

One-fourth of the subjects take placebo for 12 consecutive weeks.

Subjects are to be randomly assigned to one of the four schedules. The study is a double-blind study: neither the investigator nor the subjects should know the assignment of any subject.

The above design allows for direct comparisons between the drug and

placebo for both 6 and 12 weeks, for estimation and adjustment of carryover and/or ordering effects (i.e., drug before placebo or placebo before drug), and for measurement of within subject variability (i.e., the subject acting as his or her own control).

h. *Instructions to the subjects.* Subjects are to be given diet instructions, if any, in accordance with the labeling instructions accompanying the drug. Each subject is to keep a daily diary which is to include estimated daily caloric intake, amount of caffeine-containing drink consumed, and amount of the treatment substance under study (i.e., drug or placebo) taken, and time at which it was taken. In addition, each subject is to record daily in the diary any side effects experienced and his or her subjective evaluation of "the feeling of hunger." The evaluation of the feeling of hunger is to be on a four-point scale (none, slight, moderate, or marked).

i. *Measurements of weights during the study.* During the 12 consecutive weeks of the study the subject is to make seven visits to the investigator. The visits are to be weekly for the first 2 weeks and then every 2 weeks. They are to be at the same hour in the morning and on the same day of the week. At each visit, the subject is to be weighed (without clothing except for a standard examination gown) by the investigator or an assistant. The investigator should attempt to arrange visits in such a manner so as to minimize interaction and discussion among the subjects.

j. *Statistical analysis.* The most important outcome variable is weight loss. At least three analyses should be performed.

(1) *An analysis of the weight loss after the first 6 weeks of study.* If the drug is effective, the weight loss of those on the drug should exceed that of those receiving the placebo.

(2) *An analysis of the weight loss after the 12 weeks of the study.* If the drug is effective, the weight loss of those always on the drug is expected to exceed the weight loss of those involved in the crossover schedules (i.e., those taking the drug and placebo). Further, those who are always on the placebo should have the smallest weight loss.

(3) *A comparison of the results of the first 6 weeks with the last 6 weeks.* If the drug is effective, those involved in the crossover schedules should show greater weight loss when on the drug than when on the placebo.

The statistical techniques used in the above analyses should include repeated measure techniques, multiple comparison techniques, and analysis of variance techniques which have sensitivity to ordered alternatives.

If a claim for appetite suppressant is desired in addition, analyses similar to those described above should be performed on the variables "feeling of hunger" and "adherence to diet" (i.e., the difference between the diet instruction and the actual caloric intake).

k. *Number of subjects.* At least 25 subjects should be in each of the 4 groups defined in the "Design of Study" section (for a total sample of at least 100). This sample size requirement is based on the assumption that the average weight loss is 1 pound per week (12 pounds in 12 weeks) for those on the placebo, 1.5 pounds per week (18 pounds in 12 weeks) for those on an effective drug, and 15 pounds in 12 weeks and for those on the crossover schedule. The standard deviation of weight loss for all four groups for 12 weeks is 6 pounds. Twenty-five observations in each group will be sufficient to detect the difference between an effective drug and placebo with a Type I error of 0.05 and a Type II error of 0.20.

l. *Number of studies.* Two studies by different investigators at separate geographic locations are required.

Reference

(1) Metropolitan Life Insurance Company, "Desirable Weights for Men and Women," *Statistical Bulletin, 58:5, 1977.*

2. *Background document on the proposed protocol for evaluation of weight control ingredients.* The preceding proposed protocol for evaluating the effectiveness of drug ingredients for weight control is the result of the Panel's consideration of information from a number of sources. This information came from drug companies' submissions of the results of their research and other relevant medical literature, testimonies delivered at open sessions of the Panel, literature prepared by FDA, and advice given by the Panel's consultants. The following is a commentary on each of the sections of the preceding proposed protocol.

a. *Objective of the study.* The stated objective of the proposed protocol is "to determine the effectiveness of the substance under study in reducing weight." The claims of some firms marketing these weight reducing aids do not include weight reduction. Rather, their claims state that their drugs are effective as "appetite suppressants." Further, some firms recommend that their products should be used as adjuncts to diets because they make dieting easier. The inference, which is not necessarily made in the firms' claims, is that weight reduction will follow. These firms state in their submissions to the Panel that the appropriate variable to determine effectiveness for appetite suppressants is the subjective variable "feeling of hunger." Effectiveness is equivalent to a significant reduction in that feeling. The Panel considered these claims and arguments and decided that if a drug is useful as a weight reducing aid or even solely as an appetite suppressant, then it should be possible to demonstrate that it is effective in reducing weight in obese individuals under well-controlled experimental conditions such as given in the proposed protocol.

b. *Target and sample populations.* The target population for weight control products are persons with obesity which is unrelated to a known disease. The Panel could not find a universally accepted definition of obesity. As a working definition, the Panel viewed obesity as that physical state in which body weight in relation to height and body build is more than 10 percent above the ideal desirable weight determined from the Metropolitan Life Insurance Company table of desirable weights (Ref. *1*). The Panel decided that the sample population (i.e., population from which the sample is chosen) should consist of "persons who have no overt evidence of endocrine disorder or other organic disease predisposing to obesity, and who have exogenous obesity resulting in a weight at least 15 percent and not more than 30 percent above desirable weights." This range (15 to 30 percent) was selected to ensure meaningful statistical data. First, 15 percent was selected as a lower limit to ensure that the subjects in the study would be sufficiently obese so that weight reduction could be expected during the study. Second, inclusion of individuals whose weights exceed 30 percent of ideal would introduce too much variability into the study. These individuals have the potential for large weight reductions. Many of these reductions would be due to simple changes of diet. Unless a very large sample was used, it would be very hard to judge if any weight reductions were associated with the drug.

The Panel also considered the possibility of defining the sample population in terms of pounds overweight rather than percent overweight (e.g., 10 to 50 pounds overweight). There was no justification for believing this could result in an improvement of the study design.

c. *Study setting.* The Panel was concerned that qualified investigators in appropriate settings be used in the study. There was agreement that the drug companies would realize this and that the protocol only had to restate it.

The protocol's wording is, "The study should be conducted by qualified investigators in clinical centers or private practices."

d. *Criteria for admissibility into sample.* The objectives of admissibility criteria are to ensure that the study subjects are healthy, to ensure that they are as homogeneous as possible, to remove sources that could introduce confounding effects into the study, and to eliminate unnecessary sources of variation from the study. The proposed protocol has five admissibility criteria. The first (over 18 years of age) is routine in studies of this nature and eliminates the problem of dealing with weight fluctuations in adolescents. The second (proper medical evaluation to detect pregnancy or cardiac, renal, hepatic, or endocrine dysfunction) ensures that the subjects are healthy and not pregnant and also removes those persons who have organic reasons for being overweight. Inclusion of such persons would confound the study's results. The third criterion eliminates those subjects on medication which might influence response to the study medication or to a weight reduction diet. (The only exception is for women on estrogen therapy.) The fourth criterion eliminates those subjects who are unable to comprehend instructions and adhere to the study protocol. Inclusion of such persons would introduce bad data into the study. The final criterion eliminates those who have dieted within the past year and had a resulting weight loss of 10 percent or more. The Panel was concerned with the possibility of inclusion of those individuals who are constantly on diets and are successful for a short time period in reducing their weight. The Panel felt that such individuals have developed their own "technique for rapid weight loss" and inclusion of them in the study would supply no information about the usefulness of the study medication.

The Panel discussed extensively whether menstruating women should be included in the study. Because some of these women can show weight variations of 3 to 5 pounds monthly, many of the Panel members believed that it was best to exclude them from the study. However, other Panel members pointed out that these women constitute a significant proportion of the users of these drugs. Exclusion of them would make the study unrealistic. The Panel finally decided that they could be included. However, such a study requires more subjects than a study which excludes them. The Panel does not believe that an efficacy study must contain menstruating women as subjects.

e. *Variables to be measured before study.* Before the test medication is given, the subject's weight must be determined. This is required not only to decide upon admissibility into the study, but also for use as a reference point for determining weight loss. The pre-study weight must be as stable as possible. In order to achieve a stable estimate of the pre-study weight, the Panel decided that it should be "determined from two weighings taken on consecutive days and at the same hour in the morning." The subject is to be weighed (without clothing except for a standard examination gown) by the investigator or an assistant.

The Panel also decided that there is a collection of other variables that could influence the outcome of a subject's study response. The Panel believed these should be collected before the study. These variables are age in years, sex, height in inches, subject's usual weight, desirable weight (from the Metropolitan Life Insurance Company's table of desirable weights), percent overweight, usual degree of physical activity, subject's weight pattern over the years, subject's participation in weight reducing programs including diets and medication, estimate of subject's caloric intake for the week before the study, the subject's concept of his or her ideal weight, the subject's subjective evaluation of his or her usual feeling of hunger (none, slight, moderate, or marked), and an estimate of caffeine intake.

f. *Design of study.* The first problem facing the Panel in developing the design of the study was deciding upon the duration of it. Many of the studies reviewed in the drug companies' submissions lasted only 3 to 4 weeks. Even in the extensive review supplied by the FDA, only a few studies exceeded 6 weeks. The Panel was of the opinion that the study it was developing should be of sufficient duration so that, not only would weight reduction be established, but also the maintenance of it would be established. A drug is effective if it is instrumental in reducing weight and in aiding the individual to maintain the weight loss. It was decided that a study of 12 weeks' duration would satisfy the Panel's goal.

The next design problem facing the Panel was deciding whether the study should be a crossover or a parallel sample design. At first the Panel decided upon a placebo-controlled crossover design. The study was to be divided into two 6-week segments. With the crossover design some of the comparisons that are possible are:

(1) Drug vs. placebo for period one (i.e., on first 6 weeks);

(2) Drug vs. placebo for period two (i.e., on second 6 weeks);

(3) Drug followed by placebo (Does the drug have carryover effect?);

(4) Placebo followed by drug (Even after weight reduction with placebo in the first period, can the drug help?);

(5) Drug on period one vs. drug on period two;

(6) Placebo on period one vs. placebo on period two (If subject is on the drug during period one, will it affect the placebo effect during period two?);

(7) Comparison of group one and group two (i.e., those on drug followed by placebo vs. those on placebo followed by drug);

(8) Overall comparison of the drug and placebo;

(9) Comparison of period one and period two.

After some discussion it became obvious that the crossover design would not permit the resolution of some important problems. First, no one subject would be on either the drug or placebo for the full 12 weeks. Analysis and quantification of a 12-week drug effect would not be possible. The Panel wanted this feature to be added to the design. Second, the crossover would not supply the appropriate data to test a claim often made by the drug companies that their drugs are useful in aiding in the development of good dieting habits. (In summary the claim is that at first the drug suppresses the appetite so the subject finds it easier to diet. After a short time period, the drug effect on the appetite wears off, but by then the subject has developed good dieting habits.) In order to test this claim, a comparison must be made between two experimental groups—one group takes the drug for 6 weeks and then takes the placebo for 6 weeks, and the second group takes the placebo for all 12 weeks.

The Panel finally decided that the appropriate design should include features of both a crossover and a parallel sample design. This will allow investigation of the above two items without loss of any of the analyses possible with the crossover.

The Panel realizes that there is a serious potential problem of having a large dropout rate with a 12 week study (especially for those on the placebo for 12 weeks). Still it believes a study such as is being proposed is required to establish efficacy.

g. *Instructions to the subjects.* Routine instructions are to be given to the subjects in the study. They are to be

given the diet instructions, if any, in accordance with the labeling instructions and/or the package insert accompanying the drug. The Panel assumes that each study that uses the proposed protocol will involve the use of a low calorie diet. The subjects should also keep a daily diary which is to include the following: estimated daily caloric intake, amount of caffeine-containing drinks consumed, and the amount of the treatment substance under study (i.e., the drug or placebo) taken and the time at which it was taken. Also, the subjects are to record daily any side effects experienced and their subjective evaluations of "the feeling of hunger" (on a four point scale—none, slight, moderate, or marked). The subjects must be instructed carefully on the use of the diary. The investigators should not admit a subject into the study if it appears the subject cannot comprehend the instructions of the diet for updating the daily diary.

h. *Measurements of weights during the study.* The major requirement here is to fix the schedule of visits to the investigator as much as possible so that unnecessary variables do not confound the study.

i. *Statistical analysis.* The Panel did not want to impose itself excessively here. The major variable is weight loss per week. The analysis must be whether the drug is effective (i.e., Is it more effective than placebo?). Beyond this consideration, the drug companies may investigate any other hypotheses of interest to them. The drug firms should be aware that the sample sizes may need to be increased substantially in order to test appropriately some hypotheses (e.g., if there is a relation of weight loss to age and sex).

j. *Number of subjects.* The submissions from the drug firms did not supply any consistent data from which a determination of appropriate sample size could be made.

In order to make a determination the Panel members were asked to state what they considered to be reasonable estimates of weight loss per week for the placebo and for the drug. The joint opinion of the Panel was that if the study includes a diet, a weight loss of 1 pound per week could be expected for the individuals on the placebo and 1.5 pound per week for the individuals on an effective drug. The weight loss would be greatest at the beginning of the study, and the 1 pound and 1.5 pound figures reflect an average over 12 weeks. Further, an estimate of the range in weight loss over the 12 weeks was given by the Panel as ranging from −6 pounds (i.e., a gain of 6 pounds) to 30 pounds. This corresponds to a standard deviation of about 6 pounds over the 12 weeks. Given the above, the required number of observations can be determined. Using the calculations given in Chapter 14 of Dixon and Massey's text (Ref. *2*) for sample size determination in the one-way analysis of variance, the required sample size is at least 25 observations for each of the 4 groups defined in the section on "Design of study."

The 25 observations per group is the required number that finish the 12 weeks. In order to account for dropouts, more than 25 subjects should be included in each group at the start of the study.

K. *Number of studies.* Two studies by different investigators at two sites are required by the protocol. This is a standard requirement, and the Panel belives it is an essential feature in establishing efficacy. The samples from each of these sites should be representative of the sample population.

References

(*1*) Metropolitan Life Insurance Company, "Desirable Weights for Men and Women," *Statistical Bulletin*, 58:5, 1977.

(*2*) Dixon, W. J., and F. J. Massey, *Introduction to Statistical Analysis*, 3d Ed., McGraw-Hill, New York, 1969.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advise in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title of 21 of the Code of Federal Regulations would be amended by adding in Part 357, a new Subpart F, to read as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

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Subpart F—Weight Control Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart F—Weight Control Drug Products

§ 357.501 Scope.

(a) An over-the-counter weight control drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart in addition to each of the general conditions established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 357.503 Definition.

Anorectic drug product. An agent that reduces appetite.

§ 357.510 Weight control active ingredients.

The active ingredients of the product in the indicated dosage form, where specified, consist of the following in the dosage limits established for each ingredient in § 357.550(d):

(a) Benzocaine (in gum, lozenges, or candy).

(b) Phenylpropanolamine hydrochloride.

§ 357.520 Permitted combinations of active ingredients.

Phenylpropanolamine hydrochloride described in § 357.510(b) may be combined with caffeine described in § 340.10 provided that the product is labeled as described in § 357.555.

§ 357.550 Labeling of weight control drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "Anorectic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following statements:

(1) "For appetite control to aid weight reduction."

(2) "An aid for effective appetite control to assist weight reduction."

(3) "Helps curb appetite."

(4) "Appetite depressant in the treatment of obesity (excess weight)."

(5) "An aid to diet control in conjunction with a physician's recommended diet."

(6) "An aid in the control of appetite."

(7) "Helps control appetite."

(8) "For use as an aid to diet control."

(9) "Helps you eat less, weigh less."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 357.510.* "Do not give this product to children under 12 years of age."

(2) *For products containing phenylpropanolamine hydrochloride identified in § 357.510(b).* (i) "Do not exceed recommended dosage."

(ii) "If nervousness, dizziness, or sleeplessness occurs, stop taking this medication and consult your physician."

(iii) "If you are being treated for high blood pressure or depression, or have heart disease, diabetes, or thyroid disease, do not take this product except under the supervision of a physician."

(iv) "If you are taking a cough/cold or allergy medication containing any form of phenylpropanolamine, do not take this product."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions":

(1) *For products containing benzocaine identified in § 357.510(a).* "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding 3 months, because that should be enough time to establish new eating habits. Adult oral dosage is 3 to 15 milligrams just prior to eating or as directed by a physician."

(2) *For products containing phenylpropanolamine hydrochloride identified in § 357.510(b).* "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding three months, because that should be enough time to establish new eating habits. Adult oral dosage is 25 to 50 milligrams in a single dose and not exceeding 150 milligrams daily in divided doses 30 minutes before meals or as directed by a physician."

§ 357.555 Labeling of permitted combinations.

The labeling of combinations identified in § 357.520 contains the following:

(a) *Statement of identity.* The labeling of the product contains the established names of the ingredients and identifies the product as an "Anorectic/Stimulant."

(b) *Indications.* The indication used for this product will be a consolidation of the requirements of § 340.50(b) and § 357.550(b) of this chapter, such as "A combination of an aid for effective appetite control to assist weight reduction and a stimulant that helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness." Such a statement will be followed immediately by this statement: "This product is for use only by individuals who become fatigued because of dieting."

(c) *Warnings.* The warnings used for this product contain all those specified in § 340.50(d) and § 357.550(c) of this chapter.

(d) *Directions.* The directions used for this product contain all those specified in § 340.50(d) and § 357.550(d) (1) and (3) of this chapter.

Interested persons may, on or before May 27, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before June 28, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 3, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: February 8, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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