specified closing date for comments will be considered before taking action on the proposed rule. The proposal contained in this notice may be changed in light of the comments received. All comments submitted will be available for examination in the Office of the Assistant Chief Counsel for Southern Region, Room 550, 1701 Columbia Avenue, College Park, Georgia 30337, both before and after the closing date for comments. A report summarizing public contact with FAA personnel concerned with this rulemaking will be filed in the docket.

Availability of NPRMs

Any person may obtain a copy of this Notice of Proposed Rulemaking (NPRM) by submitting a request to the Federal Aviation Administration, Manager, Operations Branch, ASO–530, Air Traffic Division, P.O. Box 20636, Atlanta, Georgia 30320. Communications must identify the notice number of this NPRM. Persons interested in being placed on a mailing list for future NPRMs should also request a copy of Advisory Circular No. 11–2A which describes the application procedure.

The Proposal

The FAA is considering an amendment to Part 71 of the Federal Aviation Regulations (14 CFR Part 71) to establish Class E airspace at Thomson, GA, for the Thomson-McDuffie Airport. Currently the Class E airspace area for the airport is included in the Augusta, GA, Class E airspace area. The McDuffie NDB was relocated from an off-airport to an on-airport site. As a result the NDB Standard Instrument Approach Procedure (SIAP) has been revised. The subsequent airspace review revealed that less Class E airspace was now required for the Thomson-McDuffie Airport. As a result, the reduced Class E airspace area for the Thomson-McDuffie Airport no longer intersects the remainder of the Augusta Class E airspace area. Therefore, it is necessary to establish stand alone Class E airspace extending upward from 700 feet above the surface (AGL) at Thomson, GA, for the Thomson-McDuffie Airport and amend the Augusta, GA, Class E airspace area by removing the airspace previously required for the Thomson-McDuffie Airport. Class E airspace designations for airspace areas extending upward from 700 feet or more above the surface are published in Paragraph 6005 of FAA Order 7400.9D dated September 4, 1996, and effective September 16, 1996, which is incorporated by reference in 14 CFR 71.1. The Class E airspace designation listed in this document would be published subsequently in the Order.

The FAA has determined that this proposed regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. It, therefore, (1) is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a regulatory evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified that this rule, when promulgated, will not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (Air).

The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR Part 71 as follows:

PART 71—[AMENDED]

1. The authority citation for 14 CFR Part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g); 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389; 14 CFR 11.69.

§ 71.1 [Amended]

2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9D, Airspace Designations and Reporting Points, dated September 4, 1996, and effective September 16, 1996, is amended as follows:

Paragraph 6005 Class E airspace areas extending upward from 700 feet above the surface of the earth.

* * * * *

ASO GA E5 Thomson, GA [New]

Thomson-McDuffie Airport, GA
(Lat. 33°31′47″ N, long. 82°31′00″ W)

That airspace extending upward from 700 feet above the surface within a 7.5-mile radius of Thomson-McDuffie Airport.

* * * * *

ASO GA E5 Augusta, GA [Revised]

Augusta, Bush Field, GA
(Lat. 33°22′12″ N, long. 81°57′52″ W)
Bushe NDB
(Lat. 33°17′13″ N, long. 81°56′49″ W)
Daniel Field
(Lat. 33°27′59″ N, long. 82°02′21″ W)
Burke County Airport
(Lat. 33°02′28″ N, long. 82°00′14″ W)
Burke County NDB
(Lat. 33°02′33″ N, long. 82°00′17″ W)

That airspace extending upward from 700 feet above the surface within an 8.2-mile radius of Bush Field and within 8 miles west and 4 miles east of Augusta ILS localizer south course extending from the 8-mile radius to 16 miles south of the Bushe NDB, and within a 6.3-mile radius of Daniel Field, and within a 6.2-mile radius of Burke County Airport and within 3.5 miles each side of the 243° bearing from the Burke County NDB extending from the 6.2-mile radius to 7 miles southwest of the NDB.

* * * * *

Issued in College Park, Georgia, on November 18, 1996.

Wade T. Carpenter,

Acting Manager, Air Traffic Division Southern Region.

[FR Doc. 96–30524 Filed 11–27–96; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Ch. I.

[Docket No. 96N–0364]

RIN 0905–AD91

Regulation of Medical Foods

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is soliciting comments to initiate a reevaluation of its approach to the regulation of the broad group of heterogeneous products that are marketed as medical foods. FDA's goal is to arrive at a regulatory regime that will ensure that: These products are safe for their intended uses, especially because they are likely to be the sole or a major source of nutrients for sick and otherwise vulnerable people; claims for these products are truthful, not misleading, and supported by sound science; and the labeling of these products is adequate to inform consumers about how to use them in a safe and appropriate manner. The agency believes that there is a need to reevaluate its policy for regulating medical foods because of a number of developments, including enactment of a statutory definition of ''medical food,'' the rapid increase in the variety and number of products that are marketed as medical foods, safety problems

associated with the manufacture and quality control of these products, and the potential for fraud as claims that are not supported by sound science proliferate for these products.

DATES: Written comments by February 27, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written requests for single copies of FDA's Compliance Program for Medical Foods (Compliance Program No. 7321.002) to the Freedom of Information Office (HFI–35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send two self-addressed adhesive labels to assist that office in processing your requests.

FOR FURTHER INFORMATION CONTACT: Robert J. Moore, Center for Food Safety and Applied Nutrition (HFS–456), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–4605.

SUPPLEMENTARY INFORMATION:

I. Background

One of the first medical foods to be developed was the infant formula Lofenalac®, a product that was designed for use in the dietary management of a rare genetic condition known as phenylketonuria (PKU). This product contains only a very limited amount of the essential amino acid phenylalanine because the individuals with this condition have an impaired ability to metabolize this amino acid. If infants with PKU consume foods that contain phenylalanine, harmful end products of phenylalanine metabolism accumulate in the body and can cause severe, irreversible mental retardation. Dietary management to carefully limit phenylalanine intake (for example, by using a formula that provides only a limited, minimal amount of this essential amino acid) can result in normal growth and development and avoid mental retardation.

Before 1972, FDA regulated products like the infant formula Lofenalac® as drugs under section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(g)(1)(B)) because of their role in mitigating serious adverse effects of the underlying diseases. In 1972, FDA reassessed its position. At that time, such products were very limited in number and were being produced by a small number of reputable manufacturers with high standards of quality control. Additionally, the nutritional formulation requirements for this type of product were straightforward and well established by the medical community. FDA believed that the usefulness of these products in patient populations was widely accepted by health care professionals, and that close physician supervision ensured safe use in the patient population. The agency was interested in fostering innovation in the development of these products, most of which had been developed for the dietary management of diseases and conditions that are not widespread, to ensure that such products would be available at reasonable cost.

For all these reasons, the agency concluded that a revision of its regulatory approach to these products was appropriate. At the same time, the agency recognized that use of these products for feeding healthy individuals could be hazardous. For example, an infant formula that was purposely formulated to be suitable for an infant with PKU would be nutritionally inadequate for a normal infant. Thus, the agency saw that it was important to differentiate these products from foods for general use. As a result, in 1972, FDA stated that the PKU product described above would no longer be regulated as a drug but rather as a ''food for special dietary use'' [1] (37 FR 18229 at 18230, September 8, 1972). In addition, the agency began to follow a policy of regulating similar types of products as foods for special dietary use.

Since 1972, the legislative and regulatory history of medical foods has reflected the agency's efforts to develop a regulatory framework to ensure the safety and nutritional adequacy of foods that are designed to meet distinctive nutritional requirements resulting from diseases or health conditions. Medical foods are used under the supervision of a physician when such distinctive nutritional requirements cannot be met with a conventional diet. These characteristics have led the agency to exempt medical foods from many of the requirements that apply to conventional foods.

When FDA made nutrition labeling mandatory for certain foods in 1973, the agency exempted certain types of foods for special dietary use from this requirement. In the preamble to the 1973 final rule on nutrition labeling (38 FR 2124 at 2126, January 19, 1973), FDA noted that nutrition labeling developed for foods intended for consumption by the general population was not well suited for some food products, including two types of foods for special dietary use: (1) Any food represented for use as the sole item of the diet; and (2) foods represented for use solely under medical supervision in the dietary management of specific diseases and disorders. Therefore, this final rule provided that these two types of foods for special dietary use would be exempt from the general requirements for nutrition labeling and were to be labeled in compliance with regulations that the agency intended to include in 21 CFR part 125 (later redesignated as 21 CFR part 105).

The Orphan Drug Amendments of 1988 enacted, for the first time, a statutory definition of ''medical food'':

> The term ''medical food'' means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.
>
> (21 U.S.C. 360ee(b)(3))

Although Congress provided a statutory definition for medical foods, the legislative history of the Orphan Drug Amendments does not discuss the definition and, therefore, does not provide any further information regarding the types of products that the definition was intended to cover.

In the Nutrition Labeling and Education Act of 1990 (the 1990 amendments), Congress incorporated the definition of medical foods contained in the Orphan Drug Amendments of 1988 into section 403(q)(5)(A)(iv) of the act (21 U.S.C. 343(q)(5)(A)(iv)) and exempted medical

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[1] Although there was no statutory definition of a food for special dietary use in 1972, the term ''special dietary uses,'' as applied to food for humans, had been defined by regulation since 1941. In the Federal Register of November 22, 1941 (6 FR 5921), FDA promulgated a regulation stating that the term ''special dietary uses'', as applied to food for man, means particular (as distinguished from general) uses of food, and that it means, among other things, ''uses for supplying particular dietary needs which exist by reason of a physical, physiological, pathological or other condition, including but not limited to the conditions of disease, convalescence, pregnancy, lactation, allergic hypersensitivity to food, underweight, and overweight.'' This part of the regulation remains unchanged in current § 105.3(a)(1) (21 CFR 105.3(a)(1)).

The statutory definition of ''special dietary use'' in section 411(c)(3) of the act (21 U.S.C. 350(c)(3)) was added in 1976 (Pub. L. 94–278). It defines this term as a particular use for which a food purports or is represented to be used, including but not limited to the following:

(A) Supplying a special dietary need that exists by reason of a physical, physiological, pathological, or other condition, including but not limited to the condition of disease, convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control intake of sodium.

(B) Supplying a vitamin, mineral, or other ingredient for use by man to supplement his diet by increasing the total dietary intake.

(C) Supplying a special dietary need by reason of being a food for use as the sole item of the diet.

foods from the nutrition labeling, health claim, and nutrient content claim requirements applicable to most other foods. In the Federal Register of November 27, 1991 (56 FR 60366 at 60377), FDA published a proposal to implement the mandatory nutrition labeling provisions of the 1990 amendments. The proposal discussed the statutory exemption for medical foods and advised that the agency considered the statutory definition of medical foods to ''narrowly constrain the types of products that can be considered to fall within this exemption.'' In the Federal Register of January 6, 1993, FDA published several final rules implementing the 1990 amendments. The final rule on mandatory nutrition labeling (58 FR 2079 at 2151, January 6, 1993) exempted medical foods from the nutrition labeling requirements and incorporated the statutory definition of a medical food into the agency's regulations at § 101.9(j)(8) (21 CFR 101.9(j)(8)). In this regulation, FDA enumerated criteria that were intended to clarify the characteristics of medical foods. The regulation provides that a food may claim the exemption from nutrition labeling requirements only if it meets the following criteria in § 101.9(j)(8):

(i) It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube;

(ii) It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone;

(iii) It provides nutritional support specifically modified for the management of the unique [2] nutrient needs that result from the specific disease or condition, as determined by medical evaluation;

(iv) It is intended to be used under medical supervision; and

(v) It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.

(58 FR 2079 at 2185)

In the preamble to the final rule on mandatory nutrition labeling, FDA noted that it had received a number of comments asking for further clarification of the types of products that the agency considers to be medical foods. The agency acknowledged that such clarification would be helpful and announced that it intended to address the issue in the future (58 FR 2079 at 2151). In the same document, the agency also noted the need for labeling regulations for medical foods and reiterated its intention to propose such regulations.

In 1990, the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (LSRO/FASEB) published ''Guidelines for the Scientific Review of Enteral Food Products for Special Medical Purposes'' (Ref. 1). This report defined medical foods as products that are distinct from foods for special dietary use in that they ''demonstrate greater suitability for nutritional management of a specific disease than standard enteral formulas'' and are intended for patients with ''special medically determined nutrient requirements, the dietary management of whom cannot be achieved by the modification of the normal diet alone, by other foods for special dietary uses, or by a combination thereof.'' The report proposed criteria that would establish a strict standard that a food would have to meet to be considered a medical food. LSRO/FASEB's proposed definition of a medical food did not include all foods that might be useful for persons with a disease or medical condition.

II. Reasons for Re-Evaluating Regulation of Medical Foods

A. Introduction

The agency is re-evaluating its policy for regulating medical foods in light of several developments, including the enactment of a statutory definition of ''medical food,'' the impact of the 1990 amendments, the rapid increase in the variety and number of products that are marketed as medical foods and in the uses for which these products are marketed, safety problems associated with the manufacture and quality control of these products, and the resulting potential for injury to consumers and fraud as claims that are not supported by sound science proliferate for these products.

B. The Definition of ''Medical Food'' and the Impact of the 1990 Amendments: the Medical Foods Paradox

The statutory definitions of ''medical food'' (21 U.S.C. 360ee(b)(3)) and food for special dietary use (see section 411(c)(3) of the act), and the differing treatment of these two categories of products under the 1990 amendments to the act (i.e., medical foods are exempted under section 403(q)(5)(A)(iv) and (r)(5)(A) of the act, while there is no special treatment of foods for special dietary use), establish that Congress intended that medical foods and foods for special dietary use be viewed and regulated as separate and distinct categories of products. Foods for special dietary use are subject to the same nutrition labeling requirements and requirements for health claims and nutrient content claims established for most other foods by the 1990 amendments. Thus, foods for special dietary use, like ordinary foods, must be labeled with certain nutrition information in a prescribed format to ensure that such information is presented in an informative and understandable fashion. Moreover, any nutrient content claims or health claims on the label or in the labeling of a food for special dietary use must have been authorized by FDA to ensure that the claim is scientifically valid and is presented in such a way that it is truthful and not misleading.

In contrast, under the 1990 amendments, medical foods are specifically exempted from the requirements for nutrition labeling, nutrient content claims, and health claims. Thus, a medical food that is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements have been established may be sold without any nutrition information on its label or labeling, and it may bear claims that have not been evaluated under the 1990 amendments to ensure that they are scientifically valid. Moreover, there is no assurance that the formulation of a medical food has been evaluated prior to sale to ensure that it is suitable for the intended patient population. The exemption from the requirements of the 1990 amendments, therefore, creates a troubling paradox: Medical foods intended for use by sick people are subject to much less scrutiny than virtually all other foods, which are intended for the healthy general population. This lack of scrutiny creates a situation that could have adverse public health consequences if these

[2] The agency notes that experience has shown that the word that it should have used here is ''distinctive'' rather than ''unique.'' Thus, in any rulemaking that results from the advance notice of proposed rulemaking, the agency will likely propose to amend § 101.9(j)(8) accordingly.

products bear claims that are not scientifically valid, or if their labeling does not disclose nutrition or other information that is necessary for the safe and effective use of the food.

C. Universe of Products

The number and variety of products marketed as medical foods, the number and types of claims made for such products, the types of ingredients included in these products, and the number of manufacturers of these products have increased significantly since the mid-1970's. In 1974, a limited survey of pharmaceutical and food manufacturers revealed that fewer than three dozen products were being sold as medical foods (Ref. 2). As of 1989, however, well over 200 products were being sold as medical foods (Ref. 3). Table 1 lists several types of products being marketed as medical foods with examples of claims being made by vendors of these products.

However, many products marketed as medical foods may not qualify as such under the statutory definition of medical foods. Many of these products, for example, complete liquid nutrition products, are not formulated or promoted for the dietary management of a particular disease or condition but rather are formulated and marketed for use by the general population as supplements to a normal diet or as meal replacements.

Enteral nutrition is nutrition provided through the gastrointestinal tract, taken by mouth or provided through a tube or catheter that delivers nutrients beyond the oral cavity (i.e., directly to the stomach or small intestine). This document uses the term ''enteral nutrition products'' to refer to products that have been marketed as medical foods; ''statutory medical foods'' to refer to enteral nutrition products that meet the statutory definition of a medical food in section 5(b)(3) of the Orphan Drug Amendments (21 U.S.C. 360ee(b)(3)); and ''nonstatutory enteral nutrition products'' to refer to enteral nutrition products that have been marketed as medical foods but that do not meet the statutory definition of a medical food.

Enteral nutrition products labeled and marketed as medical foods are generally liquid or powdered products formulated to meet specific needs. They include nutritionally complete formulations, nutritionally incomplete formulations (such as modular products that contain only one nutrient or a small number of nutrients and that are intended for use with other formulations), formulations for metabolic disorders (including inborn errors of metabolism) in patients over 12 months of age, and oral rehydration products. While many such products are intended to provide a complete source of nutrition and are consumed orally or administered by feeding tube for this use, the labeling of such products frequently bears claims related to an intended use of the product in the management of a disease or condition, e.g., in alleviating specific symptoms and clinical manifestations of a particular disease.

TABLE 1.—EXAMPLES OF CURRENTLY AVAILABLE TYPES OF ENTERAL NUTRITION PRODUCTS FOR USE IN VARIOUS DISEASE STATES AND FOR PATIENTS WITH INBORN ERRORS OF METABOLISM [1]

Disease state	Patient population	Product characteristics	Examples of product claims
Kidney (renal) disease (e.g., chronic or acute kidney failure).	Hospitalized patients (including critical care patients) and home care patients.	Type and quality of protein.	''* * * complete balanced nutrition for renal patients * * * a moderate-protein, low-electrolyte, low-fluid, high-calorie formula * * * designed to provide balanced-nutrition for dialyzed patients with chronic or acute renal failure * * *'' ''Under careful dietary management * * * can maintain uremic patients in good nutritional status, promote anabolism and lower and stabilize blood urea nitrogen levels * * *''
Liver disease (e.g., coma or encephalopathy associated with hepatitis or cirrhosis).	Hospitalized patients (including critical care patients) and home care patients.	Type and quality of protein.	''Provides adequate protein without inducing or exacerbating hepatic encephalopathy'' An aggressive nutritional regimen * * * may be useful in the nutritional management of alcoholic liver-disease patients in reversing malnutrition, liver dysfunction, and encephalopathy.''
Hypermetabolic states (e.g., severe burns, trauma or infection).	Hospitalized patients (including critical care patients).	Type and quality of protein; added amino acids; elevated levels of specific vitamins and/or minerals.	''A nutritionally complete formula that provides a concentrated source of calories for patients with restricted fluid allowance or increased energy needs * * * useful in the dietary management of volume-restricted patients, oncology patients, hypermetabolic conditions, trauma, sepsis, and post major surgery.'' ''Specialized elemental nutrition with glutamine for metabolically stressed patients with impaired GI function * * * stimulates intestinal epithelial cell proliferation in injured rats * * * diminished mucosal atrophy associated with injury by stimulating intestinal cell replacement.''
Lung disease (e.g., chronic obstructive pulmonary disease, acute respiratory distress syndrome, cystic fibrosis).	Hospitalized patients (including critical care patients) and home care patients.	High fat, low carbohydrate content.	''A nutritionally complete, ready-to-use formula * * * uniquely formulated to provide a diet high in nitrogen and restricted in carbohydrates to aid in the control of metabolic alterations in * * * various stress states including respiratory insufficiency * * * CO_2 production is minimized while providing appropriate nutrient levels.'' ''Proven effective in the dietary management of patients with respiratory disease * * * reduced CO_2 production in chronic obstructive pulmonary disease and cystic fibrosis patients.''

TABLE 1.—EXAMPLES OF CURRENTLY AVAILABLE TYPES OF ENTERAL NUTRITION PRODUCTS FOR USE IN VARIOUS DISEASE STATES AND FOR PATIENTS WITH INBORN ERRORS OF METABOLISM [1]—Continued

Disease state	Patient population	Product characteristics	Examples of product claims
Compromised immune function. Human immunodeficiency virus (HIV) infection, acquired immune deficiency syndrome (AIDS).	Hospitalized patients (including critical care patients) and home care patients.	Enriched with specific amino acids; fortified with increased levels of vitamins.	''Specialized complete nutrition to provide effective nutritional management for people with HIV infection or AIDS * * * to support immune function.'' ''Increases CD_4/CD_8 ratio, one aspect of immune system * * * CD_4/CD_8 increased by day 5, indicating an improved T-helper cell function.'' ''7 days of use helped support return of immune function to preoperative levels; 22 percent reduction in mean length of hospital stay; 70 percent reduction in infections and wound complications.''
Diabetes mellitus	Hospitalized patients (including critical care patients) and home care patients.	Type and quantity of carbohydrate; high fiber.	''High fiber, low carbohydrate * * * for patients with abnormal glucose tolerance * * * to enhance blood glucose control * * * in persons with type I or type II diabetes mellitus and stress-induced hyperglycemia.''
Malabsorption, as found in: Inflammatory bowel disease (ulcerative colitis, Crohn's disease); radiation enteritis; short bowel syndrome.	Hospitalized patients (including critical care patients) and home care patients.	Pre-digested macronutrients; altered type or quantity of fat.	''A nutritionally complete enteral nutritional with * * * 85 percent of fat derived from (medium chain triglyceride) (MCT) oil—a lipid clinically proven to result in less severity and incidence of diarrhea and abdominal discomfort in individuals with fat malabsorption * * * resulting from conditions such as HIV infection, inflammatory bowel disease, cystic fibrosis, or short bowel syndrome.'' ''Comparision of a semi-elemental diet with Prednisolone in the primary treatment of active ileal Crohn's disease * * * this new flavored semi-elemental diet * * * may be as effective as steroids in inducing remission in ideal Crohn's disease.''
Oral rehydration solutions	Hospitalized patients (including critical care patients) and home care patients.	Solutions of water, electrolytes and a carbohydrate source.	''To quickly restore fluids and minerals lost in diarrhea and vomiting in infants and children * * * for maintenance of water and electrolytes following corrective parenteral therapy for severe diarrhea.'' ''Enteral rehydration solution * * * to prevent dehydration and to correct mild to moderate dehydration associated with fluid and electrolyte loss.'' ''Pediatric electrolyte oral maintenance solution * * * to restore body water and minerals lost in children's diarrhea and vomiting * * * prevents dehydration.''
Phenylketonuria (PKU)	Patients with phenylketonuria.	Restrict dietary phenylalanine.	''A phenylalanine-free food to aid in the nutritional management of hyperphenylalaninemia including PKU.'' ''Phenylalanine-free to allow greater intake of complete protein.'' ''Phenylalanine-free for pregnant women, women in the childbearing years and individuals over 8 years of age.''
Maple syrup urine disease	Patients with maple syrup urine disease.	Restrict dietary branched-chain amino acids (isoleucine, leucine and valine).	''To be used only for the dietary management of infants and children with maple syrup urine disease or other disorders of branched-chain amino acid metabolism under the direct and continuing supervision of a physician.'' ''A branched-chain amino acid-free medical food * * * for nutrition support of children and adults with branch-chain ketoaciduria (maple syrup urine disease).'' ''Isoleucine-, leucine- and valine-free for individuals over 8 years of age and women in the childbearing years.''
Hereditary tyrosinemia: Type I Type II.	Patients with hereditary tyrosinemia.	For Type I: Restrict dietary tyrosine, phenylalanine and methionine;. For Type II: Restrict dietary tyrosine and phenylalanine.	''A phenylalanine-, tyrosine- and methionine-free medical food * * * for nutrition support of infants and toddlers with tyrosinemia type I.'' ''A special formula powder for use in the dietary management of hereditary tyrosinemia II * * * a phenylalanine- and tyrosine-free medical food for nutrition support of children and adults with tyrosinemia type II.'' ''A special formula powder for use in the dietary management of hereditary tyrosinemia II * * * very low in tyrosine and phenylalanine * * * ''.
Homocystinuria	Patients with homocystinuria.	Restrict dietary methionine.	''A special diet powder without added methionine for dietary management of individuals with homocystinuria.'' ''A methionine-free medical food * * * for nutritional support of children and adults with vitamin B_6-nonresponsive homocystinuria or hypermethioninemia,''

TABLE 1.—EXAMPLES OF CURRENTLY AVAILABLE TYPES OF ENTERAL NUTRITION PRODUCTS FOR USE IN VARIOUS DISEASE STATES AND FOR PATIENTS WITH INBORN ERRORS OF METABOLISM [1]—Continued

Disease state	Patient population	Product characteristics	Examples of product claims
Urea cycle disorders (e.g., argininemia, ornithine transcarbamylase deficiency, methylmalonic aciduria).	Patients with urea cycle disorders.	Restrict dietary protein as tolerated without causing hyperammonemia.	''Methionine-free for individuals over 8 years of age and women in the childbearing years.'' ''A non-essential amino acid-free medical food * * * for nutrition support of children and adults with a defect in a urea cycle enzyme * * * ''

[1] This is a summary description of products available for dietary management of the listed diseases and inborn errors of metabolism. Some of these diseases and conditions have many variations, each requiring distinctive dietary restrictions or supplements to the diet. A number of products are available for several of the listed diseases and conditions, and the actual composition of these products may vary slightly from the product characteristics given in this summary.

D. Safety Problems

As discussed above, there has been a dramatic increase over the past 20 years in the number and types of products that purport to be medical foods. The number of manufacturers producing these products has also increased. As the number of manufacturers has grown, the level of industry experience in the current good manufacturing practice (CGMP) and quality control procedures necessary to produce products that contain nutrients within a narrow range of declared label values has become quite variable. Medical foods are complex formulated products, generally requiring sophisticated and exacting technology comparable to that used in the manufacture of infant formulas and drugs. Moreover, the populations that consume these products, often as the sole or a major source of nutrition, are extremely vulnerable, e.g., pediatric patients in periods of growth and development, the elderly, patients who have serious illnesses, and patients in intensive care units. Although excessive or, conversely, insufficient amounts of particular nutrients may not be a health hazard when consumed by healthy persons, serious adverse consequences (even death) may result when these vulnerable populations consume these products for long, or even short, periods of time.

Significantly, in recent years, FDA has become aware of some serious problems with foods that purport to be medical foods. In 1986, four infants died as a result of being fed an oral rehydration solution that contained lethal concentrations of potassium. FDA identified the oral rehydration solution as the cause of these deaths (Ref. 4), inspected the site where the product was manufactured, and analyzed the product's nutrient content. FDA determined that elevated amounts of potassium occurred in the product because CGMP had not been followed. Notably, weighing scales were used improperly, and persons responsible for the formulation of product lacked adequate training.

Results of a compliance program that FDA initiated for medical foods in 1988, and followup on adverse reactions reported to the agency, have identified examples of deviations from CGMP that have caused the actual nutrient content of the product to deviate significantly from the declared label value. Some deviations have been significant enough to create acute, life-threatening health hazards and have led to product recalls. For example, in 1989, problems with a nutritionally complete product containing excessive amounts of potassium and sodium were brought to FDA's attention as a result of a complaint from the Veterans Administration Medical Center in Nashville, TN. Administration of this product to a patient resulted in hyperkalemia, or elevated blood potassium levels, which can have life-threatening consequences, including fatal cardiac arrhythmias. This patient required intensive medical treatment to reduce blood potassium levels and to prevent the serious side effects of hyperkalemia. FDA inspection of the facility that had manufactured this product revealed serious flaws in CGMP. These flaws resulted in extreme variability in product composition between lots or individual packets of product, which became evident when the product was analyzed by FDA for nutrient composition. This product was recalled (Ref. 5).

In 1993, in response to a complaint to FDA from a medical center in Seattle, WA, FDA analysis of a complete nutritional product being administered enterally to patients in an intensive care unit revealed that the product contained levels of potassium that were approximately twice the amount declared on the label. The agency concluded that this product represented an acute, potentially life-threatening hazard to persons with impaired kidney function, particularly those who were not being closely monitored for serum potassium levels. As a result, a number of products were recalled (Ref. 6).

FDA is also aware of problems involving potential microbiological contamination of products that purport to be medical foods. For example, in 1993, a modular product containing protein and a modular product containing carbohydrate were recalled because they had been manufactured under conditions in which they may have become contaminated with *Salmonella* (Ref. 7).

E. Claims and the Potential for Economic Fraud

FDA has not, to date, undertaken a comprehensive review of the claims being made for products that purport to be medical foods but rather has evaluated claims for a small number of these products on a case-by-case basis, applying the following general principles:

1. A product marketed for use as a medical food in the dietary management of a disease or condition should have characteristics that are based on scientifically validated distinctive nutritional requirements of the disease or condition.

2. There should be a scientific basis for the formulation of the product and the claims made for the product.

3. There should be sound, scientifically defensible evidence that the product does what it claims to do.

The agency is concerned that some of the claims made for products that purport to be medical foods are not based on sound science, and that consumers that use products that bear such claims, and health professionals that recommend the use of such products, are being misled regarding the value of these products. In addition to the health risks created by unsafe or ineffective medical foods, consumers and third-party payers, such as insurance companies and government

health care agencies, suffer significant economic losses when products marketed as medical foods do not do what they claim to do.

A number of publications by and for health care professionals express concern about unsupported claims for foods that purport to be medical foods. For example, a recent edition of a book published by the United States Pharmacopeial Convention, Inc., *USP DI, Volume I, Drug Information for the Health Care Professional* (Ref. 8), lists enteral nutrition products that are formulated to meet nutrient requirements for individuals with specific diseases but states: ''In general, scientific evidence for efficacy of these products is weak and requires further study.'' The 1990 LSRO/FASEB report ''Guidelines for the Scientific Review of Enteral Food Products for Special Medical Purposes'' (Ref. 1) noted that products containing substances such as essential amino acids, peptides, and medium-chain triglycerides were available, and that such products were represented as being useful for the dietary management of diseases and disorders. However, the report also stated that clinical trials of these preparations were limited, and that ''none has fully confirmed or refuted the putative advantages of these products over ordinary nutritionally adequate preparations.''

III. Clarification of the Medical Food Definition

In the preamble to one of the proposed rules implementing the 1990 amendments, FDA advised that it considered the statutory medical food definition to narrowly constrain the types of products that can be considered to be medical foods (56 FR 60366 at 60377). As noted previously in this document, however, the agency recognizes that the universe of products that purport to be medical foods has expanded beyond the statutory definition of a medical food to include foods that are more appropriately foods for special dietary use. In part, this expansion has occurred because many have difficulty distinguishing between medical foods and foods for special dietary use. While the agency recognizes that some ambiguity exists in the distinction between these two types of foods, the statutory language provides several bases on which to distinguish medical foods from foods for special dietary use.

A. ''Distinctive Nutritional Requirements''

A fundamental element of the medical food definition that distinguishes this type of product from a food for special dietary use is the statutory requirement that a medical food be intended to meet distinctive nutritional requirements of a disease or condition. Under 21 U.S.C. 360ee(b)(3), distinctive nutritional requirements must be based on recognized scientific principles and established by medical evaluation. The law does not define what constitutes a ''distinctive nutritional requirement,'' however, and there is more than one possible interpretation. FDA welcomes public comment on what definition of ''distinctive nutritional requirement'' will best protect and promote the public health. The agency is suggesting two possible interpretations of this phase.

1. Physiological Interpretation of ''Distinctive Nutritional Requirement''

''Distinctive nutritional requirement'' may be interpreted to refer to the body's requirement for specific amounts of nutrients to maintain homeostasis (the state of equilibrium in the body with respect to various functions and to the chemical compositions of the fluids and tissues) and sustain life; that is, the amount of each nutrient that must be available for use in the metabolic and physiological processes necessary to sustain life.

The nutritional requirements of healthy people for specific nutrients reflect their quantitative and qualitative requirements for absorbed nutrients (i.e., the physiological requirement for the nutrient), with adjustments for common inefficiencies associated with absorption, metabolism, and retention. However, the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for the general, healthy population, the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences recognized that different or distinctive physiologic requirements may exist for certain persons with ''special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions, and drug therapies'' (Ref. 9). Thus, the distinctive nutritional needs associated with a disease reflect the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism, and excretion. These distinctive nutritional requirements may be greater than, less than, or in a narrower range of tolerance than for an otherwise healthy individual.

Under this physiological interpretation of ''distinctive nutritional requirements, ''medical foods'' are foods that are formulated to aid in the dietary management of a specific disease or health-related condition that causes distinctive nutritional requirements that are different from the nutritional requirements of healthy people. Foods for special dietary use, on the other hand, are foods that are specially formulated to meet a special dietary need, such as a food allergy or difficulty in swallowing, but that provide nutrients intended to meet ordinary nutritional requirements. The special dietary needs addressed by these foods do not reflect a nutritional problem per se; that is, the physiological requirements for nutrients necessary to maintain life or homeostasis addressed by foods for special dietary use are the same as those of normal, healthy persons. These foods are formulated in such a way that only the ingredients or physical form of the diet is different. For example, a person who has difficulty swallowing solid food may have a special dietary need for a food that is in liquid form, but this special dietary need does not change his or her physiologic nutrient requirements. Similarly, a person who is allergic to specific food proteins (e.g., gluten) may need foods specially formulated not to contain these proteins. However, the specially formulated food still would provide the same amount of protein (i.e., amino acids) as is needed by the general population because the quantitative and qualitative amount of protein required by the body is similar in both healthy and protein-sensitive patients. Thus, foods for special dietary use are foods that are intended to meet ordinary nutritional requirements through special dietary means.

2. Alternative Interpretation of ''Distinctive Nutritional Requirement''

''Distinctive nutritional requirement'' may also be interpreted to encompass physical or physiological limitations in a person's ability to ingest or digest conventional foods, as well as distinctive physiological nutrient requirements. The FASEB report on medical foods stated that medical foods are for ''patients with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients contained therein, or (who) have other special medically determined nutrient requirements'' (Ref. 1). This definition would include uses that a purely

physiological definition of ''distinctive nutritional requirements'' would exclude, such as foods intended for persons not able to ingest foods in certain physical forms (e.g., solid food), foods intended for persons who need a concentrated form of nutrition because of reduced appetite as a result of disease or convalescence), or foods intended for persons who may have other physical limitations on the amount or composition of food that they can consume. Although these types of conditions do not necessarily result in nutrient needs different from those of healthy persons, they represent a situation where it may be necessary that the food be formulated and manufactured within very narrow tolerances to ensure that the food provides most or all of the essential nutrients, as the persons for whom the food is intended may not be able to eat a variety of foods to ensure that they meet their nutrient requirements.

Therefore, it may be appropriate to define ''distinctive nutritional requirements'' to include those requirements that result from a disease or condition that cause a physical or physiological limitation in the ability of a person to ingest or digest conventional nutrient sources and result in that person needing specially formulated foods to meet part or all of their daily nutrient needs. Defining this term in this way may be appropriate because these circumstances create nutritional needs that are more narrowly defined than those of healthy persons, because the patient is relying on only a limited number of foods or a single food for sustenance. The agency asks for comments on whether persons with an impaired ability to ingest or digest specific foods because of a disease or condition, or who have physical or physiological limitations that cause them to rely on an enteral nutrition product for a significant part or all of their nutrient needs, have ''distinctive nutritional requirements'' within the meaning of the medical food definition.

B. ''Under the Supervision of a Physician''

The second element of the medical food definition that distinguishes a medical food from a food for special dietary use is the statutory requirement that a medical food be ''formulated to be consumed or administered enterally under the supervision of a physician.'' As stated in the preamble to the proposed rule implementing the nutrition labeling requirements of the 1990 amendments (56 FR 60366 at 60377), ''under the supervision of a physician'' means that the intended use of a medical food is for the dietary management of a patient receiving active and ongoing medical supervision (e.g., in a health care facility or as an outpatient). The physician determines that the medical food is necessary to the patient's overall medical care, and the patient consults the physician on a recurring basis.

Medical foods are intended for the dietary management of patients who have a short-term or long-term medical need for a particular nutrient or combination of nutrients to meet distinctive nutritional requirements. The use of a medical food requires ongoing physician oversight to ensure that the food effectively meets the distinctive nutritional requirements of the patient's disease or condition, and that the use of an enteral medical food is the appropriate means (i.e., as opposed to a patient requiring a parenteral nutrition product) to meet the patient's distinctive nutritional requirements. Therefore, medical foods are foods that are an integral component of the clinical management of a patient. Medical foods are not foods simply recommended by a physician as part of an overall diet designed to reduce the risk of a disease or medical condition, to lose or maintain weight, or to ensure the consumption of a healthy diet. Foods recommended by a physician for these purposes may be foods for special dietary use, but they are not medical foods.

C. ''Specific Dietary Management''

The third fundamental element of the definition of a medical food that distinguishes a medical food from a food for special dietary use is the statutory requirement that a medical food be intended for the specific dietary management of a disease or condition. The term ''specific dietary management'' in the statutory definition of medical foods evidences that Congress intended these foods to be an integral part of the clinical treatment of patients. Consistent with this interpretation of this term, the LSRO/FASEB Panel concluded that the objectives of incorporating the use of medical foods into patient management were, in part, to ''ameliorate clinical manifestations of the disease,'' ''favorably influence the disease process,'' and ''positively influence morbidity and mortality (patient outcomes)'' (Ref. 1). There is no language corresponding to ''specific dietary management'' in the statutory definition applicable to foods for special dietary use. Thus, although they may be useful in supplying the special dietary needs of patients who have a disease or other condition that prevents them from eating normally, foods for special dietary use, unlike medical foods, are not specifically tailored for use as the nutritional component of the patient's treatment.

D. Summary

The statutory definitions of medical foods and foods for special dietary use overlap to the extent that both categories encompass foods that are intended for use by sick people. The differences in the statutory definitions evidence, however, that Congress intended foods for special dietary use under section 411(c)(3)(A) of the act to be a broader category of foods for use by people with special dietary needs or desires, while it intended medical foods to be a narrower category of foods for use by people with particular diseases or conditions that have distinctive nutritional requirements. Since a medical food must address the ''distinctive nutritional requirements'' of a disease or condition, a medical food is suitable only for use by patients with that disease or condition. Of course, it is possible for more than one disease or condition to create the same distinctive nutritional requirements. A product that is intended to address the distinctive nutritional requirements of a particular disease is a medical food, even though some of those requirements may also be created by other diseases. A product that is designed to address a problem that is common to several diseases, but not the full range of requirements of any specific disease, would be a food for special dietary use. For example, the distinctive nutritional requirements of burn patients include a greater energy requirement due to hypermetabolism and a requirement for dietary glutamine because endogenous synthesis of this amino acid does not meet the metabolic requirement. Thus, a product formulated to meet the higher energy requirement due to the hypermetabolic state, but which does not meet the requirement for glutamine, would be a food for special dietary use and not a medical food because it does not meet the full range of distinctive nutritional requirements in patients with burn injuries.

IV. Need for Substantiation of Nutritional Efficacy and Claims Made in Product Labeling

Because of their intended use in supplying the distinctive nutritional needs of patients who are ill or otherwise medically vulnerable, it is essential that medical foods be appropriately formulated for the particular disease or condition for

which they are labeled. Moreover, because the statutory definition of a medical food provides that these foods are part of the clinical management of a disease or condition, the definition necessarily incorporates a requirement that the product actually meet the distinctive nutritional requirements for the disease or condition. It is not enough that a manufacturer merely declare or subjectively intend that the product be used for the dietary management of patients with certain diseases or conditions. If the product, as formulated and consumed, does not actually meet those distinctive requirements, it would violate the act. Under any other view, the medical foods category would merely create a safe harbor for fraudulent claims targeted at those who are most vulnerable.

Other elements of the statutory definition support this view. In defining the term ''medical food'' in the Orphan Drug Amendments, Congress included the requirement that distinctive nutritional requirements of a disease or condition exist, and that they be based on recognized scientific principles and established by medical evaluation. Thus, Congress established a strict standard for when a food qualifies as a medical food. The establishment of this strict standard for distinctive nutritional requirements necessarily implies an expectation that this standard will in fact be met.

Acceptance of the manufacturer's intent that the product meets the special needs of the disease, without objective information to support the manufacturer's intent, would establish a subjective standard that would provide no assurance that the statutory standard has been met. Moreover, such a standard would ignore the fundamental differences between a medical food and other types of food. As stated above, a medical food is intended for use as the source of nutrients that are necessary in the medical management of a particular disease or condition. Thus, it is crucial to the health of the patient. No other type of food, including food for special dietary use, has such a direct relationship to the health of an individual. It is therefore necessary that the physician be able to rely on the medical food to effectively meet the distinctive nutritional requirements of the patient.

Finally, the statutory scheme for regulation of claims relating to health and disease confirms the appropriateness of a strong standard for substantiation of the nutritional efficacy of medical foods. The act establishes a range of circumstances under which claims relating to health and disease may be made. At one end of the spectrum are conventional foods, which under section 403(r) of the act may bear a health claim only if FDA determines:

> based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles) that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

At the other end of the spectrum are drugs, whose effectiveness in diagnosing, curing, mitigating, treating, or preventing disease must be established by substantial evidence, defined as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(Section 505(d)(7) of the act (21 U.S.C. 355(d)(7)).)

Clearly, medical foods fall somewhere between these two points, and the statutory scheme therefore requires some level of substantiation for a medical food's claimed usefulness in the dietary management of disease.

When Congress enacted authorization for health claims on conventional foods, it provided that such claims would be permitted only if FDA determined that the substance-disease relationship that is the subject of the claim is supported by significant scientific agreement among experts. The House Report for the 1990 Amendments states: ''The standard is intended to be a strong one. The bill requires that the Secretary have a high level of confidence that the claim is valid'' (Ref. 10). The establishment of a ''strong'' scientific standard was necessary to ensure that claims were supported by adequate scientific evidence so that they would not be misleading, and so that consumers could have confidence in the scientific validity of the claimed substance-disease relationship. Thus, even a health claim for a food intended to be used by healthy individuals must meet a high standard.

The reasons for requiring a strong standard of substantiation apply with even more force to medical foods. The statutory definition of a medical food states that such a food must be intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. As discussed earlier, this aspect of the definition makes it clear that Congress intended that claims made for medical foods be supported by scientific evidence, and it also constitutes a scientific standard that must be met for a food to be a medical food. The nature of these products (i.e., their intended use in the nutritional management of people affected by a disease or other condition) and the exemptions (i.e., from health claim requirements applicable to conventional foods) provided for them by virtue of their status as medical foods necessitate at least as much substantiation to support claims made for medical foods as for health claims on conventional foods. It would make no sense to establish a standard for claims on medical foods that was lower than the standard for health claims that are made for foods sold to healthy people.

The agency is concerned that many claims made for products marketed as medical foods are not supported by adequate scientific evidence, and that these unsupported claims result in the inappropriate use of some products by patients and physicians when effective alternative nutritional strategies for managing the disease are available. One medical expert on enteral nutrition formulas voiced this concern by stating that since the:

> introduction of nutritional support * * * as a specific therapeutic entity in the 1960's, a number of claims have been made, and widely believed, regarding its ability to improve the natural history of many diseases. However, these claims have been disseminated in the absence of supportive data from prospective randomized controlled trials * * *; in fact, when such studies have been performed, they have by and large not been able to demonstrate that [nutritional support] does improve morbidity and/or mortality.

(Ref. 11)

A physician relies on the claims made for medical foods on their labels and in their labeling as a significant factor in deciding whether to use a particular medical food in the clinical management of a patient. Thus, it is essential that the claims made for such a product present an accurate interpretation of the scientific evidence concerning the usefulness of that product or specific formulation. It is critical for the safe and appropriate use of the medical food that the claims made for it are accurate and unbiased, and that they are based on a critical

evaluation of the science available to the manufacturer. The need for physicians and patients to have confidence that any claim that a product is a medical food formulated for the specific dietary management of a disease or condition requires that a strong standard of substantiation be in place. A strong standard of substantiation would be one that requires that all pertinent data be considered in the formulation of the product and in the development of any claims about its use.

Further, the misbranding provisions of the act do not permit a food, including a medical food, to bear misleading labeling claims (section 403(a) of the act). Claims may be misleading not only because of affirmative representations made in the labeling, but also because the labeling fails to reveal facts material in the light of such representations with respect to consequences which may result from the use of the food under the conditions of use prescribed in the labeling or under usual or customary conditions of use (section 201(n) of the act). Thus, a medical food that bears claims that are not based on all the information available, and that do not permit the consumer or physician to make an informed choice, may be misbranded.

In summary, the intended uses of medical foods, the statutory definition of a medical food, and the statutory scheme for regulating health and disease claims all point to the need for a strong standard of scientific evidence for the composition and effectiveness of medical foods to provide assurance to health care providers and patients of the nutritional utility of these products. The standard should be no less demanding than for health claims for foods intended for the healthy general population. Moreover, because medical foods are intended for use in the clinical management of seriously ill and injured patients, it may be appropriate and necessary to apply a more stringent standard to the scientific evidence used to support claims made for medical foods. The agency's preliminary view is that the scientific standard contained in the statutory medical food definition may require some of the same types of data for medical foods as are needed to support drug claims (e.g., data from clinical investigations). The agency asks for comments regarding how stringent a scientific standard is necessary to ensure the safe and appropriate use of a medical food for a particular disease or condition.

V. Agency Plans

The agency is soliciting comments to initiate a reevaluation of its approach to the regulation of the broad group of heterogenous products marketed as medical foods and whether this approach serves the best interests of the consumers of such products. If the current regulatory approach is not adequate, the agency is interested in how it can improve the regulatory regime for medical foods to best serve those interests. FDA will review and consider all comments received. While this reevaluation is ongoing, however, the agency advises that it intends to continue to take regulatory action when necessary to protect consumers from unsafe or fraudulent products marketed as medical foods.

VI. Economic Issues

Under Executive Order 12866, FDA will be required to consider the costs and benefits of any proposed regulations pertaining to medical foods when regulations are proposed. In addition, under the Regulatory Flexibility Act and the Small Business Regulatory Enforcement and Fairness Act, FDA will be required to consider the impacts on small entities of any such regulations.

The primary benefit of any proposed change in the requirements applicable to medical foods will be a reduction in the health risks posed by medical foods that meet existing requirements. In addition, changes in the requirements applicable to medical foods that specify the level of scientific support required to make claims concerning the product will mean that consumers will have assurance that the claims are valid, and that the claims that are made provide reliable information. Other benefits will derive from the elimination of fraudulent and unsupported claims which will save consumers and third-party payers money and will improve patient health because people will use products that are appropriate for their conditions instead of relying on those bearing unsupported claims that do not have a positive impact on their conditions.

FDA asks for comments and information on the current health risks posed by medical foods meeting existing CGMP, labeling, and other applicable regulations. FDA also asks for comments on the degree to which these health risks may be reduced by additional regulation of medical foods, such as quality control requirements and additional CGMP and labeling regulations.

The primary cost of any proposed change will be the difference between the current cost of producing and marketing medical foods and the anticipated cost of producing and marketing medical foods under the proposed change. For example, relevant costs may include the cost of changing labels, generating particular types of information for labels, changing production methods or facilities to accommodate new CGMP requirements, the generation of additional information to establish product safety and effectiveness, and the cost of any uncertainty or delays associated with a potential premarket notification process.

FDA asks for comments on the costs that would be generated if medical foods were subject to additional regulatory requirements, such as quality control requirements, specific CGMP requirements, and labeling regulations. FDA also asks for comments on the impacts on small entities that would result if medical foods were subject to additional regulatory requirements of the type discussed in this document.

VII. Summary

Patients rely on medical foods to meet the distinctive nutritional needs resulting from their disease or condition, and, therefore, medical foods are often a significant part of the clinical management of these patients. Despite the importance of medical foods, however, existing regulations do not provide clear guidance on what products should be considered to be medical foods or on requirements to ensure that these foods do what they purport to do and are safe for their intended use. There is no regulatory framework that establishes specific quality assurance requirements, ensures the safety of medical foods under their intended conditions of use, ensures that they provide the nutrients that they claim to provide within safe ranges, or ensures that the benefits claimed for their purported use are supported by adequate scientific evidence. Therefore, the agency asks for comments on the following questions:

1. Is FDA's current approach to the regulation of medical foods adequate to ensure that food products claimed to be medical foods are safe and that the claims that they bear are valid? Is there a need for FDA to change its approach to the regulation of medical foods to better serve the needs of the patient populations that consume such products, and if so, what should the regulatory regime for medical foods be?

2. What factors should FDA consider applying as criteria to determine what products meet the statutory definition of a medical food? Should the agency apply a physiological interpretation of ''distinctive nutritional requirements'' in determining whether a product is a medical food, or should medical foods also include products that are used for

patients with ingestion or digestion problems but with otherwise ''normal'' nutrient requirements? Would the latter interpretation be consistent with the act?

3. What requirements are necessary to ensure the safe and appropriate use of: (a) Products that meet the statutory definition of a medical food? (b) products that have been marketed as medical foods but that do not meet the statutory definition of a medical food?

Examples might include requirements that address product composition, current good manufacturing practice and quality control procedures, labeling requirements, and standards governing claims about the product and for foods that may be used as a sole item of the diet.

4. To ensure the safety and effectiveness of a medical food, should the agency require that the manufacturer notify FDA before marketing the product, and that it submit evidence that establishes that the product will be safe for its intended use and that any claims made for the product are supported by sound science? What information should be included in such a submission?

5. What standard should be used to determine the safety of a medical food?

6. What quantity and quality of scientific evidence should be required to establish that a disease or condition has distinctive nutritional requirements based on recognized scientific principles?

7. What quantity and quality of scientific evidence should be required to support the validity of claims made for medical foods?

8. What information should be included on the label of a medical food or otherwise disclosed to health care professionals and consumers? Should the amount and detail of the information to be disclosed depend on the types of claims made for the medical food or on other characteristics of the product? What methods would be most effective in communicating information on the intended uses, benefits, and other characteristics of a medical food to enable physicians and consumers to make informed decisions regarding its use (e.g., labels, package inserts, detailed summaries of the science upon which a firm is basing the claims made for its product)?

9. Should the agency develop regulations specifying quality control standards and procedures and current good manufacturing practice requirements for medical foods? What types of requirements are necessary (e.g., expiration dating, analysis of nutrient content, microbiological safety measurements, etc.)?

10. How should FDA monitor the safety and effectiveness of medical foods already on the market? What elements are necessary components of an effective postmarket surveillance system for these products? Should a postmarket surveillance system for medical foods include requirements and procedures for the collection and reporting to FDA of safety- and efficacy-related product defects, adverse reaction reports, and complaints by health care professionals and consumers? Should manufacturers be required to collect information describing the outcomes associated with the use of medical food products in designated patient categories that would be available to FDA, health care providers, and consumers?

VIII. Comments

Interested persons may, on or before February 27, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Talbot, J. M., ''Guidelines for the Scientific Review of Enteral Food Products for Special Medical Purposes,'' prepared for the Food and Drug Administration under FDA Contract No. 223–88–2124 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 1990.

2. Fisher, K. D., J. M. Talbot, and C. J. Carr, ''A Review of Foods for Medical Purposes: Specially Formulated Products for Nutritional Management of Medical Conditions,'' prepared for the Food and Drug Administration under Contract No. FDA 223–75–2090 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 1977.

3. Hattan, D. G., and D. R. Mackey, ''A Review of Medical Foods: Enterally Administered Formulations Used in the Treatment of Diseases and Disorders,'' *Food Drug Cosmetic Law Journal,* 44:479–502, 1989.

4. Health Hazard Evaluation No. 1470, Food and Drug Administration, Center for Food Safety and Applied Nutrition, 200 C St. SW., Washington, DC, April 25, 1986.

5. FDA Enforcement Report, August 23, 1989, Rockville, MD.

6. FDA Enforcement Report, May 19, 1993, Rockville, MD.

7. FDA Enforcement Report, July 28, 1993, Rockville, MD.

8. The United States Pharmacopeial Convention, Inc., *USP DI, Drug Information for the Health Care Professional, Volume I,* Rand McNally, Taunton, MS, 1996.

9. Subcommittee on the Tenth Edition of the RDA's, Food and Nutrition Board, Commission on Life Sciences, National Research Council, ''Recommended Dietary Allowances, 10th ed.,'' National Academy Press, Washington, DC, 1989.

10. H. Rept. 101–538, 101st Cong., 2d sess., 19, ''Nutrition Labeling and Education Act of 1990,'' June 13, 1990.

11. Koretz, R. L., *A Critical Look at the Trials,* Symposium #2, Immunonutrition in the ICU, In: Proceedings of the 19th Clinical Congress, American Society for Parenteral and Enteral Nutrition, Miami, FL, pp. 97–103, 1995.

This document is issued under sections 4, 5, and 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); sections 201, 301, 402, 403, 404, 405, 409, 411, 412, 501, 502, 503, 505, and 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 344, 345, 348, 350, 350a, 351, 352, 353, 355, 371); and 21 U.S.C. 360ee(b)(3) (section 5(b)(3) of the Orphan Drug Amendments of 1988, as amended by Pub. L. 100–290).

Dated: October 31, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96–30441 Filed 11–27–96; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR PART 52

[ND4–1–6459b, UT8–1–6460b, CO20–1–6461b, MT14–1–6462b; FRL–5282–2]

Clean Air Act, Section 507, Small Business Stationary Source Technical and Environmental Compliance Assistance Program for the States of North Dakota, Utah, Colorado and Montana

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule; correction.

SUMMARY: EPA approved the State Implementation Plan revisions for the States of North Dakota, Utah, Colorado and Montana (January 11, 1994 in 59 FR 1485, January 11, 1994 in 59 FR 1485, January 28, 1994 in 59 FR 4003, March