Evaluation of Incentives for Development of Orphan Medical Foods

October 1989

Prepared for

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20204

under

FDA Contract No. 223-88-2124
Task Order #5

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, Maryland 20814
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prepared by
Richard M. Leukroth, Jr., M.S.
FOREWORD

The Federation of American Societies for Experimental Biology (FASEB) recognizes that its resources are particularly suited to marshalling scientific expertise for review and assessment of topics in the biological and medical sciences. The Life Sciences Research Office (LSRO) was established by FASEB in 1962 as an operational arm of the Executive Director's staff to provide a means for conducting scientific reviews and analyses. Reports of LSRO studies are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators in specific areas of biology and medicine.

This report was prepared by Richard W. Leukroth, Jr., M.S., Staff Scientist, LSRO, FASEB in accordance with Task Order #5, FDA Contract No. 223-88-2124 for the Center for Food Safety and Applied Nutrition, Food and Drug Administration. Individuals who contributed information are noted in Chapter IX; however, this report has not been reviewed by them. The listing of their names does not imply endorsement of the contents of this report.

In accordance with the policies and guidelines developed by the LSRO Advisory Committee, this report has been reviewed and approved for submission by the Chairman of the LSRO Advisory Committee. Reports prepared by LSRO do not necessarily reflect the opinion of the individual members of the FASEB constituent societies. The author and LSRO are solely responsible for the contents of this report.

December 29, 1987

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
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I. INTRODUCTION

A. BACKGROUND

The Orphan Drug Act of 1983 (see Appendix A) was promulgated to address the needs for product development for many diseases and conditions that have limited prevalence in the United States population. Congress provided incentives for the development of orphan drugs because the limited marketing potential of products for such "orphan" conditions was hindering the availability of treatment modalities for affected individuals. Since 1983 the Orphan Drug Act (P.L. 97-414 as amended) has been credited with expediting the development and approval of over 300 new drugs and biologicals (Food and Drug Administration, 1989a; Marwick, 1989). In 1988 the Act was further amended to extend some provisions of orphan status to medical foods (U.S. Congress, 1988). The Act and the 1988 amendments are included as Appendix A in this report.

The Food and Drug Administration (FDA) has responsibility for assessing public health needs in terms of safety and nutritional adequacy of the food supply. The 1988 Amendments to the Orphan Drug Act of 1983 charged the Secretary of HHS with conducting a study to ascertain the needs of industry, patients, and academic centers that might encourage the development of medical food products with orphan status. The study requirement as described in P.L. 100-290 is as follows:

"(d) Study. -- The Secretary of Health and Human Services shall conduct a study to determine whether the application of subchapter B of Chapter V of the Federal Food, Drug, and Cosmetic Act (relating to drugs for rare diseases and conditions) and section 28 of the Internal Revenue Code of 1986 (relating to tax incentives) to medical devices or medical foods for rare diseases or conditions or to both is needed to encourage the development of such devices and foods. The Secretary shall report the results of the study to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate ..."

B. SCOPE OF WORK AND TECHNICAL APPROACH

Conduct of the required study was assigned to FDA. Because of a need for current information on orphan diseases and medical foods used for orphan medical conditions, the FDA's Center for Food Safety and Applied Nutrition (CFSAN) requested that the Life Sciences Research Office (LSRO) of the Federation of
American Societies for Experimental Biology (FASEB) study issues related to the development of orphan medical foods.

This report reviews (1) incentives for orphan medical food development in the current FDA regulatory framework; (2) ongoing research activities in industry, academic institutions, and current medical practice; and (3) identification of the diseases and conditions that could benefit from the use and further development of medical foods with orphan status. Specifically, this report addresses the following objectives:

- Identification of human diseases that may benefit from orphan medical foods,
- Criteria to define orphan status for a medical food,
- Identification of economic incentives that would most benefit orphan medical food development,
- Scope of research and development efforts that are necessary prior to the use of an orphan medical food,
- Impact of noneconomic barriers on product development,
- Comparison of U.S. and foreign development of orphan medical foods.

In preparing this report, LSRO reviewed available published literature, developed a list of information needs based on the scope of work, and identified various individuals and organizations with interests in the use and development of medical food products with orphan status. These included scientists and clinicians specializing in rare diseases, pharmaceutical and food manufacturers, patient support and voluntary organizations, organizations that represent the interests of researchers and/or industry, health insurance underwriters, federal and state governmental agencies that provide health services, and individuals with similar interests in other countries.

The study was announced in the Federal Register of August 25, 1989 (Food and Drug Administration, 1989b). Individuals and organizations were invited to submit scientific data and information that should be considered in regard to orphan medical foods. The information, data, and views received from this request were considered by the LSRO staff in preparing this report. Individuals and organizations who provided information and data in response to the Federal Register notice, as well as those contacted directly by LSRO, are listed in Chapter IX.
LITERATURE CITED


II. LEGISLATIVE AND REGULATORY FRAMEWORK

A. FEDERAL FOOD, DRUG, AND COSMETIC ACT, AS AMENDED

The Federal Food, Drug, and Cosmetic Act as amended (U.S. Department of Health and Human Services, 1986) ensures the nutritional adequacy and safety of the nation's food supply as well as the safety and efficacy of drugs, biologics, medical devices, and cosmetics. The Act differentiates between foods and drugs and provides regulatory guidance for manufacturing and marketing these products. However, the framework by which the Act provides guidance for food products used by persons with diseases and medically defined conditions is unclear (Bass, 1989; Hattan and Mackey, 1989; Mackey, 1988; Scarbrough, 1989).

Under the Act, food is defined as "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any other such article" (U.S. Congress, 1986a). Drugs are defined as "(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in (the above); but does not include devices or their components, parts, or accessories" (U.S. Congress, 1986b).

Regulations developed for drugs require extensive documentation of the chemistry, biological effects, safety, effectiveness, and toxicity (as determined by nonclinical laboratory studies and clinical studies), and review of the manner of use, label, and package insert material for FDA approval. In contrast, regulations developed for foods in accordance with the Act are based on standards of identity, quality, fill of container, and specific criteria for nutritional information on package labels. These legal definitions have been in place for many years and predate the development of foods for special medical purposes.

B. THE CODE OF FEDERAL REGULATIONS

While the language of the Act has not changed, the distinction between foods and drugs has become less clear in recent decades as some food products were developed for use by patients with certain diseases and medically defined conditions (Bass, 1989; Hattan and Mackey, 1989; Scarbrough, 1989). Prior to 1972 these products were regulated as drugs. In 1972 the FDA recognized the
need to encourage further development of these products and classified them as foods rather than drugs (Hattan and Mackey, 1989). Amendments to the Act in 1976 provided additional guidance for such products under the term "foods for special dietary purposes" (Bass, 1989). These food products included infant formulas, dietary supplements, weight loss products, and other variations of nutrient formularies (U.S. Congress, 1986c).

A "food for special dietary use" (FSDU) was defined as a food used by human beings with a particular use for which the food purports or is represented to be used for, but not limited to, the following conditions:

"(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, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control the 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; and,

(C) Supplying a special dietary need by reason of being a food for use as the sole item of the diet" (U.S. Congress, 1986c).

This definition acknowledges that food products may possess certain characteristics which are more typically associated with drugs. The FDA has maintained that FSDU with medical claims were not the equivalent of foods in general, and that such products were intended to be 1) administered enterally, 2) used under the supervision of a physician, and 3) used for the dietary management of a specific disease, disorder, or medical condition (Miller, 1983). This view was developed earlier by an expert panel of scientists which defined medical foods as products consumed or administered enterally under direct or indirect medical supervision (Fisher et al., 1977). This concept, embodied in the current Code of Federal Regulations (U.S. Congress, 1986c) in regard to FSDU would also include special nutritional products used by persons with orphan diseases.

Infant formulas constitute a special class of FSDU. The regulatory guidance for the manufacture and marketing of infant formulas developed as a result of the Infant Formula Act of 1980 is incorporated in the Infant Formula Provisions of the Code of Federal Regulations (Office of The Federal Register, 1985; U.S. Congress, 1986d) as well as the section on Foods for Special Dietary Use (U.S. Congress, 1986c). Regulations on infant formulas address requirements for manufacture of general and exempt
infant formulas, product labeling, quality control, and enforcement policy for recalls. The exempt infant formula provision identifies a type of medical food product for rare diseases and conditions. Specifically this provision states

"An exempt infant formula is an infant formula intended for commercial or charitable distribution that is represented and labeled for use by infants who have inborn errors of metabolism or low birth weight, or who otherwise have unusual medical dietary problems" (U.S. Congress, 1986d).

C. ORPHAN DRUG ACT, AS AMENDED

The Orphan Drug Act of 1983 (U.S. Congress, 1989) defined orphan disease status as a term referring to a rare disease or condition which meets either of the following criteria:

- A disease or condition that affects less than 200,000 persons in the United States, or
- A disease or condition that affects more than 200,000 persons in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

The Act stipulated that the determination of orphan disease status is made on the basis of the facts and circumstances as of the date of request for designation of the product. The Secretary of Health and Human Services was required to promulgate procedures for the implementation of this determination. The Act also stipulates that sponsors of orphan drugs will receive the following benefits for product development and marketing:

- Designation as orphan products,
- Assistance in protocol development for nonclinical and clinical investigations which must be conducted for approval,
- Marketing exclusivity protection for periods up to seven years,
- Tax incentive writeoffs equivalent to 50% of incurred costs,
- Promotion of the development of drugs and devices by the Orphan Products Board, and
- Authorization of funds to support grants and contracts for clinical studies.
In 1988, Congress promulgated amendments to the Federal Food, Drug, and Cosmetic Act to revise the provisions in regard to orphan drugs and other purposes (U.S. Congress, 1988). Specifically, those "Orphan Drug Amendments of 1988" (P.L. 100-290) amended the Orphan Drug Act of 1983 to include medical devices and medical foods. The revised section on medical foods includes provisions related to support for the costs of medical foods for rare diseases and conditions and states

- "... in the case of medical food, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance ... and,

- ... 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."

Two points are critical to the discussions that follow in this report. First, the definition of medical foods in the 1988 Amendments differs from that for FSDU in the Code of Federal Regulations. Second, P.L. 100-290 does not extend several benefits of the Act to orphan medical foods. Specifically, the 1988 Amendments do not specify that sponsors of orphan medical food products should receive the following benefits for their products:

- Assistance in protocol development for nonclinical investigations which must be conducted for approval,

- Marketing exclusivity protection,

- Tax incentive writeoffs, and

- Promotion of medical food products by the Orphan Products Board.

The U.S. Congress, in calling for a study of incentives for medical foods in P.L. 100-290, anticipated that the DHHS would address these issues in the study.
LITERATURE CITED


III. CRITERIA FOR DEFINITION OF ORPHAN PRODUCT STATUS

A. CURRENT FDA ORPHAN PRODUCT CRITERIA UNDER INTERIM GUIDELINES

The FDA has developed interim guidelines for obtaining orphan product status for drugs and biologicals. They describe procedures under which sponsors (e.g., inventors, manufacturers, organizations, clinicians, etc.) may obtain FDA's recommendations on product development. The interim guidelines are available from the Office of Orphan Product Development (OOPD) (Food and Drug Administration, 1984). The information required in a sponsor's request is listed in Appendix C. These 16 items requested by the FDA in the approval process apply specifically to drugs and biologicals, but could be modified to address orphan medical foods. The 1988 revisions to the Orphan Drug Act extend the OOPD authority to grant financial and technical assistance to sponsors who are developing medical foods and/or medical devices. Guidelines for these products are not available at this time.

Sponsors of orphan products are encouraged to consult with the OOPD after they have developed some information that supports a product concept for which they will seek orphan status. Within 30 days of the receipt of an application, FDA will determine whether there is adequate justification to conclude that the sponsor's concept is for a disease or condition that is rare in the United States, and that the rationale for product use is valid. If a positive decision is made, FDA will review the technical data provided by the sponsor and will make recommendations about additional nonclinical and clinical studies that would be desirable for approval and/or licensing of the product. Sponsors have an opportunity to incorporate these recommendations into a proposed protocol or modify their protocol to develop the necessary information. The OOPD recognizes the importance of maintaining open dialogue with sponsors during this process and has stated that these procedures are a part of an interim process which may require modification as data and experience are accumulated.

In making a determination of orphan status for a new product, the FDA reviews information on the prevalence of the targeted disease in the population, product profitability, and therapeutic efficacy (see Appendix C). This information is the basis for criteria by which new product concepts receive orphan status. These criteria of the interim guidelines for drugs and biologicals are derived from the provisions of the Orphan Drug Act.

1. Prevalence criteria

A rare disease or condition as defined in the Orphan Drug Act (P.L. 97-414 as amended) (U.S. Congress, 1989) is one that
"(A) affects fewer that 200,000 persons in the United States, or (B) affects more than 200,000 persons in the United States but for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such a disease or condition will be recovered from sales in the United States of such drug" (Section 2. Sec. 526 (a)(2); and Section 5.(b)(2)(1)).

2. Economic criteria

Costs and profits, while they are a component of the Act and are included in the OOPD guidelines, are of secondary consideration as criteria in the determination of orphan status. The vast majority of orphan drugs approved to date are perceived by the FDA to be unprofitable for their developers because the market is too small (Haffner, 1989). Determination of unprofitability is essentially open-ended because, to some extent, the firm's philosophy determines not only the acceptable profit margin but also the selection of products for development and the appeal of such products to the health care providers and to the product consumers.

3. Scientific criteria

The discussion of nonclinical and clinical testing in the Orphan Drug Act as amended, as well as the charge to the Orphan Products Board, clearly indicates that efficacy and safety of drugs and biologicals must be considered. The section on tax incentives and credits references qualified clinical testing which would also imply evaluation of efficacy and safety by FDA using established criteria and protocols.

B. CONSIDERATIONS IN APPLICATION OF CURRENT INTERIM GUIDELINES TO ORPHAN MEDICAL FOODS

1. Prevalence criteria

The 1988 amendments to the Act (P.L. 100-290) (U.S. Congress, 1988) define a rare disease or condition as

"(3) in the case of a medical food, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance under subsection (a)" (Section 5.(b)(2)(3)).

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As a guideline for drugs and biologicals, OOPD applies one criterion of prevalence, but, for medical foods, a less restrictive requirement ("occurs so infrequently") is left to administrative discretion. Because data on prevalence are incomplete, the determination of rarity is based on information submitted by sponsors. Thus, the burden of proof of orphan status shifts to the sponsor. Furthermore, the availability and authenticity of information that a sponsor might provide in support of a request become a matter of informed judgment because very few sources of prevalence data are available on most rare diseases and the data that are available are frequently incomplete, based on limited studies, or not current.

Many potential sponsors do not appreciate that the prevalence defined for drugs and biologicals may not be the same for medical foods. In the event that orphan designation is further modified to extend all provisions of the Act to medical foods, the OOPD will need to clarify this difference in procedural guidelines provided to sponsors of medical food products that may qualify for orphan designation.

The Orphan Drug Act defines a rare disease or condition as one that affects less than 200,000 persons in the United States, or an occurrence of approximately 1 case per 1200 persons. However, cystic fibrosis which occurs in about 1 in 2800 White and 1 in 17,000 Black persons in the United States (Boat et al., 1989) is not considered rare by some scientists. Persons contacted in this study provided a wide range of opinion about occurrence rates as the threshold for the definition of rare (e.g., 1 in 5000 to 1 in 20,000). Because the prevalence criterion in the Act includes diseases that are rare (less than 200,000 persons) and diseases that are not rare (over 200,000 persons) but for which expectation of profit is absent, the provision of the designated prevalence rate is nonexclusive. Eliminating the arbitrary prevalence rate as a limit was suggested by many individuals who were confused by this criterion.

While the designated prevalence of fewer than 200,000 persons appears to have an economic basis, considerable confusion prevails among potential sponsors of orphan products as to the scientific as well as economic validity of this prevalence (Frasier, 1989; Weston, 1989). This is particularly important for sponsors of medical foods because the upper limit of prevalence may not be valid and little or no information on actual prevalence is available.

2. Economic criteria

Profitability is a relative matter. Most large firms manage to make a profit even in difficult years (Noda, 1974). What is considered to be a minimum profit goal for a "large" firm could
be a significant profit goal for a "small" firm. Furthermore, even subsidiaries within large conglomerates may compete with one another in the development of product lines (Noda, 1974). In this way, costs related to development of less profitable commodities can be more readily identified for special compensation support under various government programs.

By nature of their size, "large" firms have become accustomed to associating large product volume with an efficient means of cost recovery. This application of modern operations research management (Ackoff, 1974), systems engineering efficiency (Bode, 1974), minimax theory (Noda, 1974), optimization theory (Kalman, 1974), and theory of comparative advantage (Robinson, 1974) may serve to inhibit the development of useful new products such as orphan medical foods because opportunities for production of large product volumes do not exist. However, "smaller" firms may be able to develop products effectively without associating large production volume with cost recovery. These firms capitalize on high product demands within small markets. The ability of some firms to focus on small, "niche" markets can realize product profitability in an otherwise unprofitable marketplace.

Additional economic criteria are needed to improve identification of those disease conditions receiving orphan status designation. For example, estimates and projections of the benefits derived from orphan medical foods could outweigh or never reach investment costs in product development and/or in those costs associated with making products available to affected individuals. It is instructive to recall that, prior to the development of medical foods for phenylketonuria, individuals affected by this condition were frequently institutionalized for life because of the devastating effects of this condition on brain development and function. In the case of individuals with similar conditions for which no treatment is available, lifetime institutionalization is a costly option for society. The inclusion of such economic criteria is fraught with ethical considerations which have been avoided to date in the development of guidelines for determining orphan status.

3. Scientific criteria

Inclusion of orphan medical foods in the Act necessitates re-examination of scientific criteria. Those criteria outlined in Appendix C are, in general, amenable to the approval of orphan medical food products. However, further clarification will be required to replace therapeutic efficacy with the criteria employed in regulating foods.

Inherent differences exist among the product categories such as foods, drugs, biologicals, and devices for which FDA has oversight. A medical food must be useful in dietary management of
a specific condition and safe for the intended use. Diseases, disorders, and medical conditions that benefit from medical foods are pathophysiological disorders of metabolism and nutrient utilization. To be consistent, criteria for medical foods should remain physiologically based. The FDA review of orphan medical foods should be based on the analysis of available data on the physiological effects of these products for the medical conditions indicated by the manufacturers, as supported by the research findings of scientific experts qualified in their fields of specialization.

Strengthening the Section 411 provisions of the Federal Food, Drug, and Cosmetic Act (U.S. Department of Health and Human Services, 1986) by granting some food products a "medical food" prescription status may be useful. Revision to Section 411 could be modeled after the Exempt Infant Formula provisions of the Act [see Section 412.(f)(1)(A)(B)]. Such regulatory guidance might encourage further development of these products and permit those individuals affected by physiologically based metabolic disorders a means by which product costs could be recovered as prescription items. Such an approach would alleviate several issues currently associated with these special food products (e.g., jurisdiction, health care reimbursement).

The basic tenets of safety/efficacy testing for nonclinical and clinical testing have been developed and are continually refined (Food and Drug Administration, 1978, 1982; National Research Council, 1975; U.S. Department of Health and Human Services, 1988). As strategies for safety testing evolve, the regulatory use of information obtained from these testing procedures will need to be continuously revised and/or updated (Anonymous, 1989). As these protocols for safety are applied to orphan medical foods, clinical testing procedures can be conducted under the open protocol provisions of the Act (Section 2. Sec. 528); some nonclinical procedures may not apply as animal models may not be available or adequate.

Safety testing of orphan medical foods could include a variety of endpoints such as anthropometric measurements (height, weight) and functional tests, as well as biochemical measures of nutrient utilization, nutrient levels in tissues, and enzyme activity. The endpoints employed for safety evaluation of orphan medical foods should be those that are widely used by physicians, nutritionists, dietitians, and other biomedical scientists in evaluating usefulness and safety of FSDU. In addition, sponsors seeking orphan status for medical food products should expect FDA to request that applications include detailed information based on biochemical and other measurements of the physiologic effects of medical food products on metabolic diseases and other medical disorders and conditions. When designing study protocols, regulatory scientists at FDA and product sponsors should strive to identify the most meaningful endpoints for demonstrating efficacy of orphan medical food products.
However, the most frequent criticism of regulatory scientists and sponsors who participate in the genesis and review of orphan product applications is that open-ended protocols contribute to excessive product development costs and delays in the availability of new products for individuals affected by orphan diseases (Jenks, 1989). Thus, if additional guidelines are to be developed, such guidelines should be as discrete and clear as possible so as to avoid open-ended protocols.

C. RATIONALE FOR ADDITIONAL CRITERIA

The current interim FDA guidelines for determination of orphan status of drugs and biologicals should be extended to medical foods that qualify for orphan status. For the purposes of the revised guidelines, it may be useful to replace the term "drug" with a more general term such as "orphan medical product." Orphan medical products could be defined as drugs (pharmaceutical agents), biologicals (immunological agents), medical devices (mechanical devices), medical foods (physiological agents), and other products (as determined by OOPD) that are useful in the prevention, diagnosis, mitigation, treatment, and dietary management of rarely occurring diseases (orphan diseases).

If all the provisions of orphan status are extended to medical foods, the existing regulatory guidelines for drugs and biologicals could be utilized as a framework. A coordinated framework for management of orphan drugs and biologicals already exists in FDA. Requests for orphan status are submitted to the OOPD, and the scientific evaluation is conducted by Agency scientists in the several centers as appropriate. In the case of orphan medical foods, the evaluation should be conducted by CFSAN scientists. Included within, but not limited to, the CFSAN approval process would be an evaluation of safety as well as assurance that these food products meet the specific dietary requirements for the management of the nutritional component of the designated orphan disease.

A descriptive overview of morbidity and mortality information could provide estimates of the burden to society frequently associated with these rare medical conditions. This information could be more meaningfully expressed in economic measures of financial burden of a disease within society rather than in terms of a firm's ability to profit from the disease. These costs could be expressed as health care utilization costs, lost productivity revenues, and/or the cost of lifetime institutionalization. This type of information lends itself more readily to comparison with nonorphan medical conditions. Such comparisons might be developed into a useful index that could be used by regulators to prioritize limited research resources to gain maximum benefits for society at large.
In conclusion, extension of current interim guidelines to include medical food products for use in dietary management of orphan diseases is possible. However, any revisions of guidelines should address existing impediments and unique requirements associated with medical foods.

- Prevalence criteria should be modified to provide flexibility in the weight of evidence assigned to such data in the designation of orphan disease status. In essence, informed scientific judgment should be the basis for decision making.

- Economic criteria should be expanded to include consideration of overall costs of dietary management versus absence of nutritional support and institutionalization over a long time.

- Scientific criteria should be consistent with those used in evaluation of FSDU, that is useful in dietary management of a specified condition and safe for the intended use.

Revision of the interim guidelines will require considerable time and effort. There is a need to include considerations of interested and affected individuals and organizations as well as to address potential ethical implications of decisions to encourage or discourage development of orphan medical foods. The process of revision would be enhanced if FDA would first establish guidelines for health claims on foods and criteria for determination of the status of medical foods (see Chapter V and VI).


Weston, I. 1989. Orphan drugs: why are they left on the shelf? MIMS.
IV. ORPHAN DISEASES THAT COULD BE MANAGED BY MEDICAL FOOD PRODUCTS

This chapter identifies diseases, disorders, and medical conditions that could be managed by orphan medical food products, describes supporting rationale for orphan disease designation, characterizes available products presently used or which could be used for managing orphan disease conditions, and identifies future medical food product needs for rarely occurring diseases.

A. IDENTIFICATION OF ORPHAN DISEASES, DISORDERS, AND MEDICAL CONDITIONS

Several thousand diseases, disorders, and medical conditions, including inborn errors of metabolism might be classified as orphan diseases (Mckusick, 1988; Scrivener et al., 1989). New disease conditions continue to be described at a rapid rate (Rosenberg, 1984). For example, a new apolipoprotein B-100 variant has been identified (Ladas et al., 1989). Furthermore, research reports describing new understanding about the pathophysiologic basis of diseases (e.g., cystic fibrosis, Leigh's syndrome) continue to offer new insights and opportunities for therapies (Hinman et al., 1989; Kerem et al., 1989; Miranda et al., 1989; Riordan et al., 1989; Rommens et al., 1989).

1. Sources of rare disease information

One consideration in establishing orphan disease status is derived from the definition in the Act; that is conditions with a prevalence of fewer than 200,000 individuals in the United States. The LSRO staff sought information to identify rare diseases, disorders, and medical conditions as well as clarification of the scientific basis for the prevalence level defined by the Act. One pertinent source has been developed by Elsas and Acosta (1988) who identified disorders for which the efficacy of dietary intervention has been scientifically demonstrated and accepted by the medical community (see Table 1).

Numerous government agencies collect, compile, and distribute information on the occurrence and consequences of diseases and disorders of interest to their activities. Some of these are listed in Table 2. Several studies, registries, and listings were identified, but few have compiled listings of conditions that might be categorized as orphan diseases amenable to management by means of nutritional intervention.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disorder</th>
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<tbody>
<tr>
<td>Abetalipoproteinemia</td>
<td>Hypercholesterolemia</td>
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<tr>
<td>Acrodermatitis enteropathica</td>
<td>Hyperlipoproteinemia(s)</td>
</tr>
<tr>
<td>Alkaptonuria (ochronosis)</td>
<td>Hyperphenylalaninemia(s)</td>
</tr>
<tr>
<td>Argininemia</td>
<td>Hypertriglyceridemia</td>
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<tr>
<td>Argininosuccinic aciduria</td>
<td>Hypophosphatemia</td>
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<tr>
<td>Beta-methylcrotonylglycinuria</td>
<td>Isovaleric acidemia</td>
</tr>
<tr>
<td>(\beta)-sitosterolemia</td>
<td>Lactic acidosis, intermittent</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>Lactase phenotypes</td>
</tr>
<tr>
<td>Branched-chain (\alpha)-ketoaciduria</td>
<td>Lysine intolerance (hyperlysinemia)</td>
</tr>
<tr>
<td>Carbamylphosphate synthetase deficiency</td>
<td>Methionine malabsorption</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>Methylmalonic aciduria(s)</td>
</tr>
<tr>
<td>Citrullinemia</td>
<td>Multiple carboxylase deficiency</td>
</tr>
<tr>
<td>Combined hyperlipidemia</td>
<td>Nonketotic hyperglycinemia</td>
</tr>
<tr>
<td>Cystathioninuria</td>
<td>Ornithine transcarbamylase deficiency</td>
</tr>
<tr>
<td>Cystic fibrosis(^3)</td>
<td>Orotic aciduria</td>
</tr>
<tr>
<td>Cystinosis(^3)</td>
<td>Oxalosis</td>
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<tr>
<td>Diabetes(^3)</td>
<td>Phenylketonuria</td>
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<tr>
<td>Diabasic aminoaciduria</td>
<td>Porphyrin, acute intermittent</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome; lysyl hydroxylase defect</td>
<td>Propionicacidemia</td>
</tr>
<tr>
<td>Folic acid reductase deficiency</td>
<td>Pyridoxine dependency with seizures</td>
</tr>
<tr>
<td>Folic acid transport defect</td>
<td>Pyroglutamic aciduria</td>
</tr>
<tr>
<td>Fructose intolerance</td>
<td>Pyruvate dehydrogenase deficiency, partial</td>
</tr>
<tr>
<td>Fructose-1, 6-diphosphatase deficiency</td>
<td>Refsum's disease</td>
</tr>
<tr>
<td>Galactokinase deficiency</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Sucrose-isomaltose malabsorption</td>
</tr>
<tr>
<td>Glucose–galactose malabsorption</td>
<td>Tryptophanuria with dwarfism</td>
</tr>
<tr>
<td>Glucose–6-phosphate dehydrogenase deficiency</td>
<td>Tyrosinemia, type I</td>
</tr>
<tr>
<td>Glutamate-aspartate transport defect</td>
<td>Tyrosinemia with keratosis and corneal dystrophy</td>
</tr>
<tr>
<td>Glutaric acidemia</td>
<td>Vitamin A defect</td>
</tr>
<tr>
<td>Glycogen storage disorders</td>
<td>Vitamin B12 defect</td>
</tr>
<tr>
<td>Gout(^3)</td>
<td>Vitamin D-dependent rickets</td>
</tr>
<tr>
<td>Hartnup disease</td>
<td>Vitamin K-dependent coagulation defect</td>
</tr>
<tr>
<td>Homocystinuria(s)</td>
<td>Xanthinuria</td>
</tr>
<tr>
<td>Hydroxykynuneninuria</td>
<td>Xanthurenic aciduria</td>
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<tr>
<td>Hyperbeta-alaninemia</td>
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</tr>
</tbody>
</table>

\(^1\) Modified from Elsas and Acosta (1988).

\(^2\) Treatment for some conditions may require nutrient intake modification as supplementation, restriction, and/or elimination of specified dietary components.

\(^3\) May be considered a rare disease under certain restrictive definitions and/or for various subsets of affected populations.
<table>
<thead>
<tr>
<th>AGENCIES/OFFICES/PROGRAMS</th>
<th>ACTIVITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office of Orphan Products Development, Food and Drug Administration</td>
<td>Uses available information to identify orphan medical conditions and administer the Orphan Drug Act.</td>
</tr>
<tr>
<td>National Center for Education in Maternal and Child Health,</td>
<td>Distributes information about maternal and child health care.</td>
</tr>
<tr>
<td>Public Health Service, Department of Health and Human Services</td>
<td></td>
</tr>
<tr>
<td>Supplemental Food Program for Women, Infants, and Children, United States Department of</td>
<td>Uses available information to identify nutritional needs of women, infants, and children; distribution of food package #3.</td>
</tr>
<tr>
<td>Agriculture</td>
<td></td>
</tr>
<tr>
<td>The Office of Disease Prevention and Health Promotion, Public Health Service, Department</td>
<td>Identifies information about diseases and disease prevention.</td>
</tr>
<tr>
<td>of Health Promotion, Department of Health Promotion, Department of Health and Human</td>
<td></td>
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<tr>
<td>Services</td>
<td></td>
</tr>
<tr>
<td>Health Care Financing Administration, Social Security Administration</td>
<td></td>
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<tr>
<td>National Toxicology Program, Department of Health and Human Services</td>
<td></td>
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<tr>
<td>Agency for Toxic Substances Disease Registry</td>
<td></td>
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<tr>
<td>Birth Defects and Genetic Disease Branch, Centers for Disease Control, Department of</td>
<td></td>
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<tr>
<td>Health and Human Services</td>
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<tr>
<td>Mental Retardation and Developmental Disabilities Branch, National Institutes of Health</td>
<td></td>
</tr>
<tr>
<td>National Institute of Child Health and Human Development, National Institutes of Health</td>
<td></td>
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<tr>
<td>National Center for Health Statistics, Department of Health and Human Services</td>
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<tr>
<td>Centers for Disease Control, Department of Health and Human Services</td>
<td></td>
</tr>
</tbody>
</table>
The National Center for Health Statistics, the Centers for Disease Control, and many state and local health departments collect data and information about health and disease occurrence. However, because orphan diseases are rare, most surveys obtain limited data on conditions that occur infrequently in the population.

A further difficulty in obtaining data on rare disease occurrence is the lack of specificity in the coding scheme of the International Classification of Diseases (U.S. Department of Health and Human Services, 1980). For example in the 270 series (other metabolic and immunity disorders/disorders of amino-acid transport and metabolism) ten subcategories (270.0-270.9) cover approximately 71 known disease conditions. As a consequence, many conditions must be grouped under the same code designation. Some 15 conditions currently share code 270.2 (other disturbances of aromatic amino-acid metabolism). While the system is adequate for its intended purposes, a more specific coding system would be required to obtain detailed information on rare disorders. The issue of cost effectiveness and benefit from development of a more specific coding system has yet to be considered.

Another characteristic of national data bases is the inconsistency of information about rare diseases. Detection of metabolic diseases demands diagnostic expertise (Applegarth et al., 1989; Burton, 1987; Hart and Chang, 1988; Iles et al., 1985) and sophisticated screening equipment (Parvy et al., 1988; Williams, 1989). At this time only two conditions (phenylketonuria and congenital hypothyroidism) are screened on a nationwide basis. Eight other conditions (galactosemia, maple syrup urine disease, homocystinuria, sickle cell anemia, biotinidase deficiency, tyrosinemia, cystic fibrosis, and congenital adrenal hyperplasia) are screened routinely by a few states (American Academy of Pediatrics, 1989; Schuett, 1988). Testing procedures for many other conditions are available (e.g., hypercholesterolemia) or are at various stages of development (American Academy of Pediatrics, 1989; Bickel and Watchel, 1985; Guthrie, 1972; Milunsky, 1986; Therrell, 1987; Williams, 1989). Many rare disorders are not diagnosed or are misdiagnosed; in addition, the individual may die before the correct diagnosis is made. Considerations such as cost benefit and social responsibility at the state and local level are important determinants in selecting the number of conditions included in screening programs.

Compilations that report incidence or prevalence of diseases (Elsas and Acosta 1988; McKusick, 1988; Scriver et al., 1989) do provide some information on data trends; but typically the data were collected at least two to three years before publication. Research findings of clinical investigators at regional health care centers also supply information (American Association of University Affiliated Programs, 1989; National Center for Education in Maternal and Child Health, 1986; Schuett, 1988).
However, disease prevalence information from these centers is frequently archival, unpublished, or in various stages of updating and revision. Information available from various research programs (i.e., SPRANS research programs—the New England Regional Screening Program, or the Atlanta National Birth Defect Monitoring Program) (National Center for Education in Maternal and Child Health, 1989) is useful but may reflect regional rather than national trends and may have inherent problems of study design or regional ethnic sampling bias. Soltan and Craven (1981), in a review of the extent of genetic diseases in various hospital populations, concluded that 11 to 30% of pediatric inpatients at large university-affiliated hospitals have genetic disorders, depending on the strictness of the definition of the term "genetic."

Patient support and volunteer organizations maintain newsletter mailing lists which could provide some prevalence data. Registries describing the purpose and location of these organizations have been compiled (National Center for Education in Maternal and Child Health, 1989; National Organization for Rare Disorders, 1989; Schuett, 1988). A major problem with this information, however, is the lack of physician-confirmed diagnosis for each data point. In addition, volunteer organization registries may be flawed because individuals may be listed for reasons other than the disease condition (e.g., scientific investigators, relatives of affected individuals), affected individuals may not subscribe to the organizations' services, and affected individuals may subscribe to more than one organization. Despite these problems, such registries frequently provide a national perspective about the prevalence of rare conditions. The National Organization for Rare Disorders, Inc. (NORD) maintains an information data base listing approximately 400 diseases, disorders, and conditions (National Organization for Rare Disorders, 1989). New entries are added to this list on the basis of the number of requests for technical information, the need for patient support, or the need for physician referral. Such data bases are of considerable value to affected individuals and families as a public information service.

In conclusion, a listing of diseases that affect less than 200,000 persons in the United States was not identified during this study. The several issues identified include: 1) the absence of a central registry of information for rare conditions; 2) limited access to physician and hospital patient records because of concerns over patient confidentiality; 3) missed diagnosis and/or failure to recognize rare diseases in general; and 4) the absence of actuarial information for rare diseases. The validity of the conclusions reached by the National Committee on Orphan Diseases (U.S. Department of Health and Human Services, 1989a) indicating a need for accurate information about the prevalence of rare diseases in the United States has been confirmed by the efforts of the LSRO staff to find such data. Government
agencies responsible for generating this information are hampered by a lack of resources and the need for modernization of data collecting systems. Furthermore, registries of affected individuals need to be developed to assist researchers in their investigations. National health care programs in countries such as Canada, the Netherlands, and the United Kingdom provide an advantage in collecting this information. The National Institute of Child Health and Human Development is taking a leadership role in sponsoring efforts in the development of a national registry of inherited metabolic diseases and identifying populations for birth defect studies (Mize, 1989; National Institutes of Health, 1989a). These efforts will be helpful in the future but cannot replace the need for a comprehensive national program to monitor disease occurrence and health care utilization in the United States.

2. Categories of orphan diseases, disorders, and medical conditions that could be managed by orphan medical foods

The principal commonality shared among these medical conditions is a physiological change in the utilization and metabolic processing of nutrients that disrupts metabolic homeostasis and results in a pathological condition. Table 3 summarizes the major categories that should be considered in developing a compilation of these medical conditions.

a. Inborn errors of metabolism

The autosomal recessive inborn errors of metabolism exemplify a group of readily identifiable disorders. A comprehensive listing of these disorders has been compiled by Scriver and colleagues (1989). Included among the conditions that benefit or could benefit from special nutrient formulations are the less common disorders of carbohydrate metabolism (e.g., galactosemia), amino acid disorders (e.g., hyperphenylalaninemas, tyrosinemas, histidinemas, etc.), organic acidemias (e.g., branched-chain organic acidurias, proplonic and methylmalonic acidemias, etc.), disorders of purine and pyrimidine metabolism (e.g., hereditary orotic aciduria, Lesch-Nyhan syndrome), lipoprotein and lipid metabolism disorders (e.g., neuronal ceroid lipofuscinoses), peroxisome and lysosomal enzyme disorders (e.g., adrenoleukodystrophy, Zellweger Syndrome, Refsum's disease), disorders of vitamin function (deficiency and hyperdependency states), and disorders of membrane transport and immune mechanisms (e.g., cystinurias, Alzheimer's disease). Although some conditions are currently manageable with the aid of medical foods, few are curable and treatment is not uniformly successful.
Table 3. Major Categories of Diseases, Disorders, and Medical Conditions That Could Be Managed By Orphan Medical Food Products.

- Inborn errors of metabolism\(^1\)
  - Disorders of carbohydrate metabolism
  - Amino acid disorders
  - Organic acidemias
  - Disorders of purine and pyrimidine metabolism
  - Lipoprotein and lipid metabolism disorders
  - Peroxisome and lysosomal enzyme disorders
  - Disorders of vitamin function
  - Disorders of membrane transport and immune mechanisms

- Nutrient–genome mediated developmental conditions of the maternal–fetal unit, infant, child, and adult development\(^1,2\)
  - Low birth weight infants
  - Failure to thrive
  - Mental retardation syndromes
  - Growth retardation
  - Impaired reproductive ability
  - Shortened life span

- Environmental exposures that result in long–term or permanent imbalance of metabolic homeostasis\(^1,2,3\)
  - Pharmacological agents (drugs)
  - Industrial chemicals
  - Physical agents (e.g., radiation)
  - Infectious agents (e.g., retroviruses)

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\(^1\) Items listed are an incomplete list of representative subheadings. Medical conditions that could be included within these subheadings are too numerous to be listed. For more detailed information about these medical conditions the reader is referred to Scriver et al. (1989).

\(^2\) For more detailed information about these medical conditions the reader is referred to Braunwald et al. (1987), Cohn and Roth (1983), Shils and Young (1988), Smith and Thier (1981), and Wilson (1973).

\(^3\) For more detailed information about these medical conditions the reader is referred to Goldfrank et al. (1986), Goodman and Gilman (1975), Klaassen et al. (1986), and Shepard (1983).
The treatment of many genetic conditions (i.e., Mendelian disorders not related to inborn errors of metabolism) leaves much to be desired (Hayes et al., 1985). In many cases medical foods are used to maintain and support the patient until other therapies can be used (e.g., liver, and/or fetal tissue transplant; gene therapy) (Gluckman et al., 1989; McDonald et al., 1989; U.S. Department of Health and Human Services, 1989b).

b. Nutrient-genome mediated developmental conditions

Inherited heterozygotic expressions of errors of metabolism affecting the fetus and subsequent development throughout life make up the conditions in this category (National Research Council, 1989). This category differs from autosomal recessive disorders in that the availability of sufficient quantities of nutrients is considered the critical factor for disease expression, whereas, in the previous case, disease expression is determined solely by the genome. The basis for this category is substantiated by findings cited in the National Advisory Child Health and Human Development Council (National Institutes of Health, 1988). Because these conditions are mediated by nutrient-genome interaction at the cellular level, they may benefit by the availability of medical foods; and, because a heterozygous population subset can usually be identified, some of these conditions should qualify for orphan disease status.

Some medical conditions that occur during pregnancy and postpartum are included in this category (Centers for Disease Control, 1988, 1989; Zylke, 1989). However, fetal deaths that occur during the first trimester should be omitted, as many of these are the result of faulty gametes (Hook, 1982). Nevertheless, the number of fetuses that fail to thrive during the second and third trimesters, as well as low birth weight infants or infants with reduced chances of survival, might be lowered by nutritional intervention (National Research Council, 1985; National Institutes of Health, 1988). Estimates currently indicate that the number of fetuses and neonates who fail to thrive is approximately 21% of all conceptuses in the United States (Hack et al., 1979; National Center for Health Statistics, 1989; Philip et al., 1981). Currently, few nutritional products, tests to diagnose or monitor the nutritional status of the fetus, and/or treatment regimens are available to treat the fetus in distress (National Research Council, 1985). Lack of treatment can result in fetal death, various physical deformities, mental retardation syndromes, growth retardation, impaired reproductive ability, chronic disease manifestations, and shortened life span.
c. Environmental exposures

Environmental exposures comprise the third broad category of conditions that could benefit by the availability of medical foods with orphan status. Specific agent-mediated interactions that can affect metabolic homeostasis (i.e., pharmacological agents, industrial chemicals, physical agents such as radiation, and infectious agents such as retroviruses) are included. Medical conditions resulting from exposure to chemical substances and physical and microbial agents should be included in this categorization of rare diseases because the site of toxic action for these agents occurs within cellular systems. Numerous examples of drug-nutrient interactions can be found in the clinical literature (Braunwald et al., 1987; Goldfrank et al., 1986; Goodman and Gilman, 1975; Physicians' Desk Reference for Prescription Drugs, 1989; Roe, 1988). Similar examples can be identified in the toxicological and occupational health literature (Klaassen et al., 1986; Rom, 1983). Whether the affected individual is an adult with neurologic deficit caused by pesticide exposure or an adult with AIDS, the common factor in each condition is an environmentally mediated disruption affecting cellular metabolism. Specially formulated orphan medical foods could serve as nutritional adjuncts in the treatment of these conditions.

In conclusion, three categories of rare diseases, disorders, and medical conditions that qualify as orphan diseases and that could be managed by orphan medical foods have been developed (Table 3). However, designation of orphan disease status is difficult in the absence of accurate data on prevalence of rare diseases. Individuals and organizations contacted by LSRO had frequently formed their own concepts of disease rarity, usually based on incomplete or unverified incidence or prevalence data or on available information for economic values in terms of mortality, morbidity, or health care utilization. The spectrum of opinions and information obtained by LSRO is much broader than perceived by any of the individuals contacted.

B. IDENTIFICATION OF AVAILABLE MEDICAL FOOD PRODUCTS USED FOR MANAGING RARE DISEASES, DISORDERS, AND MEDICAL CONDITIONS

In recent years nutritional support has proven to be crucial in the management of many rarely occurring diseases, disorders, and medical conditions (Clow et al., 1981; Costa et al., 1981; Dobson et al., 1977; Leonard et al., 1984; Mahoney and Bick, 1987; Matsui et al., 1983; Mudd et al., 1985; Rousson and Guibaud, 1984; Saudubray et al., 1984; Sjörving et al., 1989; Snyderman, 1985). The spectrum of potential needs is best exemplified by the various nutritional protocols currently available for the management of inherited metabolic disorders.
(Acosta, 1989; Wapnir, 1985; Wooldridge, 1988). Representative medical food products and foods for special dietary use that are currently available for rarely occurring diseases, disorders, and medical conditions are listed in Appendix B. A complete listing of available medical food products for orphan diseases is difficult to obtain because a central product listing is not available, the number of manufacturers and distributors in the marketplace is constantly changing, and the designation of orphan status for a disease is itself problematic.

For numerous reasons this compilation is incomplete, inconsistent, and flawed. Many manufacturers and/or potential manufacturers were not identified by LSRO or did not respond in time to meet the schedule for completion of this study. In addition, Appendix B does not include formulations prepared on site by hospital dietitians and pharmacists. The fluidity of contemporary corporate structure and product marketplace development presents further difficulties in identifying available products. Certain FSDU are included because these items are considered, by some authorities, to be medical foods for numerous orphan disease conditions. For these reasons, dietary modules and some nutrient supplement or nutrient substitute products are also included in Appendix B. In general, products were listed in Appendix B if the manufacturers' product description or a physician provided information that was considered to be an orphan disease indication.

The table in Appendix B is incomplete because it lists some, but certainly not all, products available internationally. Government regulations for medical food products in other countries are not always consistent with those of the United States. Furthermore, products distributed by the same manufacturer may be distributed worldwide under the same product name but have different formulations to meet specified Good Manufacturing Practices (GMP) requirements in various countries. From a strict scientific viewpoint, each formula variation should be considered a separate product. Many potential products (e.g., vitamin and mineral formulations, low-calorie, low-salt, and many gluten-free food products) are omitted from Appendix B because of uncertainty about the acceptance of such products for orphan status. However, in a broad use of the term "orphan medical foods," such products may be listed if they prove to be useful in the management of medical conditions with orphan disease status.

1. Sources of information

The Physicians' Desk Reference for Prescription Drugs (1989) identifies nine food products for use in the management of metabolic dysfunction, while other food products useful in the management of rare diseases are listed in the Physicians' Desk
Reference for Nonprescription Drugs (1985a). Some nutrition module-type products (e.g., carbohydrate substitutes, special fats, and protein products, etc.) are listed as prescription drugs and/or nonprescription drugs (Physicians' Desk Reference for Nonprescription Drugs, 1985a; Physicians' Desk Reference for Prescription Drugs, 1989).

A British listing (Anonymous, 1989a) identifies approximately sixty medical food products available in the United Kingdom. A reference text on enteral and parenteral feedings (Hui, 1988) provides cross-referenced information about some medical food products available from several manufacturers for a variety of rare diseases and conditions. This text is particularly useful as it permits some product comparisons on the basis of indication for use, composition, description, preparation and feeding information, mixing directions, storage, and packaging information, product warnings, and clinical experience. Product catalogs available directly from the manufacturer provide the most reliable and up-to-date information (Acosta, 1989; Bristol-Myers, 1988, 1989; Milupa AG, 1989; Scientific Hospital Supplies, Ltd., 1988a; Wyeth-Ayerst International, Inc., 1989). However, as many of these products are used infrequently and are tailored to meet special formulation requests, detailed information may be available only in expanded manufacturers' product listings (Birt, 1989; Scientific Hospital Supplies, Ltd., 1988b).

Although duplicative products have been developed by different manufacturers to meet the needs for a particular disease or condition (e.g., phenylketonuria), these products differ in that manufacturers maintain proprietary information regarding production, the specific formulations for phenotypic variance, or improved formulations based on advances in scientific understanding of the disease process or in nutritional management. In some cases duplicative products have been developed because medical practitioners and regulatory agencies in some nations specify the original product rather than improved product formulations.

The availability of modular component products adds a virtually limitless capacity to increase the number of products. Examples of such modules include vitamins, minerals, specific amino acids, and alternate sources of proteins, carbohydrates, and fats. Modules can also be used by scientists as a starting point to develop completely new products. Some manufacturers such as Powell and Scholefield, Ltd. in the United Kingdom are able to provide "designer diets" based on state-of-the-art medical information and interaction among physicians, dietitians, and biochemists.

2. Future product needs

Nutritional product needs or potential needs were identified for a number of orphan diseases. These include: 1) medical food products for individuals affected by inborn errors of metabolism
for which no product is currently available; 2) improved formulations for those conditions for which products are available currently; 3) specially formulated nutrition products for individuals affected by inborn errors of metabolism during times of trauma, surgery, pregnancy, and/or microbial infection; 4) special formulas for low birth weight infants; and 5) alternative products that differ in form from infant formulas.

Medical food products are available for some inborn errors of metabolism. In some cases, these products are not fully effective in ameliorating the disorders and there are other conditions for which no effective nutritional products are available (e.g., mucopolysaccharidoses, cystinuria, homocystinuria) (Gahl et al., 1988; Hayes et al., 1985; Scriver et al., 1989; Smolin et al., 1988). There is a continuing need to improve existing formulas to provide specific nutrient needs (e.g., trace elements) that are not met by many of the modified diets required by affected individuals (Acosta et al., 1987; Fishler et al., 1985; Gropper et al., 1988; Williamson et al., 1985). Available nutritional products have been shown to be lifesaving and intellect sparing (Anonymous, 1989b); however, some disease complications persist and secondary nutrient deficiencies may occur (Hayes et al., 1985; National Institutes of Health, 1988). Many conditions other than inborn errors of metabolism may also benefit by the availability of medical food products. Examples include mental retardation syndromes, some cancers, and immunological disorders. Product development for these conditions may follow traditional diet formulations that incorporate or restrict mixtures of nutrients until an effective formulation can be discovered.

More novel approaches may consider the use of nonessential nutrients and/or chemically derived nonnutrient substitutes. For example, chemically derived fat substitute products (e.g., Olesstra, Simplesse) may prove efficacious in various lipid storage disorders, while dietary lipids designed for special medical purposes may be useful in a variety of inborn errors of metabolism (e.g., adrenoleukodystrophy, Zellweger Syndrome, Refsum’s disease) and hypermetabolic conditions (e.g., burns, sepsis, and cancer cachexia) (Anonymous, 1989c; Blackburn and Stein, 1988; Holmes et al., 1987; Talwar and Swaiman, 1987; Wilson et al., 1986). The benefits derived from such products may be analogous to the use of artificial sweeteners by diabetic patients. In addition, the identification of various plant ingredients may lead to the incorporation of these substances into products for use in the nutritional support of patients with certain types of cancers (Anonymous, 1989d; National Cancer Institute, 1989). Future products may include patented transgenic plants used as foods.

The prognosis for individuals affected by inborn errors of metabolism for which management of dietary intake is presently available has improved in recent years (Anonymous, 1989b). However,
the impact of longer survival of these individuals is coming to the attention of the health care community (Ekvall et al., 1987; Ekvall and Wheby, 1987; Gortmaker and Sappenfield, 1984; U.S. Department of Health and Human Services, 1982, 1987a,b). For example, during times of medical crisis such as trauma or surgery, few if any nutrition products are suitable for these individuals. Similarly, Rudman and colleagues (1981) noted that the nutritional needs of individuals with cirrhosis differ from the norm and studies have shown that serious metabolic complications of central venous alimentation can occur (Weinsier et al., 1982). Nutrition-related and disease-specific problems have been identified as affected individuals reach reproductive age and attempt to have children (Waisbren et al., 1988).

Special nutritional formulations to prevent intrauterine growth retardation and to feed low birth weight infants are needed (National Institutes of Health, 1988; Office of Technology Assessment, 1988). This group of orphan conditions may affect both infants born with inborn errors of metabolism as well as the general infant population. Although some products are available for infants (e.g., vitamin and mineral formulations), physicians continue to identify the need to improve and/or modify currently available products (Bhatia and Fomon, 1983). New medical food products that focus on nutrient-genome interactions during fetal development are needed for intrauterine nutritional therapy (Charlton, 1987; National Research Council, 1985).

Most of the medical food products currently available are manufactured by nutrition divisions of pharmaceutical companies. As a consequence, many of these nutrition products are modeled to conform with pharmaceutical forms such as the infant formula (powder or liquid) or as drugs (pills, capsules, liquids, and injectables). Clinicians and patients have identified the need to extend the availability of medical food products beyond traditional pharmaceutical forms. Physicians frequently have trouble maintaining patient compliance because of the aesthetic, palatability, and consistency problems associated with available infant-style formulations (Hunt et al., 1985). This is especially true among adolescents. The resources and approaches to make product improvements are more frequently associated with the food industry, which, under the present regulatory framework, is permitted to make medical claims only for FSDU.

To some extent both the pharmaceutical and the food industries have recognized the need for "cross-over products." For example, many nutritional modules are available to the general public as dietary supplements or nonprescription medications (Physicians' Desk Reference for Nonprescription Drugs, 1985a). Labeling for these products frequently contains information such as "useful in dietary management" of various conditions (e.g., restricted and/or supplemented carbohydrate, protein, fat, vitamin and/or mineral intake), "for use under the direction of a physician,"
and/or other precautionary messages to identify individuals with medical conditions who should avoid such products. Among milk products available to the general population are various dairy and dairy substitute products that have been specially formulated for individuals who cannot tolerate lactose. In this case these products are not only available in drug-like forms (i.e., tablets and liquids) but also in food forms including milk, various cheeses, and ice cream (Physicians' Desk Reference for Nonprescription Drugs, 1985b). Continued change in the distinction of separate product lines for the food and pharmaceutical industries can be expected with advances in biotechnology.

Advances in food science and food technology are available to develop specialty products for some orphan diseases, but this has not caught the attention of large corporations in the food industry for numerous reasons, primarily because of economic considerations. Such products are associated with problems of low profit margins, distribution difficulties, problematic product labeling, and high costs for development. Nevertheless, with the introduction of advances in biotechnology, it may be possible to design and market cheese- or tofu-like foods for conditions such as phenylketonuria. One manufacturer in the United Kingdom (Powell and Scholefield, Ltd.) recently developed a phenylalanine-free chocolate bar as a holiday public relations gesture for distribution to individuals with phenylketonuria. The concept was well received as evidenced by a number of requests to purchase more of the product. Research groups in Japan and elsewhere are currently exploring a technique of metabolic support by use of certain amino acid-deficient peptide mixtures (Kitagawa et al., 1987). Such products are currently available only in milligram quantities and the amounts needed by affected individuals would be costly to prepare. Other programs to develop innovative nutritional therapeutic approaches for the management of inborn errors of metabolism have been initiated by various branches of the National Institutes of Health (National Institutes of Health, 1989b).
LITERATURE CITED


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V. BARRIERS AND INCENTIVES RELATED TO CURRENT REGULATORY FRAMEWORK

A. BARRIERS

A number of barriers appear to inhibit the interest in and development of medical food products useful in management of orphan diseases. These impediments include both economic and noneconomic obstacles. Because the latter affect the former, noneconomic issues such as legislative inconsistencies, regulatory deficiencies, and absence of a unified communication and data system will be discussed first.

1. Legislative inconsistencies

The Infant Formula Act of 1980 contains an exemption for products "for use by infants who have inborn errors of metabolism or low birth weight, or who otherwise have unusual medical dietary problems" (U.S. Congress, 1986). The Federal Food, Drug, and Cosmetic Act, as amended in 1988 includes provisions for medical foods consistent with the legislative intent of the Orphan Drug Act of 1983 (U.S. Congress, 1988). The amendment defines medical foods narrowly in the context of orphan medical products. Medical foods are defined in part as foods formulated to be consumed or administered enterally under the supervision of a physician. Bass (1989) concluded that the requirement for supervision by a physician is too narrow and is contrary to the direction the medical foods industry is moving in that some products are for direct consumption, at-home use, and administration by nonmedical and paramedical health care providers.

Because the concept of medical foods is complex, development of regulatory guidelines for orphan medical foods has been difficult. This difficulty is related to the recognition by FDA of four types of medical foods: 1) nutritionally complete formulas; 2) nutritionally incomplete formulas, including modular products; 3) formulas for metabolic disorders in patients over 12 months of age (other than exempt infant formulas); and 4) oral rehydration formulas (Food and Drug Administration, 1989a). Clearly, orphan medical foods could include products in each of these categories.

A second issue in the legislation is the extent to which the 1988 amendments specify how medical foods may be covered by the Act. The Orphan Drug Act contains provisions for orphan medical foods under Section 5 (Grants and Contracts for Development of Drugs for Rare Diseases and Conditions). However, the Act has no provisions that provide the Food and Drug Administration with authority to designate orphan status to medical foods under Section 1. (Short Title, Findings); Section 2.(a) Chapter V of the
Federal Food, Drug and Cosmetic Act, sec. 525 (Recommendations for Investigations of Drugs for Rare Diseases or Conditions), sec. 526 (Designation of Drugs for Rare Diseases or Conditions), sec. 527 (Protection for Drugs for Rare Diseases or Conditions), sec. 528 (Open Protocols for Investigation of Drugs for Rare Diseases or Conditions); Section 3. Title II of the Public Health Service Act, sec. 227 (Orphan Products Board); or Section 4. (a) Subpart A of part IV of subchapter A of the chapter 1 of the Internal Revenue Code of 1954 (relating to credits allowable), sec. 44H. (Clinical Testing Expenses for Certain Drugs for Rare Diseases or Conditions).

A third legislative inconsistency within the Orphan Drug Act of 1983 as amended is associated with the definition of orphan disease (See Appendix A). The Act defines a rare disease or condition as either a disease or condition which affects fewer than 200,000 persons in the United States or a disease or condition which affects more than 200,000 persons in the United States and for which there is no reasonable expectation that the cost of developing and making available a drug (read: medical food) in the United States for that disease or condition will be recovered from sales of that product in the United States.

Intuitively, the term "rare disease" implies infrequent observation. Prevalence is subject to change over time as the ability to diagnose disease becomes increasingly sophisticated, as data are accumulated, and as treatments are developed that permit longer survival of affected individuals. For example, poliomyelitis and tuberculosis were diseases with a high prevalence in the past. With the discovery of effective preventive and therapeutic approaches, they are currently considered by some to be rare diseases in the United States. Greater prevalence may occur as treatments become less effective, as in tuberculosis where new strains of Mycobacterium are evident (Iseman, 1989; Prince et al., 1989).

In the context of the above discussion, the legislative definition imposes a static definition on dynamic biological processes. Further it is open ended in that fewer than or more than 200,000 persons in the United States population may be affected. In the latter case, expectation of no cost recovery from sales in the United States is an additional criterion. In fact, a case can be made that almost any disease could be an orphan disease and it follows that requests for development of orphan drugs, biologicals, medical devices, and medical foods need only prove absence of cost recovery.

These three issues were not anticipated by Congress and these impediments were not the legislative intent in promulgating the Orphan Drug Act and its amendments. While the establishment of orphan product status has been criticized (Frasier, 1989; Haffner, 1989; Sherman, 1989; Weston, 1989), the intent of Congress in enacting this legislation has been substantiated by the
benefits derived by these products (Food and Drug Administration, 1989b; Sherman 1989; U.S. Department of Health and Human Services, 1989) and those responsible for implementing the Act (Haffner, 1989).

2. Regulatory deficiencies

As noted previously, and as documented in detail by Bass (1989), Hattan and MacKey (1989), and Scarbrough (1989), the regulatory status of medical foods has been under discussion for several years. In the absence of clear regulatory guidelines and provisions for medical foods per se, it is not too surprising that regulatory guidelines for orphan medical foods have not been developed. Without a regulatory requirement for product registration, both nationally and internationally, many of the available products are unfamiliar to the medical community. A product registration requirement has been recommended to the Food and Drug Administration (Bass, 1989; Hattan and Mackey, 1989).

Another major issue is associated with the subject of health claims for foods. A FSDU by definition makes "health claims" in the sense that the product is used in the dietary management of a disease, disorder, or medical condition. Orphan medical foods as a type of FSDU would be expected to make health claims or provide indications for use. The larger issue of health claims for foods consumed by the entire population has been under public, corporate, legislative and regulatory scrutiny for several years and no clear consensus has emerged (Food and Drug Administration, 1989c,d).

3. Terminology and its communication

Over and above the difficulties associated with definitions of medical foods, orphan diseases, and orphan medical foods, there are additional issues associated with terminology and communication of these terms among the public, the regulated, and the regulators.

Foods are defined in terms of their use by humans; drugs are defined by their intended use in or on humans (Bass, 1989). FSDU are defined as foods used for particular purposes associated with dietary management of conditions. In the context of regulatory language, FSDU, or medical foods, are used in dietary management; yet in common usage by the public and some health professionals, medical foods are used to prevent, mitigate, or treat certain
diseases or disorders. This semantic dichotomy, imposed by the language of the Federal Food Drug and Cosmetic Act and FDA's regulations, but generally ignored in common usage, has led to difficulties in communication among persons interested in medical foods and orphan medical foods. For example, the subtle but legally important distinction between "dietary management" and "treatment" constitutes an additional impediment to the understanding of the context of regulating orphan medical foods.

In collecting information for this study, it became clear that the community of interested parties was extremely large and diffuse. These individuals and organizations have no systematic means of communication. The individuals and organizations involved in the development, use, marketing, and administration of these specialty products include manufacturers and formulators in the food and pharmaceutical industries; medical practitioners; research scientists; hospital nutrition support teams and pharmacists; dietitians; and other health professionals. Further, the community of interested individuals and organizations included those with experience in delivery systems and patient-related social services; health care underwriters; various administrators and managers within federal, state, and local government agencies; patient support groups and voluntary organizations; and the patients themselves.

Communication problems at every level of interaction were identified by various individuals and organizations. These problems often relate to the fact that orphan diseases, disorders, and medical conditions occur infrequently and the corporate experience of individuals who need to interact is constantly shifting. For example, many physicians complete their training without ever seeing a patient with a rare inborn error of metabolism and will seldom have the opportunity to treat such conditions in general practice (American Academy of Pediatrics, 1965; Berry, 1987). The average medical practitioner caring for 2,000 to 3,000 families annually would see only two or three patients with phenylketonuria in a lifetime (Koch, 1989). Physicians, dietitians, and pharmacists within the hospital clinical research setting have a much greater opportunity to interact than the private practitioner outside of such setting. The patients' needs identified within the clinical setting are not always shared or appreciated by the research community in the food and/or pharmaceutical industries. Even within industry itself, food chemists and food technologists may have little interaction with scientists who focus their research efforts on drug development.

Misunderstandings and communication problems concerning rare diseases and the use of orphan medical foods were also identified among government agencies, within particular agencies, or as a result of regulatory decisions. Affected individuals represent a minority population whose needs are often unanswered despite the best intentions of government representatives operating within
the legal confines of individual agency authority. For example, food safety inspectors examining imported shipments of a medical food product formulated for a rare disease may have little appreciation that the embargo of the shipment because of labeling discrepancies may adversely affect the health of patients for whom it was prepared. Similarly, regulators may be unaware that families of affected children carry a greater financial burden than the norm, or that insurance reimbursements differ among health care plans and within different locales.

Communication problems also exist for the health care insurance industry. Individual policy coverages are developed to meet client needs; but to keep costs in line with market trends and price competition, underwriters provide a variety of options with exclusionary or incentive clauses within their policies. Policy coverage varies among companies and among policies within the same company based on regional differences and the company philosophy in providing health care (i.e., health maintenance organization, indemnity corporation).

The concept of orphan diseases is, in general, not recognized by the insurance industry. Orphan diseases, along with orphan drugs and/or orphan medical foods, are viewed as a regulatory construct derived for the convenience of the government, medical practitioners, and their patients. Medical coverage for individuals with rare diseases may or may not be reimbursable under the terms of the individual policy which is selected and/or determined by the employer, insurer oversight group, or individual seeking coverage. In general, health insurance covers diagnostic workups, treatments, and health care maintenance as described in the policy. The costs that are covered are those which are accepted and recognized medical practice with approval from government regulators and/or the medical community. For example, if a medical food is not listed by the Physicians' Desk Reference for Prescription Drugs (1989) for prescribed medications, it is typically assumed to be an experimental product or a nonprescription item. Experimental products, devices, procedures, foods, and nonprescription items are not covered by the insurance industry as described within exclusionary policy clauses.

The operating structure of the insurance industry has caused considerable communication misunderstandings for physicians, patients, and government regulators. Affected individuals, their families, and in some cases their support groups experience communication problems with representatives of the insurance industry because of the wide diversity of conditions and provisions of health insurance policies and the attendant difficulty in interpreting medical and/or legal terminology.

In some instances the isolation of each interested community has resulted in each group operating within its own set of priorities, interpreting definitions of terms, and making value judg-
mements of the overall social responsibility of others involved in
the orphan disease identification and product development pro-
cess. For example, manufacturers in both the food and pharma-
ceutical industries are deliberately cautious when selecting
terms to describe their products. This is primarily because
corporate experience has taught them to operate within the regu-
latory framework governing their industries. These groups iden-
tified product distinctions by using terms such as "foods useful"
or "foods helpful in" a condition, "foods for special dietary
uses," and "medical foods." Insurance industry representatives
and patients frequently consider medical foods as drugs used in
the treatment of disease. Clinical investigators and practicing
physicians tend to broaden the definition of "medical foods" and
"foods for special dietary uses" to include foods, formulations,
and nutrients used in dietary management of medical conditions.

4. Economic impediments

The absence of guidelines and procedures for regulating medical
foods in the broader concept is a barrier to development of or-
phan medical foods because manufacturers are uncertain as to the
potential costs of obtaining regulatory approval. Manufacturers
are reluctant to enter marketplaces where development costs
and/or product lines are not protected. Furthermore, as noted
following the infant formula regulations in 1980 (see Appendix
D), additional regulatory burden can create a barrier by adding
to product cost recovery. The impact of high costs for develop-
ment and marketing of orphan medical food products impedes fur-
ther expansion of these product lines by manufacturers.

Because orphan medical foods contain substances which are foods,
GRAS ingredients, or food additives, there is no marketing exclu-
siveness; hence little economic gain may be realized. While the
1988 amendments do provide for grants and contracts to assist in
clinical testing, the restricted market for orphan medical foods
reinforces the absence of potential economic opportunities.

Finally, the 1988 amendments do not extend the benefits pro-
vided to orphan drug sponsors to those who express an interest
in developing orphan medical foods. These absent benefits are,
in reality, barriers and include

- Assistance in protocol development for nonclinical
  investigations,
- Marketing exclusivity protection,
- Tax incentive writeoffs of development costs, and
- Promotion by the Orphan Products Board.
B. INCENTIVES

It should be obvious from the previous discussions that few if any incentives are provided by existing legislation to assist or spur development of orphan medical foods. Legislation specifying medical foods as orphan products is only 18 months old and there have been inadequate time and resources to develop policies that include potential incentives.

In addition, existing legislation and programs that might provide incentives are not widely appreciated. For example, the Technology Transfer Act of 1986 contains provisions for expediting transfer of basic research to practical applications (Anonymous, 1989a; Anonymous, 1989b; Collins and Bernard, 1989). These approaches have not been exploited by sponsors of orphan products.
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VI. BARRIERS AND INCENTIVES IN RESEARCH AND DEVELOPMENT OF ORPHAN MEDICAL FOODS

Current regulations concerning development, marketing, labeling, and use of medical foods are not extensive. FSDU and related products are required to be safe for their intended use and to be labeled for the intended uses. Most, if not all, manufacturers have assumed the responsibility for nonclinical and clinical testing to establish usefulness and safety of new products. Because most ingredients of medical foods are recognized food components, GRAS ingredients, and regulated food additives, concerns with adverse health effects are directed toward tolerance, untoward reactions, and usefulness in patients with the condition for which the product was developed. Despite the absence of definitive guidelines and protocols, manufacturers do conduct research and development activities prior to marketing medical foods. Similarly, manufacturers interact with FDA regulatory scientists in the course of product development even though premarketing clearance is not required. It is reasonable to conclude that orphan medical foods would be developed and marketed in an analogous manner.

A. CONCEPTUAL ASPECTS

A number of research activities are inherent in the process of developing an orphan medical food. The research can be expected to include characterization of the pathophysiologic disease process, understanding the unique aspects of the biochemical interactions of metabolism, exploration of sources of required nutrients, and approaches to actual dietary delivery of the product. These research activities lead to developmental activities including product formulation and testing as well as monitoring the results of product use.

1. Research activities

The formulation of a medical food product for a rare disease is an activity that requires scientific understanding of both the disease process and the nutritional requirements to manage the medical condition. The scientific literature contains numerous illustrations that trace the process of discovery and application of foods and food products that are useful in managing various diseases and medical conditions (Sarett and Knauff, 1985; Shils and Young, 1988). Examples include the use of citrus fruits in the treatment of scurvy (Honig et al., 1988a,b); the dietary restriction of phenylalanine in the treatment of phenylketonuria
(Dobson et al., 1977; Parker et al., 1977); and the use of very long-chain fatty acids in the treatment of paroxysmal disorders such as adrenoleukodystrophy, Zellweger syndrome, and Rett Syndrome (Holmes et al., 1987; Moser et al., 1989; Milhalik et al., 1989; Naidu et al., 1988; Powers et al., 1989; Talwar and Swaiman, 1987; Wilson et al., 1986).

A comprehensive understanding about the pathophysiology and biochemistry of the disease process is essential for identifying an appropriate approach to dietary management. This basic scientific information is extremely costly to obtain in terms of resource utilization and investigator time. Clinicians and scientific investigators often identify research leads based on cumulative patient findings developed over a lifetime of clinical experience or on the basis of one unique patient, new scientific evidence from an unrelated discipline in the life sciences, the availability of a newly synthesized substance, a newly discovered source or method for delivery of a nutrient, or insights from new therapeutic approaches. To establish a need for a medical food product, investigators could be expected to compile data and information from a variety of disciplines in the life sciences in order to understand the biological basis for the disease and to establish a rationale for dietary modification to restore metabolic homeostasis (Shils and Young, 1988; Smith and Thier, 1981). A broad scope of research activities is needed to support a database that includes a comprehensive understanding of the disease process (DeVoe, 1974; Shils and Young, 1988; Sidransky, 1985; Smith and Thier, 1981). If the medical food is to be used in conjunction with drug therapy, the potential for drug-nutrient interaction should be investigated (Lee, 1983; Roe, 1988; Shils and Young, 1988).

The regulation, control, and integration of nutrient utilization by various metabolic pathways are extremely complex (Orten and Neuhaus, 1975; Stolwijk and Hardy, 1974) and the scope of research activities may also take into consideration hormonal, neurological, and other factors such as infectious disease. These considerations may not be directly related to the metabolic condition but can influence the disease process and alter the pathophysiological profile of the medical condition.

The use of orphan medical foods, as a type of FSDU, can be expected to be based on accepted concepts of dietary management of diseases. Several approaches are commonly used in developing strategies of dietary management (Acosta, 1989a). These strategies may be categorized as follows:

- Correct the nutritional imbalance of metabolism by nutrient reduction, restriction, or substitution;
• Circumvent the defective metabolic pathway by using alternative pathways;

• Supplement the diet with a) "conditionally essential" nutrients, b) nutrients that are blocked by the primary metabolic pathway, and/or c) nutrients that are inadequately absorbed or not released from their apoenzyme; and

• Modulate digestive enzyme activity by a) stabilization of the enzyme system, b) enzyme supplementation, c) influencing enzyme cofactor systems, and/or d) genetic mediation of enzyme regulation via suppressor, enhancer, or promoter elements to alter enzyme production.

2. Product development

No new medical product enters the marketplace without some form of product testing which typically involves nonclinical, clinical, and analytical testing. The expense for this process is borne by federal grants, foundations, hospitals, patients, and industry.

Historically, the development of drugs has involved relatively elaborate evaluation of efficacy and safety. The traditional FDA drug testing procedures required with investigational drug applications (IND) and new drug applications (NDA) include a lengthy series of animal studies, three phases of human clinical trials, and postmarketing surveillance. Recently, FDA has incorporated some revisions to speed the approval process. These include the treatment IND and the "subpart e regulations" for parallel track access to new drugs (Ember, 1989; Young et al., 1988).

Test procedures for substances used in foods have focused on safety. While foods per se are not required to have premarket clearance, manufacturers are expected to be able to provide information on the safety of food additives and GRAS food ingredients. Evaluation of the safety of these substances is based on exposures via intake, chemical reactivity, metabolism (absorption, distribution, elimination) and biological effects. The FDA has identified three levels of concern related to the extent of exposure and degree of toxicity. FDA review of new food additives includes a premarket approval process, a determination for intended use, and evaluation of manufacturing procedures (Food and Drug Administration, 1982).

For the most part, the ingredients incorporated into orphan medical food products can be expected to be food components or products derived from foods, GRAS ingredients, and approved food additives. As such, product testing, if required, would be limited
to safety aspects of product use and nutritional suitability for the product claims. However, it should not be unexpected that such formulations would exert physiological effects that may be hazardous to persons who do not have the particular disease for which the product is formulated, or who unintentionally use or abuse such products. For this reason, the physiological basis for product claims should be substantiated by the manufacturer. Furthermore, product labeling should provide users with sufficient information about the description, composition and ingredients, physiology, indication(s), precautions, adverse reactions, directions for use (dosage), preparation, and storage of the medical food product.

Nonclinical testing in laboratory animals can provide some useful information about the activity of specific nutrients or nutrient formulations; however, the information obtained from such testing may be contradictory because metabolic processes differ among species and metabolism can be significantly altered by disease conditions. Animal models are not readily available for many rarely occurring metabolic conditions although advances in biotechnology (i.e., the transgenic laboratory animal) may provide useful study tools for investigators in the future (Gordon, 1988; Westphal, 1989). However, at this time, these models are costly to develop and are mostly unproven for metabolic disease applications.

The limitations inherent to the information obtained from laboratory animal models necessitate the use of clinical trials to substantiate product claims. Nevertheless, investigators usually obtain some safety information about product use from short-term testing in laboratory animals. In the event that product formulations contain nonconventional substances or nutrients, and/or rely on formulations that include GRAS substances or established nutrients at levels that exceed known physiological needs, additional long-term toxicity testing in laboratory animals may be necessary to establish a margin of safety and suitability for product claims.

If required, clinical study protocols should be based on recognized principles of scientific investigation. There is little in the traditional IND/NDA drug approval process that applies directly to orphan medical food testing and development. However, some parallels for safety and suitability testing have been described (American Academy of Pediatrics, 1987a). Obviously, all clinical testing procedures must conform with the federal policy for the protection of human subjects (U.S. Department of Health and Human Services, 1988). Given the consequences for untreated individuals who may be dependent on the orphan medical food product for normal health, strict adherence to randomized study protocols should be viewed as ethically inappropriate.

Depending on product formulation and expected duration of use, certain testing procedures developed for drug evaluation trials
(e.g., Phase I and Phase II type clinical testing) may be desirable prior to routine use of some medical foods. Similarly, products that exert a profound physiological effect or that are intended for long-term use will require additional surveillance testing to assure safety after the product has entered the marketplace. In the case of orphan medical foods, such clinical testing could be conducted using modified protocols involving fewer patients for shorter periods of study. Selection of evaluation endpoints would need to reflect efforts to reduce costs of data collection. For orphan medical foods, multicenter collaborative study designs may be required to obtain sufficient sample sizes for most rare diseases, disorders, and medical conditions. Essential components to these study designs should be diagnostic confirmation of study participants and homogeneity of the study population for the medical condition to be evaluated.

Following the demonstration of nutritional adequacy in patients in the clinical setting, outcome is the prime consideration for substantiating product suitability. A flexible approach should be adopted when selecting measurements of outcome for orphan medical food products. The clinical procedures used to evaluate outcome may vary based on the intended use of the product formulation and the nature of the medical condition. For some formulations, weight gain and other anthropometric measurements, general physical examination, and neurological performance may be all that is required. Other formulations may require detailed metabolic assessment including comprehensive biochemistry, hematology, urinalysis, and specific organ function tests.

Initially, for many rarely occurring medical conditions, death and/or profound morbidity must be prevented in order to determine if nutritional intervention is beneficial. Benefits can be measured in terms of survival, minimizing adverse pathophysiological effects, and/or obtaining satisfactory growth, tissue repair, or return to baseline physiological functioning. A benefit/risk ratio based on the patient's status and response to dietary management may be applied to determine the progress provided by use of the orphan medical food. Malnutrition may be a contributing factor to disease outcome (McLaren, 1988); however, the effects of overnutrition may negate product benefits and may be hazardous (Anonymous, 1989a). Study protocols may need to assess these factors in addition to those previously mentioned.

For life threatening medical conditions, and for those conditions for which no therapeutic procedures are available, it may be necessary to modify the outcome criteria to provide opportunities for investigators to advance a new product concept. If the patient will be permanently impaired or die without dietary intervention then, at least initially, modest suitability of the product may be acceptable as a forward step. Hazards can be minimized during dietary management by means of close monitoring of patients by a multidisciplinary team of knowledgeable investigators.
No orphan medical food product should be permitted to enter the marketplace without a nutritional support protocol. The availability of such protocols improves therapeutic consistency and helps to assure physician and patient compliance with the manufacturer's directions for use. Exemplary protocols have been prepared for some medical food products for inborn errors of metabolism (Acosta, 1989a,b; Wooldridge, 1988).

3. Monitoring of product use

Marketplace surveillance is an important component of orphan medical food development. Adjustment of formulations for age-specific nutrition requirements, drug and food interactions, indications for other medical conditions, and problems associated with bulk manufacturing, shelf life, and distribution may not be apparent until the product becomes established in the marketplace. The extent of postmarketing surveillance that is desirable may vary among medical food products. Those products used for abbreviated time periods should not be required to meet the same surveillance criteria as those products required for lifelong use by affected individuals. Postmarket surveillance is a reliable tool for establishing the historical data base for product safety and suitability.

B. BARRIERS AND INCENTIVES IN THE RESEARCH AND DEVELOPMENT PROCESS

The previous sections of this chapter identify fundamental considerations that are components of the process of research, development, and postmarketing surveillance which are involved in the genesis of an orphan medical food. As discussed in Chapter V, the legislative and regulatory framework has direct and indirect effects on the genesis of orphan medical food products. These effects are, in reality, a complex set of barriers, impediments, and possible incentives in and of themselves. A significant portion of these effects is associated with management of research, private and public interest, and national investment in research and development.

Issues related to barriers and incentives transcend discussion of orphan medical foods and encompass all orphan products. Most of the universal issues were identified by the National Commission on Orphan Diseases (U.S. Department of Health and Human Services, 1989) in their comprehensive review of rare disease research and product development. Rather than repeat their observations and conclusions in regard to barriers, impediments, and incentives, the following paragraphs highlight those aspects that appear to be most significant for orphan medical foods.
1. Research management

Research management is a complex and dynamic process involving fiscal and human resources. In a formal sense, research management defines objectives, provides resources, monitors costs, and produces marketable products. In an informal sense, research management must be responsive to both internal and external influences such as insufficient resources to support research or introduction of regulatory requirements or changes in the marketplace because of competition. Frequently, successful research and development requires cooperation and interaction of more than one research group. Participants in this process need to recognize the integrated nature of changes, the possible shifts in emphasis, and the impact of system dynamics that can be incentives or barriers and can be influenced by aspects of research management at different stages of product development.

Problems arise when investigators do not recognize that their role in researching the product has moved to the next stage in the development process. This occurs frequently when requests for initial or additional funding of research are made. Another aspect of the problem is the failure on the part of research managers to provide sufficient lead time for investigators to make adjustments or their lack of understanding about funding sources available from private or public sources as product development progresses.

2. Clinical studies

Clinical investigators interested in conducting trials on medical foods often face additional hurdles in obtaining approval for nutrition studies from Institutional Review Boards (IRBs). IRBs provide a mechanism for oversight of the research activities of clinical investigators. In some settings, oversight groups can provide useful support to investigators; however, in the case of clinical studies with orphan medical foods, investigators may find it troublesome and time consuming to explain to IRBs that abbreviated nutrition study protocols can be acceptable and that rigorous study protocols associated with drug trials are unnecessary.

By their nature, most clinical nutrition study protocols differ greatly from the IND protocols for drugs. At this time there is no generally accepted study protocol for conducting clinical nutrition research to serve as a guide for approval. As a consequence many investigators file for IND applications because this is the least problematic route for obtaining study approval in the clinical environment. It is a paradox that clinical nutritionists must frequently comply with protocol requirements designed for drug development because these often result in the incorporation of many costly laboratory tests of limited usefulness.
3. Career development

Investigators who seek careers in research on rare diseases, and more narrowly, nutritional management of rare diseases, face a variety of problems that reflect issues throughout the research and development system including communication, time to develop research leads, investigator desire for external encouragement and career recognition for accomplishments, availability of trained personnel, and continuity of resources in terms of funding, equipment, and facilities. Furthermore, there are distinct differences in the environments (e.g., academic, clinical, and industrial laboratories) where research on orphan medical food products might be undertaken.

The demand for orphan medical foods has risen with the increasing recognition of rare diseases in general and with the knowledge that dietary intervention can be beneficial (Greene, 1989). There are too few investigators and clinicians whose primary interests focus on rare diseases, their dietary management, and treatment. Furthermore, the insufficient number of physicians who are trained to care for the growing numbers of patients with these rare medical conditions is exemplified by the observation that pediatricians frequently remain the primary health care provider for adults with metabolic conditions (Koch, 1989). There is a need to develop fellowship programs to encourage scientists to enter this growing field of medicine (Berry, 1987; Mize, 1989).

4. Funding

Investigators and potential commercial sponsors of orphan medical food products face severe constraints in funding of research and development. The few investigators that are interested have insufficient time, other responsibilities, and limited access to funding. Sources of funding for studies on orphan medical foods are insufficient resources. For example, the House Appropriations Committee recently earmarked only $9,751,000 for all orphan product work, of which not less than $7,575,000 is to be available for all orphan products grants and contracts (Anonymous, 1989b).

The Federal Government provides both income tax credits for clinical testing and exclusivity provisions as financial incentives to manufacturers of orphan drug products (Office of the Federal Register, 1988). However, these incentives are insufficient, underutilized, misunderstood, too cumbersome, or include trade-off limitations that inhibit their utilization by manufacturers and investigators (Table 4).
Table 4. Treasury Department Report to the Orphan Products Board on the Use of the Income Tax Credit for Orphan Drug Development.

<table>
<thead>
<tr>
<th>Income Year</th>
<th>Number of Returns</th>
<th>Orphan Drug Credit</th>
</tr>
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<tr>
<td>1983</td>
<td>31</td>
<td>$236,000</td>
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<tr>
<td>1984</td>
<td>35</td>
<td>$149,000</td>
</tr>
<tr>
<td>1985</td>
<td>12</td>
<td>$204,000</td>
</tr>
</tbody>
</table>


5. Liability

The problems of product and service liability have not been addressed and remain a major barrier to orphan medical food product development (Cantrell, 1984; Scharf, 1985). One approach would be for the Federal Government to assume these costs for manufacturers, medical practitioners, and patients. Such an approach distributes the costs for these products and services more equitably throughout society.

This approach to liability, currently applied to vaccine development (National Academy of Sciences, 1985), should be considered for orphan medical products such as medical foods. Similarly, a physician's liability for the use of experimental procedures must be balanced against the interests of society as a whole and the advancement of knowledge of disease, as well as its clinical management. Limiting medical practitioners strictly to previously established procedures inhibits innovation and medical progress (Cantrell, 1984).

6. Reimbursement

Manufacturers of medical food products, clinical researchers, and patient support groups cite the lack of reimbursement for these products from Medicare/Medicaid, state and local health care programs, and other insurance underwriters as a critical barrier impeding further development or use of these products and, at least
in some cases, obstructing commercialization (U.S. Department of Health and Human Services, 1989). In many instances, the reimbursement philosophy dictates the feasibility of the provision of health care (Kane and Manoukian, 1989). Precedent has been established for the Federal Government to assume certain health care costs via the Medicare/Medicaid program. Examples include dialysis for end-stage renal disease and coverage of home intravenous drug therapy services (Office of the Federal Register, 1989). The achievements of the Medicaid program have been instrumental in reducing financial burdens of health care; however, the legislative intent of the program has yet to be fully achieved for the use of some medical products and services (American Academy of Pediatrics, 1979, 1985, 1986, 1987b; Kane and Manoukian, 1989). Similarly, availability of these medical food products to infants through the WIC program (Food Package 3) would also provide an incentive to industry. The financial impact of recent legislation, (i.e., the inclusion of orphan medical foods into the Orphan Drug Act) on programs such as Medicare and Medicaid and the USDA WIC program is yet to be realized (U.S. General Accounting Office, 1988).

However, access to general and preventive health care, and confusion about eligibility requirements for health care products and services for individuals afflicted by rare diseases, disorders, and medical conditions is a growing concern (Antoine, 1989; Grumet, 1989; U.S. Department of Health and Human Services, 1989). A broader approach may be needed to address problems inherent to the health care insurance industry and to assure health insurance equity to individuals affected by orphan medical conditions. Such a legislative proposal is presently under consideration (U.S. Congress, 1989).

7. Additional factors

There are barriers and impediments in the development process which compound those difficulties already identified. For example, marketing specialists within large corporations recognize the "bottom line" in developing a corporate product profile. Orphan medical products are viewed as community service and philanthropic activities. These are usually included into the product profile to complete rather than to initiate a product line. Corporate philanthropy to carry product lines of limited economic value is a major barrier to product development. Corporations frequently make exceptions for products with a high return as a result of increased visibility. The best example of this has been the government support of development of food products for the space program. These leveraging activities, encouraged by government and involving corporate efforts on a national priority, bring recognition of those who contribute to the resolution of these problems. There is currently no major national priority on orphan diseases, let alone orphan medical foods.
On the other hand, small and midsized companies may use larger companies as models. The small and midsize companies set product goals to position their products alongside those of larger companies by seeking out subsets of larger consumer groups for a particular type of product. As a consequence, a manufacturer's approach to the niche marketplace is significantly different from the general marketplace and these differences may be advantageous to overcome marketing problems associated with orphan medical foods. Provided the consumer can be readily identified, niche markets for medical food products are ideal for small and midsized companies because the product is consumer driven, distributed directly to the consumer, and can be manufactured in small batches. Marketing is accomplished with a minimal sales force to health care professionals and by mail order.

Even so, companies which, for whatever reasons, want to prepare orphan medical food products are faced with a confusing array of requirements for research funding, filing for patent or licensing agreements, and procuring regulatory product approval. Such activities require a familiarity with frequently cumbersome administrative processes and burdensome paperwork. There are many federal, state, and industrial programs to encourage small businesses, technology transfer, and tax incentives. The application and utility of these to investigators or manufacturers who might produce orphan medical food products should be catalogued and evaluated.

However, there are few small and midsized manufacturers with the fiscal and human resources to undertake such activities in the absence of viable economic incentives.

C. OTHER CONSIDERATIONS

Previous sections of this chapter consider the conceptual aspects, barriers, and incentives related to research, development, and postmarket surveillance of a medical food product such as an orphan medical food. The complexity of events involved in the research and development, and postmarketing activities associated with a medical food product is best illustrated by description of the milestones and factors that contributed to successful development, marketing, and acceptance of an actual medical food. Appendix D contains a detailed review of the history of the development of dietary products useful in ameliorating the effects of the inborn error of metabolism, hyperphenylalaninemia (phenylketonuria). This example was selected because the dietary management of this medical condition is accomplished by dietary modulation requiring specially formulated medical food products, and the evolution and refinement of this dietary approach can be traced over a 60-year period (Berry, 1988; Knox, 1972; Sarett and Knauff, 1985; Scriver et al., 1989).
Development of these medical food products is illustrative of the barriers (economic and noneconomic), incentives (economic and noneconomic), and other driving and modulating forces that determine and/or influence the course of product development and/or product availability. Summarizing 60 years of research and product development required an arbitrary distillation of key events into six stages:

- Disease Characterization (1930-1949)
- Hypothesis Testing (1950-1955)
- Product Development (1956-1960)
- Postmarket Surveillance (1960-1972)
- Product Refinement (1972-1980)
- Second Generation Products (1980-present)

As noted from the discussion in Appendix D, the process of developing medical food products is time- and resource-consuming, dynamic, reactive, and interactive. Factors considered incentives in the early stages of development may become barriers to further product development at later stages. Regulatory changes intended as solutions to problems identified by one community may create unforeseen problems and/or windfalls for other communities. Furthermore, shifts in program priorities can disrupt systematic availability of services to affected individuals, interfere with career objectives of investigators, and precipitate discontinuance of a particular manufacturer's product line. The complex challenges that confront the medical food industry are further confounded by aggressive competition taking place in a global market. Finally, the example provided in Appendix D suggests that in some cases, there are no shortcuts to the development of orphan medical foods for routine use.
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VII. INTERNATIONAL PERSPECTIVES ON DEVELOPMENT
OF ORPHAN MEDICAL FOOD PRODUCTS

In general, the availability of medical food products varies widely among developed and developing countries. Availability of orphan medical foods is also related to the culture as well as the characteristics of the health care delivery system. There are both similarities and differences among countries in regard to regulatory framework, support for research and development, approaches to cost recovery, as well as availability and use.

The abbreviated nature of this LSRO study did not permit sufficient opportunity to obtain extensive information from other countries and their governments. However, information indicative of current international interest in medical food products was obtained from some primary and secondary sources.

A. REGULATORY APPROACHES

In some countries, medical foods are considered to be pharmaceutical products and are regulated as drugs whereas other countries regulate these products as foods for special dietary purposes. Many countries have little or no regulatory framework or oversight for these products (Smith, 1982). It appears that the United States is the only nation that has incorporated the "orphan concept" into its regulatory framework (Weston, 1989).

Representative manufacturers and clinicians using products in several countries contacted in the course of this study identified both advantages and disadvantages about regulatory approaches as well as research and development practices that are currently used in their respective countries (Enteral Nutrition Council, 1989; Garten, 1989; Gill, 1989; Marchetti, 1989; Moser, 1989; Reiss, 1989; Scriver, 1989). The diversity of their opinions was broad and strongly reflected personal experience with regulatory systems manufacturing practices, and with aspects of research and development that left favorable or unfavorable impressions.

Medical foods used in the dietary management of inherited amino acid metabolism disorders marketed in West Germany are regulated by provisions of the "Diätverordnung." Subsection "Annex No 7" provides the regulatory framework for supplementation of the products with vitamins, minerals, and trace elements (Information provided by Reiss, 1989). Government permission and supervision are necessary in the manufacture of these products as well as conformance with guidelines on good manufacturing practices. Some manufacturers and affected individuals consider the pre-manufacture permission process a regulatory barrier to new

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product availability in West Germany. Orphan medical food products must follow the same pre-manufacture permission process as other food products even though they will be marketed as exempt products (Reiss, 1989). Anecdotal information suggests that this "pre-manufacturing notice" procedure can delay marketing of new products for two or more years.

In the United Kingdom, orphan medical food products are regulated as borderline substances. Under Regulation 20 of the National Health Service, an Advisory Committee on Borderline Substances (ACBS) has been established to determine which products are to be listed as approved substances for medical use. Only products listed as borderline substances will be reimbursed when prescribed by physicians. British physicians in the UK are not encouraged to prescribe everyday food products for some medical conditions (e.g., gluten-free foods for celiac patients) even though the ACBS has recommended that a range of specially manufactured foods should be available for prescription for those exceptional cases where medical intervention is necessary (Anonymous, 1989a; Gill, 1989; Department of Health, 1989; Monthly Index of Medical Specialties, 1989).

In Japan, the availability of foods that purport health claims to prevent disease parallels that of the United States (e.g., fiber-rich, calcium-fortified, and reduced-calorie foods) (Anonymous, 1989b). These products, termed "physiologically functional foods" (PFF), also include infant formulas and some total parenteral nutrition products. PFF are described as foods that contain ingredients generally used as foods, consumed routinely as foods, and that exhibit regulatory functions on physiological processes. At least some of these foods are designed and manufactured specifically to improve health by preventing disorders. For example, some experimental PFF are supplemented with phytochemicals from fruits and vegetables which are purported to prevent cancer. The Japan Ministry of Health and Welfare is currently reviewing issues related to medical foods in general. It is thought that they will develop a system to regulate PFF that would include methods for authorization, scientific evaluation, and product labeling (Anonymous, 1989b).

Confusion caused by the diversity of approaches used to regulate medical food products by various nations has led to difficulties in international trade of these products. Furthermore, the nutrient content of medical food products is somewhat variable among nations (Anonymous, 1989a) and the quality assurance for the manufacture of these products may be less stringent than accepted standards in the United States. However, the majority of these products are still considered safe for indicated uses and reported problems are the exception rather than the rule.

Since 1980 the Codex Alimentarius Commission has sought to enhance international trade for special categories of foods
(i.e., foods for special dietary uses, medical foods, foods for special medical purposes) by developing consensus on definitions and standards (Cheney, 1989). Approximately 25 nations are participating in the development of an international Codex, "Standard for the Labelling of and Claims for Foods for Special Medical Purposes," through its subsidiary body the Codex Committee on Nutrition and Foods for Special Dietary Uses. To date the process has advanced to step 5 (Codex Alimentarius Commission, 1989). The Codex Committee continues to refine definitions for these products, considers medical food products to be a special category of foods for special dietary uses for which specific claims are made, and recognizes that these products should be used under medical supervision. The draft definition for these products is broader than the definition used in the United States and states

"Foods for special medical purposes are a category of foods for special dietary uses which are specially processed or formulated for the dietary management of patients and may only be used under medical supervision. They are intended for the exclusive or partial feeding of patients with limited or impaired capacity to take, digest, absorb or metabolize ordinary foodstuffs or certain nutrients contained therein, or have other 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 of the two" (Codex Alimentarius Commission, 1989).

During further consideration of this definition, the Codex Committee agreed to modify the first sentence to delete the word only in regard to medical supervision (Codex Alimentarius Commission, 1989). The current Codex draft standards for product labeling of medical foods suggest that product label information state

- The intended claim for the specific disease, disorder or medical condition for which the product will be used,
- The statement "USE UNDER MEDICAL SUPERVISION,"
- A description about product rationale,
- A description about the details of nutrient modification, and
- A statement about intended use as a sole food source.

The Codex Committee draft for medical food product labeling currently recommends that manufacturers provide detailed information about product content. Specifically, the draft suggests that
"Foods for special medical purposes in which the essential characteristic involves a modification of the content or the nature of proteins, fats or carbohydrates shall bear a complete quantitative declaration of the amino acid, fatty acid or carbohydrate profile, as applicable." and

"A statement specifying the nutrient(s) reduced, deleted, increased or otherwise modified, relative to normal nutrient requirements and the reason why the nutrient(s) is (are) reduced, deleted, increased or otherwise modified" (Codex Alimentarius Commission, 1989).

In addition, the Codex draft recommends the incorporation of cautionary statements and warnings about health hazards, adverse effects, side-effects, contraindications, and drug interactions (Cheney, 1989).

In summary, the draft standards of the Codex Alimentarius for labeling of and claims for foods for special medical purposes use terminology for medical foods similar to that currently included in the Orphan Drug Act as amended (Section 5, (B)(2-3)). However, at this time, some changes in labeling requirements may be needed for United States products to conform with the proposed Codex requirements (Anonymous, 1989a; Codex Alimentarius Commission, 1989).

B. MARKETING APPROACHES

A preponderance of the items listed in Appendix B are considered exempt infant formula type products. The majority of these products are presently imported into the United States from foreign manufacturers or subsidiaries of U.S. firms. Most product prices are controlled by manufacturers outside the United States. Further, these medical food products are subject to import tariffs, high transportation fees, and handling and distribution markups. As a consequence, affected families, insurers, and the U.S. healthcare system probably pay inflated prices for these items.

There appears to be a lack of competition nationally and internationally. For all practical purposes there are two primary international manufacturers of medical food products for inborn errors of metabolism at this time. On the basis of the limited information available to LSRO, only one manufacturer is actively seeking to expand its product line and distribution network. If this situation persists, it could lead to a future monopoly over these products in the global marketplace.
In other nations, as in the United States, the manufacture and marketing of medical food products for rare medical conditions are not economical. Prime factors contributing to this problem are a) the excessive costs associated with the manufacturing process along with additional costs for compliance with good manufacturing practices and quality assurance and b) the range of special support service for physicians and pharmacies (e.g., delivery, educational materials, patient recordkeeping). Two approaches to overcome marketing barriers were identified among European nations.

In one approach, the costs for manufacture of these products by a large manufacturer with a diversified product line are currently underwritten from profits realized from a more profitable product line (i.e., infant formulas). Another approach is to utilize entrepreneurial cottage industry concepts to exploit a niche market (e.g., orphan medical foods). In the first approach, success is realized as a function of company size. In the second approach success is derived from small, efficient specialization. In some European countries, there is a strong cultural ethic that is expressed as personal interest in and motivation for development of an orphan product line.

C. RESEARCH, DEVELOPMENT, FUNDING, AND COST RECOVERY

Systems for managing scientific resources vary among nations; however, in most countries the greatest wealth of scientific resources to conduct research resides at academic and clinical institutions. In the United States academic and clinical centers are considered free enterprise institutions and are only partially subsidized by government funding. By contrast, academic centers in many other industrialized nations are frequently government operated. The determination of priorities, allocation of resources, as well as research and development activities are managed almost exclusively as government activities.

The extent of research activities required prior to the routine use of new medical food products for rare diseases is similar among most nations. However, the degree of preliminary testing of new products differs among nations. Study guidelines for clinical trials in several European countries appear to be more flexible than those in the United States. These protocols are more open in that product approval can be gained on the basis of studies with fewer patients and the extent of clinical testing is reduced. Acceptance of such protocols is of particular value to investigators of rare diseases because so few patients are available for study at any point in time and new product concepts are frequently based on the research findings from only one or a very few individuals.
A major consideration for research and development is related to issues of product liability. In those nations that have adopted a socialized medical system, the costs for medical services and liabilities are usually distributed over a broader economic base. When the government assumes a major portion of the product liability associated with research and development of an orphan medical food, manufacturers are more willing to make such products available. This major incentive to reduce manufacturer risks associated with product development is not available in the United States as it is in other nations. It is also a factor contributing to the number of products available in other countries and the extent of research activities conducted abroad. Although the science base and technical expertise in the United States remain strong in comparison to other nations, product liability is a more significant factor that impedes commercialization of orphan medical food products in this country than in others.

D. CONCLUSIONS

A variety of economic and noneconomic incentives for product development of medical foods for orphan diseases have been identified in other nations. A major advantage can be seen when government sponsors and manages the development and availability of these products. In addition, products are more readily available in nations where issues of liability are subsumed by government.


VIII. CONCLUSIONS AND RECOMMENDATIONS

The number and the complexity of issues directly and tangentially associated with orphan products, medical foods, and associated health claims are significantly greater than the topics assigned in the work scope for this study of orphan medical foods. These unresolved issues have been major impediments to addressing issues related to orphan medical foods.

The National Commission on Orphan Diseases was chartered on March 27, 1986 and delivered its comprehensive report on February 27, 1989 (U.S. Department of Health and Human Services, 1989). A significant portion of the Commission's report addresses orphan diseases and orphan drugs. Orphan status of medical foods and medical devices is mentioned only briefly. Nevertheless, because the report of the National Commission on Orphan Diseases identifies issues and possible solutions, the document is pertinent to consideration of orphan medical foods. The report makes 54 specific recommendations which, with few exceptions are applicable to encouraging research, development, and availability of orphan medical food products. The report of the National Commission on Orphan Diseases should provide a valuable reference source to the CFSAN staff as they develop policies, regulatory approaches, and guidelines for medical foods useful in the dietary management of orphan diseases.

A number of observations, conclusions, and recommendations appear throughout Chapters I-VII of this quick-response report. A majority of these address the broader scope of issues identified in the course of this study. The remainder of this chapter contains the specific conclusions and recommendations requested by CFSAN in the scope of work.

A. ADEQUACY OF CURRENT INCENTIVES

Incentives for sponsors of orphan medical foods are limited, underutilized, and inadequately funded. The 1988 Amendments to the Federal Food, Drug, and Cosmetic Act (P.L. 100-290) make grants and contracts available to sponsors of orphan medical foods for defraying costs of developing medical foods for rare diseases and conditions. Since 1988, the OOPD has provided funding for approximately 5 to 8 studies and clinical investigations that appear to be related to the development of medical foods. However, the other incentives mentioned in the Orphan Drug Act as amended have yet to be extended to orphan medical foods.

In some cases, orphan medical food products have been developed in other countries and are available in the United States by
means of licensing or marketing agreements. The extent to which this method is an economic incentive is uncertain as the process is highly variable. Reasoned judgment suggests licensing and marketing of imported products can be incentives because potential domestic regulatory barriers are circumvented. Developmental costs for the manufacturer may be lower, but costs to the consumer may be higher.

As noted in Chapters V and VI and Appendix D, what may constitute an incentive from one perspective may be viewed as a barrier from another perspective. For example, orphan designation is a particular problem as this incentive may actually serve to inhibit product development. As the Act is presently written, once a product is designated for a disease that has orphan status, the likelihood that another product for that disease will receive support diminishes. This problem has been circumvented to some extent by the designation of use for management of other specific manifestations of the same orphan disease. Furthermore, some formulations of orphan medical foods have applications to more than one orphan disease. Because of the limited nature of available funds, if one approach receives support and is successful, subsequent requests for funding of additional developmental studies are likely to be turned down.

B. IMPACT OF CURRENT BARRIERS

A number of impediments discourage development and availability of special products useful in dietary management of orphan diseases. Many of the noneconomic barriers are related to the relative recency of legislative, regulatory, and public recognition of these products. Insufficient time has elapsed for all interested parties and federal agencies to reach a consensus on what type of management system is needed for orphan medical foods and what components are needed in such a system. Economic barriers transcend the issue of orphan medical foods and orphan products in toto. These considerations are dynamic and reflect developments in international trade and global marketing strategies. Detailed discussions can be found in Chapters V and VI.

The following section summarizes current barriers and their primary impacts on development and availability of orphan medical foods.

- Absence of a Universally Accepted Definition of Medical Foods. Because orphan medical food products are a subset of medical foods, the absence of a universally acceptable definition of medical foods is impeding development, availability, and use of orphan medical foods.

- Absence of Guidelines and Procedures for Regulating Medical Foods. Current regulations governing foods for special
dietary uses may not be sufficient for adequate regulation of all types of medical foods. Because this generic issue is unresolved, the regulation of orphan medical foods remains in limbo.

- **Absence of Guidelines and Procedures for Regulating Orphan Medical Foods.** The Office of Orphan Products Development has informally extended its interim guidelines for orphan drugs to orphan medical foods. Revision of the guidelines depends on resolution of major issues associated with regulation of medical foods. The uncertainty as to extension of regulatory requirements is an economic impediment to research, development, and availability of orphan medical foods.

- **Inadequacy of Current Policy on Health Claims.** The Agency is currently addressing the major issue of health claims for foods. Until these policies and guidelines are in place, resolution of issues related to regulation of health claims for medical foods and the subset of orphan products cannot be accomplished.

- **Confusion About The Definition of Orphan Disease.** The definition of orphan disease in the 1988 amendments in regard to medical foods is open-ended and differs from that in the Orphan Drug Act. This more flexible definition of what constitutes an orphan disease is not fully appreciated by potential sponsors of orphan medical foods.

- **Current Limitations on Provisions of Orphan Drug Act.** While the amendments authorized a study of possible incentives, legislative authority to designate orphan status and provide related incentives to orphan medical foods was not included in the 1988 amendments. Because certain provisions of the Act provide economic incentives in development of orphan drugs, their absence for medical foods is a major economic deterrent to potential sponsors of orphan medical foods.

- **Diversity of Terminology.** Because there are a diverse number of interested parties, definitions of terms related to orphan medical foods (and medical foods in general) are often misused and miscommunicated. Terms that require definition include orphan diseases, orphan products, medical foods, foods versus drugs, dietary management versus treatment, and health claims.

- **Insufficient Communication Among Interested Parties.** There is a wide and diverse community of persons and organizations with interests in orphan products, including orphan medical foods. The existence of few systems for communication among these groups impairs knowledge transfer and limits awareness of product availability and public understanding of orphan diseases.
• **Limited Acceptance of the Concept of Orphan Diseases.** Despite legislative and regulatory recognition, the concept has not been embraced by the health care delivery system, particularly the health insurance industry.

• **Limited Interest in and Support for Research and Development.** While the number of persons and organizations interested in orphan diseases and orphan medical foods is relatively large, these individuals and groups have not developed coordinated programs. Thus, they have not developed effective public relations, communications, and a strong economic base. A limited number of investigators and clinicians work with orphan diseases amenable to dietary management. The number of patients is small and they are scattered throughout the country. The availability of funds from public and private sources for research and development is limited. Commercial firms with interests in orphan medical foods are also limited in number, in interest, and in resources available to this narrow area of product development.

• **Lack of Tax Incentives.** While available for orphan drugs, tax incentives have not been extended to orphan medical foods. Experience to date with orphan drug products suggests current tax incentives are underutilized, insufficient, misunderstood, cumbersome, and too restrictive for efficient application.

• **Concerns About Product Liability.** In the absence of a clear pathway for regulatory approval and guidelines for use, the issue of product liability is a major deterrent to large firms with other profitable products and to small to midsize companies that lack fiscal resources to protect themselves.

• **Lack of Third-Party Reimbursement.** This is a major deterrent to patients who might benefit from use of orphan medical foods. Lack of the availability of reimbursement for purchase of orphan medical foods is a serious problem for patients who require orphan medical foods to sustain life and a deterrent to manufacturers who want to market these products.

• **Dynamic Nature of Research and Development.** Appendix D provides an example of the dynamic nature of the process of research, development, marketing, and use of a medical food product. The dynamic nature of the process is reflected in the observations that incentives may become barriers, and barriers may become incentives in the course of development, use, and expansion of the products available.

• **Effects of International Competition in the Marketplace.** While orphan medical products are only a minor component of international trade, lower costs of research, development, marketing, and production in foreign countries appear to
be economic deterrents to domestic firms with interests in developing orphan medical foods.

C. RECOMMENDATIONS FOR FUTURE POLICIES AND INCENTIVES

Previous sections of this report have documented the existence of numerous barriers and impediments to development and availability of orphan medical foods. Similarly, the paucity of effective incentives was discussed. While incentives are needed to facilitate development by manufacturers, use by the health care delivery system, and reimbursement by third party payees, the establishment of a comprehensive policy for oversight of orphan medical foods is the central and critical need.

Two significant issues impinge on the development of policy for orphan medical foods. First, and foremost, the Agency has not promulgated a generally accepted policy for health claims for foods and a generally accepted policy for medical foods. Health claims for foods and medical foods are both complex issues, are of considerable public interest, and have required inordinate attention of the Agency for several years. Because orphan medical foods are a subset of medical foods that make medical claims in regard to intended use, the development of a policy for orphan medical foods has been delayed. The second major issue is regulatory authority and resources. The OOPD was established to coordinate activities and administer provisions of the Orphan Drug Act as amended. However, the OOPD lacks the authority and resources to provide support and extend provisions of the Act to orphan medical foods.

- **Recommendation #1:** The National Commission on Orphan Diseases (U.S. Department of Health and Human Services, 1989) has recommended the establishment of a Central Office of Orphan and Rare Diseases (COORD) to be located in the Office of the Assistant Secretary for Health, DHHS. The COORD would be responsible for the coordination of rare disease related research, and regulatory, educational and service activities of physicians, investigators, foundations, voluntary organizations, patients and families, manufacturers, insurers, and federal agencies. This recommendation should be considered by FDA and DHHS because it affords a mechanism to provide greater visibility to orphan diseases in general and, specifically, to orphan products regulated by FDA. Further, it provides a mechanism for coordination of all activities, not just regulatory issues.

- **Recommendation #2:** The Agency should reexamine its regulatory stance in regard to medical foods. Originally regulated as drugs, they are now considered foods. The advantages and limitations for overseeing these products from either perspective are identified in Appendix D. In this
example, drug status proved burdensome to manufacturers and inhibited product reformulation whereas food status encouraged product reformulation by manufacturers but inhibited cost recovery by users. The absence of distinct regulations on the various types of medical foods and procedures for their approval have affected the growth of the medical food industry in the United States. The major noneconomic barrier to further medical food product development, the lack of regulatory direction, could be overcome by the creation of a separate and distinct regulatory category for medical foods. This would probably require legislative modification to Section 201 and subsequent sections of the Federal Food, Drug, and Cosmetic Act as amended. However, if established, it would resolve issues related to health claims and medical foods by the creation of a category of products clearly separated from both foods and drugs. Resolution of this issue would enhance and accelerate efforts to develop policies specific to orphan medical foods.

- **Recommendation #3:** CFSAN and OOPD staff, with the assistance of other Agency scientists as appropriate, should assume the leadership in preparing a comprehensive policy for regulatory management of orphan medical foods. This draft policy should include the following:

  - Clarification of issues such as the definition of orphan medical foods, the meaning of dietary management, the requirements for product labeling, and regulatory status.

  - Development of a comprehensive set of guidelines for submission and approval of petitions including requirements for data on safety and efficacy, criteria for approval, and requirements for postmarketing surveillance. (Note: This recommendation presupposes establishment of a separate regulatory category for oversight of medical foods and a series of flexible criteria that are based on intended use of the orphan product.)

  - Determination of data and information needs appropriate to orphan products; that is, specification of data requirements on prevalence of the condition, the rationale for dietary management, the safety of the components of the product and, if necessary, demonstration of clinical effectiveness.

  - Provisions for communication among interested parties and coordination of research, development, use, and postmarketing surveillance by a central office, such as OOPD.

  - Provisions for incentives to potential sponsors of orphan medical food products as outlined below.
- **Recommendation #4:** Because there is a limited market for orphan medical products, and because the expectation of profit from marketing of orphan medical foods is low, additional incentives need to be developed.

  Many individuals and organizations contacted in the course of this study suggested that economic incentives include 100% recovery of research and development costs. Reasons cited include favorable economic consequences of such policies in other countries, high costs of research and development, low profit expectations, and existing needs for a multiplicity of orphan medical food products.

  As indicated above, clarification and development of regulatory guidelines could be a major incentive to potential sponsors. A flexible oversight process would permit development of information needed by the Agency to assure product safety and product claim credibility. Formulations that present a low level of concern for safety and suitability could be fast-tracked to the marketplace, while product formulations that may require greater scrutiny would receive the benefit of FDA advice in developing study protocols at early stages of development. In addition, flexible guidelines could identify needs for postmarketing surveillance as appropriate.

  Designation of medical foods (and orphan medical foods) as a separate regulatory category would provide a mechanism for FDA and sponsors to develop a system unencumbered by current regulations for foods and drugs. That is, provisions considered necessary could be included and conflicting regulatory provisions could be avoided.

  Creation of a separate category for medical foods could include prescription status for some products and the development of criteria for such status. Furthermore, cost recovery would be enhanced if regulatory revisions established prescription status for those medical food formulations that are disease-specific. This change would also distribute overall costs of research, development, and marketing over a broader economic base and should reduce the costs for product use by those who can least afford to pay.

- **Recommendation #5:** In developing a comprehensive policy on orphan medical foods, the Agency should identify possible requirements for legislative changes and should forward these to appropriate authorities with justification, for transmittal to the U.S. Congress for its consideration.
- **Recommendation #6**: The Agency should consider conducting a more comprehensive overview than this study before attempting to implement Recommendations #3, 4, and 5.
Literature Cited

IX. ACKNOWLEDGMENTS

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Those individuals who submitted comments, information, data, and views in response to the Federal Register announcement (Federal Register 54:35400, 1989) are identified by an asterisk (*). Copies of their submissions are available at the FDA Dockets Management Branch (Docket #89N-0332) and in the Open Files of the LSRO, FASEB. The other contributors provided reference materials which were incorporated into the literature files of the LSRO, FASEB.

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APPENDIX A

ORPHAN DRUG ACT
SHORT TITLE, FINDINGS

SEC. 1.(a) This Act may be cited as the "Orphan Drug Act".¹

(b) The Congress finds that –

(1) there are many diseases and conditions, such as Huntington’s disease, myoclonus, ALS (Lou Gehrig’s disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States;

(2) adequate drugs for many of such diseases and conditions have not been developed;

(3) drugs for these diseases and conditions are commonly referred to as "orphan drugs";

(4) because so few individuals are affected by any one rare disease or conditions, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;

(5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and

(6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.

AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

SEC. 2.(a) Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end the following:

SUBCHAPTER B – DRUGS FOR RARE DISEASES OR CONDITIONS
RECOMMENDATIONS FOR INVESTIGATIONS OF DRUGS FOR
RARE DISEASES OR CONDITIONS

SEC. 525.[360aa]² (a) The sponsor of a drug for a disease or condition which is rare in the States

² References in brackets [360aa–360cc] are to title 21, U.S. Code.
may request the Secretary to provide written recommendations for the non-clinical and clinical investigations which must be conducted with the drug before —

(1) it may be approved for such disease or condition under section 505,

(2) if the drug is an antibiotic product, it may be certified for such disease or condition under section 507, or

(3) if the drug is a biological product, it may be licensed for such disease or condition under section 351 of the Public Health Service Act.

If the Secretary has reason to believe that a drug for which a request is made under this section is a drug for a disease or condition which is rare in the States, the Secretary shall provide the person making the request written recommendations for the non-clinical and clinical investigations which the Secretary believes, on the basis of information available to the Secretary at the time of the request under this section, would be necessary for approval of such drug for such disease or condition under section 505, certification of such drug for such disease or condition under section 507 or licensing of such drug for such disease or condition under section 351 of the Public Health Service Act.

(b) The Secretary shall by regulation promulgate procedures for the implementation of subsection (a).

DESIGNATION OF DRUGS FOR RARE DISEASES OR CONDITIONS

SEC.526. [360bb] (a)(1) The manufacturer or the sponsor of a drug may request the Secretary to designate the drug as a drug for a rare disease or condition. If the Secretary finds that a drug for which a request is submitted under this subsection is being or will be investigated for a rare disease or condition and —

(A) if an application for such drug is approved under section 505,

(B) if a certification for such drug is issued under section 507, or

(C) if a license for such drug is issued under section 351 of the Public Health Service Act, the approval, certification, or license would be for use for such disease or condition, the Secretary shall designate the drug as a drug for such disease or condition. A request for a designation of a drug under this subsection shall contain the consent of the applicant to notice being given by the Secretary under subsection (b) respecting the designation of the drug.

(2) For purposes of paragraph (1), the term "rare disease or condition" means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made.

3 Section 526(a)(2) amended by P.L. 98–551, October 30, 1984; Sections 525(a) and 526(a) amended by Section 2 of the Orphan Drug Act Amendments, P.L. 99–91, August 15, 1985.
(b) Notice respecting the designation of a drug under subsection (a) shall be made available to the public.

(c) The Secretary shall by regulation promulgate procedures for the implementation of subsection (a).

PROTECTION FOR DRUGS FOR RARE DISEASES OR CONDITIONS

SEC. 527. [380cc] (a) Except as provided in subsection (b), if the Secretary –

(1) approves an application filed pursuant to section 505(b), or

(2) issues a certification under section 507, or

(3) issues a license under section 351 of the Public Health Service Act

for a drug designated section 526 for a rare disease or condition the Secretary may not approve another application under section 505(b), issue another certification under section 507, or issue another license under section 351 of the Public Health Service Act for such drug for such disease or condition for a person who is not the holder of such approved application, of such certification, or of such license until the expiration of seven years from the date of the approval of the approved application, the issuance of the certification or the issuance of the license. Section 505(c)(2) does not apply to the refusal to approve an application under the preceding sentence.

(b) If an application filed pursuant to section 505(b) is approved for a drug designated under section 526 for a rare disease or condition, if a certification is issued under section 507 for such a drug or if a license is issued under section 351 of the Public Health Service Act for such a drug, the Secretary may, during the seven-year period beginning on the date of the application approval, of the issuance of, the certification under section 507, or of the issuance of the license, approve another application under section 505(b), or issue a license under section 351 of the Public Health Service Act, for such drug for such disease or condition for a person who is not the holder of such approved application, of such certification, or of such license if –

(1) The Secretary finds, after providing the holder notice and opportunity for the submission of views, that in such period the holder of the approved application, of the certification, or of the license cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated; or

(2) such holder provides the Secretary in writing the consent of such holder for the approval of other applications, issuance of other certifications, or the issuance of other licenses before the expiration of such seven-year period.

OPEN PROTOCOLS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS

SEC. 528. [380dd] If a drug is designated under section 526 as a drug for a rare disease or condition and if notice of a claimed exemption under section 505(i) or regulations issued thereunder is filed for such drug, the Secretary shall encourage the sponsor of such drug to design protocols for clinical investigations of the drug which may be conducted under the exemption to permit the addition to
the investigations of persons with the disease or condition who need the drug to treat the disease or condition and who cannot be satisfactorily treated by available alternative drugs.

(b) Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by inserting before section 502 the following:

SUBCHAPTER A – DRUGS AND DEVICES.

ORPHAN PRODUCTS BOARD

SEC. 3. Title II of the Public Health Service Act is amended by adding at the end the following:

ORPHAN PRODUCTS BOARD

SEC. 227. [236]\(^d\) (a) There is established in the Department of Health and Human Services a board for the development of drugs (including biologics) and devices (including diagnostic products) for rare diseases or conditions to be known as the Orphan Products Board. The Board shall be comprised of the Assistant Secretary for Health of the Department of Health and Human Services and representatives, selected by the Secretary, of the Food and Drug Administration, the National Institutes of Health, the Centers for Disease Control, and any other Federal department or agency which the Secretary determines has activities relating to drugs and devices for rare diseases or conditions. The Assistant Secretary for Health shall chair the Board.

(b) The function of the Board shall be to promote the development of drugs and devices for rare diseases or conditions and the coordination among Federal, other public, and private agencies in carrying out their respective functions relating to the development of such articles for such diseases or conditions.

(c) In the case of drugs for rare diseases or conditions the Board shall –

(1) evaluate –

(A) the effect of subchapter B of the Federal Food, Drug, and Cosmetic Act on the development of such drugs, and

(B) the implementation of such subchapter;

(2) evaluate the activities of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration for the development of drugs for such diseases or conditions,

(3) assure appropriate coordination among the Food and Drug Administration, the National Institutes of Health, the Alcohol, Drug Abuse, and Mental Health Administration, and the Centers for Disease Control in the carrying out of their respective functions relating to the development of drugs for such diseases or conditions to assure that the activities of each agency are complementary.

\(^d\) References in brackets [236][255] are to title 42, U.S. Code.
(4) assure appropriate coordination among all interested Federal agencies, manufacturers, and organizations representing patients, in their activities relating to such drugs,

(5) with the consent of the sponsor of a drug for a rare disease or condition exempt under the section 505(i) of the Federal Food, Drug, and Cosmetic Act or regulations issued under such section, inform physicians and the public respecting the availability of such drug for such disease or condition and inform physicians and the public respecting the availability of drugs approved under section 505(c) of such Act or licensed under section 351 of this Act for rare diseases or conditions,

(6) seek business entities and others to undertake the sponsorship of drugs for rare diseases or conditions, seek investigators to facilitate the development of such drugs, and seek business entities to participate in the distribution of such drugs, and

(7) recognize the efforts of public and private entities and individuals in seeking the development of drugs for rare diseases or conditions and in developing such drugs.

(d) The Board shall consult with interested persons respecting the activities of the Board under this section and as part of such consultation shall provide the opportunity for the submission or oral views.

(e) The Board shall submit to the Committee on Labor and Human Resources of the Senate and the Committee on Energy and Commerce of the House of Representatives an annual report –

(1) identifying the drugs which have been designated under section 526 of the Federal Food, Drug, and Cosmetic Act for a rare disease or condition,

(2) describing the activities of the Board, and

(3) containing the results of the evaluations carried out by the Board.

The Director of the National Institutes of Health and the Administrator of the Alcohol, Drug Abuse, and Mental Health Administration shall submit to the Board for inclusion in the annual report a report on the rare disease and condition research activities of the Institutes of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration; the Secretary of the Treasury shall submit to the Board for inclusion in the annual report a report on the use of the credit against tax provided by section 44H of the Internal Revenue Code of 1954; and the Secretary of Health and Human Services shall submit to the Board for inclusion in the annual report a report on the program of assistance under section 5 of the Orphan Drug Act for the development of drugs for rare diseases and conditions. Each annual report shall be submitted by June 1 of each year for the preceding calendar year.

TAX CREDIT FOR TESTING EXPENSES FOR DRUGS FOR RARE DISEASES OR CONDITIONS

SEC. 4. (a) Subpart A of part IV of subchapter A of chapter 1 of the Internal Revenue Code of 1954 (relating to credits allowable) is amended by inserting after section 44G the following new section:
SEC. 44H. CLINICAL TESTING EXPENSES FOR CERTAIN DRUGS FOR RARE DISEASES OR CONDITIONS.

(a) GENERAL RULE. – There shall be allowed as a credit against the tax imposed by this chapter for the taxable year an amount equal to 50 percent of the qualified clinical testing expenses for the taxable year.

(b) QUALIFIED CLINICAL TESTING EXPENSES. – For purposes of this section –

(1) QUALIFIED CLINICAL TESTING EXPENSES. –

(A) IN GENERAL. – Except as otherwise provided in this paragraph, the term "qualified clinical testing expenses" means the amounts which are paid or incurred by the taxpayer during the taxable year which would be described in subsection (b) of section 44F if such subsection were applied with the modifications set forth in subparagraph (B).

(B) MODIFICATIONS. – For purposes of subparagraph (A), subsection (b) of section 44F shall be applied –

(i) by substituting "clinical testing" for "qualified research" each place it appears in paragraphs (2) and (3) of such subsection, and

(ii) by substituting "100 percent" for "65 percent" in paragraph (3)(A) of such subsection.

(C) EXCLUSION FOR AMOUNTS FUNDED BY GRANTS, ETC. – The term "qualified clinical testing expenses" shall not include any amount to the extent such amount is funded by any grant, contract, or otherwise by another person (or any governmental entity).

(D) SPECIAL RULE. – For purposes of this paragraph, section 44F shall be deemed to remain in effect for periods after December 31, 1985.

(2) CLINICAL TESTING. –

(A) IN GENERAL. – The term "clinical testing" means any human clinical testing –

(i) which is carried out under an exemption for a drug being tested for a rare disease or condition under section 505(i) of the Federal Food, Drug, and Cosmetic Act (or regulations issued under such section),

(ii) which occurs –

(I) after the date of such drug is designated under section 526 of such Act, and

(II) before the date on which an application with respect to such drug is approved under section 505(b) of such Act, and

(iii) which is conducted by or on behalf of the taxpayer to whom the designation under such section 526 applies.

(B) TESTING MUST BE RELATED TO USE FOR RARE DISEASE OR CONDITION. – Human clinical testing shall be taken into account under subparagraph (A) only to the extent such testing is related to the use of a drug for the rare disease or condition for which it was designated under section 526 of the Federal Food, Drug, and Cosmetic Act.

(c) COORDINATION WITH CREDIT FOR INCREASING RESEARCH EXPENDITURES. –
(1) IN GENERAL. – Except as provided in paragraph (2), any qualified clinical testing expenses for a taxable year to which an election under this section applies shall not be taken into account for purposes of determining the credit allowable under section 44F for such taxable year.

(2) EXPENSES INCLUDED IN DETERMINING BASE PERIOD RESEARCH EXPENSES. – Any qualified clinical testing expenses for any taxable year which are qualified research expenses (within the meaning of section 44F(b)) shall be taken into account in determining base period research expenses for purposes of applying section 44F to subsequent taxable years.

(d) DEFINITION AND SPECIAL RULES. –

(1) RARE DISEASE OR CONDITION. – For purposes of this section, the term "rare disease or condition" means any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date such drug is designated under section 526 of the Federal Food, Drug, and Cosmetic Act.

(2) LIMITATION BASED ON AMOUNT OF TAX. – The credit allowed by this section for any taxable year shall not exceed the amount of the tax imposed by this chapter for the taxable year reduced by the sum of the credits allowable under a section of this subpart having a lower number or letter designation than this section, other than the credits allowable by sections 31, 39, and 43. For purposes of the preceding sentence, the term "tax imposed by this chapter" shall not include any tax treated as not imposed by this chapter under the last sentence of section 53(a).

(3) SPECIAL LIMITATIONS ON FOREIGN TESTING. –

(A) IN GENERAL. – No credit shall be allowed under this section with respect to any clinical testing conducted outside the United States unless –

(i) such testing is conducted outside the United States because there is an insufficient testing population in the United States, and

(ii) such testing is conducted by a United States person or by any other person who is not related to the taxpayer to whom the designation under section 526 of the Federal Food, Drug, and Cosmetic Act applies.

(B) SPECIAL LIMITATION FOR CORPORATIONS TO WHICH SECTION 934(b) OR 936 APPLIES. – No credit shall be allowed under this section with respect to any clinical testing conducted by a corporation to which section 934(b) applies or to which an election under section 936 applies.

(4) CERTAIN RULES MADE APPLICABLE. – Rules similar to the rules of paragraphs (1) and (2) of section 44F(f) shall apply for purposes of this section.

(5) ELECTION. – This section shall apply to any taxpayer for any taxable year only if such taxpayer elects (at such time and in such manner as the Secretary may by regulations prescribe) to have this section apply for such taxable year.

(e) TERMINATION. – This section shall not apply to any amount paid or incurred after December 31, 1987.
(b) (1) Section 280C of such Code (relating to denial of deduction for portion of wages for which credit is claimed under section 40 or 44B) is amended by adding at the end thereof the following new subsection:

(c) CREDIT FOR QUALIFIED CLINICAL TESTING EXPENSES FOR CERTAIN DRUGS. –

(1) IN GENERAL. – No deduction shall be allowed for that portion of the qualified clinical testing expenses (as defined in section 44H(b)) otherwise allowable as a deduction for the taxable year which is equal to the amount of the credit allowable for the taxable year under section 44H (determined without regard to subsection (d)(2) thereof).

(2) SIMILAR RULE WHERE TAXPAYER CAPITALIZES RATHER THAN DEDUCTS EXPENSES. – If –

(A) the amount of the credit allowable for the taxable year under section 44H (determined without regard to subsection (d)(2) thereof), exceeds

(B) the amount allowable as a deduction for the taxable year for qualified clinical testing expenses (determined without regard to paragraph(1)),

the amount chargeable to capital account for the taxable year for such expenses shall be reduced by the amount of such excess.

(3) CONTROLLED GROUPS. – In the case of a corporation which is a member of a controlled group of corporations (within the meaning of section 44F(f)(5)) or a trade or business which is treated as being under common control with other trades or business (within the meaning of section 44F(f)(1)(B)), this subsection shall be applied under rules prescribed by the Secretary similar to the rules applicable under subparagraphs (A) and (B) of section 44F(f)(1).

(2) (A) The section heading of section 280C of such Code is amended to read as follows:

SEC. 280C. CERTAIN EXPENSES FOR WHICH CREDITS ARE ALLOWABLE

(B) The table of sections for part IX of subchapter B of chapter 1 of such Code is amended by striking out the item relating to section 280C and inserting in lieu thereof the following:

SEC. 280C. Certain expenses for which credits are allowable.

(c) (1) The table of sections for subpart A of part IV of subchapter A of chapter 1 of such Code is amended by inserting after the item relating to section 44G the following new item:

SEC. 44H. Clinical testing expenses for certain drugs for rare diseases or conditions.

(2) Subsection (b) of section 6096 of such Code is amended by striking out "and 44G" and inserting in lieu thereof "44G, and 44H".

(d) The amendments made by this section shall apply to amounts paid or incurred after December 31, 1982, in taxable years ending after such date.
GRANTS AND CONTRACTS FOR DEVELOPMENT OF DRUGS FOR RARE DISEASES AND CONDITIONS

SEC. 5. [360ee] (a) The Secretary may make grants to and enter into contracts with public and private entities and individuals to assist in defraying the costs of qualified clinical testing expenses incurred in connection with the development of drugs for rare diseases and conditions.

(b) For purposes of subsection (a):

(1) The term "qualified testing" means –

(A) human clinical testing –

(i) which is carried out under an exemption for a drug for a rare disease or condition under section 505(i) of the Federal Food, Drug, and Cosmetic Act (or regulations issued under such section);

(ii) which occurs after the date such drug is designated under section 528 of such Act and before the date on which an application with respect to such drug is submitted under section 506(b) or 507 of such Act or under section 351 of the Public Health Service Act; and

(B) preclinical testing involving a drug is designated under section 526 of such Act and before the date on which an application with respect to such drug is submitted under section 505(b) or 507 of such Act or under section 351 of the Public Health Service Act.

(2) The term "rare disease or condition" means any disease or conditions which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made.

(c) For grants and contracts under subsection (a) there are authorized to be appropriated $4,000,000 for fiscal year 1986 and $4,000,000 for fiscal year 1987, and $4,000,000 for fiscal year 1988.

5 Section 5(a) and (b) amended by section 5 of the Orphan Drug Act Amendments, P.L. 99-91, August 15, 1985.

ORPHAN DRUG AMENDMENTS OF 1988
AN ACT

To amend the Federal Food, Drug, and Cosmetic Act to revise the provisions respecting orphan drugs, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.
This Act may be cited as the "Orphan Drug Amendments of 1988".

SEC. 2. DESIGNATION AS AN ORPHAN DRUG.

(a) REQUEST. - Section 526(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb(a)(1)) is amended by adding after the first sentence the following: "A request for designation of a drug shall be made before the submission of an application under section 505(b) for the drug, the submission of an application for certification of the drug under section 507, or the submission of an application for licensing of the drug under section 351 of the Public Health Service Act."

(b) DISCONTINUANCE. - Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) is amended by redesignating subsections (b) and (c) as subsections (c) and (d), respectively, and by adding after subsection (a) the following:

"(b) A designation of a drug under subsection (a) shall be subject to the condition that -

"(1) if an application was approved for the drug under section 505(b), a certificate was issued for the drug under section 507, or a license was issued for the drug under section 351 of the Public Health Service Act, the manufacturer of the drug will notify the Secretary of any discontinuance of the production of the drug at least one year before discontinuance, and

"(2) if an application has not been approved for the drug under section 505(b), a certificate has not been issued for the drug under section 507, or a license has not been issued for the drug under section 351 of the Public Health Service Act and if preclinical investigations or investigations under section 505(i) are being conducted with the drug, the manufacturer or sponsor of the drug will notify the Secretary of any decision to discontinue active pursuit of approval of an application under section 505(b), approval of an application for certification under section 507, or approval of a license under section 351 of the Public Health Service Act."

SEC. 3. FINANCIAL ASSISTANCE.

(a) MEDICAL DEVICES. - Section 5 of the Orphan Drug Act (21 U.S.C. 360ee) is amended -
(1) in subsection (a), by inserting "(1)" after "assist in" and by inserting before the period a comma and "(2) defraying the costs of developing medical devices for rare diseases or conditions", and

(2) in subsection (b) (2) –

(A) by inserting "(1) in the case of a drug," after "means" in the first sentence and by adding before the period in that sentence a comma and "(2) in the case of a medical device, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical device for such disease or condition will be developed without assistance under subsection (a) ", and

(B) by striking out "under the subsection" in the last sentence and inserting in lieu thereof "under section 526 of the Federal Food, Drug, and Cosmetic Act".

(b) MEDICAL FOODS. – Section 5 of the Orphan Drug Act (21 U.S.C. 360ee) is amended –

(1) in subsection (a) (as amended by subsection (a)), by inserting before the period a comma and "and (3) defraying the costs of developing medical foods for rare diseases or conditions",

(2) in subsection (b)(2) (as amended by subsection (a)), by inserting before the period at the end of the first sentence a comma and "and (3) in the case of a medical food, any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance under subsection (a) ", and

(3) by adding at the end of subsection (b) the following: "(3) 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.".

(c) AUTHORIZATION. – Section 5(c) of the Orphan Drug Act (21 U.S.C. 360ee(c)) is amended to read as follows:

"(c) For grants and contracts under subsection (a) there are authorized to be appropriated $10,000,000 for fiscal year 1988, $12,000,000 for fiscal year 1989, $14,000,000 for fiscal year 1990.".

(d) STUDY. – The Secretary of Health and Human Services shall conduct a study to determine whether the application of subchapter B of chapter V of the Federal Food, Drug, and Cosmetic Act (relating to drugs for rare diseases and conditions) and section 28 of the Internal Revenue Code of 1986 (relating to tax credit) to medical devices or medical foods for rare diseases or conditions or to both is needed to encourage the development of such devices and foods. The Secretary shall report the results of the study to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate not later than one year after the date of the enactment of this Act. For purposes of this section, the term "rare diseases or conditions" has the meaning prescribed by section 5 of the Orphan Drug Act (21 U.S.C. 360ee).
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<td>Nutritionally incomplete high-calorie dietary formula powder with vitamins and minerals for infants and children.</td>
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<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete low-calorie dietary formula powder with vitamins and minerals for infants and children.</td>
</tr>
<tr>
<td>MSUD Diet Powder</td>
<td>&quot;</td>
<td>Branched chain amino acid disorders: Maple syrup urine disease; Hypervalinemia; Methylacetoacetic aciduria; Leucine induced hypoglycemia; Hyperleucine-iso-leucinemia; Isovaleric acidemia</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants and children.</td>
</tr>
<tr>
<td>Low PHE/TYR Diet Powder (Product 3200AB)</td>
<td>&quot;</td>
<td>Tyrosinemia; Alkaptonuria; Ochronosis; Hepatosplenomegaly</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants, children, and adults.</td>
</tr>
<tr>
<td>Low Methionine Diet Powder (Product 3200K)</td>
<td>&quot;</td>
<td>Homocystinuria</td>
<td>Nutritionally balanced complete dietary soy protein isolate formula with no added methionine for infants and children.</td>
</tr>
<tr>
<td>PRODUCT NAME&lt;sup&gt;1&lt;/sup&gt;</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>DESCRIPTION&lt;sup&gt;2&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Mono- and Disaccharide-Free Diet Powder (Product 3232A)</td>
<td>Bristol-Myers (Mead Johnson)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Disaccharidase deficiencies of lactase, sucrase, and maltase</td>
<td>Carbohydrate incomplete dietary formula powder.</td>
</tr>
<tr>
<td>PKU 1</td>
<td>&quot;</td>
<td>Phenylketonuria; Hyperphenylalaninemia</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>PKU 2</td>
<td>&quot;</td>
<td>Phenylketonuria; Hyperphenylalaninemia</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>PKU 3</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Metabolic module powder with vitamins and minerals for adolescents and pregnant females.</td>
</tr>
<tr>
<td>HIST 1</td>
<td>&quot;</td>
<td>Histidinemia</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>HIST 2</td>
<td>&quot;</td>
<td>Histidinemia</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>HOM 1</td>
<td>&quot;</td>
<td>Homocystinuria due to cystathioninesynthase deficiency</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>HOM 2</td>
<td>&quot;</td>
<td>Homocystinuria due to cystathioninesynthase deficiency</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)</td>
<td>DESCRIPTION</td>
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</tr>
<tr>
<td>LYS 1</td>
<td>Bristol-Myers (Mead Johnson)</td>
<td>Hyperlysinemia due to lysine-ketoglutarate reductase deficiency; Saccharopinuria with hyperlysinemia</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>LYS 2</td>
<td>&quot;</td>
<td>Hyperlysinemia due to lysine-ketoglutarate reductase deficiency; Saccharopinuria with hyperlysinemia</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>MSUD 1</td>
<td>&quot;</td>
<td>Maple syrup urine disease; Hypervalinemia (isoleucine and leucine to be added); Methylacetoacetic aciduria (leucine and valine to be added)</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>MSUD 2</td>
<td>&quot;</td>
<td>Maple syrup urine disease; Hypervalinemia (isoleucine and leucine to be added); Methylacetoacetic aciduria (leucine and valine to be added); Ketotic hypoglycemia, leucine induced (idiopathic form) (isoleucine and valine to be added); Hyperprolinemia type II with hyperleucine-isoleucinemia (valine to be added)</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)</td>
<td>DESCRIPTION</td>
</tr>
<tr>
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<td>---------------------------------------</td>
</tr>
<tr>
<td>OS 1</td>
<td>Bristol-Myers (Mead Johnson)</td>
<td>Propionic acidemia; Methylmalonic aciduria</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>OS 2</td>
<td>&quot;</td>
<td>Propionic acidemia; Methylmalonic aciduria</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>TYR 1</td>
<td>&quot;</td>
<td>Tyrosinemia type I; Tyrosinemia type II</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>TYR 2</td>
<td>&quot;</td>
<td>Tyrosinemia type I; Tyrosinemia type II</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>UCD 1</td>
<td>&quot;</td>
<td>Hyperammonemia Type I and Type II (arginine to be added); Citrullinemia (arginine to be added); Arginosuccinic aciduria (arginine to be added); Hyperargininemia; Hyperornithinemia</td>
<td>Metabolic module powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>UCD 2</td>
<td>&quot;</td>
<td>Hyperammonemia type I and type II (arginine to be added); Citrullinemia (arginine to be added); Arginosuccinic aciduria (arginine to be added); Hyperargininemia; Hyperornithinemia</td>
<td>Metabolic module powder with vitamins and minerals for children.</td>
</tr>
<tr>
<td>PRODUCT NAME(^1)</td>
<td>MANUFACTURER (^2)</td>
<td>INDICATION(S)(^1)</td>
<td>DESCRIPTION(^2)</td>
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</tr>
<tr>
<td>Protein-Free Diet Powder (Product 80056)</td>
<td>Bristol-Myers (Mead Johnson) (^3)</td>
<td>Methylmalonic arginino-saccinic and isovaleric aciduria; Hyperlysinemia; Maple syrup urine disease; Non-ketotic hyperglycinemia; Hypervalinemia</td>
<td>Nutritionally incomplete protein-free powder module with vitamins and minerals.</td>
</tr>
<tr>
<td>Moducal(^4)</td>
<td>&quot;</td>
<td>Protein-free calorie source</td>
<td>Nutritionally incomplete readily digestible carbohydrate powder module.</td>
</tr>
<tr>
<td>Pregestimil</td>
<td>&quot;</td>
<td>Galactosaemia; Galactokinase deficiency; Sucrose, lactose, and/or protein intolerance, and other disorders listed by the company.</td>
<td>Nutritionally complete dietary powder that is lactose-, sucrose-, fructose-, and gluten-free.</td>
</tr>
<tr>
<td>Prosobee Liquid(^4)</td>
<td>&quot;</td>
<td>Galactosaemia; Galactokinase deficiency and other indications listed by the company.</td>
<td>Nutritionally complete lactose-, sucrose-, fructose-, and gluten-free drink.</td>
</tr>
<tr>
<td>Analog XP</td>
<td>Ross Laboratories(^5)</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>Maxamaid XP (flavored and unflavored)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for children ages 1–8 years.</td>
</tr>
<tr>
<td>PRODUCT NAME(^1)</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)(^1)</td>
<td>DESCRIPTION(^2)</td>
</tr>
<tr>
<td>-------------------</td>
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<td>------------------</td>
</tr>
<tr>
<td>Maxamum XP (flavored and unflavored)</td>
<td>Ross Laboratories(^5)</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for children for use after age 8, pregnant women, and women in childbearing years.</td>
</tr>
<tr>
<td>Analog MSUD</td>
<td>&quot;</td>
<td>Maple syrup urine disease</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>Maxamaid MSUD (flavored)</td>
<td>&quot;</td>
<td>Maple syrup urine disease</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for children ages 1–8 years.</td>
</tr>
<tr>
<td>Maxamum MSUD (flavored)</td>
<td>&quot;</td>
<td>Maple syrup urine disease</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for individuals after age 8, and women in childbearing years.</td>
</tr>
<tr>
<td>Analog XPHEN, TYR</td>
<td>&quot;</td>
<td>Tyrosinemia</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>Maxamaid XPHEN, TYR (flavored)</td>
<td>&quot;</td>
<td>Tyrosinemia</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for children ages 1–8 years.</td>
</tr>
</tbody>
</table>
## Appendix B. Continued.

<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>MANUFACTURER</th>
<th>INDICATION(S)</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analog XPHEN, TYR, MET</td>
<td>Ross Laboratories(^5)</td>
<td>Tyrosinemia type I</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>Maxamaid XPHEN, TYR, MET (flavored)</td>
<td>&quot;</td>
<td>Tyrosinemia type I</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>Analog XMET, THRE, VAL, ISOLEU</td>
<td>&quot;</td>
<td>Methylmalonic acidemia; Propionic acidemia</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>Maxamaid XMET, THRE, VAL, ISOLEU (flavored)</td>
<td>&quot;</td>
<td>Methylmalonic acidemia; Propionic acidemia</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for children ages 1–8 years.</td>
</tr>
<tr>
<td>Analog XMET</td>
<td>&quot;</td>
<td>Homocystinuria due to cystathionine-(\beta)-synthase deficiency (B6 nonresponsive); Hypermethioninemia</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for infants.</td>
</tr>
<tr>
<td>Maxamaid XMET (flavored)</td>
<td>&quot;</td>
<td>Homocystinuria due to cystathionine-(\beta)-synthase deficiency (B6 nonresponsive); Hypermethioninemia</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals for children ages 1–8 years.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)</td>
<td>DESCRIPTION</td>
</tr>
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</tr>
<tr>
<td>RCF</td>
<td>Ross Laboratories&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Pyruvate dehydrogenase complex deficiency; Intolerance to carbohydrate in milk or conventional infant formulas</td>
<td>Nutritionally incomplete carbohydrate-free powder module with low iron, soy protein, vitamins, and minerals.</td>
</tr>
<tr>
<td>Similac PM 60/40</td>
<td>&quot;</td>
<td>Infants predisposed to hypocalcemia or conditions requiring lowered mineral levels</td>
<td>Infant dietary formula powder with low calcium, vitamins, and minerals.</td>
</tr>
<tr>
<td>Analog XLYS, TRY</td>
<td>&quot;</td>
<td>Glutaric aciduria type I</td>
<td>Nutritionally incomplete dietary formula powder for infants.</td>
</tr>
<tr>
<td>Maxamaid XLYS, TRY (flavored)</td>
<td>&quot;</td>
<td>Glutaric aciduria type I</td>
<td>Nutritionally incomplete dietary formula powder for ages 1–19 years.</td>
</tr>
<tr>
<td>Calcilo XD</td>
<td>&quot;</td>
<td>Hypercalcemia</td>
<td>Dietary infant formula powder with low calcium, low iron, and vitamin D free.</td>
</tr>
<tr>
<td>P.K. AID&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Powell and Scholefield, Ltd.&lt;sup&gt;7,8,9&lt;/sup&gt;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary formula for children that is phenylalanine free, gluten free, lactose free, and sucrose free.</td>
</tr>
<tr>
<td>Albumaid XP</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary formula for children that contains trace phenylalanine and is gluten free.</td>
</tr>
<tr>
<td>PRODUCT NAME$^1$</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)$^1$</td>
<td>DESCRIPTION$^2$</td>
</tr>
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<tr>
<td>Methionaid$^6$</td>
<td>Powell and Scholefield, Ltd.$^7,8,9$</td>
<td>Homocystinuria</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals.</td>
</tr>
<tr>
<td>MSUD-Aid$^6$</td>
<td>&quot;</td>
<td>Maple syrup urine disease</td>
<td>Nutritionally incomplete dietary formula powder with vitamins and minerals.</td>
</tr>
<tr>
<td>MOD XMET, THRE, VAL, ISOLE$^{10}$</td>
<td>&quot;</td>
<td>Methylmalonic acidemia; Propionic acidemia</td>
<td>Nutritionally incomplete amino acid module$^{11}$</td>
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<tr>
<td>Module MSUD$^{10}$</td>
<td>&quot;</td>
<td>Maple syrup urine disease</td>
<td>Nutritionally incomplete amino acid module$^{11}$</td>
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<tr>
<td>Module XLEU$^{10}$</td>
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<td>Isovaleric aciduria</td>
<td>Nutritionally incomplete amino acid module$^{11}$</td>
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<tr>
<td>Module XLYS$^{10}$</td>
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<td>Hyperlysinemia</td>
<td>Nutritionally incomplete amino acid module$^{11}$</td>
</tr>
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<td>Module XLYS, TRY$^{10}$</td>
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<td>Glutaric aciduria</td>
<td>Nutritionally incomplete amino acid module$^{11}$</td>
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<tr>
<td>Module XP$^{10}$</td>
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<td>Phenylketonuria</td>
<td>Nutritionally incomplete amino acid module$^{11}$</td>
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<td>Module XPHEN, TYR$^{10}$</td>
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<td>Tyrosinemia</td>
<td>Nutritionally incomplete amino acid module$^{11}$</td>
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<td>PRODUCT NAME</td>
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<td>INDICATION(S)</td>
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<td>Module-XCYS, XMETH\textsuperscript{10}</td>
<td>Powell and Scholefield, Ltd.\textsuperscript{7,8,9}</td>
<td>Cystinosis</td>
<td>Nutritionally incomplete amino acid module\textsuperscript{11}</td>
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<td>Module-XHIS\textsuperscript{10}</td>
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<td>Histidinemia</td>
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<td>Module-XLEUC\textsuperscript{10}</td>
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<td>Module-XLYS\textsuperscript{10}</td>
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<td>Hyperlysinemia</td>
<td>Nutritionally incomplete amino acid module\textsuperscript{11}</td>
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<td>Module-XMET\textsuperscript{10}</td>
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<td>Module-XTYR, Low Phen\textsuperscript{10}</td>
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<td>Tyrosinemia</td>
<td>Nutritionally incomplete amino acid module\textsuperscript{11}</td>
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<td>CYS/METH Free\textsuperscript{10}</td>
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<td>HIS Free\textsuperscript{10}</td>
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<td>Histidinemia</td>
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<tr>
<td>LEU Free (Orange Spec 09)\textsuperscript{10}</td>
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<td>Isovaleric acidemia</td>
<td>Nutritionally incomplete dietary formulation\textsuperscript{11}</td>
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<tr>
<td>LEU/ILEU/VAL(TYR/TRYP)\textsuperscript{10}</td>
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<td>PRODUCT NAME$^1$</td>
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<td>Leucine Free$^{10}$</td>
<td>Powell and Scholefield, Ltd.$^{7,8,9}$</td>
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<td>Nutritionally incomplete dietary formulation$^{11}$</td>
</tr>
<tr>
<td>METH Free$^{10}$</td>
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<td>Hypermethioninemia; Homocystinuria</td>
<td>Nutritionally incomplete dietary formulation$^{11}$</td>
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<tr>
<td>METH/VAL/ILEU/THRE Free(08)$^{10}$</td>
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<td>Nutritionally incomplete dietary formulation$^{11}$</td>
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<tr>
<td>METH/VAL/ILEU/THRE/GLY Free$^{10}$</td>
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<td>Methylmalonic acidemia; Propionic acidemia</td>
<td>Nutritionally incomplete dietary formulation$^{11}$</td>
</tr>
<tr>
<td>PHEN Low TYR Free$^{10}$</td>
<td>&quot;</td>
<td>Tyrosinemia with normal methionine</td>
<td>Nutritionally incomplete dietary formulation$^{11}$</td>
</tr>
<tr>
<td>PHEN/HIS Free (D. Francis)$^{10}$</td>
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<td>Special inborn error module</td>
<td>Nutritionally incomplete dietary formulation$^{11}$</td>
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<tr>
<td>TYR- Free, METH/PHEN Low$^{10}$</td>
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<td>Tyrosinemia</td>
<td>Nutritionally incomplete dietary formulation$^{11}$</td>
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<tr>
<td>XP (Australia)$^{10}$</td>
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<td>Nutritionally incomplete dietary formulation$^{11}$</td>
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<tr>
<td>XP$^{10}$</td>
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<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary formulation$^{11}$</td>
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<td>XISOL, VAL, MET, THRE (Alderhey)$^{10}$</td>
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<td>Methylmalonic acidemia; Propionic acidemia</td>
<td>Nutritionally incomplete dietary formulation$^{11}$</td>
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<td>PRODUCT NAME</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)</td>
<td>DESCRIPTION</td>
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<tr>
<td>XLYS, XTRYP</td>
<td>Powell and Scholefield, Ltd.</td>
<td>Glutaric aciduria type I</td>
<td>Nutritionally incomplete dietary formulation</td>
</tr>
<tr>
<td>ALA/TYR Free METH/PHEN Low</td>
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<td>Tyrosinemia with high plasma phenylalanine and tyrosine</td>
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<tr>
<td>LYS Free (RMCH)</td>
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<td>Hyperlysinemia</td>
<td>Nutritionally incomplete dietary product</td>
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<tr>
<td>LYS/TRYP Free (orange flavored and unflavored)</td>
<td>&quot;</td>
<td>Glutaric aciduria type I</td>
<td>Nutritionally incomplete dietary product</td>
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<tr>
<td>ADL Nut. Comp. and GTE</td>
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<td>Adrenoleukodystrophy</td>
<td>Nutritionally incomplete dietary product</td>
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<tr>
<td>Albumaid HIST – Low (EEC)</td>
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<td>Histidinemia</td>
<td>Formulated dietary product</td>
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<tr>
<td>Albumaid Hydrolysate Complete</td>
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<td>Cachexia; Hypoproteinemia</td>
<td>Formulated dietary product</td>
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<tr>
<td>Albumaid M ETH – Low (EEC)</td>
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<td>Homocystinuria; Hypermethioninemia</td>
<td>Nutritionally incomplete dietary product</td>
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<tr>
<td>Albumaid M ETH – Low (Non-EEC)</td>
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<td>Homocystinuria; Hypermethioninemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Albumaid PHEN, TYR–Free (EEC)</td>
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<td>Tyrosinemia with normal methionine</td>
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<td>PRODUCT NAME (1)</td>
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<td>DESCRIPTION (1)</td>
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<tr>
<td>Albumaid PHEN &amp; TYR Free</td>
<td>Powell and Scholefield, Ltd.</td>
<td>Tyrosinemia with normal methionine</td>
<td>Nutritionally incomplete dietary product</td>
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<td>Albumaid RVHB (10)</td>
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<td>Hypermethioninemia; Homocysteinemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Albumaid RVHB Complete (10)</td>
<td>&quot;</td>
<td>Homocystinuria; Hypermethioninemia</td>
<td>Formulated dietary product</td>
</tr>
<tr>
<td>Albumaid XP (Austria) (10)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Albumaid XP (EEC, Spain) (10)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Albumaid XP (Germany) (10)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Albumaid XP (Norway) (10)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Albumaid XP - Modified (Denmark) (10)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>ALS Master Mix (BCAA) (10)</td>
<td>&quot;</td>
<td>Motor neuron disease</td>
<td>Nutritional dietary product</td>
</tr>
<tr>
<td>Analog XLEU - New AA profile (10)</td>
<td>&quot;</td>
<td>Isovaleric aciduria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>PRODUCT NAME&lt;sup&gt;1&lt;/sup&gt;</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>DESCRIPTION&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Analog XLYS&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Powell and Scholefield, Ltd.&lt;sup&gt;7,8,9&lt;/sup&gt;</td>
<td>Hyperlysinemia</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Analog XP (Hydrolysate)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Analog XTYR&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Tyrosinemia</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>B.S.P.D. 73% (M.S.M.R.)&lt;sup&gt;4,10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Hypoproteinemia; Cachexia</td>
<td>Nutritional dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>BCAA Product for ALS (Pineapple)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>C26-Free LCT Emulsion&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cystic Milk&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Cystic fibrosis</td>
<td>Nutritionally incomplete dietary product for infants&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fructose Powder (RM448)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Disaccharide intolerance</td>
<td>Nutritionally incomplete carbohydrate module&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Galactosaemia Product&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Galactosaemia</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glycerol Trierucate Oil&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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### Appendix B. Continued.

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<tr>
<th>PRODUCT NAME(^1)</th>
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<th>INDICATION(S)(^1)</th>
<th>DESCRIPTION(^2)</th>
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<tr>
<td>Glycerol Trileate Oil (RM127)(^{10})</td>
<td>Powell and Scholefield, Ltd.(^7,8,9)</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
</tr>
<tr>
<td>GTE Emulsion(^{10})</td>
<td>&quot;</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
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<tr>
<td>High Tyrosine P.K. Aid I(^{10})</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product for 2nd &amp; 3rd trimester of pregnancy(^{11})</td>
</tr>
<tr>
<td>Histinaid 73% (M.S.M.R.)(^{10})</td>
<td>&quot;</td>
<td>Histidinaemia</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
</tr>
<tr>
<td>Hydrolysate XP Module(^{10})</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
</tr>
<tr>
<td>KECA Version of Trauma Product(^{4,10})</td>
<td>&quot;</td>
<td>Burns</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
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<tr>
<td>KECA/Isotonic Post-Trauma TP(^{4,10})</td>
<td>&quot;</td>
<td>Burns</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
</tr>
<tr>
<td>Lorenzo Oil (4GTO:1GTE)(^{10})</td>
<td>&quot;</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
</tr>
<tr>
<td>Lorenzomaid Emulsion(^{10})</td>
<td>&quot;</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
</tr>
<tr>
<td>Lorenzomaid Spread(^{10})</td>
<td>&quot;</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritionally incomplete dietary product(^{11})</td>
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<td>PRODUCT NAME</td>
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<td>INDICATION(S)</td>
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<tr>
<td>M.S.U.D. Aid 73% (M.S.M.R.)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Powell and Scholefield, Ltd.&lt;sup&gt;7,8,9&lt;/sup&gt;</td>
<td>Maple syrup urine disease</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maxamaid ESS XP&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Maxamaid Leucine-Free, Gly High&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Organic acidaemias</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Maxamaid UCD (flavored and unflavored)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Urea cycle disorders</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Maxamaid XHIS&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Histidinaemia</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Maxamaid XLEUC&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>Isovaleric acidemia</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Maxamaid XLYS&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Hyperlysinemia</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Maxamaid XLYS, XTRY (Norway)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Glutaric aciduria type I</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Maxamaid XLYS, XTRYPT&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Glutaric aciduria</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Maxamum RVHB (Dublin)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Hypermethioninemia</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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### Appendix B. Continued.

<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>MANUFACTURER</th>
<th>INDICATION(S)</th>
<th>DESCRIPTION</th>
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<tr>
<td>Maxamum XLYS</td>
<td>Powell and Scholefield, Ltd.</td>
<td>Hyperlysinemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Maxamum XLYS, TRY</td>
<td>&quot;</td>
<td>Glutaric aciduria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Maxamum XMET</td>
<td>&quot;</td>
<td>Hypermethioninemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Maxamum XMET, THRE, VAL, ISOLEU</td>
<td>&quot;</td>
<td>Propionic aciduria; Methylmalonic aciduria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Maxamum XPHEN, TYR</td>
<td>&quot;</td>
<td>Tyrosinemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Maxamum XTYR</td>
<td>&quot;</td>
<td>Tyrosinemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Methioninaid 73%</td>
<td>&quot;</td>
<td>Homocystinaemia; Hypermethioninemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Methioninaid (II)</td>
<td>&quot;</td>
<td>Hypermethioninemia</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Modified Maxamum</td>
<td>&quot;</td>
<td>Melanoma</td>
<td>Nutritional dietary product</td>
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<tr>
<td>Modified Maxamum</td>
<td>&quot;</td>
<td>Psychiatric disorders</td>
<td>Nutritional dietary product</td>
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<td>PRODUCT NAME</td>
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<tr>
<td>MSUD Aid 73% (II) (M.S.M.R.)</td>
<td>Powell and Scholefield, Ltd.</td>
<td>Maple syrup urine disease</td>
<td>Nutritionally incomplete dietary product</td>
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<tr>
<td>Neocata</td>
<td>&quot;</td>
<td>Protein malabsorption</td>
<td>Nutritional dietary product</td>
</tr>
<tr>
<td>Nut. Complete Adrenoleuco</td>
<td>&quot;</td>
<td>Adrenoleucodystrophy</td>
<td>Nutritional dietary product</td>
</tr>
<tr>
<td>Prod+GTO</td>
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<tr>
<td>P.K. Aid II (Australia)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
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<tr>
<td>P.K. Aid I (Breast Milk</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Profile)</td>
<td></td>
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<tr>
<td>Parkinson's Disease Product</td>
<td>&quot;</td>
<td>Parkinson's disease</td>
<td>Nutritional dietary product</td>
</tr>
<tr>
<td>PKU Aid II (M.S.M.R.)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>PKU Aid 73% (M.S.M.R.)</td>
<td>&quot;</td>
<td>Homocystinemia;</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypermethioninemia</td>
<td></td>
</tr>
<tr>
<td>PKU Bar (apricot and orange)</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product</td>
</tr>
<tr>
<td>Potato Starch MDX</td>
<td>&quot;</td>
<td>Carbohydrate intolerance</td>
<td>Nutritionally incomplete carbo- hydrate substitute module</td>
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</tbody>
</table>

"1" Numbers refer to footnotes.
<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>MANUFACTURER</th>
<th>INDICATION(S)</th>
<th>DESCRIPTION</th>
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<tr>
<td>Protein Free Chocolate Slab&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Powell and Scholefield, Ltd.&lt;sup&gt;7,8,9&lt;/sup&gt;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Protein Free Milk&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Protein intolerance</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Rice Starch MDX&lt;sup&gt;4,10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Allergy</td>
<td>Nutritional incomplete carbohydrate substitute module&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Synthetic Albumaid XP (Non Hydro)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>TYROSIN Aid (M.S.M.R.)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Tyrosinemia with normal methionine</td>
<td>Nutritionally incomplete dietary product&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>S-14</td>
<td>Wyeth-Ayerst International, Inc.&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Leucine-sensitive hypoglycemia</td>
<td>Infant dietary formula powder with low leucine, vitamins, and minerals.</td>
</tr>
<tr>
<td>S-29</td>
<td>&quot;</td>
<td>Renal acidosis with hyperphosphatemia; Pseudohypo-parathyroidism; Diabetes insipidus; Hypercalcemia; Severe cardiac decompensation</td>
<td>Infant dietary formula powder with exceptionally low renal solute load.</td>
</tr>
<tr>
<td>S-44</td>
<td>&quot;</td>
<td>Hypercalcemia</td>
<td>Dietary infant formula powder that is vitamin D free, and has exceptionally low renal solute load.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)</td>
<td>DESCRIPTION</td>
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<tr>
<td>Wysoy</td>
<td>Wyeth–Ayerst International, Inc.</td>
<td>Galactosaemia; Galactokinase deficiency; Milk or lactose intolerance</td>
<td>Milk protein–, lactose–, and gluten–free nutritionally complete dietary powder.</td>
</tr>
<tr>
<td>Rite–Diet (gluten free and low protein)</td>
<td>Welfare Foods</td>
<td>Phenylketonuria; Galactosaemia; Amino acid intolerances and other disorders listed by the company.</td>
<td>A variety of low protein, gluten–free pasta and bread and cake mixes.</td>
</tr>
<tr>
<td>Lpf</td>
<td>Milupa AG</td>
<td>Disorders of amino acid metabolism and other disorders listed by the company</td>
<td>Low–protein powder formulation.</td>
</tr>
<tr>
<td>Caloreen</td>
<td>Roussel</td>
<td>Disorders of amino acid metabolism and other disorders listed by the company</td>
<td>Protein–, gluten–, lactose–, sucrose–, galactose–, and fructose–free; electrolyte–low glucose polymer dietary powder.</td>
</tr>
<tr>
<td>Isomil</td>
<td>Abbott</td>
<td>Galactosaemia; Galactokinase deficiency; Milk and lactose intolerance</td>
<td>Milk protein–, lactose–, and gluten–free nutritionally complete dietary powder.</td>
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<tr>
<td>PRODUCT NAME</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)</td>
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<td>Polycose</td>
<td>Abbott&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Disaccharide intolerance; Disorders of amino acid metabolism and protein intolerance, and other disorders listed by the company</td>
<td>Dietary powder that is lactose and gluten free and with carbohydrate as glucose polymers.</td>
</tr>
<tr>
<td>Aglutella&lt;sup&gt;10&lt;/sup&gt;</td>
<td>G.F. Dietary&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Phenylketonuria and similar amino acid abnormalities, and other disorders listed by the company</td>
<td>Gluten-, sucrose-, and lactose-free; protein-, sodium-, and potassium-low pasta products.</td>
</tr>
<tr>
<td>Aglutella Azeta&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Phenylketonuria and similar amino acid abnormalities, and other disorders listed by the company</td>
<td>Gluten-free, protein-, sodium-, and potassium-low cream filled wafers.</td>
</tr>
<tr>
<td>PKU Drink&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Milk substitute drink</td>
</tr>
<tr>
<td>Juvela Low Protein</td>
<td>&quot;</td>
<td>Phenylketonuria, and similar amino acid abnormalities, and other disorders listed by the company</td>
<td>Protein-, low, gluten-, lactose-, and milk-free loaf and bread/cake mix.</td>
</tr>
<tr>
<td>Aminogran&lt;sup&gt;10&lt;/sup&gt;</td>
<td>A &amp; H&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary powder of essential and non-essential amino acids, and phenylalanine free.</td>
</tr>
<tr>
<td>Aminogran Mineral Mixture&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&quot;</td>
<td>Phenylketonuria</td>
<td>Mineral and supplement for use with Aminogran.</td>
</tr>
<tr>
<td>PRODUCT NAME$^1$</td>
<td>MANUFACTURER $^1$</td>
<td>INDICATION(S)$^1$</td>
<td>DESCRIPTION$^2$</td>
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<tr>
<td>Aproten$^{10}$</td>
<td>Ultrapharm$^{16}$</td>
<td>Phenylketonuria and similar amino acid abnormalities, and other disorders listed by the company</td>
<td>A variety of pasta and cake products that are low protein and gluten free.</td>
</tr>
<tr>
<td>Ostertag$^{10}$</td>
<td>Farley$^{16}$</td>
<td>Galactosaemia; Galactokinase deficiency; Lactose and sucrose intolerance</td>
<td>Milk protein-, sucrose-, lactose-, and gluten-free dietary powder.</td>
</tr>
<tr>
<td>Aminex$^{10}$</td>
<td>Cow and Gate$^{16}$</td>
<td>Phenylketonuria and similar amino acid abnormalities, and other disorders listed by the company</td>
<td>Protein-, phenylalanine-, sodium-, and potassium-low; sucrose- and lactose-free biscuit.</td>
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<tr>
<td>Formula S$^{10}$</td>
<td>&quot;</td>
<td>Galactosaemia; Galactokinase deficiency, and lactose intolerance</td>
<td>Lactose-, gluten-, fructose-, and sucrose-free nutritionally complete dietary powder.</td>
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<tr>
<td>Galactomin 17$^{10}$</td>
<td>&quot;</td>
<td>Galactosaemia; Galactokinase deficiency; and lactose intolerance</td>
<td>Lactose-low and sucrose-free nutritionally complete dietary powder.</td>
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<tr>
<td>Galactomin 19$^{10}$</td>
<td>&quot;</td>
<td>Galactose intolerance</td>
<td>Nutritionally incomplete dietary mixture with washed caseinates, vegetable oils and fructose as the main carbohydrate source.</td>
</tr>
<tr>
<td>PRODUCT NAME(^1)</td>
<td>MANUFACTURER</td>
<td>INDICATION(S)(^1)</td>
<td>DESCRIPTION(^2)</td>
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</tr>
<tr>
<td>Minafen(^{10})</td>
<td>Cow and Gate(^{16})</td>
<td>Phenylketonuria</td>
<td>Nutritionally incomplete dietary powder for infants and young children.</td>
</tr>
<tr>
<td>Polycal(^{10})</td>
<td>&quot;</td>
<td>Disaccharide intolerance; Disorders of amino acid metabolism and protein intolerance, and other disorders listed by the company.</td>
<td>Carbohydrate as maltodextrin syrup in powder form.</td>
</tr>
</tbody>
</table>

\(^1\) Product name and indications for use are identified from manufacturers' product labeling or information catalogs or listings in available literature.

\(^2\) Protein, fat, and carbohydrate sources for similar products may vary among manufacturers, users should consult product label for full information.


\(^4\) Product has application not only to orphan disease but also to many other medical diseases, disorders, and medical conditions.


\(^6\) Previously distributed by Milner Scientific Company, Ltd., but now incorporated into the Scientific Hospital Supplies, Inc., product line and currently distributed in the United States by Dietary Specialties, Inc., Rochester, NY.

Appendix B. Continued.


9 Products manufactured by Powell and Scholefield, Ltd. are licensed exclusively to Scientific Hospital Supplies, Ltd. Some products are distributed in the United States to Ross Laboratories by Scientific Hospital Supplies, Inc. These include Analog XP; Maxamaid XP; Maxamum XP; Analog MSUD; Maxamaid MSUD; Maxamum MSUD; Analog XPHEN, TYR; Maxamaid XPHEN, TYR; Analog XPHEN, TYR, MET; Maxamaid XPHEN, TYR, MET; Analog XMET, THRE, VAL, Isoleu; Maxamaid XMET, THRE, VAL, Isoleu; Analog XMET; Maxamaid XMET; Analog XLYS, TRY; Maxamaid XLYS, TRY. Formulations of these products may vary slightly to conform to the regulatory standards of different nations. For description, see listing under Ross Laboratories.

10 Product available outside the United States.

11 Full product description was not received in time for inclusion in this appendix.


13 Distributed in the United States by Dietary Specialties, Inc., Rochester, NY.

14 Some products manufactured by Milupa are distributed in the United States by Bristol–Myers/Mead Johnson. These include PKU 1, PKU 2, PKU 3, HIST 1, HIST 2, HOM 1, HOM 2, LYS 1, LYS 2, MSUD 1, MSUD 2, OS 1, OS 2, TYR 1, TYR 2, UCD 1, and UCD 2. For description, see listing under Bristol–Myers (Mead Johnson).


Appendix C

Interim Guidelines for Obtaining Recommendations for Investigations of Orphan Drugs

CONTENTS OF SPONSOR REQUEST

Any sponsor seeking recommendations regarding the nonclinical and clinical investigations that are necessary to obtain approval or licensing of a drug or biological product for a rare disease or condition should submit the following information in duplicate to:

Office of Orphan Products Development/HF-35
Food and Drug Administration, Room 15-61,
5600 Fishers Lane,
Rockville, Maryland 20857

1. The sponsor's name and address.

2. A statement that the sponsor is requesting written recommendations on orphan drug development under section 525 of the Federal Food, Drug, and Cosmetic Act.

3. The sponsor's primary contact person, and the person's title, address, and telephone number.

4. The generic and trade name of the drug and a list of the drug's components or description of the drug by formulation.

5. The proposed dosage form and route of administration.

6. Present regulatory status of the drug, e.g., investigational new drug in the U.S.; marketing experience or investigational studies conducted outside the U.S.

7. A description of the disease or condition for which the drug is to be investigated and the proposed indications for use for such disease or condition.

8. The basis for concluding that the drug is for a disease or condition that is rare in the U.S., including the following:

   (i) The size and other known demographic characteristics of the patient population affected, and source of the information.

   (ii) The summary of the sponsor's basis for believing that the disease or condition named in paragraph 7 occurs so infrequently that there is no reasonable expectation that the costs of drug development and marketing will be recovered in future sales of the drug in the United States. This information may be waived if the prevalence of the disease or condition in the U.S. for which the drug is intended is approximately 200,000 or less. For higher prevalence conditions the estimated costs and sales data as provided by the interim guidelines for Section 526 of the Act should be submitted.
The exclusion for a patient prevalence of less than 200,000 applies not only to a disease or condition per se but also to a subpopulation. For certain drugs used for prophylactic purposes, such as vaccines and blood products, the figure of 200,000 or less applies to the number of patients per year receiving the product.

9. A detailed summary and analysis of available data on the pharmacologic effects of the drug.

10. A detailed summary and analysis of available nonclinical and clinical data pertinent to the drug and the disease to be studied. The sponsor should include copies of pertinent published reports.

11. An explanation of how the data in paragraphs 9 and 10 support the rationale for use of the drug in the rare disease or condition.

12. A definition of the population from which subjects will be identified for clinical trials (if known).

13. A detailed outline of any protocols under which the drug has been or is being studied for the rare disease or condition and interpretation of resulting data.

14. The sponsor's conclusions on the scope of preclinical and clinical trials needed to establish the safety and effectiveness of the drug or biological product.

15. Detailed protocols for each proposed clinical trial, if available.

16. Specific questions to be addressed by FDA in its recommendations for nonclinical and clinical studies.
APPENDIX D

CHRONOLOGY OF RESEARCH AND DEVELOPMENT ACTIVITIES ASSOCIATED WITH A MEDICAL FOOD PRODUCT USEFUL IN DIETARY MANAGEMENT OF PHENYLKETONURIA (PKU).

NOTE: Preceding the description of events that occurred during each stage in the research and development process is an overview of various incentives, barriers, and contributing factors that influenced the course of research and development during that stage.

Stage 1. Disease Characterization (1930-1949)

<table>
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<tr>
<th>Incentives:</th>
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<tbody>
<tr>
<td>1. Clinicians seek to improve health care to affected individuals</td>
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<tr>
<td>2. Investigator gains career advancement</td>
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<table>
<thead>
<tr>
<th>Barriers:</th>
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<tbody>
<tr>
<td>1. Lack of understanding about the medical condition</td>
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<tr>
<td>2. High cost of basic research (facilities, equipment, personnel)</td>
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<td>3. Time to develop needed information</td>
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<td>4. Availability of modified food source</td>
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<tr>
<th>Contributing Factors:</th>
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<tbody>
<tr>
<td>1. Parental approval to research new procedure</td>
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<td>2. Center of excellence with directed research goals</td>
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By 1930 institutions for the mentally retarded were faced with the problem of caring for a multitude of individuals for whom no available medical treatment was successful. Early literature describes some of these individuals as “idiots” who were unable to stand, walk, or talk and who spent much of their time groaning, crying, or inflicting self-injury (Bickel et al., 1953). During 1929 a significant research breakthrough took place with the observation that certain infants could not tolerate infant formula products containing cow’s milk. The availability of a special soy-based infant formula inspired some clinical investigators to further characterize other conditions for which no treatment or cure was available (Cook and Sarett, 1982). Følling (1934) reported that certain institutionalized patients with severe mental retardation expressed high levels of phenylpyruvic acid in their urine. During subsequent years Følling’s research findings were confirmed by other investigators who
characterized the pattern of genetic inheritance and biochemistry of the metabolic error (Jervis, 1939, 1947; Penrose and Quastel, 1937). With the initial pathophysiological characterization of the metabolic disorder, Woolf and Vulliamy (1951) developed the hypothesis that the mental retardation associated with the condition might be prevented by modifying phenylalanine intake. However, a major barrier to formulating a dietary product with low phenylalanine was the availability of phenylalanine-free protein sources.


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<tr>
<th>Incentives:</th>
<th>Barriers:</th>
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<tbody>
<tr>
<td>1. Investigators seek to improve health care to affected individuals</td>
<td>1. High cost of basic research (facilities, equipment, personnel)</td>
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<tr>
<td>2. Investigator gains career advancement</td>
<td>2. Need for technology transfer</td>
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<tr>
<td>3. Some seed money becomes available for basic research</td>
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<table>
<thead>
<tr>
<th>Contributing Factors:</th>
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</thead>
<tbody>
<tr>
<td>1. Availability of study subjects and study materials</td>
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<tr>
<td>2. Institutional Review Board approval to test new procedure</td>
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Collaborative efforts among clinical, academic, and industry investigators occurred during the early 1950s. A biochemical technique for removing phenylalanine from casein hydrolysate was identified by Smallwood and colleagues, and a source of phenylalanine-free protein was made available by a manufacturer in the United Kingdom (Bickel et al., 1953). With the availability of this "crude" phenylalanine-free food source, Bickel and colleagues (1953) reported a case study of a PKU patient that demonstrated improved growth and neuromuscular coordination when fed a diet low in phenylalanine. These findings were confirmed by Woolf and colleagues (1955) who also included psychometric and electroencephalographic measurements in their study. During the same year an American research group working on a parallel path reported similar case study findings using a nutritionally balanced synthetic diet composed of a mixture of amino acids (Armstrong and Tyler, 1955). Reports describing this new procedure of dietary modification in peer-reviewed scientific literature identified a new medical product of interest for some pharmaceutical manufacturers.

Incentives:
1. Profitability from product sales
2. Enhanced corporate image as a responsible citizen
3. Third party reimbursement for product users

Barriers:
1. R&D cost associated with safety and efficacy testing
2. Small user community

Contributing Factors:
1. Product and misuse liability
2. Regulatory oversight by FDA

During the mid 1950s the PKU dietary product was considered to be a drug. Manufacturers identified methods to produce bulk quantities of the medical food product with a consistent nutrient profile. Questions about product safety and suitability were studied by industrial research teams in collaboration with clinicians at various hospital centers. Some nonclinical studies were conducted to gain information about nutritional adequacy and to assure safe use during clinical testing (Sarett and Knauff, 1985). In subsequent years, the product underwent the clinical trials required by the FDA under the Investigational New Drug Application process. These findings substantiated significant health improvement for affected individuals, the product received FDA approval, and was subsequently marketed to affected individuals as a prescription item (Centerwall, 1958).

**Incentives:**
1. Affected individuals no longer require institutionalization
2. Third party repayment covers medical food and physician costs
3. Additional funding was made available to academic investigators for research activities

**Barriers:**
1. Classification of the medical food product as a drug
2. Technology to identify affected infants

**Contributing Factors:**
1. FDA product assurance maintained under Good Manufacturing Practices
2. Affected individuals express the need for additional products

After 1958 the PKU dietary product underwent continued surveillance testing in clinical settings. Investigators soon determined that the toxic effects of phenylalanine (mental retardation) could be significantly reduced if affected infants could receive the PKU dietary product shortly after birth and that the brain damage could be prevented but not reversed. A blood test was developed to identify PKU infants and in 1963 a newborn screening program was implemented (Guthrie, 1972; Guthrie and Susi, 1963). Experience with the medical food indicated that termination of the PKU medical product in the diet could be harmful (Murphy, 1969). To address this and other issues, a collaborative study at 15 hospital centers was initiated in 1967 (Williamson et al., 1977). During this period, the needs of affected individuals after infancy were assessed further. As new insights about the disease process were identified from various pathophysiological measurements, investigators identified the need to adjust and/or reformulate the product to meet the nutritional demands for older individuals (Dobson et al., 1977; Parker et al., 1977). Ascribing drug status to the medical food product became a barrier to further product improvement because any adjustment to the formulated product would require application for FDA approval of the revised formulation as a new drug product. Filing an application for new drug status for each refinement to the medical food product would inhibit a manufacturer's ability to recover product development costs, add to consumer product costs, and result in lengthy retesting and regulatory approval delays.

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<th>Incentives:</th>
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<tr>
<td>1. Reclassification of the product as a food</td>
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<tr>
<td>2. Investigators find funding to pursue development of products for other metabolic disorders</td>
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<tr>
<td>3. Affected individuals become productive citizens</td>
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<tr>
<th>Barriers:</th>
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<tr>
<td>1. Affected individuals lose third party payment for use of the medical food product</td>
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<tr>
<td>2. Product costs escalate</td>
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<td>3. Requirements of Infant Formula Act</td>
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<tr>
<th>Contributing Factors:</th>
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<tbody>
<tr>
<td>1. Affected individuals demand greater variety of products</td>
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<tr>
<td>2. FDA increases oversight of infant formula products</td>
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</table>

Encouraged by the availability of additional funding, investigators participating in the collaborative PKU study expanded scientific knowledge about this metabolic disorder and developed an animal model to study the neurological effects of the disease (Berry et al., 1977; Koch et al., 1985). Knowledge gained from the concept of using the PKU dietary product was applied to other metabolic disorders and a variety of new products became available. In 1972 the FDA reclassified the PKU medical food product as a food for special dietary uses (Office of the Federal Register, 1972; U.S. Congress, 1986a). This regulatory change brought these products in line with other food products and clarified the needs for limited product testing and regulatory approval. This action spurred further development of new product formulations as manufacturers were able to respond more quickly to meet changing needs of affected individuals. However, as a consequence of this regulatory decision, insurance underwriters were no longer responsible to provide reimbursement costs for product use as well as other related medical services. This action acted as a barrier to further development as the costs for product use, manufacture, and formulation refinement were now borne exclusively by the families of affected individuals and/or by Departments of Health at the State level. Product costs escalated dramatically during this period as the total number of affected individuals using the product increased (Koch, 1989). Parallel to these developments were advances in the understanding of nutritional requirements of infants (American Academy of Pediatrics, 1967, 1971, 1976a,b). Standards for infant formula composition were established with the inclusion of the Infant Formula Act (U.S. Congress, 1986b) into the Federal Food, Drug, and Cosmetic Act. This amendment sets specifications to assure overall safety and adequacy of infant formula products for nutrient, vitamin, mineral, and food additives that may be used, as well as oversight of manufacturing hygiene, packaging, and labeling. Some provision was made for dietary products that are exempt from the nutritional requirements for general infant formulations. Manufacturers' compliance with these regulations contributed to a further escalation of product costs during this period.

Incentives:
1. Affected individuals seek additional medical food products
2. Some funding available for medical food development via the Orphan Drug Act (1988)
3. Some NIH funding available for metabolic disease research (1988)

Barriers:
1. The PKU medical food
2. Status quo: manufacturers' previous investment in product development
3. Lack of third party repayment for product use
4. Insufficient regulatory direction for medical food products
5. Research funding cuts and/or shifts in funding priorities

Contributing Factors:
1. Escalating costs of research
2. Lack of incentives to train investigators
3. Advances in biotechnology
4. Increasing awareness of the importance of nutrition and health

During the 1980s unexpected problems were further characterized by clinical investigators working with the PKU dietary product (Gropper et al., 1988; Guthrie, 1988). This was most apparent in women reaching childbearing age (American Academy of Pediatrics, 1985). Additional dietary products derived from previous formulations were designed to meet some of the needs of pregnant women and protocols were designed to address potential problems associated with pregnancies in the PKU patients. The collaborative maternal PKU study continues to provide new insights into the complex problem of pregnancy and PKU (Waisbren et al., 1988). Recent research has identified new approaches to resolve problems associated with maintaining phenylalanine levels in-utero and in the brain (Jordan et al., 1985; McSwigan et al., 1981; Vorhees and Berry, 1989). In addition, affected individuals have pointed out product palatability problems associated with odor, bad taste, and adult use of infant style product forms. Manufacturers have incorporated flavoring into the existing product formulations (Acosta, 1989; Scientific Hospital Supplies, Ltd., 1989). Advances in biotechnology now permit the synthetic manufacture of low-phenylalanine peptides (Kitagawa et al., 1987) but technology transfer to manufacturers is delayed by lack of incentives and high costs to implement product development. In addition, manufacturers are not encouraged to expand product lines because of restrictive regulations for associating health claims with food products, the increasing trend by third party insurers to circumvent reimbursement for use of products that are foods, and the small market potential for such products.

During this period, funding for basic research activities was gradually cut back as the success of the medical food product was recognized. Thus, the availability of PKU medical food products became a barrier to further development. In fact, with the exception of nutrient refinement of the PKU dietary medical food product, there has been no significant improvement in disease management since the PKU dietary product was introduced (Berry, 1987). New approaches to disease treatment (e.g., prevention of phenylalanine absorption) have been identified, and the technology transfer for information learned from further study of PKU–specific signs and symptoms could lead to better understanding in other research areas (e.g., weight control). Pursuit of such approaches is limited by the availability of funding and the lack of career incentives for investigators (Berry, 1987).
LITERATURE CITED

Acosta, P.B. 1989. The Ross metabolic formula system: nutrition support protocols (with product label information). Available from: Ross Laboratories, Columbus, OH.


