DEVELOPMENT OF MEDICAL FOODS FOR RARE DISEASES

PROCEEDINGS OF A WORKSHOP

June 9–11, 1991

Sponsored By

National Institute of Child Health and Human Development
National Institute of Diabetes and Digestive and Kidney Diseases
Office of Orphan Products Development of the
Food and Drug Administration
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U.S. Nutritional Group of the Bristol–Myers Company
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Conducted

By

The Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Comprehensive and quick response reports are based upon literature reviews and the scientific analyses by knowledgeable investigators active in specific areas of biology and medicine. Proceedings from workshops and symposia include synopses of presentations, references, and opinions provided by participants.

These proceedings were developed from a workshop held June 9-11, 1991 at the Federation Conference Center, 9650 Rockville Pike, Bethesda, Maryland. The workshop was sponsored by the National Institute of Child Health and Human Development, the National Institute of Diabetes and Digestive and Kidney Diseases, the Office of Orphan Products Development of the Food and Drug Administration, the International Life Sciences Institute, the U.S. Nutritional Group of the Bristol-Myers Company, and the Nabisco Biscuit Company. This report on the workshop was prepared in accordance with provisions of NIH Contract No. N01-HD-91-3105.

The workshop proceedings are presented in two parts: 1) synopses of the invited papers on current understanding and gaps in knowledge, and 2) conclusions and recommendations on research approaches and priorities derived from summaries of working group discussions.

The invited papers and the working group recommendations were developed independently of the sponsors. The speakers, discussion leaders, rapporteurs, and LSRO accept responsibility for the accuracy of their respective portions of these proceedings; however, listing of these individuals does not imply that they specifically endorse each conclusion and recommendation. These proceedings were reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each Constituent Society of FASEB) under authority delegated by the Federation Board. Upon completion of these review procedures, the proceedings were approved and transmitted to the sponsors by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, as the proceedings of a workshop, it reflects the expertise of the participants and does not necessarily reflect the opinion of each individual member of the FASEB Constituent Societies.

December 31, 1991

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Research Office
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INTRODUCTORY REMARKS

Kenneth D. Fisher, Ph.D.

Director
Life Sciences Research Office
Federation of American Societies for Experimental Biology
Bethesda, Maryland

On behalf of the member Societies of the Federation of American Societies for Experimental Biology, LSRO is pleased to present the proceedings from the workshop on "Development of Medical Foods for Rare Diseases." This workshop is being sponsored by the National Institute of Child Health and Human Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the Office of Orphan Products Development of the Food and Drug Administration, the International Life Sciences Institute, the U.S. Nutritional Group of the Bristol-Myers Company, and the Nabisco Biscuit Company. This range of sponsorship reflects the broad interest of the biomedical and the nutritional communities in this particular topic.

As most of you are aware, in 1983 the U.S. Congress promulgated the Orphan Drug Act to address the need for development of drugs for various diseases and conditions of limited prevalence in the United States. Congress provided incentives to industry for the development of orphan drugs because of the limited potential for these products in the marketplace and because availability of treatment modalities was limited by the absence of effective drugs. Congress also provided support for clinical and experimental research on the development of orphan drugs and approaches to treatment.

In 1988, the Act was amended to extend certain provisions to medical devices and medical foods. Specifically, the revised sections of the Act on medical foods included provisions related to support for the costs of research and development on medical foods for rare diseases. Rare diseases where medical foods might be useful were defined as, "... any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such a disease or condition will be developed without assistance." The term, medical food, was further defined as "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 upon recognized scientific principles, are established by medical evaluation."
Despite the passage of the 1988 amendments to the Orphan Drug Act, now referred to as the Orphan Products Act, knowledge of the medical foods provisions of the Act throughout the biomedical and nutritional communities is limited and fragmentary. Collaborative efforts among the National Institutes of Health, the Food and Drug Administration, and various food and pharmaceutical manufacturers are just now beginning to produce results.

This workshop was organized as a result of the tentative nature of progress on development of medical foods for rare or orphan diseases. The workshop brought together individuals from several disciplines so that investigators in food science and food technology could gain a better appreciation of the clinical needs for specific medical food products. In addition, the workshop sought to acquaint clinical investigators with new and novel approaches in food science and biotechnology for product development, and it was designed to make these investigators aware that while manufacturers have the capability to produce new and novel medical foods, they have difficulty in utilizing these techniques because of fiscal and regulatory obstacles. Another goal of the workshop was to acquaint all parties with the regulatory framework in which such products must be developed, tested, and marketed. The workshop was structured to provide maximum opportunity for both presentation of information and informal discussions among participants.

The introductory speaker provided a brief overview of the history of the development of medical foods from the perspective of one who was intimately involved. Five speakers from different disciplinary viewpoints were asked to address specific aspects of medical foods for rare diseases. We asked that their presentations be provocative, raising more questions than answers and leaving answers to discussions held later in the session. The presentations were followed by summaries of discussion groups. These groups consisted of workshop participants and were designed to give a more in-depth consideration of needs, problems, opportunities, and solutions for issues related to development of medical foods. The summaries also reflect the open discussions of the collective participants on the final day of the workshop.
INTRODUCTORY REMARKS

Ephraim Levin, M.D.

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Twenty-five years ago, when I was working in a medical school, I became acquainted with a clinical investigator who was attempting to sustain patients with chronic renal failure. At that time, neither routine renal dialysis nor successful renal transplantation was yet widely available. My clinical colleague had developed an experimental program which combined bimonthly intermittent peritoneal dialysis with a low-protein formula diet. This regimen could keep patients alive for prolonged periods on the very edge of catastrophic uremia. The formula diet was liquid, bland, and inoffensive, but terribly monotonous. Patients would soon tire of it and sneak off at night for forbidden items such as hamburgers or ice cream. As they were producing little or no urine, they decompensated. My colleague, a dedicated physician, would rescue them at all hours and all days of the week throughout the year by an extra series of peritoneal dialysis. Despite the modest success of this treatment regimen, the lack of patient compliance and the clinical burden became too much for him, and he informed the patients one by one that if they did not conform to this treatment protocol, he would drop them from the study. I remember one patient in particular, a World War II veteran, who cried in anguish and anger, "But you're going to kill me!"

The behavior of this patient, who was being threatened with a very rapid negative feedback from noncompliance, was different in degree but not in kind from that we see today in those people who are unable to control their smoking or overindulgences in food or drink for the sake of their long-term health. Even more difficult to manage clinically are those patients whose very life depends on special diets or especially formulated foods that have unpleasant smells or tastes. Like my colleague's patients, these people often do not have the luxury of delayed feedback from failure to comply with dietary prescriptions. An even larger group consists of persons with inborn errors of metabolism and other rare diseases whose only chance at growth, development, and survival is made possible by a limited number of available foods, monotonous in consistency, physical appearance, taste, and smell.

Each inborn error of metabolism is rare, but in the aggregate they are fairly common. Recent estimates suggest there are about 150 dietary products available to patients with about fifteen to twenty such metabolic conditions. There is, perhaps, a greater number of metabolic disorders and conditions for which few or no
nutritional products are available. In a real and practical sense, there are pressing needs for a wider variety of more acceptable medical foods and a broader array of specialty products with which to manage these unique medical conditions.

To the extent that this is a research problem, it is the primary responsibility of certain branches of the National Institutes of Health. However, current budgetary stringencies make it difficult to direct substantial sums into Requests for Applications or Contract Proposals, the traditional mechanisms that NIH program staff have used to stimulate work in neglected areas of basic or clinical research. These mechanisms may stimulate interest, but they can lead directly to only a small number of funded grants or contracts in the chosen area. The Institutes need to explore other ways of fostering work in certain areas of need, such as better medical foods for rare diseases.

One of the methods we are trying to develop for this purpose is analogous to the catalytic activity of an enzyme, which lowers the activating energy required to drive a process by maintaining the reactants in proximity in the optimal position for interaction. That is what we are attempting to do at this meeting by bringing together clinicians who understand the needs of the patients with academic and industry scientists who have the skill to develop responses to those needs. We know that there is expertise in the food technology industry and in university laboratories investigating food science, food technology, and biotechnology that can be marshalled to develop an array of palatable foods from selected precursor materials. We would like to see some of that expertise applied to making dietary management more successful and life more tolerable for patients whose entire existence is dominated by the need to compensate for their metabolic errors by controlling what they consume as foods and beverages.

I was told recently that food technologists have stated that they could manufacture a phenylalanine-free cheese any time someone wanted one. Well, we want one. We also want other phenylalanine-free foods which would help a pregnant woman with phenylketonuria, who has trouble with dietary compliance, protect her unborn child from irreversible cerebral damage from hyperphenylalaninemia. We would like to have a variety of products with good organoleptic properties which would meet the special nutritional and metabolic needs of patients with all the metabolic disorders that are responsive to dietary therapy. The needs are clear, the expertise is available, the techniques can be found and applied to this problem, and the regulatory apparatus can be used to further these goals.

Perhaps, over the next day or two, we can identify specific research needs and gaps in knowledge, and stimulate interest in research grants and small business proposals for development of special medical foods. Hopefully, we can also find ways to initiate some collaborative activities that are self-sustaining
or that can be maintained by industry. We have an opportunity and an obligation to put our vast expertise and limited resources together to address important needs of a significant segment of our population.
AN HISTORICAL OVERVIEW OF MEDICAL FOODS

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Office of Nutrition and Food Sciences
Food and Drug Administration
Washington, DC

BACKGROUND

The concept of medical foods -- that is, enteral nutritional support of seriously ill patients under medical supervision -- has been recognized for several decades. However, from an historical point of view, there is not a very good understanding either domestically or internationally of exactly what medical foods are. A brief historical overview of the origin, development, and current status of medical foods is in order from the perspective of someone who has been involved in the clinical and regulatory aspects for many years.

The fundamental concept that undergirds the use of medical foods is based on the sound and reasonable medical principle, "if the gastrointestinal tract is functional, use it." Medical foods are, in fact, life support systems and should be viewed as such. Contemporary clinical nutritional thinking holds that there are five different types of medical foods:

- Nutritionally complete formulas
- Modular formulas
- Special products for inborn errors of metabolism
- Oral rehydration solutions
- Very low-calorie diets (<400 kcal/d).

While the focus of this workshop is only on those special products for inborn errors of metabolism, from a regulatory perspective, all types of medical foods are an enigma. Prescription drugs are very strictly regulated. Infant formulas as a subclass of foods for special dietary use are by far the most strictly regulated segment of the food industry in this country. The Infant Formula Act of 1980, amended again in 1986, establishes requirements for FDA to promulgate approximately 20 different regulations that govern infant formulas. Yet the enigma is that medical foods in their totality are not regulated at all; they are another subclass of foods for special dietary use and are in the gray zone between prescription drugs and conventional foods. For practical purposes, medical foods in today's world are regu-
lated simply under the good manufacturing practice regulations from the 1970s which govern all foods.

Yet manufacture of medical foods is an economically large industry. In 1984, an estimated five million patients were receiving medical foods for some period of the year. The magnitude of the industry in 1990 has been estimated to be about $1 billion per year. Accurate figures are hard to determine as enteral products are used in hospitals, in nursing homes, and are available over-the-counter for home use. This is a reflection, in part, of the absence of regulation.

Another historical observation of importance is the diverse nature of biomedical disciplines that have contributed to the development of medical foods. From a clinical point of view, inborn errors have been known for over 70 years. During World War II, the concept of what we now call medical foods came into being in military medicine for surgery, war-induced trauma in particular, and subsequently for overall sustenance of patients in general.

In the 1950s and 1960s clinical nutrition was preoccupied with parenteral nutrition and enteral products took a back seat. Current clinical practice includes more balanced nutritional/metabolic approaches based on macronutrient and micronutrient needs. However, most products are formulated on the basis of the Recommended Dietary Allowances, simply because we know so little about nutritional needs for specific medical conditions. Thus, enteral feeding is often a clinical art as well as a scientifically based practice.

Some progress is being achieved through expanded understanding of the basic biochemical and physiological mechanisms of disease-nutrient interactions. Recently, investigations of the interactions of nutrition and immunology in trauma and burn patients and epidemiological studies of the use of medical foods have increased in scope and number. Definitive information on the prevalence of specific disorders, particularly inborn errors of metabolism, in which the application of medical foods can be useful, continues to be a major stumbling block. Clearly, better epidemiological data are needed.

This workshop is an important undertaking as there is considerable expertise available among scientists in clinical medicine, food science, food technology, food and chemical engineering, marketing and nutrition that can be brought to bear on development of medical foods for rare diseases. Both academia and industry have an incredible wealth of knowledge and resources if ways can be found to bring these together. But one must be mindful of the history of development and regulation of medical foods to make any progress in this area.
REGULATORY HISTORY

Medical foods have existed for many years. Clinicians have known what they are, what they are for, and how to use them. Clinicians have developed life support systems, but very little attention has been paid in regulating and assuring the quality and safety of these products for the purposes for which they are intended.

Some key events in the regulatory history of medical foods are depicted in Table 1. Note that this is mostly a history of exemptions. Indeed, under the Infant Formula Act, infant formulas other than those for normal babies are called "exempt infant formulas". This is a rather curious choice of words because they are really not exempt from anything except for the classic standard nutrient profile of conventional infant formulas. Therefore, inborn error products that are specifically marketed for the infant and other products that are marketed, for example, for the low-birth-weight baby, are covered under the rigid requirements of the infant formula law and regulations.

The concept of medical foods as a distinct category of foods for special dietary use was developed in 1971. The first step FDA took was in 1972 when products for infants who had inborn errors were deregulated from prescription drugs to foods for special dietary use. The motivation for this action was quite simple. We had at that time in this country only one product for PKU, Lofenalac™ regulated as a prescription drug. In Canada, there were five products for PKU and in the United Kingdom eight or ten. The problem of dietary monotony had become an extremely difficult one to deal with in the United States, but other countries seemed to have succeeded in broadening their dietary armamentarium. Another aspect of this motivation of deregulation was to get these products out from under drug law, because the expense of developing new products under drug law is enormous.

And, in the case of food law, as a rule, it isn't, particularly when dealing with nutritional products that are formulated with well-understood nutrients.

In 1973 medical foods got their first recognition in the Federal Register simply by being exempted from the provisions of nutritional labeling. This brought medical foods into regulatory existence.

In 1976, the Proxmire Amendment was passed to reduce FDA's authority to regulate the composition and potency of dietary supplements. This legislation recognized the existence of medical foods and exempted them from the provisions of that particular amendment.
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<th>Year</th>
<th>Event</th>
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<td>Concept development</td>
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<td>1972</td>
<td>&quot;Deregulation&quot; of inborn error products from prescription drugs to foods for special dietary use</td>
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<td>1973</td>
<td>Exemption from nutrition labeling (therefore recognized to exist as a class of foods for special dietary use)</td>
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<td>1976</td>
<td>Exemption from vitamin and mineral provisions of the Food, Drug, and Cosmetic Act (FD&amp;C) (Proxmire Amendment)</td>
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<td>1984</td>
<td>Draft medical foods regulation prepared in FDA (core concept: a pre-approval process)</td>
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<td>1984</td>
<td>Final labeling rule re medical supervision for very low calorie diets (&lt;400 kcal/d)</td>
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<td>1987</td>
<td>Draft medical foods regulation rejected within FDA</td>
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<td>1987</td>
<td>Exemption from first proposal on &quot;health messages&quot;</td>
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<td>1988</td>
<td>Definition of &quot;medical foods&quot; by law (Orphan Drug Amendments to the FD&amp;C Act of 1988)</td>
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<tr>
<td>1990</td>
<td>Exemption from second proposal on &quot;health messages&quot;</td>
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<td>1990</td>
<td>Exemption from proposal for mandatory nutrition labeling</td>
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<td>1990</td>
<td>Exemption from Nutrition Labeling and Education Act of 1990 (requires numerous reproposals/new proposals)</td>
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<tr>
<td>1991</td>
<td>Uncertainty -- will reexempt in new nutrition labeling proposal</td>
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1 Subsequent to this meeting, FDA did so; see Federal Register, Vol. 56, No. 229, November 27, 1991, page 60392; FDA also stated its intent to develop regulations governing medical foods, pages 60377-60378.
In 1984, a medical foods regulation was prepared by FDA which established a pre-approval process for medical foods. Concurrently came the final labeling regulations pertaining to very-low-calorie diets that incorporated the concept of warning labels and the necessity of use only under medical supervision. In 1987, the 1984 draft medical foods regulation was rejected within FDA, in large part, because of the general deemphasis on government regulations at that time.

Medical foods were again exempted from the proposals on health messages in 1987, but finally emerged and were defined in the 1988 Orphan Drug Amendment to the Federal Food Drug and Cosmetic Act. This history of exemptions continues today, as medical foods have been exempted in provisions of the Nutrition Labeling & Education Act of 1990.

As of the moment, there is a lot of uncertainty about the future of the regulation of medical foods. It is fairly clear from the new nutrition labeling regulations that FDA will probably reexamine medical foods. But FDA is still stuck with a basic problem; now medical foods are recognized in law. When something exists in law, it's a lot different from something proposed in regulations. It creates a real solid problem for FDA, and I was delighted to hear the Commissioner state recently that he intended to pursue appropriate regulation of medical foods.

RELATED HISTORICAL EVENTS

Despite the lack of regulatory action to define and guide the development of medical foods other than the protection of exemptions, there has been a number of activities that have influenced the development of the concept of medical foods.

In 1977, FDA requested that LSRO/FASEB undertake a review of foods for medical purposes with emphasis on specially formulated products for nutritional management of medical conditions. This report provided a foundation for the 1984 draft regulations prepared by FDA. In 1987, FDA requested that the Committee on Nutrition of the American Academy of Pediatrics prepare a report entitled "Guidelines for the Clinical Evaluation of New Products Used in the Dietary Management of Infants, Children, and Pregnant Women with Metabolic Disorders". This report provided major support for implementation of the infant formula regulations and for the proposed pre-approval process for medical foods.

The FDA introduced the whole idea of the regulation of medical foods at the United Nations level in 1980, specifically by getting it onto the agenda of the Joint FAO/WHO Codex Alimentarius Commission's "Committee on Nutrition and Foods For Special Dietary Uses," (CCNFSDU). In existence for about thirty years with approximately 140 member countries, the Codex establishes regulatory standards and guidelines for food in order to facilitate world trade. A major symposium on medical foods was
sponsored by the Food & Drug Law Institute in 1988, and in 1989 the International Union of Nutritional Sciences (IUNS) sponsored a working group that considered the matter of medical foods in great detail. In 1989 there was a symposium on this matter in the 14th International Congress of Nutrition in Seoul, South Korea.

Two other reviews, conducted for FDA, have been completed by LSRO/FASEB. In 1989, a report, "Evaluation of Incentives for Development of Orphan Medical Foods" was published to comply with the spirit of the Orphan Drug Amendments. In 1990, the report, "Guidelines for the Scientific Review of Enteral Food Products for Special Medical Purposes" was developed to support the FDA's review of approaches to regulation of medical foods.²

Two recent events of regulatory significance are of considerable importance. First, the CCNFSDU at its most recent meeting approved a standard, which we would call a regulation on medical foods, and submitted it to the parent Codex Commission. Second, as anticipated, the Codex Commission gave its final stamp of approval to the standard in July 1991.

This results in an interesting set of events. The U.S. Government as a Codex member, specifically the FDA and USDA, is obligated to take action when a Codex standard is approved. The FDA and USDA can do one of several things. They can propose it as written by going through public rulemaking. They can say that any product that is imported into the U.S. that meets the standard will be permitted entry. But then no regulation is required, just a simple statement that such products, if they are labeled properly and otherwise are in accordance with the standard, can enter this country. The third thing they can do is issue a regulation that takes exception to specific provisions of the Codex standard, with public disclosure of the reasons for disagreement. In the past, the United States has generally adhered closely to the provisions of the international Codex agreements.

While this regulatory history may be quite dry and uninspiring, it is pertinent to the workshop agenda. Its pertinence relates to the evolution of the definition of what is a medical food. Consider the several definitions that have evolved since 1977 as presented in Table 2.

Note that only one definition, the Orphan Drug Amendments of 1988, has legal standing in the U.S., and it differs from the one about to be adopted by the Codex. In the current regulatory

² Note: Subsequent to this meeting, FDA established a Medical Food Task Group in August 1991 to develop a regulatory strategy for medical foods.
Table 2. Definitions of Medical Foods

A. 1977 LSRO/FASEB

"Medical foods are foods that are specially formulat- ed or prepared products consumed or administered enterally under direct or indirect medical supervision in the dietary management of individuals with specific diseases, disorders, or medical conditions in which the existence of associated nutritional requirements is established by medical evaluation."

B. 1984 FDA Proposal

"A medical food is a food or nutrient intended for enteral use in the treatment, prevention, cure or mitigation, primarily by dietary management, of a disease or a disorder or medical condition related to a disease. A medical food may be used only under a physician's supervision. The definition of medical foods does not include infant formulas as defined in section (201)aa of the Act."

C. 1987 Codex Committee on Nutrition and Foods for Special Dietary Uses (prepared by the International Union of Nutritional Sciences)

"Foods for Special Medical Purposes" means a category of foods for special dietary uses which are specially processed or formulated for the dietary management of patients with a specific disease(s), disorder(s) or medical condition(s) (including malnutrition) and which are presented as such. Foods for special medical purposes are distinguished from other foods for special dietary purposes by the requirements that they shall be used under medical supervision."


"The term 'medical foods' 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."
Table 2. Definitions of Medical Foods (Continued)

E. 1988 Codex Committee on Nutrition and Foods for Special Dietary Uses (changes originating from the European Economic Community)

"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 be used only 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 modification of the normal diet alone, by other foods for special dietary uses, or by a combination of the two."

F. 1990 LSRO/FASEB

"Medical foods are a category of foods for special dietary uses, processed or formulated for the management of patients, designed for use under continued medical supervision, and that demonstrate greater suitability for nutritional management of a specific disease than standard enteral formulas. They are intended for use as either the exclusive or supplemental source of nutrition for patients with limited or impaired capacity to ingest, 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 thereof."
climate, medical foods for rare diseases would need to conform to the definition in the Orphan Drug Amendments of 1988.\footnote{Note: FDA has now proposed to promulgate this definition for regulatory purposes; see the Federal Register, Vol. 56, No. 229, November 27, 1991, page 60392.}

One final comment on the plethora of definitions is in order. This may sound trite, but it is extremely complicated in the regulatory environment to get a definition of anything that is clear, concise, acceptable and doesn't move around from week to week. It's no wonder clinicians and industry are confused. My own prejudice is toward the 1987 Codex Committee definition which defines medical foods as foods for special medical purposes. Subsequently developed definitions suggest that most medical foods are for patients who have something the matter with their gastrointestinal tract, whereas in fact, that is usually not the case. It's far better to talk about specific diseases and disorders and conditions including malnutrition, than to imply that there is something the matter with the digestive system in most patients, which is simply not true.

Let me turn briefly to some other historical events of relevance, particularly to the issues surrounding the topic of medical foods for rare diseases and disorders. In 1983, the National Organization for Rare Disorders (NORD) was founded. It has focused its efforts on the absence of insurance coverage for users of medical foods for metabolic disorders; the absence of insurance coverage for products purchased in health food stores (e.g., carnitine); the recognition of more disorders manageable with medical foods; and the absence of medical foods regulations.

Partially because of the efforts of NORD, the National Commission on Orphan Diseases was authorized by the Congress in 1983. The report of the Commission in 1989 has been a major spur to consideration of prevention, treatment, and management of rare diseases at the Federal level. Most recently, as a result of the Commission's report, the Orphan Products Board has been established.

In summary, there is a need for a reasonable regulatory frame of reference for medical foods, including the orphan products. It makes little sense scientifically or legally to have a life support system between foods and drugs that is not regulated at all.

The potential for changes is tempered by the knowledge that any progress is going to be slow and painstaking until such time as the following occur:

(1) Promulgation of a regulatory frame of reference, hopefully not nearly as severe as those applied to infant formulas.
(2) NIH and the private sector put significant resources into the medical foods area for basic and applied medical research and evaluation.

(3) Industry is provided with really substantive incentives for development and marketing.

(4) And, third party payees realize that they are dealing with a life support system, and they pay accordingly.

I wish you all great success in this workshop ....
NEEDS FOR NUTRITIONAL MANAGEMENT
OF
PATIENTS WITH RARE DISEASES

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The experience of physicians caring for patients with inborn errors of metabolism, principally inherited disorders of amino acid metabolism continues to spur the development of new medical foods. In these diseases, degradation of one or more amino acids is impaired because of a single metabolic defect such as the absence of an enzyme. This metabolic error leads to the accumulation of toxic substrates; the toxic substrate may be the amino acid or one of the intermediate substrates in the degradation pathway. The prototype disease of this group is phenylketonuria (PKU), which results from a deficiency of phenylalanine hydroxylase.

Nutritional management of these rare diseases consists of two parts; restriction of foods containing the offending agent and provision of nutritional supplements to support growth and development. Dietary restriction of a specific amino acid requires a drastic reduction of foods containing protein and the use of diet powder and special low-protein prepared foods, e.g., low-protein pastas or breads. Because these diets are often nutritionally incomplete, they are supplemented with sources of carbohydrate, fat, vitamins, and minerals. Such composites or mixtures result in an unpalatable and monotonous diet.

To further demonstrate the need for new approaches to the development of a wider variety of medical foods, I would like to exploit my experience in the nutritional management of inborn errors of metabolism. It should be noted that while the emphasis in this presentation is on disorders of amino acid metabolism, it is not intended to diminish the importance of developing medical foods for other diseases.

PKU is a disease caused by the accumulation of phenylalanine and its by-products. The consequences of high plasma levels of phenylalanine include severe mental retardation. With the introduction of newborn screening and availability of low-phenylalanine diet powder, severe mental retardation in PKU is no longer a problem in treated patients.

It is now estimated that by five years of age, a PKU patient who has been able to maintain plasma phenylalanine levels below 1000 µmol/L (some workers in the field recommend levels <600 µmol/L) will have an IQ well within normal limits. The
importance of maintaining metabolic control was demonstrated by Holtzman et al. (1986) who found that when compared to unaffected siblings, IQ deficits occurred in older PKU children as a function of age of loss of metabolic control. They observed that the highest and lowest correlations between patient and parent IQ were in those on diet at age eight years and those off diet at age six years, respectively.

The maintenance of a low-phenylalanine intake is a simple matter for infants and toddlers because they do not discriminate their dietary wants on the basis of sensory or gustatory characteristics of infant formulas. As these children grow older, compliance becomes a problem because they receive their nutrition from a diet in which the major source of protein is a phenylalanine-free diet powder and must exclude or restrict commonly consumed protein sources. The following is an example of a typical daily menu for a PKU child.

**Breakfast:**
- 8 oz. orange juice
- 1 cup cereal
- banana
- 8 oz. phenylalanine-free formula

**Lunch:**
- 1 cup low-protein noodles
- 1/2 cup spaghetti sauce
- 1/2 cup canned fruit
- 4 oz. phenylalanine-free formula

**Dinner:**
- medium baked potato
- 3/4 cup broccoli
- 1 tbl. margarine
- 1/2 cup canned pears
- 4 oz. phenylalanine-free formula

Although some substitutions of fruits and vegetables and creative preparations of low-protein pastas and bread partially relieve the monotony of this diet, acceptability and compliance remain a medical problem. Non-compliance with diet is a consequence of many factors; however, the diet itself plays an important role in creating a need for new approaches to developing medical foods. One such novel approach is the development of a low-phenylalanine soy protein by Nakhorst et al. (1989).
Other well-characterized inborn errors of metabolism and their dietary requirements include: maple syrup urine disease (MSUD) which requires the limitation of dietary valine, leucine, and isoleucine; propionyl-CoA carboxylase deficiency (PCA) and methylmalonyl-CoA mutase deficiency (MMA), which require limitation of leucine and isoleucine; and four disorders of leucine degradation which require limitations of leucine. All of these disorders could be treated with a branched-chain amino acid-deficient food along with supplemental valine for those with PCA and isoleucine and valine for patients with MMA. But again, these diets lack sensory appeal and variety; thus, compliance is a problem.

Another class of diseases are those in which the problem is not the accumulation of a specific amino acid but rather a failure (or nearly so) to properly excrete nitrogen waste, i.e., dietary nitrogen not used for net protein synthesis. These are the urea cycle disorders (Brusilow and Horwich, 1990) for which recent therapeutic advances have included the use of drugs that activate other pathways of nitrogen excretion that substitute for the defective urea synthetic pathway. To maximize the effectiveness of these new treatments, it is necessary to prescribe an unpalatable low-protein diet; thus, these patients are also particularly good candidates for the development of new dietary approaches and products.

From a clinical perspective, the reward for development of new medical foods is the patient's well being; however, practically speaking, in order to manufacture such products with little prospect for financial reward, incentives must be created for producers. From a regulatory perspective one issue that has confused the picture is the definition of a rare disease.

As defined in the Orphan Drug Act (P.L. 97-414 as amended) (U.S. Congress, 1989), a rare disease is one that "(A) affects fewer than 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)].

The 1988 amendment to the Food Drug and Cosmetic Act (P.L. 100-290)(U.S. Congress, 1988) defines 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)].

The importance of these definitions is seen in terms of incentives given to manufacturers for the development and subsequent marketing of these products. These definitions also impact on the public's perception of the importance of these conditions
which will also affect public and private research funding opportunities.

While it is generally assumed that inborn errors of metabolism such as PKU are rare disorders, a comparison of the incidence of these diseases with diseases pediatricians regularly encounter suggests otherwise. The incidence of PKU, 1 in 12,000, (Scriven et al., 1990) is greater than that of all forms of leukemia of childhood, 1 in 15,000 (Young and Miller, 1975) and not much different from that of insulin dependent diabetes mellitus, 1 in 10,000 (Travis et al., 1987). Similarly, urea cycle disorders occur at a frequency of approximately 1 in 25,000.

The incidences of many other childhood diseases are approached by those of the rarer inborn errors of metabolism. Wilms' tumor occurs in 1 out of 128,000 infants, bone malignancies in 1 out of 78,000 (Young and Miller, 1975), and juvenile rheumatoid arthritis in 1 out of 40,000 infants (Singsen, 1990). All of these more well known diseases occur at a frequency equivalent to the following inborn errors: branched chain alpha-keto acid dehydrogenase deficiency (MSUD), (Danner and Elsas, 1990), propionyl-CoA carboxylase (PCA) deficiency, methylmalonyl-CoA mutase (MMA) deficiency (Rosenberg and Fenton, 1990), and four disorders of leucine metabolism (Sweetman, 1990). Because of their rarity or at least a regulatory and public perception thereof, these diseases await further advances in development of effective nutritional strategies and products.

Another consequence of the current regulatory framework is the cost in time and money of the petition and approval process. Expeditious production and delivery of medically essential foods and drugs to the patients who require them are fundamental objectives of clinical research and development. In the case of medical foods for rare diseases, one possible solution is a peremptory or pre-marketing approval of newly developed medical foods. This approval could come as a result of an evaluation by an inter-agency approval panel composed of experts who are aware of the risks and benefits of these products. Panelists would include representatives from NAS, academia, industry, NIH, and the FDA. Such a procedure could significantly enhance the FDA's ability to approve these products without the enormous expense that the current approval process entails.

A final issue related to the financial burden of these disorders is the cost and payment for the required medical foods. The average cost to feed a four-year old child phenylalanine-free formula is approximately $3,000/year. Additional food costs would include: low-protein pastas @ $5.00/pound (as compared to normal pastas at about $1.00/pound); low-protein breads @ $3.35/pound ($1.50 for regular bread); and low-protein baking mix @ $3.23/pound (compared to $0.30/pound for flour). Notwithstanding the fact that these are prescribed medical foods for potentially catastrophic diseases, third party payers usually do not cover these costs.
The focus of this brief review has been the primary clinical motivation for the development of new medical foods; the enhancement of long-term outcomes of patients with rare diseases through the availability of palatable, varied diets, accessible to patients at a reasonable cost. Additional concerns were expressed about potential regulatory issues that might hinder progress in reaching these objectives. Hopefully, through the discussion of these issues and the interdisciplinary ties created through efforts such as this workshop, the goal of a long and healthy life for these children may be accomplished.

LITERATURE CITED


NEW FOOD TECHNOLOGIES

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INTRODUCTION

There have been several definitions of medical foods reported at this workshop; I would like to offer one more:

Medical foods are designed to provide nutritional support to individuals who are unable to ingest adequate amounts of food in a conventional form or to provide specialized nutritional support to persons who have special physiological, chemical, immunological and/or nutritional needs.

The official definition of a medical food as it appears in the Orphan Drug Amendments of 1988 21 U.S.C. 360ee(b), is "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."

Depending on the patients' needs, medical foods may supplement a diet, be the sole source of nutrition, or control a disease state. A compromised individual who would require medical foods might be characterized by an increased caloric or protein requirement, a decreased ability to absorb nutrients, a lack of mobility, a malfunction of processing organs (liver, intestines), an inborn error of metabolism, such as phenylketonuria (PKU) or maple syrup urine disease (MSUD), or an allergy to certain food constituents.

To the food technologist there is a spectrum of products that may be produced. Liquid parenteral products, which are regulated as drugs, are at one end of the spectrum. These products must supply nutrients in as low a molecular state as possible so that they may readily enter the bloodstream. Because of the route of administration, these products must be sterile and in a liquid form. On the other end of the spectrum are the normal solid foods which contain a full complement of nutrients, generally in higher molecular weights, and probably not suitable for patients with rare diseases. Most of the available foods are either powders that are mixed with water just prior to tube or oral feeding or liquids that are reconstituted from powders and then sterilized for use as either enteral or parenteral nutrient sources.
REGULATORY ISSUES

How and where these specialized foods fit into the existing regulatory framework is a complex and evolving issue. Prior to 1972, medical foods were classified as prescription drugs; however since 1972, they have been classified under section 21 CFR 105.3 of the Food and Drug Act, as special dietary foods. The first product of this kind was Lofenalac developed in 1957 for treatment of PKU. Today, there are over 180 products produced by more than 20 different manufacturers. As with all foods, the FDA currently has the authority to regulate the safety and labeling of medical foods; the latter area includes both content and product health claims.

As far as adulteration, the production of medical foods must follow the guidelines of good manufacturing practices (GMP), and therefore must not contain any poisonous or deleterious substances. Interestingly, if a product contains more than three percent meat, it is technically subject to USDA inspection and regulation. Currently, medical foods on the market that contain meat are treated by the USDA on a case-by-case basis and because of the small volume, are put under FDA jurisdiction.

The GMPs that relate to food manufacturing are very broad and are covered in section 21 CFR 100, which deals with making the product under conditions which are not going to lead to the presence of poisonous or deleterious substances or microorganisms in the final product. Sterile foods are covered under 21 CFR 113 which deals with any foods that are non-acidic (pH >4.6) and includes specific guidelines for how to achieve sterility. Any new sterilization process would have to be approved prior to commercial use, although in the case of medical foods it is possible that if a new specific sterilization process were developed, there might be special regulatory consideration under the current statute.

If one manufactures a product that does not meet the established standards, i.e., GMPs, the FDA can use special procedures called emergency permit regulations that allow for termination of interstate transport of those products. For improperly manufactured infant foods, perhaps the most regulated category of foods covered by the Food, Drug and Cosmetic Act, the FDA has the authority to look at records as well as evaluate the processes involved with the suspected foods. GMPs related to the manufacture of infant foods are covered in 21 CFR 106 and 107.

In addition to the law, there are several compliance policy guidelines for medical foods. These are not regulations but an attempt to get compliance in terms of product labeling and composition. These guidelines have divided medical foods into four categories: nutritionally complete, nutritionally incomplete, formulas for metabolic (genetic) disorders, and oral rehydration solutions. Nutritionally complete foods contain protein or other nitrogen source (caseinate, soy protein), carbohydrate
hydrolyzed corn starch, sugar), and fat (corn and canola oils, and medium chain triglycerides).

MEDICAL FOODS: PRECURSORS TO PRODUCTION

From a management perspective there are several key factors that must be considered before embarking upon the production of a medical food. These might be referred to generically as formulation considerations and would include: the nutritional profile required for the product; the functionality and compatibility of ingredients; the bioavailability and safety of ingredients; the commercial availability of ingredients; the cost of the ingredients and processes; and the regulatory status of the particular item being considered.

There are many problems that may arise if these factors are not carefully considered. For example, the Maillard reaction which occurs between reducing compounds (sugars, aldehydes, and ketones) and amino acids, leads to loss of amino acids and the production of certain hepatotoxins. Another problem is associated with the commercial purity of the ingredients used. Up until recently, the amino acids used in enteral/parenteral formulations were derived from digestion of proteins, a difficult process. However, with the advent of genetic engineering and its application in fermentation processes, commercial quantities of amino acids became more available. Unfortunately, eosinophilia-myalgia syndrome which killed over 50 people, was caused by the ingestion of tryptophan derived from a genetically manipulated organism. This tryptophan, even though crystalline and >99 percent pure, did contain some compound that was etiologically implicated in this disaster. In my view lack of good GMPs in the manufacturing of this product may have contributed to this impurity, suggesting that better GMPs are needed for all ingredients used.

Nutrient stability is another major concern to be considered in the developmental stages of a new food product. For foods that are formulated in a hospital pharmacy for immediate use, nutrient stability is only a concern in the distribution of the ingredients, which if dry is probably minimal. However, for those products that are manufactured as liquids and subsequently transported and stored, product stability may be a major problem that needs to be addressed in the earlier stages of development. In the case of sterilized parenteral solutions, there is a characteristic brown color associated with long-term storage. This pigmentation is not only associated with nutrient instability but may also reduce the bioavailability of essential minerals in the solution.

A related issue to stability is the variability of methods used for analysis. In order to ensure that the ingredients listed on the label are in fact there at the right levels, the product must be subjected to standardized analyses. Work by researchers at the USDA has demonstrated that the coefficient of variation (CV)
for analysis of a given nutrient is a function of the concentra-
tion of the nutrients in the finished product. As the percentage
decreases, the CV increases dramatically. For example, a per-
centage of between 10^{-6} - 10^{-8} for a nutrient results in a 20-30%
CV. Obviously, the FDA will be concerned about this issue, so
that the manufacturer must be able to not only formulate the
product but also be able to ensure that what is on the label is
correct.

The food industry has been responsive to the real and perceived
needs of the consumer with respect to health and nutrition. When
consumer demand has been high, the technology has been available
to meet those needs. Examples of consumer driven products
include foods that are low-salt, low-cholesterol, sugar- or fat-
free. The FDA, as mandated by the Nutrition Labeling and
Education Act of 1990, will be more active in defining the terms
and regulating health claims on food products. From a food
technology perspective there are several broad areas that
may be applied to the development of new medical foods:
separation/combination technologies and biotechnology.

SEPARATION/COMBINATION TECHNOLOGY

Within the broad area of separation there are several basic
tools: physical separation, solvent extraction, and methods for
recombination of separate ingredients into a new form. There has
been very little work done in the area of separation technology
for the removal of the kinds of nutrients that would be required
for the treatment of the inborn errors of metabolism. There are
ample historical precedents for the impact of inadvertent separa-
tion of nutrients during processing. The classic example is the
worldwide problem of beri-beri or thiamine deficiency associated
with the milling of rice. To date, there has not been a concert-
ed effort to use separation technologies to remove single nutri-
ents that might have an adverse effect for persons with rare
diseases. This can be accomplished through the advent of new
methods such as image analysis which can locate specific compo-
nents in foods that could then be isolated and extracted. This
is an area that is currently under investigation.

A new and exciting area related to solvent extraction is called
super-critical CO₂ extraction. In this process, carbon dioxide
(CO₂) is subjected to very high pressure at a temperature range
of between 20-50°C until it crosses a certain point in the tem-
perature-pressure curve to become super-critical. At this point
the CO₂ still has the properties of a gas in terms of its mobili-
ity but also has the solvent properties of a liquid. CO₂ is a
linear molecule that has a dielectric constant of zero, and so it
behaves as a very good non-polar organic solvent. Consequently,
since anything that is non-polar can be dissolved in it, under
proper temperature and pressure this method can be used to sepa-
rate various lipid fractions as well as other non-polar materi-
als. Super-critical CO₂ is now being used for extraction and
production of low-fat or low-cholesterol cheeses and other dairy products. It could also be applied to separate proteins. There is work on using this technique along with liquid chromatography systems for separations that could be done on a bench scale. Obviously, once an analytical procedure is developed on a bench scale there is the potential for application to a larger commercial scale.

Another example where separation/recombination technology may be applicable is in the creation of medium-chain triglycerides. The starting point would be a source of triglycerides that would contain both long- and medium-chain fatty acids. These compounds would then be subjected to saponification in an alkaline solution resulting in free fatty acids. The free fatty acids would then be separated with a high pressure liquid chromatography system that would use super critical CO₂ or some other method. The separated medium-chain fatty acids could then be re-esterified with glycerol to form the desired medium-chain triglycerides that could subsequently be used for a specific medical purpose. Other designer fats could be made in this way. One company is about to petition the FDA for a fat composed of capric, caprylic, and behenic acids that contains only five calories per gram.

Another separation technology that could be useful for the development of medical foods is membrane filtration, a process by which reverse osmosis can be used to separate out electrolytes or different charged species depending on the size of the membrane used. Ultrafiltration membranes are now available on a commercial scale for various molecular weight size separations. This process can be used to separate proteins, sugars, or other larger water-soluble substances. Ultrafiltration is currently being used to remove lactose from milk which helps to eliminate the graininess associated with temperature fluctuations in ice cream during distribution and storage. Ultrafiltration can also eliminate the brown color that occurs during heat sterilization as a consequence of the Maillard reaction.

Obviously, the filtration systems can be only applied to liquid food systems. There are, however, membranes which can be used to separate out microorganisms that often appear. Millipore filtration, which is available at a bench scale in many hospitals can be applied on a commercial scale to help in product sterilization.

With the advent of these new separation technologies, the food industry can now devise and create new ingredients that could be used in medical foods. Examples of such new ingredients would include: ketone bodies for specific gastrointestinal conditions; immunoglobulins separated from cow colostrum for subsequent use for medical conditions; micro-algae derived specific short- and long-chain fatty acids which are then separated from the culture; and an ever growing list of natural low-caloric-density sweeteners obtained from plants (e.g., stevioside from plant leaves).
An important and often overlooked concern with the development of new ingredients derived from foods is that once an ingredient is separated from its parent food for use as a food additive, it no longer is regulated as a food. These separated substances are viewed by the FDA as unapproved food ingredients that require prior approval as an additive or GRAS substance before being marketed. An example of the problems that can arise if this issue is not properly addressed by the food industry is the regulatory controversy associated with Simplesse™. Simplesse™ is a fat substitute composed of microparticulated whey and egg proteins that required an FDA approval before becoming commercially available.

BIOTECHNOLOGY

Biotechnology offers a myriad of possible techniques that could be applied to either the addition or removal of specific factors that could be used in the development of new medical foods. Possible approaches could include the following:

1. Offending nutrients could be removed by manipulation of plant genetics.

2. Genetic engineering could be used to add genes for specific factors in certain plants.

3. Microorganisms can be used to create new and unique proteins such as a low-phenylalanine, modified wheat protein (low or gluten-free) or new peptides that could serve as flavor enhancers.

As noted earlier with products derived from foods, substances that result from biotechnology will also require FDA regulation. Currently, the FDA is ruling on these substances on a case-by-case basis. The exact regulatory mechanism for approval remains to be elucidated. Clearly, the FDA will be involved in a prior approval process. Currently, there is only one biotechnologically derived protein approved for food use, Chymosin™, which is used as an enzyme for the coagulation of milk in the cheese-making process.

Another way in which biotechnology might be used would be in the production of enzymes and enzyme reactors that could be used to create food ingredients. One example of this is the production of cocoa butter from soy bean oil with the aid of microbiologically derived enzymes. Other examples include the inclusion of microbially derived lactase in dairy products to degrade lactose and the plastein reaction for construction of new proteins. The latter process involves the creation of a new protein from amino acids with the use of biotechnological processes. Enzymes can be created and added to packaging material to react with the food in such a way as to produce a product that would be free of an offending substance. Lactase is currently being used in such a
fashion for the marketing of lactose-free foods. These types of technologies await the definition of the situations to which they may be applied.

PRESERVATION TECHNOLOGY: ISSUES IN PRODUCT PACKAGING AND DELIVERY

The form in which a medical food is delivered to the patient is a major area of concern since very few items other than recon-stitutable powders or liquids are available. Realistically, given the rareness of the diseases for which medical foods are needed, it is the small manufacturer who has the flexibility to produce several products that will be most actively involved in this arena. This small manufacturer will need distribution systems that will allow delivery of the products in a stable form throughout the United States and perhaps the world.

There are several types of distribution/preservation systems, including dry stable powders, frozen products, refrigerated products, and sterilized shelf-stable products.

Dry Food Products are simple to produce by spray-, air-, or freeze-drying techniques. The products can be distributed as separate ingredients or blends of different components. If they are packaged in a foil laminate, these products will be protected, and if the moisture content is controlled appropriately, the product will have a relatively long and stable shelf-life. Intermediate-moisture semisolid products, produced by extrusion, could also be made, but the higher moisture would result in greater chemical instability.

Freeze-drying is a method that can be used to produce stable products with long shelf-lives providing temperature considerations are addressed. In addition, air or freeze drying can result in a crisp-hard texturized product that can be eaten in the form of a bar, relieving the monotony of liquid feeding systems.

Frozen foods: this is an area that does not at this point have any obvious applications in medical foods; however, through the design of new medical foods for rare diseases, there is a potential for frozen products in the future. One possibility could utilize a newly developed low-phenylalanine dairy product to produce an ice cream for PKU patients.

Refrigeration: If one of the goals in the development of new nutritional treatments for these rare diseases is to make biotechnologically-derived special vegetables or fruits available to be eaten in the fresh state, then refrigeration techniques will be required to allow a broad distribution of these products. Because cost presents a particular obstacle for the small manufacturers, refrigerated delivery systems will probably have little potential for development in the medical foods area.
STERILIZATION:

- **Canning:** Sterile blended medical foods can be made by simply grinding and blending the ingredients in water, putting them in a can, and then heat-treating. Canning technology was started in 1810 by Nicholas Appert. The mechanics of canning became commonplace long before an understanding of the reactions underlining the process evolved. At its most basic level, sterilization involves the delivery of enough heat at the slowest heating point in the can to deliver at least a 12 log cycle reduction of *Clostridium botulinum*, the spore forming pathogen, at the slowest heating point in the can.

The major technical obstacle associated with canning is that a standard can of food requires heating at a temperature of 220-240° F, for 30-40 minutes or more depending on the container size. Aside from sterilization, this type of heating can result in undesirable changes in the composition and quality of the finished product. One solution to this dilemma is to reduce the amount of time required to achieve the same degree of sterility. In general, as the distance from the outside to the slowest heating point is reduced, the time to deliver the same amount of heat is reduced by the power of two. Thus, if the dimensions are reduced by a factor of two, the amount of time that is required to give a heat kill equivalent to traditional canning sterilization is reduced by a factor of four with subsequently less heat damage to the product. Many parenteral and enteral products now come in narrow dimension plastic containers.

- **Retort pouch:** The U.S. Army Natick Laboratory has been instrumental in introducing the use of the retort pouch in this country. The retort pouch, which is used widely throughout the world, is a flexible multilaminate (one layer is foil) metal-like container with a narrow dimension that allows for the delivery of the same amount of heat kill with significantly less heat than noted above. As with many of the newer technologies in food processing and packaging, the Army has been instrumental in the development of these products. Meals ready to eat, or MREs, have been used successfully by the military for providing foods to troops in the field.

These types of delivery systems can be used to some extent in the medical foods area. Recently, retortable high-oxygen-barrier films have become available without metals, so that the pouch can be heated in a microwave oven, thereby affording ready access at the point of consumption. An additional clinical benefit of the clear plastic container is the ability to view the contents of hanging bottles. While plastic bottles eliminate breakage problems, they also contribute to municipal solid waste.
High-temperature short-term (HTST) sterilization:
In discussing heat sterilization, it should be noted that
the different biological/biochemical reactions have
different sensitivities to temperature change during
heating. Microbiological death increases by a factor of
about 80 times for every 10 degree rise in temperature;
whereas, chemical reactions generally go up by a factor of
2 to 3 times for a 10 degree rise in temperature. In
practice, it can be demonstrated that at high temperatures,
sterilization will take place in a very short time (e.g.,
2-3 seconds at 350° F) without the occurrence of untoward
chemical reactions. This is known as HTST sterilization.
This could mean that vitamin C in solution would not lose
any biological activity and destructive reactions such as
the Maillard reaction discussed earlier would not occur.

Sterile liquid medical food products can be prepared
aseptically by a 2-step process that involves pumping the
liquid through a heat exchanger at 300-400° F to sterilize
it, then into a sterile chamber to be packaged in a
previously sterilized container. Applications of this
aseptic technique currently include the widely available
juice boxes that have been so commercially successful.
These types of boxes are now being used for enteral medical
foods.

Plastic containers: The availability of microwave
technology to the general public has been the driving force
behind the effort of the food industry to develop and
expand the uses of the plastic tray container. This
results in a meal which is shelf-stable at room temperature
and can be heated directly in a microwave. The relevance
of this area to medical foods is not clear at this time;
however, the ability to provide sterile meals in a single
container is attractive. The technology for providing food
in this manner can be adapted on a small scale.

Irradiation: Among the sterilization techniques,
irradiation has been the focus of a considerable amount of
attention and controversy. Irradiation has historically
been used to sterilize drugs, packaging material, and other
items in the dry state. In the case of foods, undesirable
chemical reactions may accompany irradiation, because of
the dose levels needed to sterilized foods. The U.S. Army
Natick Laboratories have demonstrated that these
unpalatable side effects can be circumvented by irradiating
food at liquid nitrogen temperatures. The major obstacles
preventing the implementation of this technology on a
larger scale are related to public perception of the danger
of irradiation and fears about building large-scale
irradiation plants. However, on a small scale, sterile
meals have been supplied to hospitals with isolation units
used for immuno-compromised patients. Some of these
sterile items have also been used in the NASA space
program.
• **Microwave sterilization**: Another process that is being employed in Europe is microwave sterilization. This allows for faster heating throughout the product, while reducing the time of heat transfer, thereby solving the constant dilemma about changes in quality and nutritional value caused by heat-induced chemical reactions.

• **Ohmic heating**: A process not yet approved in the United States, is also used in Europe and involves the passage of a very high voltage current through a liquid-solid medium during aseptic sterilization. An example of this method is the old Presto™ hot dog cooker in which the hot dog was cooked by the passage of an electrical current through two electrodes inside the apparatus. This method could also be used for the manufacture of liquid/particulate mixtures, like soups with very high quality if HTST sterilization is accomplished.

• **High pressure sterilization**: Originally proposed as a sterilization method 30 years ago, high pressure can be an effective method to kill microorganisms on fresh foods. With the advent of biotechnologically-derived medical foods, this method may become a useful adjunct to available sterilization technologies. There have been reports of large-scale units in operation in Japan; however their applications have not been documented.

• **Flashblast**: A recently developed technology that involves the application of high-intensity white light pulsed at an intensity roughly equivalent to that of an atomic bomb. The pulses of light are converted into heat at the surface of the fresh food to sterilize it. This method awaits approval by the FDA.

**FRONTIER TECHNOLOGIES**

Interactive packaging is a concept that would have applications in the refrigerated medical foods area. In order to develop medical food that is natural in form, the product will probably require refrigeration and the application of some method that can extend shelf-life and allow for long distance storage and transport. There are new technologies being developed that use the package itself to control oxygen and consequent spoilage. In Japan, many food packages contain a sachet with iron to scavenge oxygen, thereby increasing shelf-life 2-5 times. Another example is a sachet, inserted into a package of bread, that emits ethanol in amounts sufficient to retard mold growth. This sachet can extend shelf-life of bread from about seven days to more than two months. Other examples of shelf-life extenders are antioxidants emitters.

A frontier that has just begun to receive attention may be referred to as aroma therapy. Many of the flavor houses are
researching the effects of various odor compounds on changing mood and behavior. An obvious clinical application of this type of technology would be in cachectic cancer patients who develop sensory aversions to food. Clearly, the enhancement of our ability to control the sensory characteristics of previously monotonous and unpleasant medical diets would be a boon to those who must feed children with rare metabolic disorders.

Concluding Remarks:

Some final comments are needed about the safety and feasibility of producing new medical foods. Establishment of safety will require extensive pre-market testing. A major question to be addressed concerns the appropriateness of the available animal models. Another issue is the risk assessment model to be used. Finally, the number of products required must be elucidated. If what is needed is a small number, e.g., 50 new cases of a disorder/year, it is going to be a very difficult task to get an industry to make these special foods without incentives.

Clearly, a greater coordination of needs and technological logistics will be required to meet the needs of these special clinical populations. The technology exists and the needs are there. Through the concerted efforts initiated by interactions such as this workshop we will reach our goal of good nutrition for all those who need it.
INTRODUCTION

Over the last forty years the number of enteral nutrition products available for the dietary management of inborn errors of amino acid and carbohydrate metabolism has increased. In most of these disorders an important enzyme defect blocks a metabolic pathway at a specific point. The incidence of any one of these metabolic errors is relatively low; but for those infants who are affected, these diseases pose a serious threat and may require lifetime dietary management. The development of products applicable to these conditions involves decisions on product design and specifications, a cycle of developmental steps, concerns that may arise with individual products, and the testing necessary to allow the commercialization of special formulas.

IDENTIFICATION OF DIETARY NEED

Before the design of any specific product can be initiated, there must be a history of information and clinical research to establish the metabolic cause of the disorder. With the aid of new diagnostic methods, progress has been made in the ability to analyze the patient's medical information. After additional clinical testing, analysis of patients' records, and a review of relevant medical literature and case histories, a metabolic problem can be defined and dietary therapies recommended.

Table 1 lists some of the most common inborn errors of amino acid metabolism together with brief comments on dietary treatment and the desired properties of therapeutic products. Table 2 lists several urea cycle and organic acid disorders, which, although not new to the medical community, are somewhat newer to industrial research and development. Table 3 summarizes some inborn errors of carbohydrate metabolism for which products have been developed.

The malabsorption that accompanies a number of illnesses such as pulmonary, hepatic, and renal disorders is also of interest for possible product development. Other specific conditions that would require nutritional intervention as a result of malabsorption include cystic fibrosis, steatorrhea, and intolerance to intact proteins.
Table 1. Inborn Errors of Amino Acid Metabolism

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>Reduce dietary phenylalanine</td>
</tr>
<tr>
<td></td>
<td>Lower or eliminate phenylalanine in product</td>
</tr>
<tr>
<td>Maple Syrup Urine Disease</td>
<td>Lower dietary branched-chain amino acids</td>
</tr>
<tr>
<td></td>
<td>Remove leucine, isoleucine, and valine from product</td>
</tr>
<tr>
<td>Tyrosinemia, Type I, Type II</td>
<td>Control dietary levels of tyrosine and phenylalanine</td>
</tr>
<tr>
<td></td>
<td>Lower or eliminate these amino acids in product</td>
</tr>
<tr>
<td>Homocystinemia</td>
<td>Achieve normal plasma levels of methionine and cystine</td>
</tr>
<tr>
<td></td>
<td>Lower or remove methionine from product</td>
</tr>
<tr>
<td>Histidinemia</td>
<td>Reduce plasma levels of histidine</td>
</tr>
<tr>
<td></td>
<td>Remove histidine from product</td>
</tr>
<tr>
<td>Hyperlysinemia</td>
<td>Restrict dietary lysine</td>
</tr>
<tr>
<td></td>
<td>Formulate product free of lysine</td>
</tr>
</tbody>
</table>
Table 2. Urea Cycle and Organic Acid Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea cycle disorders</td>
<td>Reduce hyperammonemia without producing protein malnutrition</td>
</tr>
<tr>
<td></td>
<td>Product low in protein, containing mainly mixtures of essential amino acids</td>
</tr>
<tr>
<td>Organic acidemia</td>
<td>Place limitations on protein or essential amino acids in diet</td>
</tr>
<tr>
<td>(ex., Propionic acidemia and</td>
<td>Restrict amounts of isoleucine and methionine, threonine and valine, or leucine</td>
</tr>
<tr>
<td>Isovaleric acidemia)</td>
<td>in product</td>
</tr>
</tbody>
</table>
Table 3. Inborn Errors of Carbohydrate Metabolism

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactosemia</td>
<td>Provide galactose-restricted diets</td>
</tr>
<tr>
<td></td>
<td>Products without lactose or galactose-containing carbohydrates</td>
</tr>
<tr>
<td>Hereditary Fructose Intolerance</td>
<td>Eliminate free fructose and all potential precursors from diet</td>
</tr>
<tr>
<td></td>
<td>Product free of sucrose, sorbitol, and fructose-containing foods</td>
</tr>
<tr>
<td>Glycogen Storage Disease</td>
<td>Products should have recommended levels of carbohydrate</td>
</tr>
</tbody>
</table>
PRODUCT DEVELOPMENT

Product Design: As indicated by the examples in the tables, the focus of product development is on the elimination of a previously identified nutrient. After identification of the specific dietary restriction, a great deal of time is spent defining the product's requirements and formulating production guidelines. Input is supplied by research and development staff, including nutritionists, physicians, clinical researchers, regulatory staff, and food scientists. Outside expertise and scientific input are also essential.

Regulatory issues are another important aspect in product design because many products may be marketed worldwide. A relevant regulatory issue that is considered during product development is product labeling. Among the components of the label is the choice of an optimal caloric distribution for the product. For example, if the product will be used by infants, lipid and carbohydrate sources with levels approximating those in human milk will most likely be desired. The label claims will usually relate to how the product is positioned for the market and will be based on levels in infant formula or use RDA guidelines for children and adults.

The product ingredients have a significant impact on what the final nutrient levels in the product will be. The product label claims should reflect inherent natural levels of a nutrient, such as the level of phosphorus naturally present in soy protein isolate. Adjustments in product formulation may also be needed to obtain the ideal calcium to phosphorus ratio, or the ideal electrolyte balance. The sources finally chosen to provide the major nutrients can also be influenced by the desired product osmolality. A more detailed description of product composition is seen in Table 4.

Generally, for disorders of carbohydrate metabolism, most infant formulas are nutritionally complete whereas the products for amino acid disorders must be complemented with other dietary foods. Several factors may influence micronutrient levels in any given product. Processing can impact on nutrient stability and subsequent product composition. An example would be the vitamin C overage necessitated by heat-sterilization of liquids. Another factor affecting product composition is bioavailability. For example, the zinc and phosphorus levels in soy protein isolate products are increased because of the phytate present in soy protein isolate. Because of analytical variations, a product may be formulated to contain a higher level of a trace nutrient relative to label claim. This increases confidence that the analysis of the product will confirm the minimum required label level.

Formulation Development: Once the product is designed, the staff proceeds to formulate the planned product. Nutrient sources are
Table 4. Product Examples

<table>
<thead>
<tr>
<th>Disease</th>
<th>Product Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>Products may be liquid or powders, are available for infants, children or adults, are composed of protein sources, (either casein hydrolysate or amino acid mixtures) with calories provided by vegetable oil and or carbohydrates and fortified with minerals and vitamins. These products are generally nutritionally incomplete and must be used in conjunction with other foods and/or nutrient sources to provide recommended levels of essential nutrients.</td>
</tr>
<tr>
<td>MSUD</td>
<td>Products are powders for infants and children usually containing amino acid mixtures free of BCAA, minerals, and vitamins. Other calorie sources may be provided. These products are nutritionally incomplete.</td>
</tr>
<tr>
<td>Homocystinemia</td>
<td>Products may be liquid or powders for infants, children, or adults. Protein sources are from soy protein isolates or amino acid mixtures. Calories are provided by vegetable oils and/or carbohydrates. Formulations are fortified to meet daily requirements for vitamins and minerals. These products are also nutritionally incomplete.</td>
</tr>
<tr>
<td>Urea Cycle Disorders</td>
<td>Powders produced for infants and children are mixtures of only essential amino acids fortified with minerals and vitamins. Other caloric sources may be provided.</td>
</tr>
<tr>
<td>Carbohydrate Disorders</td>
<td>Liquids or powders that may be nutritionally complete. In the case of galactosemia, all products are galactose-free. For those with hereditary fructose intolerance, products are free of all potential sources of fructose.</td>
</tr>
</tbody>
</table>
selected for macronutrients and major, trace or ultra-trace minerals. Vitamins are added and optional flavorings, acidulants, stabilizers, and emulsifiers are included depending on product form or positioning. For products with a specified level of a particular amino acid, only protein sources such as soy protein isolate, protein or casein hydrolysates, and purified amino acid mixtures can be used to meet this nutrient restriction. Vegetable oils and fractionated oils can provide lipid. A variety of mono- and disaccharides, glucose polymers, and modified starches can serve as carbohydrate sources.

In addition to nutritional factors, other considerations related to ingredient selection include: commercial availability, process compatibility, regulatory status of components, and economic factors such as product cost.

With respect to product form, a liquid product may require the addition of a stabilizer (carrageenan) or an emulsifier (like lecithin) to enhance stability. Similarly, if the product contains fat and amino acids, a modified food starch may be used for stability purposes. Products are continually tested for composition, and adjustments made when necessary. For example, the levels of a mineral may need to be adjusted to take into account natural variations in a particular source material. Products based on amino acids or protein hydrolysate generally have low scores for sensory acceptance, and sweeteners and flavors might be added to improve acceptance for children or adults. Chemical stability especially in the case of products with free amino acids and reducing sugars is a particular concern addressed by staff food scientists.

The vitamin and mineral levels in products for infants are normally patterned after levels stipulated within the guidelines of the Infant Formula Act. When products are intended for other than infants, RDA's are usually followed in mineral and vitamin fortification. For those products designed to provide all or almost all of an individual's daily nutrient requirements, the RDAs serve as the guidelines for nutritional adequacy.

**Processing and Packaging:** Enteral products for rare diseases are usually processed and packaged in conventional manners. Processing of liquid products usually involves homogenization and sterilization steps; however, most of the products are available only in forms ready to use after reconstitution. Only a limited amount of process technology to improve mixability of powders is used in developing the powder forms. Examples of these processes include: spray drying, dry blending, granulation, and formulation of agglomerated powders.

The packaging choices for these products usually relate to manufacturers experience and capabilities. The packaging selected can add significantly to product costs. Issues affecting the packaging process include: package size (single or multiple serving units); type of package (can, or plastic containers);
technical label copy and claims; and use instructions (usually provided on secondary packaging).

Among the concerns in the latter stages of product development are batch uniformity and shelf life. The desirable shelf life for powders is usually two years, a factor related more to marketing reasons than product stability, as many of these products are manufactured infrequently due to low product volume requirements.

Preclinical and Clinical Studies: For all special dietary formulations, preclinical testing, including determinations of nutrient bioavailability and assessment of protein quality (usually through establishment of protein efficiency ratios), is completed. Although not required by law, many manufacturers mandate that clinical testing, including sensory acceptability, tolerance, and growth studies, clinical effectiveness, and patient evaluation must also be completed before the products are marketed.

Commercialization: An important aspect of commercialization is the installation of quality control procedures to ensure that raw materials meet specifications and that the finished products are in compliance with standards. Before any product is marketed, extensive shelf-life studies to ensure retention of nutrient, chemical, and sensory qualities must be completed. When assessment of this information is complete, the appropriate shelf life is set for the liquid or powder products.

Production manufacturing systems, such as premixes for amino acids, vitamins, and minerals are often used in making these products. In designing a premix, the amount of each nutrient to be added can be calculated on the basis of target levels needed in the final product.

A primary goal of distribution is to provide these special products directly from the company to hospitals, or to the centers which will use them. Some products go through large pharmacies. Once a product is in production, research continues to provide support to improve product qualities if needed.

SUMMARY AND FUTURE OUTLOOK

Currently, industrial research and development supports more than fifty products for the treatment of rare diseases. Furthermore, the food industry accepts all quality control and regulatory responsibilities, provides for continuing research, product improvement and the development of new products, and where possible, integrates applicable new technology. The dietary treatment of inborn errors of metabolism offers a challenging opportunity and responsibility to the medical community and food industry. As science and clinical research progress, and new technologies emerge, new and improved products will be made available for the treatment of infants, children, and adults with rare diseases.
It is apparent that industry does an excellent job of providing the essential desired features, along with the additional nutrient needs, in developing products. Unfortunately, in many cases, it is difficult to justify the cost involved because of the low commercial volume of these products. If incentives and additional resources were available in this area, efforts could be made to: (1) make the products taste better and improve the sensory properties; (2) provide products in alternative food forms, especially for children and adults; (3) attempt to reduce product costs by developing formulas with less costly materials and packages, and finally, (4) adapt available new food technology to this class of products.
REGULATORY REQUIREMENTS FOR MEDICAL FOODS

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Center for Food Safety and Applied Nutrition
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Washington, DC

INTRODUCTION

In the keynote address for this workshop, Dr. Forbes covered the history of development of the concept of medical foods as a regulatory classification. I also want to approach the subject from a quasi-historical perspective; but for my talk, history begins on November 8, 1990 -- when President Bush signed into law the Nutrition Labeling and Education Act of 1990 -- the NLEA (U.S. Congress, 1990). This is the most important food labeling legislation to become law in over 50 years, going back to the passage of the Federal Food, Drug, and Cosmetic Act of 1938. But it also represents a watershed in the development of the concept of medical foods.

Therefore, I would like to give a brief description of what the new Act says, and does not say, about medical foods. Then I would like to briefly discuss some of FDA's tentative interpretations, and plans for implementation, of the requirements imposed on the Agency by the NLEA. And finally, I will mention a few of the issues that the Agency must address, regardless of any specific regulatory scheme that may be adopted.

Medical Foods are mentioned by name in two sections of the NLEA -- 403(q) which deals with nutrition labeling and 403(r) which covers claims, including descriptors such as "low calorie" and the more explicit health claims.

DEFINITION

First, looking at 403(q):

403(q)(5)(A) "Subparagraphs (1), (2), (3), and (4) shall not apply to food ---- (iv) which is a medical food as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b), ...."

Paragraph (5)(A)(iv) has at least two major consequences. First and foremost, it incorporates the definition of medical foods that was adopted in the Orphan Drug Act (U.S. Congress, 1988) into the Federal Food, Drug, and Cosmetic Act:
"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".

This is important for a couple of reasons. First, the concept of medical foods is formally and legally recognized within the context of the primary law governing foods and drugs in this country. This ends the debate about whether there should be a regulatory category designated as medical foods or whether these products should be regulated simply as foods or as drugs. There is now congressional recognition that "medical foods" should exist as a separate regulatory entity. Second, at least from legal and FDA perspectives, this ends, for the time being, the debate about the definition of the term "medical foods". As Dr. Forbes detailed, defining the concept of medical foods has been a difficult and controversial task. Yet, the definition is crucial to the understanding of the universe of products that medical foods should encompass. Now, whether we find this definition to be perfect or not, this is the definition that FDA must use as we approach the regulation of medical foods -- at least until Congress changes the law. Still, the definition is open to some degree of interpretation, which I will discuss later.

INTERPRETATION OF CONGRESSIONAL INTENT

The second consequence of paragraph (5)(A) is accomplished through the cross-references to paragraphs (1), (2), (3), and (4). In this way, NLEA exempts medical foods from nutrition labeling. Clearly, Congress is saying that the nutrition information that will be required to be on the label of conventional foods is not necessarily the nutrition information that should appear on medical foods. But Congress is silent on just what information should be required for medical foods.

Paragraph 403(r)(5)(A) is equally troublesome:

403(r)(5)(A) "This paragraph does not apply to infant formulas subject to section 412(h) and medical foods as defined in section 5(b) of the Orphan Drug Act."

It says, without reservation, that the regulations FDA is instructed to implement to govern label claims do not apply to medical foods.

Thus we have a congressionally-created paradox. Those foods, which one could very convincingly argue should be the most accurate in terms of the nutrition information that they provide and in the claims that they make, are suddenly completely exempt from very strict legislation that applies to all other foods. Because
of these exemptions, there is a possibility that some segments of industry may attempt to position inappropriate products as medical foods. This concerns FDA very much. We are already aware of manufacturers who have at least considered the idea of declaring their products to be medical foods, sending a few brochures to health care professionals, and then claiming exemption, particularly from FDA regulations on claims. This would do nothing but increase current confusion for consumers, for the regulated industry, and for the health insurance industry about coverage for medical foods.

**SOME UNOFFICIAL FDA PERSPECTIVES**

Today I can not give FDA's "official" interpretation of these sections -- that will be established through the notice and comment rulemaking process of the next few years. But we can present some of the Agency's preliminary thinking. We believe that the proper labeling of the nutrient content and purported uses of medical foods, perhaps in a different manner or in more detail than is required for other, more traditional foods, and appropriate directions for use, as well as assurances of the quality of medical food products, are all of vital public health interest. We believe that Congress shares this view and has, in fact, aided the Agency in moving in this direction by formally recognizing medical foods in the law. Therefore, for efficient enforcement of the Act, the Agency intends, as a first step, to adopt the statutory definition by incorporating it and providing clarification of it in our regulations. We hope, in this way, to make the definition and our intentions more understandable and clear.

But how does FDA tentatively interpret the definition of medical foods?

Above all we consider that the statutory definition of medical foods narrowly constrains the types of foods that can be considered to fall within this category. In general, in order to be considered a medical food, a product must, at a minimum, meet the following criteria: the product is a food for oral or tube feeding; the product is labeled for the dietary management of a medical disorder, disease, or condition; and the product is labeled to be used under medical supervision.

The definition makes clear that medical foods are foods that are specifically and specially formulated and processed (as opposed to naturally occurring foodstuffs used in their natural state). They are for the partial or exclusive feeding of a patient who is seriously ill or who requires the product as a major treatment modality. They are fed by means of oral intake or by enteric feeding tube infusion; that is, they provide nutrition via the gastrointestinal tract, by mouth, or through a tube or catheter that delivers nutrients beyond the oral cavity. The term medical foods does not pertain to all foods or nutrients provided to sick patients.
Single ingredient nutrient products that are promoted for use in therapeutic doses for the treatment of specific disease states will continue to be regulated under existing drug law. Being a nutrient is not sufficient, in and of itself, to qualify a product as a medical food. Further, all injectable nutrient formulations will continue to be regulated as drugs. Parenteral nutrients are drugs and not medical foods. Although it might be argued that total parenteral nutrition products are sources of nutrients, just as foods are, and that they require the supervision of a physician for use, the statute specifies the route of administration as a determinant in categorizing some products for regulatory purposes and parenteral nutrients will continue to be regulated exclusively as drugs.

Medical foods are distinguished from foods for special dietary uses or from foods that make health claims by the requirement that medical foods must be used under medical supervision. The intended use of a medical food is for the dietary management of a patient receiving active and ongoing medical supervision (e.g., in a health care facility or as an outpatient), and the medical food is determined by the physician as necessary to overall medical care. The patient is not dismissed from the physician's care and sees him/her on a recurring basis for instructions on the use of the medical food.

Medical foods are not foods that are simply recommended by a physician or other health care professional as part of an overall diet designed to reduce the risk of a disease or medical condition or as weight-loss products. Also, medical foods are not dietary supplements for the general population that can be openly purchased from retail shelves or by mail order, even though they may be recommended by a physician for a specific condition or disease. The intended use and degree of medical oversight for these latter products is not sufficient to qualify them as medical foods, and such products will continue to be regulated as foods for special dietary use.

Medical foods are intended for the dietary management of patients by providing nutrition specifically modified to include as many nutrients as necessary while mitigating adverse signs and symptoms that might result from the provision of some nutrients not ingested, digested, absorbed, or metabolized normally by the patient.

As the law requires, in determining whether products address distinctive nutritional requirements, based on recognized scientific principles, as established by medical evaluation, the agency will review data from clinical trials addressing safety and suitability, review submissions by recognized medical experts and expert panels, and review the literature, as appropriate; through such a review the Agency will determine whether a medical food product is safe and suitable for its intended uses, not adulterated or misbranded within the meaning of the act, and that claims are true and not misleading.
Just because we can state clearly that certain drug products, such as parenteral nutrients, are not medical foods, it does not follow that medical foods cannot have certain properties of drugs. Some objectives or end points for clinical trials of medical foods are the alleviation or amelioration of the clinical manifestations of disease. The concepts of amelioration or alleviation are consistent with the concept of mitigation. The term mitigate is used in the definition of a drug found in the Food, Drug, and Cosmetic Act. Medical foods are a special category of products. Although medical foods do not necessarily cure, they do indeed mitigate the effects of a disease or medical condition and they do have the attributes of both foods and drugs. Traditionally FDA's policy has been to regulate medical foods as a subcategory of foods for special dietary use. However, in light of the existing statutory definition for foods for special dietary use and the definition for medical foods that has been subsequently enacted by Congress, FDA is reevaluating its policy. In creating a regulatory scheme, FDA must carefully consider using both food and drug authorities of the law.

Now that we have talked about FDA's interpretation of the new Act, let us briefly address what FDA is likely to do in the area of medical foods. I think we may have a hint if we look at the Commissioner's recent Food and Drug Law Institute Food Update speech (Anonymous, 1991). On April 24, the Commissioner said:

"Medical foods represent another product type for which the status quo is clearly unsatisfactory. These products are made of food ingredients, but they are labeled for the dietary management of specific diseases and are used under medical supervision. They exist somewhere in that legal gray area between foods and drugs."

"People who depend on medical foods are especially vulnerable. These products, which sustain life, are very much like infant formulas. But like infant formulas, they should be submitted to sound quality control."

"After considerable internal debate, FDA will develop a program to ensure that medical foods are safe and perform their intended function, that they are properly labeled, and that they meet specified standards of quality."

Although this sounds like something that the Center for Food Safety and Applied Nutrition might have written, I can assure you that this statement was inserted into the talk on the Commissioner's own initiative. Clearly medical foods are on the Commissioner's mind. And this is the man who, when the misuse of the term "fresh" was brought to his attention, went out and put the squeeze on the "fresh" orange juice industry. I, for one, believe that when the Commissioner indicates that FDA will develop a program, we can look for that program in the very near future.
The Commissioner mentioned a program covering at least three aspects of medical foods: safety, including quality control, labeling, and effectiveness or suitability. What are some examples of requirements that FDA might look at in each of these areas?

Under safety requirements a basic tenet would be, of course, freedom from microbial and environmental contaminants. However, beyond the general requirements for more traditional foods, we would also want to consider constancy of composition of products and close conformity between nutrient contents and label declarations, because, unlike the more traditional foods these products are used in situations where a more precise knowledge of the contents is particularly important to the physician. We would also insist on some form of final product testing to ensure that compositional errors do not occur. There would, of course, be some form of quality control requirements, which would be appropriate to the type of product and severity of compromised health of patient. Another important consideration is that there must be nutrient stability throughout the storage, reconstitution, hang-time, and shelf-life of the products. Finally, for such critical products, FDA must have ready access to records related to quality control and product testing.

Under potential labeling requirements, there must obviously be some form of extensive nutrient content and compositional information. There should be a prominent statement to "USE UNDER MEDICAL SUPERVISION" and directions for use of the product that are adequate, appropriate, and not misleading. These directions would include the intended claims for the specific disease, disorder, or medical condition for which the product is intended. If nutrients are modified, reduced, deleted or increased, the label must discuss, with rationale, these changes. The labeling or label must provide any information about known contraindications for use or known side effects.

Establishing suitability and effectiveness for medical foods may be the greatest challenge facing FDA. The kinds of information required may very well depend on the type of medical food under consideration and will almost certainly derive from a medical understanding of the dietary management of the disease. The primary goal of using a medical food is to provide an optimum profile of nutrients to meet the metabolic needs of the patient so that malnutrition does not become a cofactor in the disease process. However, recent research efforts are focusing on the effects of nutritional therapies that extend beyond treatment or prevention of deficiencies of dietary components and are looking to nutrients that may elicit biological responses similar to pharmacological agents. As this happens, the boundary between food and drugs becomes less distinct, and definitive conclusions about the efficacy of the medical food become more difficult to establish. However, this is a challenge that not only FDA, but also the academic community and the industry must face. This
workshop is an important step in understanding the development of medical foods and we look forward to the outcome of our deliberations. Thank you.

LITERATURE CITED


INTRODUCTION

The Infant Formula Act (IFA) of 1980 (U.S. Congress, 1980), in conjunction with the amendments of 1986, has made infant formulas the most highly regulated category of food products. Infant formulas are the only product category in all of FDA product jurisdiction with the explicit statutory requirements that manufacturers notify the FDA if they have knowledge of a product being adulterated and/or misbranded and that mandates that recalls be instituted to the retail level if FDA determines a health hazard to exist. Because orphan medical foods are often comparable to the so-called "exempt" category of infant formulas in composition, methods of manufacture and conditions of use, a review of the regulatory requirements for infant formulas is appropriate in considering the regulatory status of orphan medical foods.

The passage of the Infant Formula Act of 1980 (IFA) (U.S. Congress, 1980) was in direct response to an incident which became known in the summer of 1979 involving two brands of infant formula which, for a period of time, contained an inadequate amount of the essential nutrient chloride. This caused a substantial number of infants to develop hypochloremic metabolic alkalosis, a very serious condition with virtually unknown long-term physical and developmental consequences. The subsequent recall of the involved products was less than fully and expeditiously implemented which exacerbated the situation. The 1986 amendments primarily clarified and expanded regulatory requirements in the quality assurance area. A very detailed and interesting chronology of the events surrounding the passage of the IFA and its implementation up to the 1986 amendments appeared in The Food Drug Cosmetic Law Journal (Levin, 1987).

As it exists today, the IFA, which is Section 412 of the Federal Food Drug and Cosmetic Act (the Act), is not a shining example of a precise, orderly, and well-written statutory scheme. In fact, it is the antithesis of all of these in that it contains subsections that have subsections, each with further subsections. The IFA can be best made relevant to this conference by examining its requirements in response to the simple question, "What do I have to do to be on the market?" (Appendix A).
EXEMPT INFANT FORMULAS

The IFA also delineates a table of 29 nutrients which formulas must contain. The table specifies a lower limit for each and an upper limit for those for which safety is a concern. It was a codification of the current recommendations of the Committee on Nutrition (CON) of the American Academy of Pediatrics.

In recognition of the fact that some formulas are for infants with unusual nutritional needs, the IFA establishes a category of formulas to which the table does not apply. This category is defined as:

"any infant formula which is represented and labeled for use by an infant

(A) who has an inborn error of metabolism or a low birth weight, or
(B) who otherwise has an unusual medical or dietary problem" [Section 412(h)]

Since many of the nutrient testing and Good Manufacturing Practice (GMP) (Office of the Federal Register, 1990) requirements specify compliance with the nutrient table, the law also exempts these formulas from such requirements but authorizes the FDA to promulgate separate regulations to cover them. FDA responded by simply promulgating a regulation that requires an exempt formula to meet all these above mentioned requirements unless the manufacturer submits a medical, nutritional, scientific, or technical rationale (including animal and or human studies where appropriate) justifying the exemption.

The Exempt Infant Formula regulations create a two-tier category of products: those generally available at the retail level and those not generally available at the retail level. Most orphan medical foods for infants would be in the second category.

The distinction between these two categories is very minor and pertains mostly to production scale. That is, a product which not marketed at retail will likely be manufactured on equipment not covered by existing GMPs. Thus, manufacturers of these products must devise customized quality control procedures to effectuate the same end as the GMP regulations and submit these to the FDA.

The exempt formula regulation also states that this section does not apply to formulas specifically and individually prepared for one or more specific infants on a physician request. Such products, I believe, are considered to be analogous to a compounded prescription and thus not really commercially available. This section certainly might control some orphan medical food formulas.
Shortly after the passage of the IFA, the FDA notified all manufacturers and requested the submission of a nutritional/medical rationale for those exempt formulas already on the market. The agency provided guidance on what information it was seeking by way of an attachment to the request letter. A copy of the attachment is appended as Appendix B to this paper. To my knowledge, no exempt formulas on the market at that time were removed from distribution as a result of the responses to the FDA request.

As of this date, only one new exempt infant formula has been successfully brought to the market through this regulatory process. The product, a nutritionally complete protein hydrolysate formula, is marketed by Ross Laboratories under the trade name Alimentum™. It is labeled for infants and children with severe food allergies, sensitivity to intact protein, protein malabsorption or fat malabsorption. It is important to recognize that from a regulatory perspective, this product is an exempt infant formula, not a medical food. Appendix C lists the clinical studies submitted to the FDA in this notification. It is included as an example of the qualitative and quantitative nature of studies which were undertaken. There were several meetings with FDA representatives during the course of evaluation of the submission made.

ISSUES FOR THE FUTURE

Although the current regulatory scheme provides a sufficient safety net for the protection of consumer health and well-being, there are areas where current standards of compliance or applicability may be impeding the development and utility of orphan medical foods. I will identify some areas that I see as ripe for review and which, if modified, would remove what is now, or could be, substantial roadblocks.

A. Food Additive Regulations

The marketing of orphan medical foods must be done in compliance with the food additive section of the Act (Section 409). This section is designed to provide the utmost safety of the food supply, and rightly so. Time does not permit explanation of the regulatory mechanisms for the approval by FDA of food additives, nor the intricacies of the current meaning of the well known "Delaney clause", which prohibits additives in foods which have been shown to cause cancer in man or animals. However, I wish to point out an area where the unique characteristics of medical foods, in my opinion, justify a less than literal application of this section and a less than dogmatic adherence to the FDA's Red Book (Food and Drug Administration, 1982) in the conduct of toxicity studies.

Medical foods differ from conventional foods in the following important respects:
1. Medical foods are usually formulated "from scratch."

2. Many ingredients have no utility in the conventional food supply.

3. Medical foods present a legitimate medical benefit/risk situation which must be assessed.

Rare diseases characterized by aberrant nutrient metabolism may call for simple, or perhaps not so simple, analogues of ordinary nutrients. The metabolism of these analogues may provide the nutrient benefit without fueling the metabolic anomaly. This may greatly increase a patient's quality of life or even be life saving itself. Should the time, expense, and regulatory review period associated with extensive, long-term, multi-generational, multi-species carcinogenicity studies like those required for additives that would be ubiquitous in the conventional food supply, be really necessary? I think not and I think that this is an area which will become problematic to FDA as nutritional science advances. Incorporation of consideration of the benefits/risk evaluation into the determination of acceptable animal studies for constituents of medical foods would be beneficial.

B. Mechanism for Conducting Clinical Studies

Because of legal prohibitions against the interstate shipment of unapproved food additives, the FDA utilizes the traditional drug IND mechanism for the conduct of studies. This mechanism provides the reviewing Drug Division and, presumably, the appropriate Food Center scientists, with sufficient details of clinical plans. The already difficult-to-determine food versus drug question for these additives becomes more difficult when the drug scientists apply traditional drug standards to the question of formulation changes, bioavailability requirements, and the like. Are these the appropriate standards to apply to these products? Will unanswered IND questions/issues come back to haunt the sponsor or Food Center scientists? I don't know the answers, but I suggest a Food Center regulatory mechanism comparable to but separate from the IND mechanism would simplify these often very unproductive issues. In so doing, commercial developers of these products would be far more likely to initiate studies rather than being intimidated by the bureaucracy and uncertainties of apparent drug requirements. Research oriented companies are reluctant to pursue projects with business/regulatory uncertainties over and above the unknowns of scientific research and take little solace in the often repeated statement, "It's unclear, but we can probably work this out."

C. Who Pays?

Like most health care issues of today, cost and who pays it, are issues driving many activities, or probably more precisely, lack
of activity in the medical food and orphan medical food areas. Medical foods are not drugs and should not be required to be developed as though they are. Payers use this fact as a mechanism to avoid payment. Like all good rules, the one that says we will only reimburse for FDA-approved drugs, should have legitimate exceptions if the facts and benefit to the patient so warrant. If the conditions under which a legitimate medical food would be reimbursed were established and known, industry could appropriately evaluate alternative potential medical food products and be confident that accepting the financial risk of research will indeed grant a reasonable return on investment. In the case of orphan medical foods, this would allow an accurate forecast of actual financial loss in the majority of situations where there is no financial return to manufacturers.

LITERATURE CITED

Food and Drug Administration. 1982. Toxicological principles for the safety assessment of direct food additives and color additives used in food. Available from: Food and Drug Administration, Washington, DC.


I. Premarket Registration and Notification

A. Manufacturers are required to register the name and address of the manufacturing facility.

B. At least 90 days prior to the marketing of a "new" infant formula, a manufacturer must notify the FDA by a submission containing the following information:
   1. Quantitative formulation
   2. Description of change if the product is "new" by reason of reformulation or processing change
   3. Assurance of compliance with any applicable quality factor regulation and batch testing requirements
   4. Assurance regarding good manufacturing practice (GMP) compliance

C. After processing, but prior to distribution of a "new" infant formula, manufacturers must submit a summary verification of nutrient contents and compliance with GMP regulations.

D. For formulation and or processing changes not defined as "new" which the manufacturer determines "...may affect whether the formula is adulterated under subsection (a) ..." must submit notification information in B. above before the change is implemented.

II. Manufacturing Regulations

A. GMP regulations must be promulgated and cover the following:
   1. Analytical verification of all 29 required nutrients in every batch.
      a. Vitamins A, E, B₁, and C at the "finished product" stage.
      b. All individually added nutrients and the premix "indicator nutrient" at some time during manufacture.
      c. All relied upon nutrients in a nutrient premix prior to use in manufacture.
   2. Testing to verify nutritional adequacy over shelf life period.
   3. In-process controls designed to prevent adulteration of each batch.
   4. Regularly scheduled compliance audits.

B. Requirements for retention of the following records for one year beyond shelf life. These must be provided to FDA investigators upon request when they inspect the plants:
   1. Documentation of GMP compliance

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1 "new" also includes a reformulated or processing change of an existing product where experience or theory would predict a possible significant adverse impact on levels of nutrients or availability of nutrients.
2. Certificates of analysis by premix suppliers (suppliers must also keep records to confirm accuracy of certificates).

3. Microbiological records for ingredients used in powdered formulas.

4. Records showing compliance of packaging material to food additive requirements.

5. Results of quality assurance audits (only a written assurance of conducting the audit must be provided to FDA).

6. Complaints and records of complaint investigation of those "...which may reveal the possible existence of a hazard to health."

III. Postmarketing Obligations

A. Promptly notify FDA if manufacturer "... has knowledge which reasonably supports the conclusion ..." that product fails to meet nutrient table or is otherwise adulterated or misbranded.

B. Immediately recall to the retail level any lot which FDA determines presents a risk to human health.

C. Ask retailers to post a recall notice at the point of purchase if the product presents a risk to health.

IV. Miscellaneous

The IFA directs the FDA to promulgate regulations to establish requirements for "quality factors" for infant formulas, including quality factor requirements for required nutrients.
APPENDIX B. 1982 FDA GUIDELINES\(^1\) FOR INFORMATION ON CURRENTLY MARKETING EXEMPT INFANT FORMULAS

Format for Submission of Safety and Suitability Information

In order to assist FDA personnel and thereby expedite the review and evaluation of your data, we suggest that you submit information in the following format:

1. A description of the proposed purpose of the product, including the proposed text of the labeling.

2. Annotations to the information in the summary and technical sections of the submission that support the inclusion of each labeling claim.

3. An in–depth discussion of the scientific and medical rationale for the product, including the following:
   
a. A summary of scientific reasoning for the development of the product for its intended use, with citation of appropriate references.

   b. Potential clinical benefits resulting from the use of this product, including supporting information that may be available from standard clinical textbooks or other recognized authorities.

   c. A supporting bibliography, with inclusion of full reports of key references. Please provide complete English translations of reports derived from foreign language journals.

4. Information on safety and suitability based on a history of use of the product, including any reports of adverse reactions or product contamination. Where appropriate this should also include a list of the countries in which the product has been used and the length of time available on the market. Additionally, you should include a discussion of the manner in which these adverse experiences (safety or suitability) were monitored and the results of such monitoring.

5. The safety and bioavailability of nutrients as documented by animal and/or human studies demonstrating normal growth and development and freedom from adverse effects (when the product is appropriately modified, if necessary, to provide a complete diet). Complete copy of reports (in English) should be provided.

6. Clinical data, including a description and analysis of each clinical study, a statement of the hypothesis being tested, a detailed protocol, means used to evaluate the study, assessment of statistical power relative to the hypothesis tested (if appropriate), and a summary of the results. Complete copy of reports (in English) should be provided. Information on the study locales and a description of any credentials supporting the qualifications of clinical centers and investigators should be provided.

7. A "Conclusions" section summarizing the safety and efficacy information. This section should present the investigator's summary of the data which demonstrate substantial evidence for effectiveness of the product for its intended purpose, a discussion of any proposed additional studies, and a description of postmarketing surveillance planned. Discussion of reviews by

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\(^1\) Unpublished attachment to an FDA request to manufacturers (shortly after passage of the Infant Formula Act of 1980) for submission of a nutritional/medical rationale for those exempt infant formulas already on the market.
APPENDIX C. STUDIES SUBMITTED ON BEHALF OF THE EXEMPT INFANT FORMULA ALIMENTUM™, A PROTEIN HYDROLYSATE FORMULA WITH IRON, TO QUALIFY AS AN EXEMPT INFANT FORMULA

I. Nutritional Studies
   A. Short-term feeding study of acceptance and tolerance
   B. Growth and development in normal full-term infants
   C. Metabolic balance study

II. Clinical Studies (Suitability vs Efficacy)
   A. Double blind, placebo-controlled oral challenge in documented cow's milk and other food allergic patients
   B. Specific patient populations
      1. Protein induced colitis
      2. Food protein intolerance
      3. Malnutrition/malabsorption

III. Other Studies
   A. In vitro studies documenting the molecular weight profile of protein components of a number of products
   B. Animal study. Measurement of serum protein antibody levels in hyperimmunized white rabbits by sensitive ELISA methods
Expert Panels relative to product or formulation in use should be included at this point. Concerns associated with inappropriate use (if applicable) should be summarized in this section.
RECOMMENDATIONS FROM THE WORKSHOP ON DEVELOPMENT OF MEDICAL FOODS FOR RARE DISEASES

The following compilation of recommendations to the workshop sponsors and other concerned agencies and parties resulted from the deliberations of the four breakout discussion groups and the open discussion of the assembled workshop participants.

I. CLARIFICATION OF REGULATORY ISSUES - An overriding theme was the lack of clarity in the regulations.

A. **Endorse** the concept of a third category of orphan medical foods which may be part of a larger group of medical foods. This category would have regulatory requirements less stringent than current drug or food additive regulations and more stringent than current food regulations.

B. **Create** a permanent expert advisory council to provide advice on establishment of uniform standards and safety of orphan medical foods. Initial attention should be directed to products designed for the treatment of inborn errors of metabolism. This council should include members from academia, industry, FDA, NIH, clinicians, and advocacy groups such as NORD.

Five years after introduction, a product should be re-evaluated. The advisory council would make recommendations for continuing approval or for extension or withdrawal of the product.

C. ** Expedite** approval of orphan medical foods developed by non-approved technologies by means of the expert advisory council.

D. **Establish** uniform international regulations of medical foods for rare diseases.

E. **Clarify** and **recognize** current existing regulations pertaining to medical foods, including regulation of food additives, the law as it relates to Good Manufacturing Practices (GMP), and the relevance of the Infant Formula Act.

F. **Model** any new regulatory scheme related to orphan medical foods after the Humanitarian Device Exemption of the 1990 Safe Medical Devices Act. For example, in such a model, orphan medical foods should be exempt from pre-marketing approval requirements except:
1. With regard to the application of Good Manufacturing Practices (GMP) which should be expanded to include compositional standards and analytical procedures related to product claims;

2. Safety requirements, including a redefinition of adulteration to take into account those substances that enhance efficacy of the product;

3. Efficacy studies which should be based on:
   a. Product's ability to sustain life;
   b. Product's role in sustaining growth in children and maintenance of adults;
   c. Identification of biochemical markers related to the specific medical conditions for which the product is intended; and,
   d. The product's efficacy should also be based on its ability to maintain normal parameters of biochemical and nutritional status in children and adults with a rare disease.

G. Recommend that an appeals process be created to exempt certain compounds that have been shown to be efficacious in the management of orphan disease from regulation as food additives and from the IND/NDA process.

H. Exempt infant formulas for rare diseases from the Infant Formula Act and regulate them as orphan medical foods.

I. Encourage the Health Care and Finance Administration (HCFA) to establish a "standard of care" which includes reimbursement for medical foods.

II. SUGGESTIONS ABOUT INCENTIVES FOR RESEARCH AND DEVELOPMENT

A. Facilitate and expedite the development of new products and/or alternative forms of present products by:

1. Creation of closer ties between academia and industry in order to identify needs and facilitate development. Suggested models for such a relationship included the Pharmaceutical Manufacturers Association Commission on drugs for rare diseases.

2. Utilization of pre-existing organizations such as the Enteral Foods Council or Infant Formula Council as clearinghouses for information about product development.
B. **Establish** tax credits for 100% of development costs for sponsors of orphan medical foods, with provision for banking unused tax credits in cases where the sponsor has insufficient current tax liability. This should include the cost of clinical studies such as those required especially for the infant products.

C. **Guarantee** sponsors developing products that they will not lose money on marketed products by:

2. Mandated reimbursement from insurance industry. Reimbursement for medical foods is appropriate when not providing these foods would likely be life-threatening or debilitating in the near term. The insurance industry should be represented when considering this issue.
3. Exemption from rebates to state Medicaid programs.
4. Direct payment from the states.

D. **Reduce** development costs through regulatory means by creation of "research for the benefit of the patient" which would fall under the section of the Food, Drug, and Cosmetic Act 409(i), and serve as a pre-IND for a medical food that would essentially take the development out of the drug side and put it in the food side of the Act. There is approval for testing new foods under the Act, but the FDA has not created regulations to implement this provision, 409(i).

E. **Increase** activity by advocacy groups in the generation of private foundation-type support for research and development.

F. **Identify** other sources of governmental funding, e.g., NIH small business or training grants, USDA/HATCH funds for use at land grant universities.

G. **Support** orphan product research and development by a prorated fee based on industrial sales by food companies.

H. **Increase** payments for medical foods through state agencies and programs involved in screening and treatment of rare diseases.

I. **Create** an Interdisciplinary Committee composed of governmental, academic/clinical, and industrial experts to review and assess needs and strategies for development and evaluation of medical foods for rare diseases. This could be designed to fit into the FDA structure,
or outside the FDA, but should be charged to open channels of communication and facilitate the regulatory process.

J. Protect industry from loss of alternative opportunity which occurs when limited resources that might be applied to the development of a profitable product are used for development of a product with a limited market.

K. Create centralized testing and distribution centers with collective clinical expertise to help lower costs.

L. Encourage creation of a research institute for medical foods funded by industry, foundations, and the government; designed to address concepts of formulation, processing and packaging, sensory quality, storage stability, analytical needs, regulatory matters, cost and clinical testing issues. Such an institution would be especially useful in those cases of foods that would be unlikely to be developed by individual firms.

III. ROLE OF TECHNOLOGY

A. Continue development of alternate food forms. Examples include surimi prepared with synthetic protein or sources other than fish; snack foods such as granola and candy bars prepared with constituents selected for low phenylalanine, alternate sources of carbohydrate, etc.

B. Explore the use of lyophilization/compression processes for alternate food forms.

C. Re-examine the range of rare diseases in terms of prevalence and potential for nutritional intervention with novel foodstuffs. Utilize biotechnological approaches to develop such foodstuffs. For example, can high-lysine corn be genetically engineered to have proteins with altered amino acid composition?

D. Explore opportunities to develop new nutritional approaches to treatment of rare diseases through investigation of novel food sources, for example:

1. Use algal and fungal proteins;
2. Use biotechnology to produce designed neopeptides;
3. Emulate techniques used to produce sucrose and corn syrup; and,
4. Modify existing protein sources (legumes, beans, chicken, etc.) to include factors needed for human growth and development; that is, incorporation of specific genes for immunoglobulins, growth hormones, enzymes, etc.

E. **Address** enhancement of flavor and sensory perception using new technologies for encapsulation of bitter and off-flavor components. **Explore** the use of the plastein reaction and the synthesis of new dipeptides.

F. **Apply** new packaging technologies to extend shelf life and maintain nutritional composition and form by utilizing technologies to remove deleterious substances or unwanted components.

G. **Use** biotechnology to create proteins by selecting needed combinations of amino acids that have acceptable taste and sensory characteristics.

IV. OTHER RECOMMENDATIONS

A. **Re-examine** and **refine** the definition for rare diseases in terms of prevalence figures arrived at through consultation with experts in the field. The current criterion of diseases or conditions affecting less than 200,000 persons is probably too high. One suggestion was that the value should be expressed as new incidences per year per 100,000 population.

B. **Standardize** labeling utilizing 100 grams of the dry product as the portion size unit of measure.

C. **Create** a centralized distribution center staffed by clinicians and other health care providers. The center should have the capacity to distribute directly or indirectly (through a pharmacist) to patients and families. The available inventory should include medical foods for rare diseases and commonly recognized foods specifically used for these disorders, e.g., low-protein pastas, cheeses, bread, flour, and ice cream. An additional service should be distribution of educational materials.
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