

IEM Digest

The enigma of medical foods

The explosion in genetic knowledge and new technologies has the potential to make newborn screening universal and to expand the number of disorders screened for regardless of ability to pay [1]. Newborn screening systems represent a predictive and preventative model of health care that has evolved in step with advances in science to identify individuals at risk for various genetic disorders and to provide various interventions before symptoms appear.

Lifelong support for many of the genetic metabolic disorders consists of nutrition interventions that involve dietary modifications and the use of synthetic diets (medical foods), which provide the majority of needed nutrients. Commercially available medical foods are therefore indispensable, hence medically necessary, for treatment of these disorders. Although most dietitians and clinical geneticists recognize the need for medical foods and use them regularly, regulation of the nutrient contents of these products and reimbursement of their cost by insurance companies have received little attention. Despite an anticipated rise in the use of medical foods to treat inborn errors of metabolism (IEMs), there is still uncertainty about regulation of the nutrient content of these foods and reimbursement for them. The key issues, both present and future, pertaining to medical foods are summarized here as they relate to IEMs.

Regulatory history of medical foods

Prior to 1972 medical foods were classified as prescription drugs by the Food and Drug Administration (FDA) to ensure that a physician supervised their use [2,3]. This required manufacturers to complete drug trials and apply for an Investigational New Drug license to market new products, an expensive and time-consuming procedure. Medical foods were next reclassified as Special Dietary Foods in 1972, with an eye toward relaxing labeling requirements to facilitate further research and development [2,3]. These products were often referred to as ‘orphan,’ since they are developed for rare disorders that affect fewer than 200,000 persons in the United States [4]. The legal definition of a medical food was added to the Orphan Drug Amendments of 1988: “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” [2,3]. These products were classified as medical foods (but are still referred to inconsistently as formulas, metabolic medical foods, protein substitutes, etc. instead of medical foods) because of their placement between conventional foods and drugs. To expand the manufacturing market for medical foods and to promote their development, the FAO/WHO Codex Commission approved international standards for foods for special medical dietary uses in 1991 [3]. Agreement on a definition for medical foods by an international committee could facilitate global harmonization, thereby creating a larger market to promote production [4]. In 1996 the FDA solicited comments on the regulation of medical foods to ensure the safety and adequate labeling of these products [2,3,5]. This represented an effort to distinguish, at a physiological level, between the two classes of enteral products: medical foods, which meet complete nutrient requirements while providing for specific nutritional needs associated with the disease, and foods for special “dietary” use, which provide routine (ordinary) nutritional content with altered forms of liquid supplements [5]. Furthermore, issues related to measuring the nutritional efficacy of these products were raised at this time. Since 1996, no further actions have been taken. See Table 1 for a regulatory history timeline.

Medical foods and nutrition management

Nutrition management of these rare genetic diseases typically consists of restricting natural (intact) protein, which can lead to nutritionally incomplete diets. When medical foods are used as the major nutrient source, they not only limit the intact protein but also provide specialized amino acids, carbohydrates, fats, vitamins, minerals, and conditionally essential nutrients for optimal growth and development. Furthermore, it is now recognized that these restrictive diets require lifelong compliance; yet despite efforts by companies manufacturing these medical foods to introduce variety, convenience, and better flavors, non-compliance remains an issue. It is estimated that there are over 200 metabolic medical foods produced by more than 20 manufacturers. Medical foods are now available in different categories, including nutritionally complete and nutritionally incomplete, as well as in different forms,

Table 1
Medical foods: Timeline of regulatory history

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| 1938 | U.S. Food, Drug, and Cosmetic Act defined medical foods as prescription drugs to ensure that a physician would oversee their use. This required an Investigational New Drug license for manufacturers to market new products |
| 1941 | Food and Drug Administration (FDA) defined “special dietary uses” for foods |
| 1957 | Lofenalac, the first medical food for phenylketonuria, was approved for use in infants |
| 1972 | The FDA reclassified medical foods as Special Dietary Foods and defined medical foods as “foods represented for use solely under medical supervision to meet nutritional requirements in specific medical conditions.” Labeling requirements were relaxed to foster research and development |
| 1973 | Nutrition labeling made mandatory, with the exception of foods for Special Dietary Use |
| 1976 | Statutory of “special dietary use” added to the Food, Drug, and Cosmetic Act by the FDA |
| 1988 | Orphan Drug Act amended to legally include the definition of medical food (law) |
| 1990 | Nutrition Labeling and Education Act amended to include the definition of medical food and to exempt medical foods from labeling, health claims, and nutrient content claims required by the Act |
| 1991 | FAO/WHO Codex Commission approved international standards for special dietary foods |
| 1996 | FDA solicits comments on regulation of products marketed as medical foods |

such as sachets, ready-to-feed, capsules, bars, etc. These differences reflect variability in nutrient profiles, bioavailability, nutrient stability, and cost [6]. This picture is further complicated by the fact that some IEMs do not require complete medical foods, and nutrient intervention for these disorders involves a modular approach not previously used, including supplementation with single nutrients, such as carnitine, leucine, isoleucine, and co-enzyme Q, at doses much higher than recommended by the RDA (for amino acids). This category of nutritional, currently referred to as nutraceuticals, merits further attention. Nutraceuticals are juxtaposed between medical foods and drugs; they are required for the treatment of IEMs, but do not provide total nutrition support. Medical foods are the major source of nutrition for patients with metabolic disorders, yet the paradox is that regulatory guidelines require compliance with good manufacturing practices (GMPs) and the adulteration and misbranding sections of the Food, Drug, and Cosmetic Act only. Medical foods are unique in that they cannot be classified as either conventional foods or prescription drugs, thereby requiring the creation of a distinct class of special foods that meet the unique nutrient needs of individuals with an IEM. Clinical trials for nutritional efficacy are only required for products used by infants under one year of age. The nutrient needs of patients with an IEM who are older than one year are not addressed by the FDA.

Reimbursement and health care system issues

Medical foods are a necessity for the management of many genetic disorders identified through the public health-based newborn screening systems. The financial burden of these disorders on families for the required medical foods can be large. The average annual cost to patients with various metabolic disorders can vary and is approximately \$7000/year based on our annual clinic data. In the United States, payment for these medical foods varies across states. Some states may pay for medical foods through programs such as Newborn Screening, Genetic

Services, Children with Special Health Care Needs, Medicaid, and Women, Infants, and Children (WIC), all of which receive support from various federal agencies, including the Health Resources and Services Administration, the Centers for Medicare and Medicaid Services, and the Food and Nutrition Service [7]. Eligibility for assistance is usually income-based. Most of the obstacles to obtaining medical foods are faced by the underinsured, families who carry private insurance but for whom third-party payers may not recognize the need for specialized care, and families whose insurance plans require large co-payments. Despite the fact that legislatures in more than 30 states have established statutes requiring private insurers to treat prescribed medical foods similar to prescription drugs, families continue to face barriers to reimbursement. This is because the provisions are heterogeneous and vary by treatments covered, amount, and period of coverage. Annual caps for reimbursement can average from \$1500 to \$25,000, depending on family income, and may be applicable to medical foods [7].

Reimbursement for adults varies even more widely and also differs by state. The most common age limits are either 18 or 21 years. State plans that fail to cover adults, providing coverage only upon proof of a pregnancy [8], have a detrimental effect. It has been demonstrated clearly in women with PKU that the risk of the fetus being affected by maternal phenylketonuria (MPKU) syndrome is greatly reduced when women have blood phenylalanine concentrations under control prior to conception [9]. High plasma concentrations of phenylalanine during pregnancy have an effect similar to fetal alcohol exposure. Therefore, a policy that provides medical food to pregnant women via the WIC program for patients with PKU and other genetic metabolic disorders needs to be considered in order to provide full support for medical foods throughout life, including preconception. Clinicians working with PKU patient populations have expressed their support of reimbursement for medical foods throughout life via a policy statement by the American Academy of Pediatrics (AAP) issued in

2001 (www.aap.org), the Society for Inherited Metabolic Disorders in 2007 (www.simd.org), and Genetic Metabolic Dietitians International in 2007 (www.gmdi.org).

Conclusion

The logic behind FDA exemptions from the nutrient and labeling requirements for medical foods was to encourage the development of new products in an assortment of forms and flavors. To ensure compliance with these lifelong synthetic diets and thus to improve outcomes, such variety is essential. However, if due attention is not paid to guaranteeing the age-appropriate nutrient adequacy of these products, their anticipated health benefits may well never manifest. Furthermore, the lack of ready product availability due to financial barriers also hinders the treatment and arrest of diseases diagnosed through public health programs. Ultimately, nutritional studies are urgently required to gauge the efficacy of medical foods for maintaining normal biochemical status. Data from such studies could be used as the basis for developing nutrient recommendations for this patient population and for labeling the medical foods they take. Efforts to provide immediate access to appropriate nutritionally adequate medical foods can significantly improve long-term outcomes in patients diagnosed through newborn screening.

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