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Medical Foods: Products for the Management of Chronic Diseases

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Medical foods are a specific category of therapeutic agents created under the Orphan Drug Act of 1988, which separated medical foods from drugs for regulatory purposes. Products in this category share the requirements that they are intended for the nutritional management of a specific disease, are used under the guidance of a physician, and contain ingredients that are generally recognized as safe (GRAS). An example of medical foods are formulations intended to manage patients with inborn errors in amino acid metabolism. Newer medical foods are designed to manage hyperhomocysteinemia, pancreatic exocrine insufficiency, inflammatory conditions, cancer cachexia, and other diseases.

Key words: dietary supplements, generally recognized as safe (GRAS), medical foods, nutritional management

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INTRODUCTION

Humans have sought and used botanical sources for therapeutic purposes for thousands of years. The successful products, usually found by trial and error, may be normal, unaltered food sources (e.g., flavonoids from tea or bee propolis) or may have to be extracted by some means, usually boiling (e.g., salicylic acid from willow bark), but all withstand the test of time for therapeutic effectiveness. Medical foods are a special category of nutritional products, containing ingredients that are generally recognized as safe (GRAS), and they reside in a regulatory area between dietary supplements and prescription drugs.

HISTORY OF MEDICAL FOODS AND THEIR REGULATION

The regulation of medical foods and dietary supplements has been reviewed previously.[1] Since 1941, foods for "special dietary uses" were defined in the Federal Register.[2] Prior to 1972, the Food and Drug Administration (FDA) regulated these and other medical foods as drugs under section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act, 21U.S.C.321(g)(1)(B). In an attempt to promote product innovation, and because medical foods were generally used under close physician supervision, the FDA reclassified them as "foods for special dietary use" in 1972.[3] In 1988, amendments to the Orphan Drug Act were passed by the US Congress that provided the formal legal definition of a medical food given above.[4] In 1990, the FDA published the final amendments to the Nutrition and Labeling Act of 1990[5] and incorporated the statutory medical food definition into Section 403(q)(5)(A)(iv) of the Act, 21U.S.C.343(q)(5)(A)(iv).[5] The FDA published several final rules regarding nutrition labeling requirements and also incorporated the statutory definition of a medical food into other regulations in 1993 at Section 101.9(j)(8).[6] This regulation stated that a medical food can be exempt from nutrition labeling,[7] nutrient content claims, and health claims rules if it meets all of the following requirements[8]:

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

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2) "It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone";
3) "It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition as determined by medical evaluation";
4) "It is intended to be used under a medical physician's supervision"; and
5) "It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food."

All efficacy claims for medical foods must be based on recognized scientific principles and sound laboratory and clinical data.[4] Medical foods must be comprised of components designated as GRAS. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition and agreement on that safety by experts in the field. Many ingredients have been determined by the FDA to be GRAS, and are listed as such by regulation in Volume 21 CFR Section 582. Other ingredients may achieve self-affirmed GRAS status via a panel of experts who co-author a GRAS Report. Finally, a few ingredients have been specifically permitted by FDA as medical food ingredients, e.g., folic acid in Volume 21 CFR Section 172.345(f). In addition to the GRAS standard for medical foods, the FDA initiated a compliance program in 1988 to ensure the safety of all products being released as medical foods.[6,9,10] This oversight requires that all medical foods be manufactured under food Current Good Manufacturing Practice (CGMP) regulations. In fact, most medical foods are manufactured by pharmaceutical companies and therefore comply with prescription drug CGMP.

Physicians are sometimes unaware that some of the products they regularly prescribe are actually classified as medical foods and not drugs. In an environment of heightened product safety awareness, medical foods are now gaining in clinical prominence and acceptance as a potentially safer way to manage the metabolic processes underlying many chronic disease states.

CHARACTERISTICS OF MEDICAL FOODS

By definition, a medical food must meet a specific nutritional need of a particular disease or condition. These distinct nutritional requirements "should be based on recognized scientific principles and established by medical evaluation."[4] Under the rules of the Orphan Drug Act, there are numerous ways that a "distinctive nutritional requirement" can be defined or interpreted.[8] The prevailing interpretation recognizes that these products may contain specific nutrients or natural products that would allow the patient to return to a metabolic or physiological homeostasis that was in disequilibrium due to disease. This is a reasoned stance, since the nutrient requirements and metabolism in a disease state are usually quite different from those of healthy individuals. Other interpretations of distinctive nutritional requirements refer to people who have "impaired capacities to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients contained therein, or (who) have other special medically determined nutritional requirements."[11] Therefore, if in the judgment of medical experts, a product contains GRAS food ingredients that offer therapeutic value(s) by correcting a metabolic imbalance or restoring homeostasis to a metabolic process involved in a disease state, then the dietary need requirement should be met.

Medical foods must be used under the ongoing supervision of a licensed physician for the dietary or nutritional management of a patient with a disease whose pathogenesis involves unique nutritional (i.e., metabolic) requirements. Therefore, medical foods are meant to be an integral part of an overall disease management plan rather than a disease risk reduction strategy, and a licensed physician is the only practitioner who can adequately monitor and regulate their use. The statutory definition does not allow for naturopathic or chiropractic physicians to supervise the administration of medical foods. Consistent with this intent, many state laws explicitly state that medical foods must be prescribed by a licensed medical physician. In cases of chronic metabolic conditions where a registered dietitian is involved in patient care, such as is often the case with diabetes mellitus, he or she may initiate the use of a medical food under a licensed physician's supervision.

CONTRASTING MEDICAL FOODS WITH SUPPLEMENTS AND DRUGS

Medical foods are often confused with dietary supplements, perhaps because both may contain nutritional ingredients; however, the terms are not interchangeable and fall within discrete regulatory classifications. Medical foods have a specific statutory definition contained in the Orphan Drug Act of 1988, later reaffirmed in 1992 and again in 1996, while supplements are defined in a lengthy statute, the Dietary Supplement Health and Education Act (DSHEA). Medical foods are formulated for

Table 1. Differences Between Medical Foods, Dietary Supplements, and Drugs

Product Class Attribute	Dietary Supplement	Medical Food	Drug
Governing regulation	Dietary Supplements Health & Education Act (DSHEA, 1994)	Orphan Drug Act (amendments, 1988)	Federal Food, Drug and Cosmetic Act (1938 as amended by FDA Modernization Act of 1997)
Intended population	Healthy	Diseased	Diseased
Ingredients	Nutritional	Nutritional, not in ordinary diet	Mostly synthetic, can be nutritional
Product basis	"General expectation" of desired product performance	Dietary need = metabolic imbalance can be restored by special nutrients	Safe & effective for disease & patient population
Safety standard	"General expectation" of safety (ingredients on market prior to DSHEA)	GRAS (generally recognized as safe) as food ingredients = safe for public use	Approved via NDA, ANDA or used as DESI ("grandfathered")
Scientific requirements	None	Recognized science = follows good scientific practices, accepted in clinical practice or peer review	Preclinical & clinical phases I, II, III
Physician supervision	None	Required	Required if prescription drug
Dosing	Oral	Oral or enteral	Any
Distribution	Health food stores, mass market	Hospitals, retail pharmacies	Hospitals, retail pharmacies

a specific diseased population and must be shown by sound scientific and medical evaluation to meet the distinctive nutritional needs of that population, whereas supplements are intended for a healthy population and require no efficacy testing. Medical foods must be administered under the supervision of a licensed medical physician, and many states require a prescription for this purpose, while supplements can be bought "over the counter." Medical foods make medical claims (i.e., to manage a disease), while supplements may make only structure/function claims (i.e., to support normal, healthy function of a body part or metabolic process). Supplements may also claim to lower the risk of a disease, while medical foods may not, given that they are already intended for a diseased population. In 1990, an FDA-sponsored panel suggested that medical foods "ameliorate clinical manifestations of the disease, favorably influence the disease process, and positively influence morbidity and mortality (patient outcomes)."[11] Supplements are subject to strict labeling requirements, while medical foods are specifically exempt from these restrictions.

Products classified as drugs have an entirely separate set of criteria. As defined by the FDA, drugs are substances that diagnose, cure, mitigate, treat, or prevent disease. Drugs need not be constituents of foods and do not have a defined essential metabolic function. The management of a metabolic process is not an essential property of a drug. Some major differences and similarities in drugs, dietary supplements, and medical foods are summarized in Table 1.

EXAMPLES OF MEDICAL FOODS

An early example of a medical food is the formula Lofenalac®, which is used for the dietary management of phenylketonuria (PKU), a genetic defect in the metabolism of phenylalanine. The diet used in feeding infants with PKU, who have a defective/deficient phenylalanine hydroxylase enzyme, contained low amounts of phenylalanine and sufficient tyrosine in order to manage this metabolic error in a scientifically rational manner. Infants with PKU not in a managed program are characterized by high levels of phenylalanine and its alpha keto metabolites in plasma and urine. They have an increased risk of physical and neurological developmental problems. Lofenalac® is designed specifically to manage the abnormal metabolic milieu in the patient with PKU. Table 2 lists some currently prescribed medical foods.

There has been a steady rise in the number of products marketed as medical foods since the 1990s. In its 1996 Announcement of New Proposed Regulations

Table 2. Sample Prescription Medical Food* Products

Product	Uses†	Key Ingredients	Form	Reimbursement
Ultrase MT® NDC 58914-045-10 Axcan Pharma www.axcan.com	Exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, steatorrhea	Lipase Protease Amylase	Enteric coated capsule	Medicaid most HMO/PPO
Limbrel™ NDC Primus Pharmaceuticals, Inc. www.limbrel.com	Osteoarthritis	Baicalin Catechin Epicatechin	Capsules	Most HMO/PPO
Conison™ Capsules NDC 58177-0044-03 Ethex (KV Pharm.) www.ethex.com	Pernicious anemia megaloblastic anemias	Intrinsic factor Vitamins B_{12} and C Folic acid Iron fumarate	Capsules	Medicaid most HMO/PPO
Renax® NDC 0642-2746-90 Everett Labs www.everettlabs.com	End-stage renal disease renal insufficiency	Chromium Selenium Zinc Vitamin E Folic acid Cyanocobalamin (B_{12}) Pyridoxine (B_6)	Caplets	Medicaid some HMO/PPO
Folgard RX 2.2® NDC 0245-0016-11 Upsher-Smith www.upsher-smith.com	Elevated homocysteine	Folic acid Cyanocobalamin (B_{12}) Pyridoxine (B_6)	Tablets	Medicaid some HMO/PPO
Cerefolin™ NDC 0525-0503-90 Pan American Laboratories www.cerefolin.com	Mild to moderate cognitive impairment, vascular dementia, Alzheimer's disease	L-methylfolate Riboflavin (B_2) Pyridoxine (B_6) Cyanocoblamin (B_{12})	Tablets	Medicaid some HMO/PPO
BCAD 2 NDC 0087-008341 Mead Johnson www.meadjohnson.com	MSUD, other errors of branched-chain amino acid metabolism	Hydrolyzed guar gum Soy lethicin Potassium Calcium Magnesium Vitamin E Folic acid Niacin	Powder	Medicare (Part B)

Table 2. (Cont'd) Sample Prescription Medical Food* Products

Product	Uses†	Key Ingredients	Form	Reimbursement
Resource Support® NDC 00212-1755-62 Novartis www.novartis.com	Cachexia due to cancer	EPA DHA Amino acids Soluble fiber	Liquid	Medicare (Part B)
Oxepa® NDC 70074-0543-87 Ross Labs (Abbott) www.ross.com	Lung injury for patients on ventilation such as with pneumonia, sepsis, and hypoperfusion	EPA Soy lethicin Vitamins A, B_6, B_{12}, C, D3, E L-carnitine Niacin Zinc Folic acid Magnesium Calcium	Liquid	Medicaid Medicare (Part B)
Isosource® VHN NDC 00212-1875-42 Novartis www.novartis.com	Post-surgical pressure ulcers; wound healing; calorie restriction; long-term tube feeding (high protein, isotonic complete needs)	Soy fiber, lecithin Guar gum Magnesium L-carnitine, taurine Vitamins A, B12, D3, K1 Folic acid Calcium	Liquid (sealed container for tube feeding)	Medicare (Part B)

*Classified as a medical food according to an analysis FDA criteria based on the manufacturer's uses, claims, and marketing materials.
†Represents the disease for which the product provides nutritional management.

(ANPR), the FDA expressed concern about the number and nature of products on the market being called medical foods, noting that many lacked the scientific support required to document their claims as required by statute. Additional guidelines were to be forthcoming, but in 2000 the agency withdrew the ANPR and to date no further regulation has been approved. That concern notwithstanding, many products have survived scrutiny by medical practitioners and have moved into mainstream medical use, as evidenced by the fact that they are reimbursed by most US health care plans and often Medicare or Medicaid. Some medical foods are recognized as medical nutrition therapy (MNT) by the Older Americans Act, Administration on Aging, the US Department of Agriculture, and various state units on aging. MNT is a multi-step process beginning with assessment of the nutritional status of the individual who has a condition, illness, or injury that puts him or her at nutritional risk. MNT is often an important component of the management of chronic diseases such as heart, lung, and kidney diseases, stroke, diabetes, osteoporosis, osteoarthritis, and some types of cancer.

More recently, medical foods have been moving in the commercial direction of prescription drugs while retaining their FDA medical food regulatory status. These products are being offered in tablet or capsule form through retail pharmacies. For example, mixtures of the vitamins folic acid, vitamin B_6, and vitamin B_{12} in tablet or capsule form are offered as medical foods to manage high blood levels of homocysteine. Hyperhomocysteinemia is associated with cardiovascular disease, stroke, and other diseases.[12-15] This vitamin mixture is not specifically intended for the prevention of vitamin deficiency syndromes; it is intended to lower plasma homocysteine levels by enhancing established metabolic pathways for homocysteine. Therefore, there is a rational scientific basis to use these products to manage elevated plasma homocysteine levels. The use of folic acid to lower the toxicity of low-dose methotrexate therapy in rheumatoid arthritis therapy is another example of the use of nutritional ingredients as a medical food.[16,17] These vitamin mixtures are correctly classified as medical foods because: 1) they are products marketed for the management of a metabolic disequilibrium; 2) there is a scientific basis for the formulations; 3) there is evidence that the product does what it claims to do; 4) the ingredients are GRAS; and 5) they are used under a physician's supervision.[12,17]

Medical foods are used in the practice of traditional medicine in Africa, Asia, and the Far East. For example, some medical foods are extracted from the bark of the *Acacia* tree and the root of the *Scutellaria* plant. *Acacia* spp. is widely known in Africa as the "fever tree," and extracts of the bark are reported by the native population to be efficacious in the treatment of a variety of ailments.[18,19] *Scutellaria* spp. is known as Huang-Qin ("golden root"), Hwang-geum, and Wogon in traditional Chinese, Korean, and Japanese medicines, respectively.[20,21] Root extracts from *Scutellaria* spp. are also components in a variety of treatments. Chemical components of these plants are reported to have anti-inflammatory and antioxidant activities, as well as minimal toxicity, and lend credibility to claims of such by practitioners of traditional medicine.[20-26] In Japan, extracts from these plants are listed in the official Japanese Pharmacopoeia, are prescription-controlled products, and can be reimbursed by the National Health Insurance.

THE FUTURE OF MEDICAL FOODS

Although medical foods have been used in the United States for decades, they are poorly understood as a product category. Confusion about their classification and regulation derives in part from the fact that these products were regulated as drugs prior to 1988. The word "food" in "medical food" may contribute further to category confusion.

The continuing use and need for medical foods can be attributed to: 1) incomplete success of some drug therapies in the treatment of disease; 2) the success (or even partial success) of natural, botanical-based ingredients and their constituents in managing metabolic disequilibrium associated with many conditions or diseases; and 3) the generally low toxicity of the GRAS ingredients in medical foods. These factors combine to produce a favorable risk/benefit ratio for the product category and will create an environment fostering further development of these agents.

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