

The Current Regulatory Framework of Medical Foods: Challenges and Opportunities

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MEDICAL FOODS WORKSHOP:
**Science, Regulation
and Practical Aspects**

AUGUST 13-14, 2019 WASHINGTON, DC

Points to cover

- Regulatory History of Medical Foods
- FDA's perspective on what is, and is not, a medical food
- Key elements of the regulatory framework
 - Statutory definitions vs. Regulatory Interpretations
 - Distinctive Nutritional Requirements (DNR)
 - Modification of the Diet Alone (MODA)
 - Delineating between categories of “food”; Avoidance of drug claims
- Challenges confronting the medical food category
- Opportunities for medical foods to improve patient health outcomes and quality of life

History of Early Regulation

Pre-1972 –Lofenalac[®], a product used for dietary management of the inborn error of metabolism (IEM), phenylketonuria (PKU), regulated as a drug

Late 1972 –Lofenalac[®] moved from drug category into “Foods for Special Dietary Use” (FSDU)

1988 –Orphan Drug Act Amendments created and defined the category of “medical foods”, separate from drugs, yet associated with disease

1988-Orphan Drug Act Amendment created a statutory definition of medical food

“The term *medical food* means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation”

21 U.S.C. 360ee(b)(3)

See Link for expanded background of defining medical foods in the context of funding for research for rare disorders:

<https://www.law.cornell.edu/uscode/text/21/360ee>

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Key Regulatory Differences between Medical Food and Drugs

	Drugs	Medical Foods
Premarket Approval Required	X	-
Premarket review of safety and efficacy*	X	-
Premarket review of label claims	X	-
Product registration	X	-
Mandatory adverse event reporting	X	-

** Except for food and color additives used as ingredients in medical foods must be reviewed, and exempt infant formulas, sometimes classified as medical foods, are reviewed for normal growth efficacy*

Regulation of Medical Foods

- Medical foods must not be adulterated
 - Manufacturers must ensure their products are safe under the intended conditions of use
 - Manufacturers must follow cGMPs, with registration and periodic inspection of facilities
- Medical foods must not be misbranded
 - Manufacturers must ensure that label claims are truthful and not misleading
 - Labels must conform with all applicable food labeling regulations
 - Exemptions from nutrition labeling, health claims, nutrient content claims
- FDA's authority is post-market surveillance

Tools used by FDA for Post Market Enforcement

- Marketplace Monitoring
- Adverse Event Report Monitoring
- Facility Inspections
- Import Entry Reviews and Examinations
- Regulatory Correspondence and Meetings
- Import Alerts (detention without physical examination)
- Warning Letters
- Seizures
- Injunctions

Additional Legislative and Regulatory Activity

1990 –Nutrition Labeling and Education Act (NLEA) exempted medical foods from the nutrition labeling, health claim, and nutrient content claim requirements applicable to most other foods

1993 –Food labeling regulations, implementing NLEA, identified 5 criteria that must be met to qualify as a medical food (21 CFR 101.9(j)(8))

References to actual Federal Register Citations, in context, for Medical Food

- For reference, go to this website for the actual pdf of the Jan 6 1993 Federal Register Notice: <http://cdn.loc.gov/service/ll/fedreg/fr058/fr058003/fr058003.pdf>
- I recommend downloading this file into Adobe Acrobat Reader, to make it more manageable
- That produces a document with 1138 pages, starting at page 1 (not the actual Fed Register pages, but of the downloaded pdf file). By putting in the following page numbers, you will save a lot of time scrolling through the entire Federal Register, but this will give you the actual language being referenced:
- P. 249 21 *CFR Parts 1 and 101 Food Labeling: Mandatory Status of Nutrition Labeling and Nutrient Content Revision, Format for Nutrition Label. Agency: Food and Drug Administration, HHS; Action: Final Rule (Summary and Supplementary Information)*
- P. 345 Part 101.9 – Food Labeling; 101.9 Nutrition Labeling of Food (a) *“Nutritional information relating to food shall be provided for all products intended for human consumption and offered for sale unless an exemption is provided for the product in paragraph (j) of this section.”*
- P 354 (j) Following Foods are Exempt...
- P. 355 (8) Medical Foods

Final regulations implementing NLEA issued Jan 1993 defined medical food to qualify for certain label exemptions, 21 C.F.R. 101.9(j)(8)

Specifically, this regulation provides that a food is a medical food only if:

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

Medical Foods

- Are not products simply recommended as part of overall diet to
 - Manage symptoms of a disease or condition
 - Reduce the risk of a disease or condition
- Not all foods fed to patients with a disease that requires dietary management are medical foods
- Medical foods are different from certain other specialized food categories

2016 Medical Foods Guidance

- Published May 13, 2016, to help manufacturers better understand compliance with regulations
- Stated as “Non-binding Recommendations”
- Easy to read Q&A format
- Provides information on
 - Definition of medical foods
 - Types of diseases and conditions appropriate and inappropriate to be considered for a medical food
 - Label statements reserved only for drugs: “Rx Only” and NDC numbers, with rationale

Contains Nonbinding Recommendations

Frequently Asked Questions About Medical Foods; Second Edition Guidance for Industry

Additional copies are available from:
Office of Nutrition and Food Labeling, HFS-800
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740
(Tel) 240-403-2373
<http://www.fda.gov/FoodGuidance>

You may submit written comments regarding this guidance at any time. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
May 2016

Link to FDA's page with direct link to download Final Guidance pdf

<https://www.fda.gov/food/cfsan-constituent-updates/fda-issues-final-guidance-frequently-asked-questions-about-medical-foods>

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Foods for Special Dietary Use (FSDU) Defined in 21 CFR §105.3(a)(1) 1977-1979

The term special dietary uses, as applied to food for man, means particular (as distinguished from general) uses of food, as follows:

- (i) uses for **supplying particular dietary needs which exist by reason of a physical, physiological, pathological or other condition**, including but not limited to the conditions of diseases, convalescence, pregnancy, lactation, allergic hypersensitivity to food, underweight, and overweight;
- (ii) uses for **supplying particular dietary needs which exist by reason of age**, including but not limited to the ages of infancy and childhood;
- (iii) uses for **supplementing or fortifying the ordinary or usual diet** with any vitamin, mineral, or **other dietary property**. Any such particular use of a food is a special dietary use, regardless of whether such food also purports to be or is represented for general use

Found at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=105&showFR=1>

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Other Legislative Developments

- 1994 Dietary Supplement and Health Education Act (DSHEA)
 - Provided a statutory definition for dietary supplements, distinguishing them from other, conventional foods
 - Effectively removed these products from the category of foods for special dietary use into a new classification
 - Did NOT bring dietary supplements under the definition of medical foods

What is a Dietary Supplement?

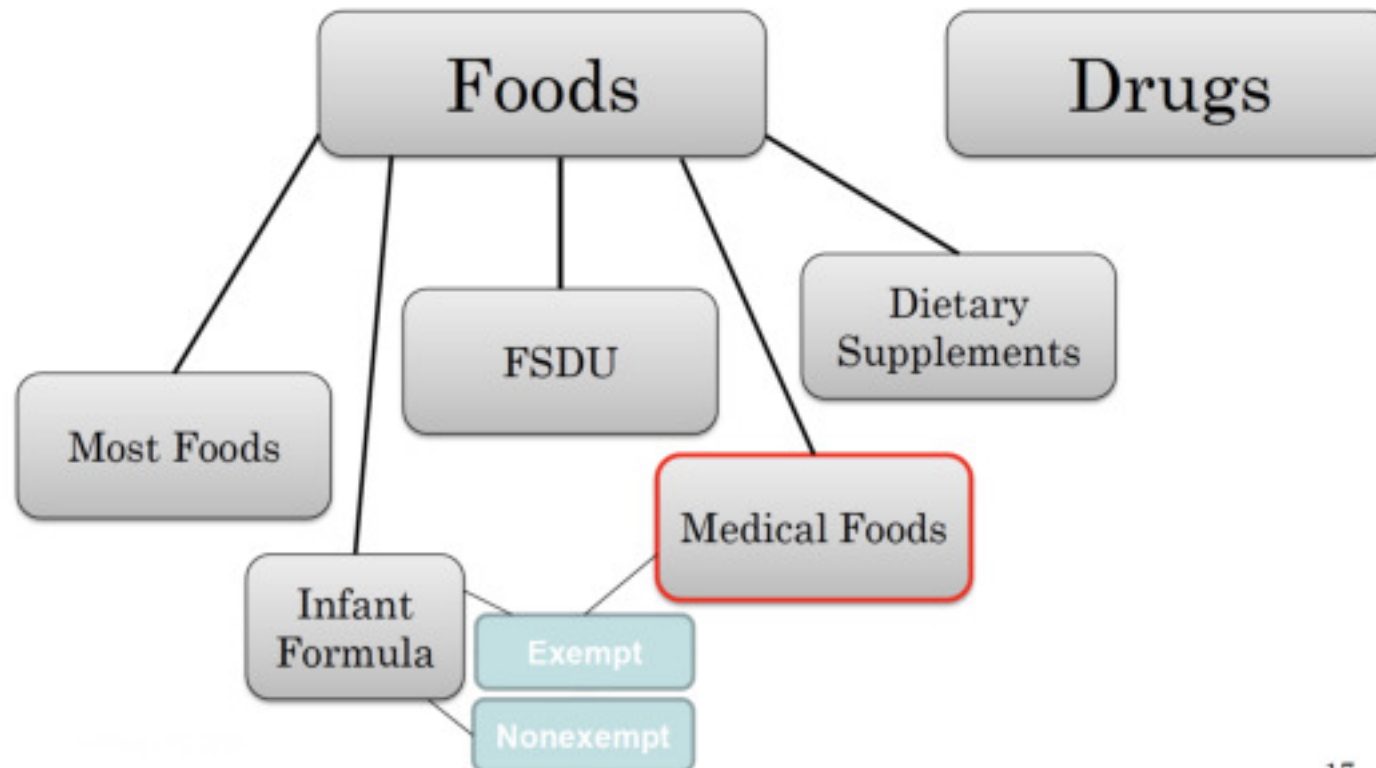
- Section 201(ff) of the Federal Food, Drug and Cosmetic Act (21 USC 321(ff)):
 - 1) Means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
 - (A) a vitamin;
 - (B) a mineral;
 - (C) an herb or other botanical;
 - (D) an amino acid;
 - (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
 - (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)
 - (2)(B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and
 - (C) is labeled as a dietary supplement

FDA's Graphic of Regulatory Domains



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Other Regulatory Activity – ANPRM “Regulation of Medical Foods” — Fed Reg 61 Nov 29, 1996, 60661-60671

Link: <https://www.govinfo.gov/content/pkg/FR-1996-11-29/pdf/96-30441.pdf>

FDA published an Advance Notice of Proposed Rulemaking (ANPRM), “**Regulation of Medical Foods**”, announcing its intent to re-evaluate policy for regulating medical foods and inviting public comments to their proposal in light of:

- Rapid increase in the variety and number of products,
 - Uses for which they were being marketed,
 - Reports of safety problems,
 - Potential for consumers to be injured/misled due to unsupported claims
- Key Sections in the 11 page, 3 columns, small print, Federal Register document include:
 - I. Background
 - II. Reasons for Re-Evaluating Regulation of Medical Foods
 - A. Introduction
 - B. The Definition of “Medical Food” and the Impact of the 1990 Amendments: the Medical Foods Paradox
 - C. Universe of Products
 - D. Safety Problems
 - E. Claims and the Potential for Economic Fraud
 - III. Clarification of the Medical Food Definition
 - A. “Distinctive Nutritional Requirements”
 1. Physiological Interpretation of “Distinctive Nutritional Requirement”
 2. Alternative Interpretation of “Distinctive Nutritional Requirement”
 - B. Under the Supervision of a Physician
 - C. Specific Dietary Management
 - D. Summary
 - IV. Need for Substantiation of Nutritional Efficacy and Claims Made in Product Labeling

Other Regulatory Activity – 2004 Withdrawal of ANPRM Medical Foods Regulations

Fed Reg vol.69, no. 227, Nov 26, 2004, 68831 [Link: https://www.govinfo.gov/content/pkg/FR-2004-11-26/pdf/04-26234.pdf](https://www.govinfo.gov/content/pkg/FR-2004-11-26/pdf/04-26234.pdf)

In Link above, go to FR page 68834, item 14. Regulation of Medical Foods— Docket No. 96N–0364, November 29, 1996, 61 FR 60661

2004 –ANPRM withdrawn without consideration of comments received

“Because of competing priorities that have tied up FDA’s limited resources, the agency has been unable to consider, in a timely manner, the issues raised by comments on the ANPRM, and does not foresee having sufficient resources in the near term to do so. Therefore, the agency is withdrawing this ANPRM.”

However, FDA believes that the basic principles described in the ANPRM provide an appropriate framework for understanding the regulatory paradigm governing medical foods. Therefore, FDA advises that it will continue to refer to the basic principles described in the ANPRM and in FDA’s Medical Foods Compliance Program (CP7321.002) when evaluating medical foods.

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Points to Consider

- Statutory definition states MF “...intended for the specific dietary management of a disease or condition...” whereas,
- Regulatory Definition states MF “... intended for the dietary management of a patient...” since “food” is prohibited from claiming any role in the prevention, treatment, mitigation, or cure of disease
- Key terms that remain without clear definition 25-30 yrs later:
 - **distinctive (unique) nutritional requirements**
 - recognized scientific principles
 - **established by medical evaluation**
 - **other special medically determined nutrient requirements**
 - **Dietary management cannot be achieved by modification of the normal diet alone**
 - **management of the unique nutrient needs that result from the specific disease or condition**
- Different interpretations of nutrient, essential/conditionally essential, nutrient precursor, bioactive dietary substance, alternate fuel sources at cellular level, compensatory alternate biochemical substrates, pre-probiotics, signaling molecules

Morck's Ten-ionic Nutrition Definition

Impairment in any system can impact overall nutritional status

- Education - What foods are appropriate
- Selection - Make the right choices
- Mastication - Chewing/Dental issues
- Ingestion - Process for taking food into the body
- Deglutition - Process of Swallowing
- Digestion - Breaking complex foods into simple molecules
- Absorption - Taking nutrients across gut wall into blood
- Transportation- Carrying nutrients to target organs/cells
- Utilization - Metabolism for energy, defense, renewal, growth
- Excretion - Removal of waste by-products

Overview: Challenges & Opportunities

- Challenges for

- Companies
- Regulators
- Payors
- Financial Success

- Opportunities

- Companies
- Safe, effective products
- Route to market faster than drugs
- Patient health outcome benefits

Challenges

- Clear understanding of the Medical Food category:
 - How is it different from Food, Dietary Supplements, Food for Special Dietary Use, Drugs?
- Conducting appropriate research
 - Designing, conducting, reporting results from appropriately powered clinical trials
- Developing claims & communicating benefits
 - Permitted/prohibited statements
- Market access/target populations
 - Patients, Healthcare providers, consumers,
- Pricing and who pays?
 - Patient, medical care provider, health insurance company, self-insured employee benefit

Opportunities

- Research Scientists
- Regulators
- Policy Makers
- Industry
- Patients

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Opportunities

- Research Scientists
 - Be aware of the need to report clinical results from a nutritional systems perspective
 - Evaluate “nutrient” requirements of an individual, including genetic & microbiome factors, to include metabolically beneficial dietary components, with scientifically robust publications citable by regulatory agencies to support regulations
- Regulators
 - Understand that DNR for a patient is aimed towards achieving his/her optimal health, not comparison to a population mean of otherwise “healthy” individuals
 - Accept that physician recommendation and ongoing supervision of a properly formulated medical food preempts arbitrary “modification of diet alone” constraints
 - Consider creative ways to increase staffing and priority for evaluating/“approving” disease-impacting nutritional solutions, possibly through a notification process

Opportunities

- Policy Makers

- Welcome safe, lower cost than drugs, “therapeutic nutrition”, for cost-effective, reimbursable patient care with improved health outcomes
- Press for bi-partisan congressional support to pass legislation or otherwise direct FDA to draft enabling regulations, with clear definitions and guidance for industry, to assure compliance
- Support public and private health insurance coverage for “medically necessary nutrition products” and the equipment and supplies needed to administer them to qualified patients

- Industry

- Sponsor clinical trials that demonstrate specific formulations compensate for disease-related physiological impairments, and help restore “nutritional balance” at the cellular, tissue, organ, and/or whole body level
- With regulatory guardrails clearly understood, accelerate product innovation pipelines to expand nutritional therapies suitable for patients facing any disease or condition throughout their lifespan

Opportunities

- Patients

- Mobilize efforts to actively press scientists, regulators, policy makers, and industry to accelerate development of cost-effective, nutrition-based products that improve quality of life and regain “nutritional balance” in the face of disease
- Recognize that overall dietary management, including appropriate medical foods or targeted nutritional therapies, puts your body in the best condition to improve health
- Take an active role with your physician and healthcare professionals to understand how improving your “metabolic nutrition” helps in managing your disease

In Summary

- Medical Foods were defined 3 decades ago, regulations 25 years ago
 - But those definitions/regulations have not kept pace with scientific advances
- The role of “nutrients” in food impact more than preventing deficiency diseases; scientific evidence of patient benefit is extensive
- Challenges remain in aligning regulations consistent with nutritional benefits for patients with diseases/conditions
- Opportunities must be explored to equip regulators to make safe, effective, patient benefits a top priority



Thank You!

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