

# FOOD AND DRUG LAW JOURNAL

## EDITOR IN CHIEF

Judy Rein

---

## EDITORIAL ADVISORY BOARD

### CHAIR

Laurie Lenkel  
*FDA – OC*

### VICE CHAIR

Robert Giddings  
*Hutchison PLLC*

### FACULTY ADVISOR

Joseph A. Page  
*Georgetown University Law  
Center*

---

Anthony Anscombe  
*Sedgwick LLP*

James Flaherty  
*Fresenius Medical*

Francis Palumbo  
*University of Maryland  
School of Pharmacy*

Peter Barton Hutt  
*Covington & Burling*

Abraham Gitterman  
*Arnold & Porter LLP*

Sandra Retzky  
*FDA – CTP*

Barbara Binzak  
Blumenfeld  
*Buchanan Ingersoll &  
Rooney PC*

Kimberly Gold  
*Norton Rose Fulbright  
LLP*

Joan Rothenberg  
*FDA - CFSAN*

Catherine Clements  
*Express Scripts*

John Johnson  
*FDA Imports*

Jodi Schipper  
*FDA – CDER*

Kellie Combs  
*Ropes & Gray LLP*

Alan Katz  
*toXcel, LLC*

Christopher van Gundy  
*Keller and Heckman*

Nathan Cortez  
*Southern Methodist  
University*

Sara Koblitz  
*Fish & Richardson*

James Woodlee  
*Kleinfeld Kaplan & Becker LLP*

Brian Dahl  
*Dahl Compliance  
Consulting LLC*

Valerie Madamba  
*Blue Apron*

Emily Wright  
*Pfizer*

Sandra dePaulis  
*FDA – CVM*

Alan Minsk  
*Arnall Golden Gregory  
LLP*

Kimberly Yocum  
*TC Heartland LLC*

Ian Fearon  
*British American Tobacco*

Nicole Negowetti  
*The Good Food  
Institute*

Lowell Zeta  
*Hogan Lovells*

James O'Reilly  
*University of  
Cincinnati*

Patricia Zettler  
*Georgia State  
University Law School*

## OFFICERS OF THE FOOD AND DRUG LAW INSTITUTE

CHAIR: Jeffrey N. Gibbs, Hyman, Phelps & McNamara, P.C.

TREASURER: Frederick R. Ball, Duane Morris LLP

GENERAL COUNSEL/SECRETARY: Joy J. Liu, Vertex Pharmaceuticals

IMMEDIATE PAST CHAIR: Allison M. Zieve, Public Citizen Litigation Group

PRESIDENT & CEO: Amy Comstock Rick

# GEORGETOWN UNIVERSITY LAW CENTER

## STUDENT EDITOR IN CHIEF

Dana Shaker

---

## STUDENT MANAGING EDITORS

Jacob Klapholz

Christine Rea

---

## STUDENT NOTES EDITOR

Lauren Beegle

## SYMPOSIUM EDITOR

Alexander P. Kramarczuk

---

## STUDENT EXECUTIVE EDITORS

Courtney L. Blandford  
Thomas Crimer

Lindsay Laddaran  
Jackson Lavelle

Christopher R. Lombardi  
Emily Salomon

---

## STUDENT SENIOR STAFF EDITORS

Colleen Hespeler  
Yang Li

Arvind S. Miriyala  
Sheaniva H. Murray  
Laya Varanasi

Bonnie Fletcher Price  
Mariah Trisch

---

## STUDENT STAFF EDITORS

Seth Appiah-Opoku  
Natalie Camastra  
Emma Chapman  
Daniel Elkus  
Adam Harris  
Lacey Henry

Laura Higbee  
Nicholas Hill  
Meaghan Jerrett  
Daniel Krisch  
Yinan Lin  
Allison Parr

Nicholas Prust  
Erik Rynko  
Thomas Sanford  
Shaun Weiss  
Tiffany Weston

---

## LLM EDITORS

Holly Hedley  
Dena Kirpalani  
Julia Kuelzow  
Laura Malavé

Hayley Scheer  
Andrew Hennessy-Strahs  
Cheng Zeng

---

## FACULTY ADVISOR

Joseph A. Page

---

## FACULTY ADVISORY BOARD

Oscar Cabrera  
Vicki W. Girard  
Lawrence O. Gostin

Lisa Heinzerling  
John R. Thomas  
Rebecca Tushnet

David C. Vladeck  
Timothy M. Westmoreland

---

## O'NEILL INSTITUTE ADVISOR

Eric N. Lindblom

## O'NEILL INSTITUTE LIAISON

Ana S. Ayala

# Proposed Industry Best Practices in Development and Marketing of Medical Foods for the Management of Chronic Conditions and Diseases while Awaiting Regulation

BRUCE P. BURNETT  
AND ROBERT M. LEVY\*

## ABSTRACT

*Ideal therapeutics have low toxicity and can effectively manage condition(s) or disease(s). The Food & Drug Administration (FDA) marketing category of therapeutics called “medical foods” (MFs) meets such a definition. Medical foods have existed in Federal law since passage the Orphan Drug Act in 1988,<sup>1</sup> which created a category of nutritional therapeutics separate from drugs. Unfortunately, MFs are not widely understood by the medical community or utilized in all patients who need them due to lack of a FDA-approval process, unclear and contradictory guidance especially with regard for need for an investigational new drug (IND) application,<sup>2</sup> and no clear regulations regarding their development and marketing.<sup>3</sup> The goals of this article are to propose “Best Practices” to guide the medical food industry in the development and marketing of products as well as to serve as a starting point for suggestions regarding further FDA regulation so that therapeutics which are shown to be generally recognized as safe (GRAS),<sup>4</sup> provide food ingredients to meet a*

---

\* Bruce P. Burnett, Ph.D. 1992, Yale University; M.Ph. 1989, Yale University; B.S. 1987, Eastern Washington University. Robert M. Levy, M.D. 1967 University of Chicago; B.S. 1963, Cornell University. The authors note that those assertions that would typically require a citation under legal conventions follow generally-accepted medical and scientific conventions and/or are a product of the authors’ combined professional experience.

<sup>1</sup> See The Orphan Drug Act, 21 U.S.C. § 360ee(b)(3) (1988) (“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 law amended an earlier Orphan Drug Act, 21 C.F.R. Part 316 (1983).

<sup>2</sup> See U.S. DEPT OF HEALTH & HUMAN SERVS. et al., GUIDANCE FOR CLINICAL INVESTIGATORS, SPONSORS, AND IRBS INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS)—DETERMINING WHETHER HUMAN RESEARCH STUDIES CAN BE CONDUCTED WITHOUT AN IND (2013), <http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf> (placed restrictions on medical foods requiring an investigational new drug application for testing of disease endpoints in clinical trials).

<sup>3</sup> See Bruce P. Burnett, Robert M. Levy & Sarah L. Morgan, *Medical Foods Come Under Assault in the U.S.*, NUTRITION INSIGHT, SUPPLEMENT TO THE WORLD OF FOOD INGREDIENTS (July/August 2016) (summarizing the history of the medical food category, the current state of FDA regulation, and challenges that exist in the managed care industry in the U.S.).

<sup>4</sup> See 21 U.S.C. §§ 321(s), 348 (2012) (stating “any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of

*distinctive nutritional requirement for a specific condition/disease and are proven effective for the management for that condition/disease can be used to benefit patients who need them.*

## INTRODUCTION

The first product to use the term “medical food” (MF) was Lofenalac®, a specially formulated meal replacement therapy with low phenylalanine approved by FDA under the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) in 1957 for management of phenylketonuria.<sup>5</sup> The origin of MFs, however, can be traced to the passage of the first FDCA in 1938. Shown in Table 1 are the major events in the evolution of MFs to today’s FDA-regulated category.<sup>6</sup>

Table 1  
History of Medical Food Marketing Category, Statutes, Regulations and Guidance

<i>Date</i>	<i>History of Medical Food Marketing Category, Statutes, Regulations and Guidance</i>
1938	Initial Federal Food, Drug and Cosmetic Act
1941	Food and Drug Administration (FDA) defined “special dietary uses” for foods
1957	First Approved Medical Food in Name, Lofenalac®
1958	First GRAS List of Foods
1972	Conversion of the Majority of Medical Foods to the Newly Established Marketing Category of Foods for Special Dietary Users
1969–1982	Analysis of GRAS Substances in the American Diet
1988	Passage of the Update to the Orphan Drug Act, which Established Medical Foods Separate from FDA-approved Drugs
1990	Nutrition Labeling and Education Act re-codifies Medical Foods in Law but Exempts them from Nutrition Labeling
1993	21 CFR 101.9(j)(8); the First Regulation for the Medical Food Category
1996	Advanced Notice of Proposed Rule Making Proposes New Regulations for Medical Foods
1997	FDA Begins Posting GRAS Affirmations
1997–	FDA Lists Medical Foods as Physician Prescribed Therapeutics

its intended use, or unless the use of the substance is otherwise excepted from the definition of a food additive.”).

<sup>5</sup> See 21 U.S.C. § 201(g)(1)(B) (1957). Phenylketonuria is an inherited genetic disease caused by mutations in the gene encoding the enzyme phenylalanine hydroxylase which processes phenylalanine from the diet. Phenylalanine builds up in the body to toxic levels and has been identified to cause mental retardation as well as other system symptoms and defects. See *Phenylketonuria*, MAYO CLINIC (Nov. 26, 2014), <http://www.mayoclinic.org/diseases-conditions/phenylketonuria/basics/definition/con-20026275>.

<sup>6</sup> See Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938). The FDCA gave authority to the U.S. Food and Drug Administration (FDA) to oversee the safety of food, drugs, and cosmetics. The introduction of this act was prompted by 70 to over 90 adults and children who died after consuming an elixir containing diethylene glycol as relayed in a Report of the Secretary of Agriculture on Deaths Due to Elixir Sulfanilamide-Messengill. S. DOC. NO. 75-124, at 1 (1937). This Act replaced the Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906).

2007	
2003	FDA Withdraws ANPR Without Comment
2007	FDA Published FAQ Draft Guidance on Medical Foods
2008	FDA Publishes Medical Food Program Guidance Manual for Drug Inspectors Guidance
2013	FDA Publishes FAQ Second Edition Draft Guidance on Medical Foods
2013	FDA Publishes Requirement in Guidance for an IND for Clinical Trials for Medical Foods
2016	FDA Finalizes FAQ Guidance on Medical Foods

This 1938 law that established the Food and Drug Administration (FDA) in its regulatory role for safe oversight of the nation's food and drugs<sup>7</sup> also gave it authority to police cosmetics and therapeutic devices.<sup>8</sup> New drugs had to be shown to be safe before marketing and tolerance levels had to be set for unavoidable "poisonous substances."<sup>9</sup> The Act also authorized FDA to investigate misbranding and put the onus on industry to defend their statements about product efficacy and safety.<sup>10</sup> It further required companies to describe food with simple identity statements, add labeling for the quantity of foods in containers, and uphold certain standards of quality.<sup>11</sup> Lastly, the Act gave FDA power of factory inspection and the ability to obtain injunctions from courts to cease operations of food and drug companies if necessary.<sup>12</sup> Along with the Wheeler-Lea Act of 1938, which gave the Federal Trade Commission (FTC) powers essentially to prosecute companies for unfair or deceptive acts or practices in commerce,<sup>13</sup> this new regulatory structure of FDA and FTC established powers at the Federal level for protection of the nation's food and drug supply, made companies accountable for business practices in competition with other companies and protected consumers from deceptive advertising in selling products.

Medical foods were first regulated as "foods for special dietary uses" which were initially reviewed and approved for safety only under the 1938 FDCA where the specific content of these products had to be defined in the label.<sup>14</sup> In the 1950s, it was recognized that defects in metabolic processing of nutrition led to inborn errors of metabolism (IEM)<sup>15</sup> and specially formulated foods in the form of MFs were created

---

<sup>7</sup> See generally David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 LAW & CONTEMP. PROBS. 2 (1939), <http://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=1937&context=lcp> (history of legislation, incidents and passage of the Federal Food, Drug and Cosmetic Act of 1938).

<sup>8</sup> See 21 U.S.C. §§ 201(h), 325(h) (both for "Device"), 361(a), 5(a)-(b), 60x(a) (1938) (for "Cosmetic").

<sup>9</sup> See 21 U.S.C. § 351(a) (1938).

<sup>10</sup> See 21 U.S.C. § 331(a) (1938).

<sup>11</sup> See 21 U.S.C. § 341 (1938).

<sup>12</sup> See 21 U.S.C. § 372a (1938).

<sup>13</sup> See Federal Trade Commission Act, Pub. L. No. 75-447, 52 Stat. 111 (1938) (attempting to regulate false and misleading advertising).

<sup>14</sup> See 21 U.S.C. §§ 402(b)(4), 5342(b)(4) (1938).

<sup>15</sup> See Lewis Waber, *Inborn Errors of Metabolism*, 19 PEDIATRIC ANNALS 105, 105 (1990) (IEMs are rare, inherited genetic disorders in which mutations of certain metabolic genes that encode enzymes

to provide or exclude specific nutrients to children to mitigate these inherited genetic diseases.<sup>16</sup> At this point until modernization of FDA in the 1960s, all MFs were approved under the same law used for Lofenalac® approval.<sup>17</sup> These products consisted of basic formulations which contained amino acids, vitamins, minerals, carbohydrates, and salt solutions for a variety of conditions where solid food could not provide proper nutrition.<sup>18</sup> These initial therapies led to enteral formulations for patients who were unable to ingest or swallow solid foods due to injuries (i.e., burn victims) that inhibited the body's ability to process nutrition, and/or for IEM.<sup>19</sup>

All MFs are required to be composed of safe food ingredients, but development of this safety standard has a long history. In 1958, the Food Additives Amendment to the FDCA was passed so that "any substance intentionally added to food is a food additive and is subject to premarket approval by FDA unless the use of the substance is generally recognized as safe (GRAS)."<sup>20</sup> This was the first attempt to create a list of foods and substances consumed in the United States that were considered safe. All food products were required to be composed of GRAS<sup>21</sup> substances or of substances authorized by prior sanction.<sup>22</sup> By 1961, FDA completed amendments to food safety regulations which included a formal list of food substances that were GRAS under certain conditions of use.<sup>23</sup> This led manufacturers to request FDA's opinion as to the GRAS status of their foods which did not appear on the list authored by FDA. In 1969, the Nixon administration asked FDA to report on the safety of food and food additives in the American diet.<sup>24</sup> FDA contracted the Life Sciences Research Office (LSRO) of

---

for processing nutrients in the body do not function properly to produce building blocks for the tissue or energy).

<sup>16</sup> See Mohammed Almannai et al., *Newborn Screening: A Review of History, Recent Advancements, and Future Perspectives in the era of next Generation Sequencing*, 28 CURRENT OPINION PEDIATRICS 694 (2016).

<sup>17</sup> See 21 U.S.C. § 201(g)(1)(B) (1957).

<sup>18</sup> Kathryn M. Camp et al., *Nutritional Treatment for Inborn Errors of Metabolism: Indications, Regulations, and Availability of Medical Foods and Dietary Supplements Using Phenylketonuria as an Example*, 107 MOLECULAR GENETICS & METABOLISM 3, 5 (2012).

<sup>19</sup> See generally Campbell SM, *An anthology of advances in enteral tube feeding formulations An anthology of advances in enteral tube feeding formulations*, 21 NUTRITION IN CLINICAL PRACTICE 411 (2006).

<sup>20</sup> See generally Food Additives Amendment of 1958, Pub. L. No. 85-929, 72 Stat. 1784 (1958) (codified as amended in various sections of title 21 U.S.C. Major thrust was to development a review and approval process for new food additives).

<sup>21</sup> Generally recognized as safe means that "any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use . . ." *Generally Recognized as Safe (GRAS)*, FDA, <http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/> (last updated: Oct. 17, 2016).

<sup>22</sup> See 21 U.S.C. § 321(s); 21 C.F.R. § 170.30 (establishing standards for ingredients formulated into medical foods).

<sup>23</sup> See, e.g., 26 Fed. Reg. 938, 938 (1961); 24 Fed. Reg. 9368, 9369 (1959).

<sup>24</sup> See 36 Fed. Reg. 12,093, 12,093 (1971) ("A current review of GRAS substances is necessary because of new scientific knowledge, the development of modern toxicological techniques, and the expanded usage of some GRAS substances beyond the exposure patterns considered when the GRAS list was originally promulgated."); 35 Fed. Reg. 18,623 (1970) (announces prior GRAS criteria for the comprehensive and complete review of food substances). President Nixon ordered FDA to undertake this review. *Consumer Protection*, 5 WKLY. COMPILATION PRESIDENTIAL DOCUMENTS 1516, 1522 (1969) ("I

the Federation of American Societies for Experimental Biology (FASEB) to help with this analysis.<sup>25</sup> During the 1970s, FDA established the procedures for affirming the GRAS status of a substance submitted to and reviewed by FDA.<sup>26</sup> By 1982, FASEB's LSRO had reported to FDA the safety of approximately 400 substances in the diet.<sup>27</sup>

From the early 1980s until 1997, FDA accepted petitions for the analysis of substances to be reviewed for GRAS status or on its own accord reviewed and either approved or rejected food substances or additives publishing these notifications *via* Federal Register.<sup>28</sup> In 1997, FDA also proposed establishing a system by which a person or company could submit notification of use of the proposed GRAS substance to the agency, obtain a review and receive a non-confidential response indicating that there were no questions regarding the safe use or that there was insufficient evidence for a GRAS determination of the substance.<sup>29</sup> FDA began publishing these notifications on their website in 1998.<sup>30</sup> FDA recently finalized the regulation for submission and review of GRAS status of food substances formalizing the voluntary notification program.<sup>31</sup> The GRAS program is relatively unchanged except for clarifying certain terminology such as "GRAS notifications" which are now "GRAS notices," "GRAS determinations" are now called "conclusions of GRAS status" or "GRAS conclusions," and the "exemption" of GRAS substances from the law on food additives is now termed an "exclusion." In addition, the final GRAS rule specifies specific content needed in GRAS notice to FDA:

1. Signed Statements and Certification: trade secrets, intended conditions of use, and the basis for the conclusion of GRAS status;
2. Identity, Method of Manufacture, Specifications, and Physical or Technical Effect: characterization of the notified substance and method of manufacture;
3. Dietary Exposure: dietary exposure based on common use in food;
4. Self-Limiting Levels of Use: amount of the notified substance that would make a formulation unpalatable or technologically impractical;
5. Common Use in Food Before 1958: common use in food to be the basis for the GRAS conclusion, the pre-1958 consumption must be by a significant number of consumers;

---

have asked the Secretary of [HEW] to initiate a full review of food additives . . . re-examining the safety of [GRAS] substances . . .").

<sup>25</sup> See George W. Irving, Jr., *News - The Generally Recognized as Safe List*, 34 FED'N PROC. 1308, 1308 (1975).

<sup>26</sup> See 21 C.F.R. § 170.35 (developing a GRAS affirmation process for substances that directly or indirectly become a component in food).

<sup>27</sup> See Frederic R. Senti, *Insights on Food Safety Evaluation*, 3 REG. TOXICOLOGY & PHARMACOLOGY 133, 133 (1983).

<sup>28</sup> See generally 21 C.F.R. pt. 184 (human food), pt. 584 (animal feed and pet food).

<sup>29</sup> See Substances Generally Recognized as Safe, 62 Fed. Reg. 18,938, 18,938 (April 17, 1997).

<sup>30</sup> UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE, FOOD SAFETY: FDA SHOULD STRENGTHEN ITS OVERSIGHT OF FOOD INGREDIENTS DETERMINED TO BE GENERALLY RECOGNIZED AS SAFE (GRAS) (2010) ("From 1998—the first year a company submitted a notice of a GRAS determination—through 2008, companies chose to submit 274 GRAS determinations to FDA under the 1997 proposed voluntary notification program, or about 25 annually. According to FDA, it has received notices for substances such as carbohydrates, lipids, proteins, and chemicals. At any given time, FDA may have pending notices—notice under review for which FDA has not yet issued a final opinion.").

<sup>31</sup> See Substances Generally Recognized as Safe, 81 Fed. Reg. 54,960, 54,960 (Aug. 17, 2016) (to be codified at 21 C.F.R. §§ 20, 25, 170, 184, 186, and 570).

6. Narrative: description for the basis for the conclusion of GRAS status;
7. Supporting Data and Information: published and unpublished safety data on the notified substance.<sup>32</sup>

Although FDA eventually recognized MFs as a distinct category requiring GRAS safety, the regulatory framework for MFs has significant gaps such as specific rules and guidance on substantiation.

The history of clinical substantiation of drugs formally began in 1962 with the passage of the Kefauver-Harris Drug Amendments, FDA regulations that established a new system to approve drugs for safety and efficacy in phase I-III studies.<sup>33</sup> The category of MFs was subject to this new law.<sup>34</sup> During the years of 1972-74, FDA converted most MFs to a new over-the-counter (OTC) category of "Foods For Special Dietary Use."<sup>35</sup> FDA felt at the time that the risk of these foods causing harm was minimal thus allowing for the conversion to foster development of these products without onerous restrictions for approval and marketing.<sup>36</sup> Foods for special dietary use are foods that do not require physician supervision or require premarket approval under the modernized drug approval process, but provide needed nutrients for special situations to: (i) supply a particular dietary requirement 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) supply a particular dietary needs which exist by reason of age, including but not limited to the ages of infancy and childhood; (iii) supplement or fortifying the ordinary or usual diet with any vitamin, mineral, or other dietary property.<sup>37</sup> FDA did express concerns of healthy individuals using the new formulations, especially those for phenylketonuria,<sup>38</sup> so it modified its decision placing some nutritional formulations back under physician supervision as MFs. Other MFs remained in the drug category and were, even as GRAS substances, subject to the same phase I, II, and III development pathway required after FDA modernization.<sup>39</sup> This onerous development pathway was not commercially viable, especially for rare diseases, and led to a lack of MF development during this time.

---

<sup>32</sup> See Substances Generally Recognized as Safe, 81 Fed. Reg. 54,960 (Aug. 17, 2016).

<sup>33</sup> See generally Kefauver Harris Amendment, Pub. L. No. 87-781, 76 Stat. 780 (1962).

<sup>34</sup> *Id.*

<sup>35</sup> See 21 C.F.R. § 125 (1974); currently defined under 21 C.F.R. § 105.3(a) (2005).

<sup>36</sup> See Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,662 (November 29, 1996) ("FDA believed that the usefulness of these products in patient populations was widely accepted by health care professionals, and that close physician supervision ensured safe use in the patient population. The agency was interested in fostering innovation in the development of these products, most of which had been developed for the dietary management of diseases and conditions that are not widespread, to ensure that such products would be available at reasonable cost.").

<sup>37</sup> See C.F.R. § 105.3 (foods for special dietary use).

<sup>38</sup> See Drugs for Human Use, 37 Fed. Reg. 18,229, 18,230 (Sept. 8, 1972) (removing phenylketonuria formulations from the category of foods for special dietary users and placed it back to the medical food category).

<sup>39</sup> Phase I studies entail testing safety and dosage in a small group of healthy volunteers. Phase II studies involve testing a larger group of the specific target disease for safety and efficacy. Phase III studies are long-term, large studies in the specific target disease population for safety and efficacy. The Drug Development Process Step 3: Clinical Research, FDA, <http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm> (last updated Oct. 14, 2016).



Presumably to overcome these obstacles and spur further development of MFs, an amendment was added to the 1988 update to the Orphan Drug Act and used as a vehicle formally to establish the MF category separate from FDA-approved drugs and Foods for Special Dietary Use (Table 1).<sup>40</sup> It is noteworthy that creation of the MF Marketing category occurred six years in advance of the establishment of the Dietary Supplement Marketing Category in 1994 under the Dietary Supplement Health and Education Act, a rather unregulated category by comparison sometimes confused with MFs.<sup>41</sup> The Orphan Drug Act of 1988 defined MFs as “a food which is formulated to be consumed or administered eternally 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.”<sup>42</sup> In 1991, the MF category was reaffirmed in the Nutrition Labeling and Education Act (NLEA), which further defined the MF category but exempted these products from the nutrition labeling required by conventional foods purchased in the grocery store.<sup>43</sup> The NLEA, which effectively amended the FDCA, was also the basis for the regulation that FDA finalized in 1993 for MFs.<sup>44</sup> This regulation further defined the category, stating that a food is a MF exempt from nutrition labeling only if:

- a. 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;
- b. 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;
- c. 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;
- d. It is intended to be used under medical supervision; and
- e. 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.

At this point, the MF category was separate from drugs and other foods, but needed further regulation to define the requirements for scientific and clinical evidence. In 1996, FDA issued a public discussion document, which was meant to define certain terms in the Orphan Drug Act of 1988, the NLEA and the one regulation. This

---

<sup>40</sup> See 21 U.S.C. § 360ee(b)(3).

<sup>41</sup> See 21 U.S.C. § 301.

<sup>42</sup> See 21 U.S.C. § 360ee(b)(3).

<sup>43</sup> See 21 U.S.C. § 343(q)(5)(A)(iv).

<sup>44</sup> See 21 C.F.R. § 101.9(j)(8).

document was the Advance Notice of Proposed Rulemaking for MFs (ANPR).<sup>45</sup> Contained in this document were suggested definitions for a “distinctive nutritional requirement,” the need for clinical evidence of efficacy and the requirement of “medical supervision” of MF products.<sup>46</sup> The ANPR was publicly discussed for approximately seven years and then withdrawn by FDA without further comment, leaving the category lacking definition and direction on these important issues.<sup>47</sup> Therefore, industry was left to interpret the Orphan Drug Act, the NLEA, the regulation 21 CFR 101.9(j)(8), the ANPR, and warning letters issued by FDA to companies not following basic requirements for the MF category.

In 2007, in an attempt to advise industry and others on what constituted MFs, FDA issued nonbinding guidance in the form of Frequently Asked Questions (FAQs) About Medical Foods but did nothing to define terms in the Orphan Drug Act of 1988, the NLEA and from 21 CFR 101.8(j)(8) or to provide guidance on what constitutes proof for a “distinctive nutritional requirement” or clinical efficacy.<sup>48</sup> In 2008, FDA finalized a Medical Food Program Guidance Manual to be used by its field inspectors in case they encountered MF products at drug product facilities.<sup>49</sup> This manual restated the content of the previous laws and guidance documents, prevented import of MFs from overseas distributors and gave the drug inspectors guidance on how to sample products and inspect labels. In 2013, the second edition of FDA FAQs About MFs was released; the guidance was finalized in 2016.<sup>50</sup>

The history of MF is extensive dating back to the inception of FDA. The remainder of the article will discuss the current guidance and regulation, controversies as well as suggested industry best practices in the development and marketing of MF products to

---

<sup>45</sup> See Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,661–62 (Nov. 29, 1996).

<sup>46</sup> *Id.*

<sup>47</sup> See Withdrawal of Certain Proposed Rules and Other Proposed Actions, 69 Fed. Reg. 68,834, 68,834 (Nov. 26, 2004). FDA declared in this filing that: “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 (CP 7321.002) when evaluating medical foods. With regard to the specific points made in the comment regarding regulation of medical foods, the comment is correct that the act exempts medical foods from the nutrition labeling, health claim and nutrient content claim requirements that are applicable to most other foods. However, all statements on food labels (including medical foods) must be truthful and not misleading (see section 403(a)(1) of the [A]ct). FDA advises that medical foods with false and misleading labeling are subject to enforcement action. The agency also advises that withdrawal of this ANPRM does not change the requirement that all ingredients used in medical foods must be approved food additive, GRAS, or otherwise exempt from the food additive definition. Medical foods that do not comply with this requirement are subject to enforcement action.”

<sup>48</sup> See FDA, GUIDANCE FOR INDUSTRY: FREQUENTLY ASKED QUESTIONS ABOUT MEDICAL FOODS (May 2007), reprinted in NUTRIENT PHARMACOLOGY, <http://nutrientpharmacology.com/fda.html>.

<sup>49</sup> See FDA, COMPLIANCE PROGRAM GUIDANCE MANUAL 7321.002, MEDICAL FOODS PROGRAM – IMPORT AND DOMESTIC (FY 06/07/08) (2008), <http://www.fda.gov/downloads/Food/ComplianceEnforcement/UCM073339.pdf>.

<sup>50</sup> See Frequently Asked Questions About Medical Foods, 81 Fed. Reg. 29,866; *Frequently Asked Questions About Medical Foods Second Edition: Guidance for Industry*, U.S. FOOD & DRUG ADMIN. (2016), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>.

help assure vital nutritional therapeutics category for patients. In addition, we will call for formal regulation of the MF category suggesting the best practices as a jumping off point to new rule making.

## OVERVIEW OF CURRENT GUIDANCE AND REGULATIONS FOR MEDICAL FOODS

The final guidance of FAQs About MFs; Second Edition represents FDA’s current thinking on the category.<sup>51</sup> Though guidance is non-legally binding, FDA uses this document as the basis for office actions such as warning letters and providing advice to industry.<sup>52</sup> Table 2 contains the current requirements for the development and marketing of MFs.

Table 2

<i>Requirement</i>	<i>Description</i>
Formulation	<input type="checkbox"/> Specially formulated, processed GRAS substance(s) <sup>53</sup> <input type="checkbox"/> Approved food and/color additives <sup>54</sup> <input type="checkbox"/> Form of MFs: <sup>55</sup> nutritionally complete; nutritionally incomplete formulas; or metabolic formulas for IEM
Labeling	<input type="checkbox"/> Exempt nutrition panel labeling <sup>56</sup> <input type="checkbox"/> Ingredient(s) list in order of predominance <sup>57</sup> <input type="checkbox"/> Net weight of ingredients <sup>58</sup> <input type="checkbox"/> Prominent and conspicuous labeling <sup>59</sup> <input type="checkbox"/> English or predominant language label <sup>60</sup> <input type="checkbox"/> Principal information panel requirements <sup>61</sup>

<sup>51</sup> See FDA, *supra* note 49.

<sup>52</sup> *Guidance for Industry: Frequently Asked Questions About Medical Foods; Second Edition*, U.S. FOOD & DRUG ADMIN. (May 2016), <http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm054048.htm>; See 56 Fed. Reg. 60366, 60377 (Nov. 27, 1991); *Frequently Asked Questions About Medical Foods Second Edition: Guidance for Industry*, U.S. FOOD & DRUG ADMIN. (2016), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>.

<sup>53</sup> *Id.* at 4 (“Medical foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for a patient who requires use of the product as a major component of a disease or condition’s specific dietary management.” GRAS substances as determined by qualified experts under the conditions of its intended use (GRAS), or be a substance authorized by a prior FDA action.); see 21 C.F.R. § 101.9(j)(8).

<sup>54</sup> See generally 21 C.F.R. §§ 73–74, 172.

<sup>55</sup> See FDA, *supra* note 45 at Part I p. 2.

<sup>56</sup> See Nutrition Labeling and Education Act of 1990, Pub. L. No. 101-545, 104 Stat. 2353; 21 U.S.C. § 343(r)(5)(A).

<sup>57</sup> See 21 C.F.R. §§ 101.3, 101.4.

<sup>58</sup> See 21 C.F.R. § 101.105.

<sup>59</sup> See 21 C.F.R. § 101.15.

<sup>60</sup> See 21 C.F.R. § 101.15(c)(1)(2).

<sup>61</sup> See 21 C.F.R. §§ 101.1, 101.2, 101.18 (2016).

	<input type="checkbox"/> Listing of potential allergens <sup>62</sup> <input type="checkbox"/> Name, place of business of manufacturer, packer, or distributor <sup>63</sup> <input type="checkbox"/> Cannot include NDC numbers <sup>64</sup>
Manufacture	<input type="checkbox"/> Registration and adhere to current Good Manufacturing Practices <sup>65</sup> <input type="checkbox"/> Compliant with Food Safety Modernization Act <sup>66</sup> <input type="checkbox"/> When applicable, follow Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers, Acidified Food and Emergency Permit Control regulations <sup>67</sup>
Physician Supervision	<input type="checkbox"/> Medical and physician supervision required <sup>68</sup>

The current state of regulation in the MF category does not sufficiently guide industry in the development, manufacture and marketing of MFs. Due to the lack of clarity of regulation for this category, there are controversies which have arisen since the MF category was formalized in law.<sup>69</sup>

#### A. Current Controversies in Medical Foods

Though regulations exist for composition, labeling, and manufacturing of FDA-regulated MFs, there are several current controversies regarding the category. These controversies include: 1) a lack of FDA approval for medical food products; 2) little recognition by FDA and medical community that nutritional intervention can be safely used to manage chronic conditions or diseases; 3) no standards for clinical substantiation of medical foods; 4) lack of a formal definition of what constitutes a distinctive nutritional requirement for specific conditions or diseases; 5) confusion about what constitutes medical or physician supervision and how these products are marketed to patients.<sup>70</sup> These controversies have created challenges for companies in the development of MFs, in the recognition of these products as viable therapies for disease intervention, in patients obtaining these products from physicians or pharmacy and in securing coverage through managed care and government insurance programs.

---

<sup>62</sup> See Food Allergen Labeling and Consumer Protection Act, Pub. L. No. 108-282, 118 Stat. 906 (2004) (codified as amended at 21 U.S.C. § 301) (milk, eggs, fish, shellfish, tree nuts (e.g., almonds, walnuts, pecans), peanuts, wheat, and soy).

<sup>63</sup> See 21 C.F.R. § 101.5.

<sup>64</sup> See FDA, *supra* note 46 at 8.

<sup>65</sup> See generally, 21 C.F.R. pt. 1 Subpart H, part 110.

<sup>66</sup> See Food Safety Modernization Act, Pub. L. No. 111-353, 124 Stat. 3885 (2011) (codified as amended at 21 U.S.C. § 301).

<sup>67</sup> See generally, 21 C.F.R. §§ 108, 113–114.

<sup>68</sup> *Id.*

<sup>69</sup> *Id.*

<sup>70</sup> Etan Yeshua, *New FDA Draft Guidance for Medical Foods Suggests that Some Common Products and Certain Label Statements Violate FDA Regulations*, FDA LAW BLOG (Aug. 14, 2013), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2013/08/new-fda-draft-guidance-for-medical-foods-suggests-that-some-common-products-and-certain-label-statem.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/08/new-fda-draft-guidance-for-medical-foods-suggests-that-some-common-products-and-certain-label-statem.html).

### 1. *Lack of FDA Approval*

Medical foods are not FDA-approved products.<sup>71</sup> Rather, these are highly regulated products, which are required to demonstrate safety through an expert GRAS panel review and efficacy *via* clinical studies.<sup>72</sup> FDA regularly monitors claims for products in the MF category and issues warning letters if they find companies overstep current guidance and regulations.<sup>73</sup> Companies that are compliant with current regulations obtain minimally a self-affirmed GRAS status for their MF and perform studies to substantiate an intended use though this is not specifically required by under current FDA regulations. Most medical food companies support product disease or condition use with carefully designed case studies and/or conventional randomized, double-blind, placebo or active comparator controlled studies of sufficient magnitude to generate statistically significant data for efficacy and publish these studies in peer-reviewed scientific journals. Unfortunately, the CFSAN has never defined the studies needed to demonstrate efficacy. Even if these products have GRAS status and efficacy studies that substantiate label claims, the lack of FDA-approval adversely impacts understanding, acceptance, and utilization of MF by the wider medical community.<sup>74</sup> Physicians are primarily trained only to utilize FDA-approved substances, making any therapeutic agent lacking this certification suspect or less desirable.<sup>75</sup> As a consequence, MFs tend to be therapeutics of last resort after multiple drug therapy failures or adverse reactions. If efficacy were sufficiently demonstrated for MF, they would be more appropriately suited as first-line therapies because of their relatively benign safety profiles.<sup>76</sup>

This lack of FDA approval particularly complicates reimbursement for medical foods. The Medicare Modernization Act of 2003, which set forth the system of

<sup>71</sup> *Is It Really 'FDA Approved?'* - *FDA Doesn't Approve Medical Devices*, U.S. FOOD & DRUG ADMIN. (Jan. 17, 2017), <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm047470.htm>.

<sup>72</sup> Peter Arhangelsky, *FDA's Expansion of IND Regulations Impose Yet Another Major Regulatory Hurdle for Medical Food Companies*, EMORD & ASSOCIATES (Oct. 22, 2013), <http://emord.com/blawg/fdas-expansion-of-ind-regulations-impose-yet-another-major-regulatory-hurdle-for-medical-food-companies/>.

<sup>73</sup> See FDA, COMPLIANCE PROGRAM GUIDANCE MANUAL 7321.002, MEDICAL FOODS PROGRAM – IMPORT AND DOMESTIC (FY 06/07/08) (2008), <http://www.fda.gov/downloads/Food/ComplianceEnforcement/UCM073339.pdf>; Alexander Gaffney, *FDA in Sustained Crackdown Against Marketers of Medical Foods*, Regulatory Affairs Professionals Society (Jan. 21, 2014), <http://www.raps.org/focus-online/news/news-article-view/article/4520/>. *Frequently Asked Questions About Medical Foods Second Edition: Guidance for Industry*, U.S. FOOD & DRUG ADMIN. (2016), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>.

<sup>74</sup> See Bruce P. Burnett, Robert M. Levy & Sarah L. Morgan, *Medical Foods Come Under Assault in the U.S.*, NUTRITION INSIGHT, supplement to THE WORLD OF FOOD INGREDIENTS (2016) (summarizing the history of the medical food category, the current state of FDA regulation, and challenges that exist in the managed care industry in the United States).

<sup>75</sup> See ACG-FDA Visiting Fellowship Program, American College of Gastroenterology, <http://gi.org/membership/committees/fda-related-matters-committee/acg-fda-visiting-fellowship-program/> (last visited Feb. 1, 2017).

<sup>76</sup> Aaron S. Kesselheim et al., *Physicians' Knowledge About FDA Approval Standards and Perceptions of the "Breakthrough Therapy" Designation*, 315 J. AM. MED. ASS'N 1516, 1516–18 (2016). It generally-accepted medical convention that evidence-based medicine is required to prove safety and efficacy of FDA-approved drugs or biologics. Yet, no medical society or the FDA has opined on the type of sufficient efficacy evidence required for a medical food which is already considered generally recognized as safe and would not require earlier safety studies needed for drug approval. If efficacy standards (i.e., trial types, number of subjects, etc.) could be specifically developed for this category, the use of these products would occur earlier in the patient treatment regimen.

Medicare pharmacy coverage of patients over age 65 (Part D), does not allow reimbursement for non-FDA approved therapies, including those considered therapeutic nutrition such as MF.<sup>77</sup> Insurance companies and pharmacy benefits managers typically have systems for review specifically for FDA-approved agents.<sup>78</sup> The lack of FDA approval is often used by third party payers as an excuse for denying payment for MF, thus decreasing patient access to an entire class of therapies even with proven effectiveness and demonstrable safety advantages.<sup>79</sup> Interestingly, medical supplies such as pumps and tubing to administer MFs to a patient are covered under Part B, but in most circumstances the therapeutic agent itself is excluded from coverage.<sup>80</sup> There are examples of some coverage for enteral nutrition if it is a “qualified medical expense” in hospitals and skilled nursing facilities under Medicare Part A.<sup>81</sup> This lack of Part D and very limited Part A and B coverage of MFs through government insurance programs has become cover for commercial payers to exclude these products from formularies, even in circumstances where the MF offers proven unique therapeutic efficacy (i.e., no drug equivalent) or comparable efficacy to FDA-approved drugs with distinctly better safety profiles for management of specific conditions and diseases.<sup>82</sup> As a consequence, those patients on Medicare and Medicaid are likely to have trouble accessing medical food products to manage their chronic conditions or diseases. Recent passage by Congress of the National Defense Authorization Act restored coverage of certain MFs for IEM and gastrointestinal conditions and diseases which may help patients of military families, but the program is still currently in its infancy and it is difficult to foresee which MFs will be covered.<sup>83</sup> An act of Congress would still be required to give FDA the power to review and/or approve medical foods for specific intended uses.

---

<sup>77</sup> See Medicare Prescription Drug, Improvement, and Modernization Act, Pub. L. No. 108-173, 117 Stat. 2066 (2003).

<sup>78</sup> *Frequently Asked Questions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082690.htm#6>; *How We Build a Formulary*, EXPRESS SCRIPTS (Jul. 26, 2016), <http://lab.express-scripts.com/lab/insights/drug-options/how-we-build-a-formulary>.

<sup>79</sup> Susan A. Berry et al., *Insurance Coverage of Medical Foods for Treatment of Inherited Metabolic Disorders*, 15 GENETICS MED. 978, 978–82 (2013) (summarizing the landscape of coverage for medical foods intended for inborn errors of metabolism demonstrating limited coverage of these therapies); Adesoji O. Adelaja & Amish Patel, *Political Economy of Medical Food Reimbursement*, 42 U.S. J. FOOD DISTRIBUTION RES. 37, 37–55 (2011) (summarizing the insurance industry’s attitude for paying for medical foods).

<sup>80</sup> Adesoji O. Adelaja & Amish Patel, *Political Economy of Medical Food Reimbursement*, 42 U.S. J. FOOD DISTRIBUTION RES. 37, 37–55 (2011); *Coverage Determination (NCD) for Enteral and Parental Nutritional Therapy (180.2)*, CENTERS FOR MEDICARE AND MEDICAID SERVICES (1984), <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=242&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Keyword=enteral&KeywordLookUp=Title&KeywordSearchType=And&bc=gAAAABAAAAAAAA%3d%3d&>.

<sup>81</sup> See CENTERS FOR MEDICARE AND MEDICAID SERVICES, MEDICARE CLAIMS PROCESSING MANUAL 30.7, 100.2.2 (2016), <https://perma.cc/H6HE-YCY8>.

<sup>82</sup> *Coverage Summary: Medications/Drugs (Outpatient/PartB)*, UNITEDHEALTHCAREONLINE, [https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/UnitedHealthcare%20Medicare%20Coverage/Medications\\_UHCMA\\_CS.pdf](https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/UnitedHealthcare%20Medicare%20Coverage/Medications_UHCMA_CS.pdf) (last visited Feb. 8, 2017).

<sup>83</sup> National Defense Authorization Act for Fiscal Year 2017, H.R. 2943, 114th Cong. (2016).

## 2. Lack of Recognition of Nutritional Intervention

Nutrition science and the link of dietary intervention in different disease states has increased substantially from the time that FDA first approved Lofenalac® and other basic nutrient MFs for diseases linked to IEM under a specific statute prior to 1972.<sup>84</sup> The interplay of other purified nutritional substances compounds such as carotenoids, flavonoids, vitamin metabolites (e.g., L-methyl folate), fatty acids, amino acid metabolites (e.g.,  $\beta$ -hydroxy- $\beta$ -methylbutyrate), functional proteins (e.g., oral immunoglobulins, whey protein with TGF $\beta$ ), and other compounds from foods formulated in MFs are well-studied in different disease states.<sup>85</sup> There is abundant evidence that healthy foods in their natural state act to promote physiological homeostasis and maintain health.<sup>86</sup> Once purified, concentrated and standardized to levels that cannot be obtained by a dietary change, however, some of these GRAS nutritional substances become therapeutic and are capable of managing a wide variety of diseases, the statutory-intent of the MF category which is also stated in FDA guidance on the category. In the Second Edition of the MF FAQs, FDA recommends that these products can be developed for *some specific* IEM, but not for diabetes, pregnancy or malnourished states (i.e., scurvy, pellagra).<sup>87</sup> FDA stated that these

<sup>84</sup> See 21 U.S.C. § 201(g)(1)(B) (1957).

<sup>85</sup> Hidekatsu Yanai, *Nutrition for Sarcopenia*, 7 J. CLINICAL MED. RES. 926 (2015); Dale Wilson et al., *Evaluation of Serum-Derived Bovine Immunoglobulin Protein Isolate in Subjects with Diarrhea-Predominant Irritable Bowel Syndrome*, 6 CLINICAL MED. INSIGHTS: GASTROENTEROLOGY 49 (2013); Larry Goodet et al., *New Therapeutic Option for Irritable Bowel Syndrome: Serum-Derived Bovine Immunoglobulin: Case Study*, 21 WORLD J. GASTROENTEROLOGY 3361 (2015); Leonard B. Weinstock & Victoria S. Jasion, *Serum-Derived Bovine Immunoglobulin/Protein Isolate Therapy for Patients with Refractory Irritable Bowel Syndrome*, 4 OPEN J. GASTROENTEROLOGY 329 (2014); Ira Shafran et al., *Management of Inflammatory Bowel Disease Patients with Oral Serum-Derived Bovine Immunoglobulin*, 8 THERAPEUTIC ADVANCES GASTROENTEROLOGY 331 (2015); David Asmuth et al., *Oral Serum-Derived Bovine Immunoglobulin Improves Duodenal Immune Reconstitution and Absorption Function in Patients with HIV Enteropathy*, 27 AIDS 2207 (2013); David Asmuth et al., *Serum-Derived Bovine Immunoglobulin Isolate Increases Peripheral and Mucosal CD4+ T-Cell Counts*, AM. ASSOC. IMMUNOLOGISTS (2015); J.K. Triantafyllidis et al., *Beneficial Effect of a Polymeric Feed, Rich in TGF- $\beta$ , on Adult Patients with Active Crohn's Disease: A Pilot Study*, 19 ANNALS GASTROENTEROLOGY 66 (2006); J.K. Triantafyllidis et al., *Maintenance Treatment of Crohn's Disease with a Polymeric Feed Rich in TGF- $\beta$* , 23 ANNALS GASTROENTEROLOGY 113 (2010); Robert M. Levy et al., *Flavocoxid is as Effective as Naproxen for Managing the Signs and Symptoms of Osteoarthritis of the Knee in Humans: A Short-Term Randomized, Double-Blind Pilot Study*, 29 NUTRITION RES. 298 (2009); Robert M. Levy et al., *Efficacy and Safety of Flavocoxid, A Novel Therapeutic, Compared with Naproxen: A Randomized Multicenter Controlled Trial in Subjects with Osteoarthritis of the Knee*, 27 ADVANCES THERAPY 731 (2010); Herbert Marini et al., *Effects of the Phytoestrogen Genistein on Bone Metabolism in Osteopenic Postmenopausal Women: A Randomized Trial*, 146 ANNALS INTERNAL MED 839 (2007); Osvaldo Borrelli et al., *Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial*, 4 CLINICAL GASTROENTEROLOGY HEPATOLOGY 744 (2006). This list of peer-reviewed and published clinical trials is meant to inform the reader that proper clinical research is being performed on specially formulated dietary ingredients that are currently marketed as medical foods to show efficacy for these interventions in different disease states and conditions.

<sup>86</sup> Heiner Boeing et al., *Critical Review: Vegetables and Fruit in the Prevention of Chronic Diseases*, 51 EUROPEAN J. NUTRITION 637, 637–63 (2012); Tristan Chalvon-Demersay et al., *A Systematic Review of the Effects of Plant Compared with Animal Protein Sources on Features of Metabolic Syndrome*, 147 J. NUTRITION (2017), <http://jn.nutrition.org/content/early/2017/01/24/jn.116.239574.abstract?sid=ec98ab53-4ca1-4070-a808-85f2e524cecf>; Timothy J. Key et al., *Diet, Nutrition and the Prevention of Cancer*, 7 PUB. HEALTH NUTRITION 187, 187–200 (2004).

<sup>87</sup> See *supra*, note 46 at 10–11. FDA has made the judgment that diet alone can provide the needed nutrition to provide for the nutritional requirements in diabetes and pregnancy as well as correct

conditions can be corrected with change in diet.<sup>88</sup> Though certain deficiencies can be rectified by proper diet, FDA sometimes fails to recognize that dietary modification alone is often insufficient to correct or manage established diseases such as diabetes. In addition, patients sometimes, due to physical or physiological limitations, dietary habits or socioeconomic factors, will not or cannot consume a properly nutritious diet. In such cases, MFs provide specially formulated nutrition which can supplement dietary modification to manage these conditions. Finally, though physicians normally suggest changes in diet and exercise as a way to both prevent and treat certain diseases, their knowledge of dietary interventions is normally not substantial based on their medical education. Medical students normally do not take nutrition classes and their knowledge is lacking in even basic nutrition, let alone in other nutritional substances that may be part of MF products.<sup>89</sup>

### 3. *No Standards for Clinical Studies*

The ANPR of 1996 recommended that the intended use for each MF be substantiated with clinical studies.<sup>90</sup> FDA withdrew the ANPR without comment in 2003 but has since provided no recommendations regarding the types of clinical studies needed to support label claims. Since MFs have food-like safety, to require companies to perform phase I and phase II studies in their development may not be necessary since these trials necessarily focus on safety for drugs. Most randomized-controlled clinical trials testing MFs for their efficacy tend to be smaller phase III-like (pilot studies) powered to obtain statistical endpoints.<sup>91</sup> Companies have also utilized, without challenge from CFSAN, open-label, case control studies, case series, and comparator trials with drug therapies to demonstrate efficacy of their products published in peer-reviewed journals.<sup>92</sup> Despite having GRAS status, MF clinical trials also track routine safety parameters and manufacturers generally maintain robust post-marketing adverse event surveillance programs.

Although most legitimate MF companies are compliant with FDA standards for clinical substantiation, there have been examples where companies do not follow the basic tenets, regulations, and guidance for the category. Generally, these involve cases

---

nutritional deficiencies which exist in malnourished states. FDA did not provide published sources for their opinions in the cited guidance.

<sup>88</sup> *Frequently Asked Questions About Medical Foods Second Edition: Guidance for Industry*, FOOD & DRUG ADMIN. (2016), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>.

<sup>89</sup> David M. Eisenberg, *Nutrition Education in an Era of Global Obesity and Diabetes: Thinking Outside the Box*, 90 ACAD. MED. 854–60 (2015); Kelly M. Adams et al., *The State of Nutrition Education at US Medical Schools*, 2015 J. BIOMEDICAL EDUC. 1–7 (2015), <https://www.hindawi.com/journals/jbe/2015/357627/>.

<sup>90</sup> Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,670.

<sup>91</sup> Thabane L, Ma J, Chu R, et al., *A Tutorial on Pilot Studies: the What, Why and How*, 10 BMC MED. RES. METHODOLOGY (2010), <https://bmcmredresmethodol.biomedcentral.com/articles/10.1186/1471-2288-10-1>. Reference 85 lists clinical trials which support current medical foods. These studies typically enrolled 50 to 300 subjects, which are considered pilot or “vanguard” studies. Since FDA has not given specific guidance on clinical trials for medical foods, most companies that market these products use the equivalent of pilot studies to establish efficacy. Safety is established by a review of safety data in establishing generally recognized as safe status with an expert panel, normally composed of food toxicologists.

<sup>92</sup> See, e.g., Shaw AL et al., *Absorption and Safety of Serum-Derived Bovine Immunoglobulin/Protein Isolate in Healthy Drugs*, 9 J. of Clinical and Experimental Gastroenterology 365 (2016).



where FTC or FDA finds evidence of reliance on unverified scientific reports in which a small number of companies avoided any clinical substantiation to support claims leading to the use of language that constituted false advertising and deceptive practices in connection with the sale of products and/or use of proscribed drug language such as “treat” and “cure” in advertising products.<sup>93</sup>

In a more recent challenge to provide clinical substantiation for MFs, the Center for Drug Evaluation and Research (CDER) issued Guidance for Clinical Investigators, Sponsors, and IRBs Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND which directly challenges the MF category.<sup>94</sup> This guidance to institutional review boards (IRBs) requires all foods to file an investigational new drug application (IND) to perform a clinical study if evaluating disease endpoints other than safety of the formulations or studies of the taste, aroma, and/or “nutritive value.”<sup>95</sup> The term “nutritive value,” is not present in the FAQ guidance from CFSAN.<sup>96</sup> The definition of “nutritive value” comes from FDA regulation and is defined as that “sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy.”<sup>97</sup> The use of the word “nutritive” for the testing of MFs confuses researchers and industry representatives who must substantiate claims for chronic conditions and diseases through clinical investigation.<sup>98</sup> It is unclear as to what type of research falls under the jurisdiction of “nutritive value” other than providing essential nutrients or calories which is required in some, but not all chronic conditions and diseases. Interestingly, in the FAQ Guidance Concerning the Orphan Products Grants Program, MFs are specifically exempted from the requirement for an IND.<sup>99</sup> This is in direct conflict with CDER’s IND guidance to IRBs.<sup>100</sup>

Due to protests from food researchers, patient groups who utilize food for therapy, and others, a *stay* has recently been issued on the IND guidance to IRBs for studies of

---

<sup>93</sup> See Order Re Summary Judgment Motions at 8–9, *F.T.C. v. Wellness Support Network, Inc.* No. 3:10-cv-04879-JCS (2014) (Nos. 163, 169), [https://www.ftc.gov/system/files/documents/cases/140307wsn\\_motion.pdf](https://www.ftc.gov/system/files/documents/cases/140307wsn_motion.pdf).

<sup>94</sup> See FDA, GUIDANCE FOR CLINICAL INVESTIGATORS, SPONSORS, AND INSTITUTIONAL REVIEW BOARDS (IRBS) ON INVESTIGATIONAL NEW DRUG APPLICATIONS – DETERMINING WHETHER HUMAN RESEARCH STUDIES CAN BE CONDUCTED WITHOUT AN IND (2013), <http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf>.

<sup>95</sup> *Id.*

<sup>96</sup> *Id.*

<sup>97</sup> See 21 C.F.R. § 101.14 (2016) (defining certain terms and levels of nutrients related to food). The term nutritive value is misplaced in this case as medical foods are required to provide for a distinctive nutritional requirement which is unique to manage a specific condition or disease. Therefore, not all medical foods will provide nutritive value in “sustaining human existence by such processes as promoting growth” but they must manage a condition or disease by definition in the Orphan Drug Act of 1988 and under 21 C.F.R. §101.9(j)(8).

<sup>98</sup> *Frequently Asked Questions About Medical Foods Second Edition: Guidance for Industry*, FOOD & DRUG ADMIN. (2016), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>.

<sup>99</sup> FDA has asked and stated: “Do I need an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE) in order to qualify for an OOPD grant?” Yes, an IND/IDE is needed except for medical foods that do not need premarket approval and medical devices that are classified as non-significant risk (NSR). See *FAQ Concerning the Orphan Products Clinical Trials Grants Program*, FDA, <https://perma.cc/3EK9-A4PL> (last updated Oct. 17, 2016).

<sup>100</sup> *Id.*

conventional foods, but not for MFs.<sup>101</sup> This has set up a contradiction for the MF category: if a company files an IND to perform clinical studies to substantiate claims of efficacy for a MF, the company is admitting the product is a drug.<sup>102</sup> This would necessitate FDA-approval as opposed to FDA oversight, and thus make a potentially valid MF a drug. Yet, MFs are still required to support label claims for an intended use with clinical studies or risk FDA/FTC action.<sup>103</sup> This guidance has created confusion, not only for MF companies, but also for IRBs which are reluctant to monitor MF studies as they have in the past for fear of acting in violation of what might become statutory law at some future date.<sup>104</sup> The result has been millions of dollars in delay and negotiation costs with IRBs. In addition, this guidance is affecting the U.S. scientific infrastructure by discouraging or preventing academic researchers from performing therapeutic nutritional clinical trials.<sup>105</sup> This encourages U.S. MF companies to take clinical trials overseas, which results in U.S. job losses and further hampers FDA in its charge to monitor the safety of foods including MF products.<sup>106</sup>

#### 4. Lack of a Definition for Distinctive Nutritional Requirement

A theme running through nearly all warning letters issued by CFSAN to companies marketing MFs for disease management is that there is no documented “distinctive nutritional requirement” for the intended use cited by the company.<sup>107</sup> In the ANPR, CFSAN posited the following two possible definitions for distinct nutritional requirements:

##### a. Physiological Interpretation of ‘Distinctive Nutritional Requirement’

“Distinctive nutritional requirement” may be interpreted to refer to the body’s requirement for specific amounts of nutrients to maintain homeostasis (the state of equilibrium in the body with respect to various functions and to the chemical

<sup>101</sup> See FDA, *supra* note 74, at 13.

<sup>102</sup> *Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)*, U.S. FOOD & DRUG ADMIN. (2015), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm>.

<sup>103</sup> *FTC Prevails Against Marketers of Medical Foods*, SHEHADEH GIANNAMORE, PLLC (2014), <http://giannamore-law.com/ftc-prevails-against-marketers-of-medical-foods/>; Kristi Wolff, *FTC Judgment Adds to Growing Number of Medical Good Regulatory Actions*, AD LAW ACCESS (March 11, 2014), <http://www.adlawaccess.com/2014/03/articles/ftc-judgment-adds-to-growing-number-of-medical-food-regulatory-actions/>.

<sup>104</sup> Tish Eggleston Pahl, *The FDA’s Final IND Guidance – A Bitter Pill for Food and Nutrition Research*, OFW LAW (Jan. 8, 2014), <http://www.ofwlaw.com/2014/01/08/the-fdas-final-ind-guidance-a-bitter-pill-for-food-and-nutrition-research/>. There is a history of FDA action against IRBs who do not follow FDA regulations and guidance. The article reflects the current unease and confusion by industry and researchers in attempting to substantiate efficacy for medical foods.

<sup>105</sup> *Id.*; see also Letter from Connie Weaver, Distinguished Professor in Nutrition Science, Purdue University, to Janet Woodcock, Director of the Center of Drug Evaluation and Research, FDA (Nov. 6, 2013) <http://www.hpm.com/pdf/blog/FDA%20IND%20Connie%20Weaver%20letter.pdf> (explaining the effect of nutrition research by IND Guidance to IRBs).

<sup>106</sup> Amanda Gardner, *Many Clinical Trials Moving Overseas*, U.S. News (Feb. 18, 2009 5:00 pm), <http://health.usnews.com/health-news/managing-your-healthcare/research/articles/2009/02/18/many-clinical-trials-moving-overseas>.

<sup>107</sup> Maile Gradison Hermida & Xin Tao, *FDA Issues Final Guidance on the Definition and Labeling of Medical Foods*, HOGAN LOVELLS BLOG (June 10, 2016), <https://www.hoganlovells.com/en/blogs/focus-on-regulation/fda-issues-final-guidance-on-the-definition-and-labeling-of-medical-foods>.

compositions of the fluids and tissues) and sustain life; that is, the amount of each nutrient that must be available for use in the metabolic and physiological processes necessary to sustain life.<sup>108</sup>

b. *Alternative Interpretation of “Distinctive Nutritional Requirement”*

“Distinctive nutritional requirement” may also be interpreted to encompass physical or physiological limitations in a person’s ability to ingest or digest conventional foods, as well as distinctive physiological nutrient requirements.<sup>109</sup>

These two definitions suggest that a MF composed of GRAS substances from food could be used to restore and maintain normal balance to metabolic or physiological pathways<sup>110</sup> or, that a MF could be formulated in a way to allow for its consumption or digestion if there are physical or physiological limitations in the patient.<sup>111</sup> It is possible that a MF could be marketed to manage diseases which result from an imbalance in anabolic and catabolic pathways such as those which occur in bone loss, arthritis, cardiovascular dysfunction, inflammatory bowel disease, venous insufficiency or even Alzheimer’s disease in addition to IEM or patients who require tube feedings. Based on the above definition, a MF could help to restore a homeostasis with regard to the chemical compositions of the fluids and tissues and thus manage disease. Morgan and Baggett suggested in a review of the MF category 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.”<sup>112</sup> These conclusions, however, are contrary to the CDER issued guidance to IRBs which restricts MFs to provide formulations only for “nutritional purposes.” Therefore, companies are stuck between guidance from the drug division which contradicts guidance from the food division and Orphan Drug grants programs regarding the development of MFs.

5. *Confusion about what Constitutes Medical or Physician Supervision*

The Orphan Drug Act of 1988 defined a MF as “a food which is formulated to be consumed or administered enterally under the supervision of a physician . . . .”<sup>113</sup> FDA has been very consistent in requiring physician oversight of this therapeutic category presumably because these specially formulated agents are administered to patients with chronic conditions or diseases.<sup>114</sup> To give concentrated food substances, GRAS or not, may put patients in jeopardy if the physician is not involved.<sup>115</sup> For example, it

---

<sup>108</sup> *Id.*

<sup>109</sup> See Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,661–62 (Nov. 29, 1996).

<sup>110</sup> For clarification: In patients who have lack the ability to process food and nutrients.

<sup>111</sup> For clarification: A patient may not be able to chew, swallow or have a stomach which allows passage of food.

<sup>112</sup> Sarah L. Morgan & Joseph E. Baggott, *Medical Foods: Products for the Management of Chronic Diseases*, 64 NUTRITION REV. 495, 496 (2006).

<sup>113</sup> 21 U.S.C. § 360ee(b)(3). For clarity, only the first part of the language is shown to emphasize the requirement by law of physician supervision of medical foods.

<sup>114</sup> See Morgan, *supra* note 111, at 495–501 (2006).

<sup>115</sup> See Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,661–62 (Nov. 29, 1996).

is well-known that certain foods substances inhibit the CYP450 enzymes responsible for processing many drugs.<sup>116</sup> In addition, the right formulation of a medical food may need to be prescribed by a physician to assure its safe use.<sup>117</sup> An example of this is the correct tyrosine to phenylalanine ratios in a formulation to assure maintenance of cognitive function in phenylketonuria.<sup>118</sup> Absence of physician oversight in administration of a product intended for use by diseased individuals could potentially result in adverse effects, if the cause and consequences of which go unrecognized would be poor medical practice and might even be considered unethical. Though MFs have a generally benign safety profile assured by their GRAS status, they are effective therapeutic agents with significant physiologic effects and, as such, have the potential for side effects especially in more fragile, diseased individuals.<sup>119</sup> Availability of such medical foods “over-the-counter” would allow the decision to use such products, in which doses and concomitant use with other medications, would be made by untrained individuals with potentially harmful consequences. Conversely, the use of certain medical foods where healthy people self-medicate could have deleterious effects (i.e., if they do not get enough of one nutrient by using meal replacement MF for phenylketonuria). In the regulation derived from the NLEA, 21 CFR 101.9 (j), MFs are “intended to be used under medical supervision; and . . . 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.”<sup>120</sup> The ANPR of 1996 recommends MFs be used under medical and physician supervision.<sup>121</sup> FDA’s website from 1997-2007 stated, “A medical food is prescribed by a physician when a patient has special nutrient needs in order to manage a disease or health condition, and the patient is under the physician’s ongoing care.”<sup>122</sup> In the first FAQ guidance for MFs in 2007, FDA stated that “the product must be intended to be used under medical supervision.”<sup>123</sup> In the Import and Domestic, Compliance Program, and Guidance Manual, “medical supervision” is again cited.<sup>124</sup> And in the current FAQ guidance, FDA states regarding the requirement for an oral or written prescription:

---

<sup>116</sup> See Barbara Ameer & Randy A. Weintraub, *Drug Interactions with Grapefruit Juice*, 33 CLINICAL PHARMACOKINETICS 103, 103 (1997). Drug interactions shown by inhibition of liver enzymes, the CY450 isozymes, is of great concern when combining food, medical foods, dietary supplements or drugs in patients with specific treatments for disease(s). Medical foods and drugs are required to specifically test for these interactions to establish generally recognized as safe status and safety, respectively.

<sup>117</sup> *Frequently Asked Questions About Medical Foods Second Edition: Guidance for Industry*, FOOD & DRUG ADMIN. (2016), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>.

<sup>118</sup> See Monica Luciana et al., *Associations Between Phenylalanine-to-Tyrosine Ratios and Performance on Tests of Neuropsychological function in Adolescents Treated Early and Continuously for Phenylketonuria*, 72 CHILD DEV. 1637, 1637 (2001).

<sup>119</sup> See Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,661–62 (Nov. 29, 1996).

<sup>120</sup> *Id.*

<sup>121</sup> *Id.*

<sup>122</sup> *Medical Foods*, FDA CTR. FOR FOOD SAFETY & APPLIED NUTRITION (1997 Guidance), <https://perma.cc/NU7K-9JBS>.

<sup>123</sup> FDA, *supra* note 44.

<sup>124</sup> *Id.*

No. The requirement for a written or oral prescription in section 503(b) of the FD&C Act and its implementing regulations at 21 CFR 201.100 only applies to the dispensing of prescription drug products. The Orphan Drug Act provides that medical foods must be formulated to be consumed or administered enterally under the supervision of a physician, but there is no requirement for a prescription.<sup>125</sup>

Yet, CFSAN does not state whether these products can be made available or dispensed by prescription to meet the requirement for medical or physician supervision. Recently, one of the drug listing companies, First Databank, which informs payers whether products are prescription or not, has interpreted language in the MF FAQs to mean that MFs are OTC products.<sup>98</sup> This has caused payers to decrease patient access to these products by instantly dropping insurance coverage since they do not pay for OTC products.<sup>126</sup> This misinterpretation has led to patients with very serious conditions, which require meal replacement MFs for such conditions as phenylketonuria, not being able to pay for their MF due to high costs.<sup>127</sup> If the situation persists, this *pseudo-regulatory*, and possibly illegal (since it obviates the statutory requirement for physician oversight), decision by First Databank, a publicly traded company, may result in patient harm.

FDA requires MF to be supervised by a physician. From the FAQs:

FDA considers the requirement that a medical food be formulated to be consumed or administered enterally under the supervision of a physician to mean that 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) by a physician who has determined that the medical food is necessary to the patient's overall medical care. The patient should generally see the physician on a recurring basis for, among other things, instructions on the use of the medical food as part of the dietary management of a given disease or condition.<sup>128</sup>

FDA also states in the FAQs: "Medical foods are not those simply recommended by a physician as part of an overall diet to manage the symptoms or reduce the risk of a disease or condition."<sup>129</sup>

---

<sup>125</sup> FDA, *supra* note 46.

<sup>98</sup> See FIRST DATABANK, <http://www.fdbhealth.com/> (last visited Oct. 29, 2016); *Medical Fields Revisited*, NETWORK PHARMACY WEEKLY (June 30, 2016), [https://www.express-scripts.com/art/prc/June302016\\_Network\\_Pharmacy\\_Weekly.pdf](https://www.express-scripts.com/art/prc/June302016_Network_Pharmacy_Weekly.pdf).

<sup>126</sup> See *Medical Foods Labeling Change*, PREMERA BLUE CROSS, <https://perma.cc/8Y92-JSMY> (FDA did not convert the category of medical food products to over-the-counter. Nowhere in any FDA writings on the category does this thinking exist. In personal communications with FDA, they have said they do not want medical foods as OTC products as they are intended for someone who has a chronic disease or condition, unlike dietary supplements which are intended for healthy people).

<sup>127</sup> See Jennifer Payne, *Voice of the Patient on State Response to Unmet Needs*, MEDICAL FOODS POLICY, <https://rare diseases.org/assets/files/rare-action-network/JP-NORD-Medical.Foods-State.Policy.pdf> (last accessed Feb. 2, 2017); *Improve Our Future and Save Healthcare Dollars*, NATIONAL PKU ALLIANCE, [https://npkua.org/portals/0/pdfs/talking\\_points.pdf](https://npkua.org/portals/0/pdfs/talking_points.pdf) (last accessed Feb. 2, 2017).

<sup>128</sup> FDA, *supra* note 46.

<sup>129</sup> *Id.*

These statements strongly suggest that FDA does not want MF to be OTC. Therefore, a MF manufacturer is stuck in a “Catch-22” with regard to making its products available to ill patients based on the First Databank decision. How can one assure medical supervision of MF required under law<sup>130</sup> by converting these products to OTC? The traditional way MFs are distributed in a hospital is by chart order, a form of prescription.<sup>131</sup> In the outpatient setting, physician supervision can best, and perhaps, only be guaranteed by a requirement for prescription. FDA does not prohibit dispensing MFs by prescription as long as they are not labeled “Rx only.”<sup>132</sup>

FDA states in the FAQs:<sup>133</sup>

The labeling of medical foods may *not* bear the symbol “Rx only.” Section 503(b)(4)(A) of the FD&C Act (21 U.S.C. 353(b)(4)(A)) provides that a prescription drug is misbranded if the label of the drug fails to bear, at a minimum, the symbol “Rx only” to indicate that the product may not lawfully be dispensed without a prescription. Unlike prescription drugs, medical foods are not required by federal law to be dispensed by prescription. Therefore, the use of the symbol “Rx only” in the labeling of a medical food would misbrand a medical food under section 403(a)(1) of the FD&C Act because it would be a false and misleading statement about that product.

FDA further states:<sup>134</sup>

However, because medical foods are required by statute to be formulated to be consumed or administered enterally *under the supervision of a physician*, FDA would not object to the use of language to communicate this requirement in the labeling of a medical food product that is not false or misleading (e.g., “must be used under the supervision of a physician”).

Language of “available by prescription” or “dispensed by prescription” under physician supervision meets this standard, though there is no strict requirement for a prescription.<sup>135</sup> FDA has never stated that MFs are OTC products and making these products available OTC would violate current law and regulation as well as potentially put patients and/or healthy individuals at risk by consuming these products incorrectly.<sup>136</sup> The current situation created by First Databank’s misinterpretation of current MF laws, regulations and guidance is leading to a huge disruption for patients, physicians, pharmacists, and industry. The biggest concern, however, is that patients

---

<sup>130</sup> See 21 C.F.R. § 101.9(j)(8) (2016).

<sup>131</sup> *Frequently Asked Questions About Medical Foods Second Edition: Guidance for Industry*, FOOD & DRUG ADMIN. (2016), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>.

<sup>132</sup> *Id.*

<sup>133</sup> FDA, *supra* note 46.

<sup>134</sup> *Id.*

<sup>135</sup> FOOD & DRUG ADMIN., *supra* note 130.

<sup>136</sup> 21 U.S.C. § 360ee(b)(3) (stating that “a food which is formulated to be consumed or administered enterally under the supervision of a physician...”); 21 C.F.R. § 101.9(j)(8) (“A medical food is exempt from the nutrition labeling requirements of 21 CFR 101.9 only if . . . . It (*medical food*) is intended to be used under medical supervision; and 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.”).

are losing access to therapies that they require to manage their chronic diseases and conditions.

There is a need for clarification of terms that define MFs, such as what constitutes a distinctive nutritional requirement for a specific disease or condition. In addition, nutritional intervention should be embraced as a part of stepwise therapy prior to administering drugs with potentially greater side effect profiles when appropriate. Utilization of nutritional intervention will have to be based on clinical substantiation for MFs using a standard appropriate for the category. In order for this to occur, FDA will have to help define a specific clinical path for these products. Finally, physicians need to recognize the importance of nutritional intervention with MF and must be involved in administering and monitoring the use of these products as part of ongoing care. In order to achieve these goals, there is a need for industry to first adhere to certain standards and perhaps in the long run, a need for further FDA regulation.

### *B. SUGGESTED INDUSTRY BEST PRACTICES IN THE DEVELOPMENT AND MARKETING OF MEDICAL FOODS*

The MF category is currently governed by statutes, regulations, and guidance. Unfortunately, some of this regulation/guidance is poorly defined and coordinated with regard to actions by CDER and CFSAN as discussed with IND requirements. There is also no review or approval process of MF, which has created confusion among manufacturers, drug listing companies, payers, physicians, and pharmacists as to what constitutes a valid medical food.<sup>137</sup> Due to the various contradictions in guidance, limited regulations, and confusion in the MF category, we propose additional “Best Practices” that add to current requirements to aid industry in developing MF products. These best practices suggest the minimum necessary requirements and provide guidance on current gaps in FDA regulation to develop, manufacture, as well as market a MF. These best practices should be considered by all companies in the industry when developing products (Table 3).

Table 3

Requirement	Best Practice Recommendations to Industry
Formulation	<input type="checkbox"/> Formulation of MFs with GRAS ingredients. We propose a safety dossier for determination of GRAS must be published in a peer-reviewed journal or reviewed by FDA which will then affirm a conclusion of GRAS status.
Distinctive Nutritional Requirement	<p>We propose the following definition for what constitutes a “distinctive nutritional requirement” based on language in the ANPR:<sup>138</sup></p> <p><i>A distinctive nutritional requirement for a MF is the physical, physiological or metabolic requirement of a generally recognized as safe, specially formulated nutritional substance(s) needed to restore and/or maintain homeostatic processes (the state of equilibrium in the body with respect to various functions</i></p>

<sup>137</sup> See Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,661–62 (Nov. 29, 1996).

<sup>138</sup> See Regulation of Medical Foods, 61 Fed. Reg. 60,661, 60,667 (Nov. 29, 1996).

	<p><i>and to the chemical compositions of the fluids and tissues) for the management of a specific chronic condition or disease.</i></p> <p>We propose establishment of a distinctive nutritional requirement for a MF in a specific condition or disease by one of the following:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Expert panel, published peer-reviewed article examining the preponderance of evidence in peer-reviewed, published literature;</li> <li><input type="checkbox"/> Company-sponsored, peer-reviewed, and published manuscript;</li> <li><input type="checkbox"/> Presentation at scientific and/or medical congresses of data that supports the distinctive nutritional requirement(s);</li> <li><input type="checkbox"/> At least one peer-reviewed, prospective, published, randomized, clinical study (i.e., placebo, active comparator or case controlled) that adequately demonstrates the existence of such distinctive nutritional requirement(s)</li> </ul>
Clinical Substantiation	<p>We propose that companies substantiate their intended use of a MF by any of the following:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Peer-reviewed, published, retrospectively gathered, HIPAA-compliant case studies, histories or series where the medical food is used alone or added to standard-of-care to management of a chronic condition or disease;</li> <li><input type="checkbox"/> Peer-reviewed, published registry studies done under IRB supervision with or without informed consent (IC) where data is added by choice of the physician as observations in the management of a chronic condition or disease as part or added to standard-of-care;</li> <li><input type="checkbox"/> Peer-reviewed, published investigator-initiated trials (IITs) performed under IRB supervision with IC;</li> <li><input type="checkbox"/> Peer-reviewed, published collaborative clinical trials sponsored by the manufacturer with shared costs by the investigator, institution, granting agency, etc., performed under IRB supervision with IC;</li> <li><input type="checkbox"/> Pre- or post-marketing, peer-reviewed, published randomized, clinical studies done under IRB supervision with IC, whether or not sponsored by the manufacturer of the medical food that assesses the product's ability to provide for the distinctive nutritional requirements in the management of a chronic condition or disease. Such clinical studies may be placebo or active comparator-controlled, dose ranging or open-label with comparison to pre-existing clinical status in design.</li> </ul>
Labeling	<p>We propose that:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> all MFs should have a package insert to assure proper instructions for the intended use.</li> <li><input type="checkbox"/> the package insert should also contain the distinctive nutritional requirement met by administration, clinical substantiation, and adverse events as well as the Medwatch Program contact information;</li> </ul>



	<ul style="list-style-type: none"> <li><input type="checkbox"/> MFs may use a stocking number such as a UPC code to allow for retrieval of the product through pharmacies.</li> </ul>
Manufacture	<p>We propose that:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> all raw materials used in a MF must be tested for identification, microorganisms, residual solvents, and prohibited impurities, including, but not limited to, toxic heavy metals using USP standards and have a verifiable chain of custody history;</li> <li><input type="checkbox"/> MF manufacturing and packaging must undergo validation pursuant to a properly executed validation protocol;</li> <li><input type="checkbox"/> all equipment used in the manufacture and storage of a MF must be properly validated (IQ, OQ, and PQ) and must be approved for food use;</li> <li><input type="checkbox"/> all packaging components (resins) for a MF shall undergo proper USP testing prior to use and are approved for food use, and;</li> <li><input type="checkbox"/> MFs must be manufactured and packaged in facilities with an effective quality control system in place that meet current manufacturing requirements;<sup>139</sup></li> <li><input type="checkbox"/> labeling must contain an expiration date or “use by date” supported by industry standard stability test data;</li> <li><input type="checkbox"/> all new MFs must undergo a manufacturing development and validation process including scale-up validation;</li> <li><input type="checkbox"/> all batches of MFs must undergo industry standard testing (assay, dissolution, micro, stability) prior to release;</li> <li><input type="checkbox"/> finished medical food products must not contain any microorganisms listed in FDA’s “Bad Bug Book”;<sup>140</sup></li> </ul>
Physician Supervision	<ul style="list-style-type: none"> <li><input type="checkbox"/> MFs are NOT allowed to be OTC as this does not meet the standard of medical supervision under current regulation;<sup>141</sup></li> <li><input type="checkbox"/> We propose that MFs may be “administered under the direction of a physician” or other licensed healthcare provider by chart order, call-in to the pharmacy, paper prescription and/or electronic prescription systems;</li> <li><input type="checkbox"/> We propose that MFs labeling may contain language such as “administered by prescription,” “dispensed by prescription” or “dispensed by Rx” to meet the standard of medical supervision under current regulation.<sup>142</sup></li> </ul>
Marketing	<p>We propose that:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> MFs MAY be marketed directly to consumers according to the intended use as long as the product is dosed and supervised by a physician or other licensed healthcare provider;</li> </ul>

<sup>139</sup> See generally, 21 C.F.R. §§ 101, 110, 111, 119, 190.

<sup>140</sup> See generally FDA, BAD BUG BOOK: HANDBOOK OF FOODBORNE PATHOGENIC MICROORGANISMS AND NATURAL TOXINS (2d ed. 2012), <http://www.fda.gov/Food/FoodborneIllnessContaminants/CausesOfIllnessBadBugBook/>.

<sup>141</sup> See 21 C.F.R. § 101.9(j)(8) (2016).

<sup>142</sup> *Id.*

	<input type="checkbox"/> MFs CANNOT be OTC products; <input type="checkbox"/> MF advertising should include “fair balance” of information about risks as compared with information about benefits.
--	---

There is a concern that industry proposed best practices may be inadequate to assure that companies formulate, substantiate, manufacture, and market medical foods in an ethical manner similar to drugs. For example, companies may choose to not perform well-controlled clinical studies due to the current FDA IND guidance from the drug division,<sup>143</sup> or they may not want to invest in the money required to prove efficacy in well-constructed clinical studies.<sup>144</sup> Or, companies may not publish their safety data or submit a GRAS notice to FDA. Therefore, in addition to the best practices proposed above to guide industry in developing MF products, we recommend an eventual stronger regulatory structure be put in place by FDA to define terms in the Orphan Drug Act such as what constitutes a “distinctive nutritional requirement” and “physician supervision.”<sup>145</sup> In addition, we suggest that FDA define a clear regulatory pathway for review and/or approval, which includes specific requirements for clinical efficacy and safety substantiation. We also ask that FDA work with industry partners, nutrition scientists, physician societies, nutrition societies, and patient organizations to help construct a regulatory structure for MFs that meets the needs of all involved, but especially patients with chronic conditions and diseases. Finally, we urge Congress to give FDA the ability through new statutes to review and approve products in the MF category. Based on the safety profile of these products and if they are proven to be efficacious, this should decrease costs to the healthcare system. In the interim, these proposed best practices should be utilized by companies to develop, test, and market MFs.

## CONCLUSION

Medical foods have been utilized for decades in the U.S. and contributed to the safe management of chronic conditions and diseases in millions of patients. Products that meet the statutory definition of MF have proven efficacy for their intended disease targets and have low toxicity as a consequence of being composed of GRAS ingredients. Thus, MFs are capable of improving quality of life of patients with a minimum of adverse effects. After languishing for years since the establishment of the MF category by an update to the Orphan Drug Act due to a lack of FDA direction, it is time that “Best Practices” be utilized by industry for the development, manufacture, and marketing of these products toward an eventual formalized approval process unique to the MF category. Formal regulatory definitions for various terms including “distinctive nutritional requirement,” “dietary management of a condition or disease,” “based on recognized scientific principles,” “use under medical or physician

---

<sup>143</sup> *Id.*

<sup>144</sup> Tish Eggleston Pahl, *The FDA’s Final IND Guidance – A Bitter Pill for Food and Nutrition Research*, OFW LAW (Jan. 8, 2014), <http://www.ofwlaw.com/2014/01/08/the-fdas-final-ind-guidance-a-bitter-pill-for-food-and-nutrition-research/>.

<sup>145</sup> *Id.*

supervision,” and established by medical evaluation in the Orphan Drug Act,<sup>146</sup> regulation<sup>147</sup> as well as the current MF FAQs<sup>148</sup> are needed so that industry understands the rules of the road for product development and marketing of these formulations. In addition, Congress needs to act to give CFSAN the ability for pre-market review and/or approval of MF products. These changes must come quickly as headwinds against MF nutritional therapeutics have reached a point where patients have more and more limited access, which could result in harm. It would behoove all parties involved to meet and help establish a robust MF category as FDA approved drugs are insufficient to meet the needs of millions of American patients with chronic diseases and conditions.

Other countries are well on their way in making their equivalent to medical foods standard-of-care. Europe, which adapted the MF category from the U.S. as “foods for special medical purposes,” is in the process of finalizing an approval system for such products utilizing the European Food Safety Authority for review of ingredients, safety and substantiation.<sup>149</sup> China just finalized a process for review emphasizing not only specific information on formulation, manufacturing, and the need for the food for special medical purposes, but also submission of clinical trial reports.<sup>150</sup> The U.S., which has utilized these products for patient care for decades, is in danger of actually dissolving a category of needed, safe nutritional therapies. It appears time, then, for the United States to recognize the validity of a MF industry that uses modern scientific methodology to understand and apply the molecular basis for nutritional therapeutic interactions to diseased populations. Best Practices followed by industry are the starting point while FDA and all parties involved begin to define regulations and everyone waits on Congress to act to grant authority for review/approval of the MF category.

---

<sup>146</sup> Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended 21 U.S.C. §§ 301 et seq., 360aa).

<sup>147</sup> See 21 C.F.R. § 101.9(j)(8).

<sup>148</sup> FDA, *supra* note 46.

<sup>149</sup> *Scientific Opinion of the European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies Scientific and Technical Guidance on Foods for Special Medical Purposes in the Context of Article 3 of Regulation (EU) No 609/2013* (Nov. 2015), <http://www.efsa.europa.eu/en/efsajournal/pub/4300>.

<sup>150</sup> See Measures for the Administration of the Registration of Foods for Special Medical Use (China Food and Drug Administration Order No. 24), <http://www.sda.gov.cn/WS01/CL0053/146741.html>.