



# Nutraceutical and Functional Food Regulations in the United States and Around the World

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# Understanding Medical Foods under FDA Regulations

# 11

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## 11.1 History of medical foods

It took the Food and Drug Administration (FDA) 50 years after the passage of the Federal Food, Drug, and Cosmetic Act (FDCA) to formally define “medical foods.” Prior to 1972, what we now would consider medical foods were regulated as prescription drugs under section 201(g)(1)(B) of the FDCA because of their role in mitigating serious adverse effects of diseases.<sup>1</sup> Furthermore, prior to 1972, to market new products, manufacturers of medical foods were subject to onerous requirements, such as conducting complete drug trials, Investigational New Drug license applications, and New Drug Applications. Extremely time-consuming and cost-restrictive, such requirements choked the life out of medical food product innovation.

In 1972, the FDA reassessed its position on medical foods. This action was prompted by the agency’s interest in fostering innovation in the development of medical foods and ensuring that such products were available to the public at a reasonable cost. However, due to safety concerns, the agency still sought to differentiate medical foods from general use foods. For example, the FDA reasoned that Lofenalac, an infant product designed for use in the dietary management of a rare genetic condition known as phenylketonuria (PKU), would be hazardous for healthy infants since it would be nutritionally inadequate for them. Therefore, the agency reclassified medical foods provided *enterally* (i.e., ingested via the digestive tract) as “foods for special dietary use,” but injectable medical foods remained classified as drugs

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<sup>1</sup>Advanced Notice of Proposed Rulemaking, Regulation of Medical Foods, 61 Fed. Reg. 60661, 60662 (Nov. 29, 1996).

subject to the FDA's Drug Efficacy Study (DESI) program.<sup>2</sup> In short, enterally administered nutrition was transferred to the food category while parenteral nutrition (i.e., injected into the body) retained its drug status.

Just one year later, when the agency made nutrition labeling mandatory for certain foods, it exempted certain types of foods for special dietary use from this requirement.<sup>3</sup> In the preamble of the final rule, the FDA noted that nutrition labeling developed for foods intended for consumption by the general population was not well suited for some food products. Two foods for special dietary use were exempted from the nutrition labeling required for other food: (1) any food represented for use as the sole item of the diet and (2) foods represented for use solely under medical supervision in the dietary management of specific diseases and disorders.

A statutory definition of medical foods was finally promulgated in the Orphan Drug Amendments of 1988, Section 5b, Orphan Drug Act.<sup>4</sup> A medical food was defined as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."<sup>5</sup> This statutory definition remains unchanged. Unfortunately, the legislative history of the amendments does not discuss the statutory definition of medical foods, thus failing to provide any additional information regarding the types of products Congress intended the definition to cover.<sup>6</sup>

Soon after the Orphan Drug Act Amendments, the FDA formally launched its initiative to improve the content and format of food labels with the publication of an Advanced Notice of Proposed Rulemaking (ANPR).<sup>7</sup> As part of this overall initiative, the agency sought to resolve consumer confusion about food labels, aid consumers in health food decisions, and encourage product innovations so that manufacturers were

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<sup>2</sup>The FDA recognized foods for "special dietary use" as early as 1941. Per regulation, the FDA stated that the term "special dietary uses" as applied to food for man, meant, among other things, "uses for supplying particular dietary needs which exist by reason of a physical, physiological, pathological or other condition, including but not limited to the conditions of disease, convalescence, pregnancy, lactation, allergic hypersensitivity to food, underweight, and overweight." Amendment to the General Regulations, Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act, 6 Fed. Reg. 5921 (Nov. 22, 1941). This part of the regulation remains unchanged in the Code of Federal Regulations. See 21 C.F.R. § 105.3(a)(1) (September 17, 2013).

<sup>3</sup>8 Fed. Reg. 2124, 2126 (January 19, 1973).

<sup>4</sup>21 U.S.C. § 360ee(b)(3). Foods for special dietary use were often referred to as "orphan" because they were developed for the treatment of rare disorders that affect fewer than 200,000 persons in the United States. T.P. Labuza, *Food Laws and Regulations: The Impact on Food Research*, 36 Food Drug Cosmetic L.J. 293 (1981).

<sup>5</sup>21 U.S.C. § 360ee(b)(3). The amendments also introduced a subcategory called "orphan medical foods" to be used in the management of "...any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such a disease or condition will be developed without assistance." *Id.*

<sup>6</sup>61 Fed. Reg. 60662.

<sup>7</sup>54 Fed. Reg. 32610 (August 8, 1989).

given an incentive to improve the quality of the food and provide consumers with more healthy food choices.<sup>8</sup> In the ANPR, the FDA asked the industry for guidance on a wide range of food-labeling issues to assist the agency in determining what, if any, changes to food labeling requirements were necessary, and it was quickly followed by four public hearings. With obvious public support for a thorough modernization of food labeling, the FDA published proposed regulations on July 19, 1990.<sup>9</sup>

It was during the comment period for the proposed regulations that Congress passed the Nutrition Labeling and Education Act of 1990 (NLEA), and on November 8, 1990, the legislation was signed into law by President George H. Bush. Not only did the NLEA affirm the FDA's authority to mandate nutrition labeling on most foods and clarify the agency's role in regulating nutrient content claims and health claims on food labels, it also incorporated the definition of medical foods contained in the Orphan Drug Amendments of 1988 into Section 403(q)(5)(A)(iv) of the FDCA and exempted medical foods from the nutrition labeling, health claim, and nutrient content claim requirements applicable to foods generally.<sup>10</sup>

Quickly thereafter, the FDA published a proposal to implement the mandatory nutrition labeling provisions of the NLEA, focusing specifically on the statutory exemption for medical foods.<sup>11</sup> The proposal advised that the agency considered the statutory definition of medical foods to “narrowly constrain the types of products that can be considered to fall within this exemption,”<sup>12</sup> a sentiment that the FDA has since reiterated time and again. Further, the FDA explained how medical foods are distinguished from the broader category of foods for special dietary use and from foods that make health claims. In the FDA's opinion, “under the supervision of a physician” within the NLEA meant “that the intended use of a medical food is for the dietary management of a patient receiving active and ongoing medical supervisions (e.g., in a health care facility or as an outpatient). The physician determines the food that is necessary to the patient's overall medical care,”<sup>13</sup> and the patient visits the doctor for instructions on the use of the medical food. In its closing remarks on medical foods, the FDA stressed the vital public health interest in proper labeling of the nutrient content and purported uses of medical foods, which it noted may require a different manner and more detail than more traditional foods, adequate and appropriate directions for use, and product quality assurance. Thus, the agency declared that it intended to develop regulations covering these aspects “in the near future.”<sup>14</sup>

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<sup>8</sup>Virginia Wilkening, *The Nutrition Labeling and Education Act of 1990* (November 27, 1991), [http://www.nutrientdataconf.org/PastConf/NDBC17/8-2\\_Wilkening.pdf](http://www.nutrientdataconf.org/PastConf/NDBC17/8-2_Wilkening.pdf) (last visited September 17, 2013).

<sup>9</sup>55 Fed. Reg. 29456 (July 19, 1990).

<sup>10</sup>Nutrition Labeling and Education Act § 2(a)(1990).

<sup>11</sup>56 Fed. Reg. 60366 (November 27, 1991).

<sup>12</sup>*Id.* at 60377.

<sup>13</sup>*Id.*

<sup>14</sup>*Id.*, at 60378.

In the Federal Register of January 6, 1993, the FDA published the final rule on mandatory nutrition labeling, which exempted medical foods from the nutrition labeling requirements and incorporated the statutory definition of medical foods into the agency's regulations at Section 101.9(j)(8).<sup>15</sup> In the regulation, the FDA enumerated criteria intended to clarify the characteristics of medical foods. Accordingly, a food was defined as a medical food and, thus, not subject to the nutrition labeling requirements only if:

1. It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding tube.
2. It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone.
3. It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation.
4. It is intended to be used under medical supervision.
5. It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.<sup>16</sup>

This definition remains unchanged. In addition, the agency acknowledged that further clarification on the specific types of products the FDA considers medical foods would be helpful. Accordingly, it expressed its intention to address the issue in the future, but also noted its objective to develop much-needed medical food-labeling regulations.<sup>17</sup>

Citing the enactment of a statutory definition of medical food, the rapid increase in the variety and number of products marketed as medical foods, safety problems associated with the manufacture and quality control of these products, and the potential proliferation of fraudulent claims not supported by sound science, the FDA issued an ANPR on the "Regulation of Medical Foods" in 1996.<sup>18</sup> The agency also sought to clarify the distinct differences between medical foods and foods for special dietary purpose. Though this ANPR was withdrawn in 2004,

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<sup>15</sup>58 Fed. Reg. 2079, 2151 (January 6, 1993).

<sup>16</sup>21 C.F.R. § 101.9(j)(8).

<sup>17</sup>58 Fed. Reg. 2151.

<sup>18</sup>61 Fed. Reg. 60662.

it largely remains the guiding force for industry understanding of the agency's views of medical food regulation.<sup>19</sup>

In the 1996 ANPR, the FDA acknowledged that the universe of products purporting to be medical foods had surpassed the statutory definition of a medical food to include foods that would more appropriately be categorized as foods for special dietary use. Looking to statutory language, the FDA sought to outline distinctions between these two types of foods, beginning with the meaning of “distinctive nutritional requirements” in the FDCA’s definition of medical food. Pursuant to the statute, distinctive nutritional requirements must be based on recognized scientific principles and established by medical evaluation. Unfortunately, as the FDA noted in the ANPRM, the law does not define distinctive nutritional requirements. As a result, the agency proposed two possible interpretations of the phrase: (1) physiological interpretation and (2) alternative interpretation.

In the physiological interpretation, the FDA advised that distinctive nutritional requirements could be understood as referring to the body’s need for specific amounts of nutrients to maintain homeostasis and sustain life. Under this interpretation, medical foods are

*foods that are formulated to aid in the dietary management of a specific disease or health-related condition that causes distinctive nutritional requirements that are different from the nutritional requirements of healthy people. Foods for special dietary use, on the other hand, are foods that are specially formulated to meet a special dietary need, such as a food allergy or difficulty in swallowing, but that provide nutrients intended to meet ordinary nutritional requirements. The special dietary needs addressed by these foods do not reflect a nutritional problem per se; that is, the physiological requirements for nutrients necessary to maintain life or homeostasis addressed by foods for special dietary use are the same as those of normal, healthy*

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<sup>19</sup>69 Fed. Reg. 68834 (November 26, 2004). The FDA declared 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.

*persons. These foods are formulated in such a way that only the ingredients or physical form of the diet is different.*<sup>20</sup>

On the other hand, the agency stated in the alternative interpretation that distinctive nutritional requirement may be construed to encompass physical and physiological limitations in a person's ability to ingest or digest conventional foods, as well as distinctive physiological nutrient requirements.<sup>21</sup> Similarly, the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (LSRO/FASEB Panel) noted in its 1990 *Guidelines for the Scientific Review of Enteral Food Products for Special Medical Purposes* that medical foods are for "patients with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients contained therein, or (who) have other specialized medically determined nutrient requirements."<sup>22</sup> After quoting this purpose, the FDA stated that the definition of distinctive nutritional requirement would include

*foods intended for persons not able to ingest foods in certain physical forms (e.g., solid food), foods intended for persons who need a concentrated form of nutrition because of reduced appetite as a result of disease or convalescence, or foods intended for persons who may have other physical limitations on the amount or composition of food that they can consume. Although these types of conditions do not necessarily result in nutrient needs different from those of healthy persons, they represent a situation where it may be necessary that the food be formulated and manufactured within very narrow tolerances to ensure that the food provides most or all of the essential nutrients, as the person for whom the food is intended may not be able to eat a variety of foods to ensure that they meet their nutritional requirements.*<sup>23</sup>

The second element that the FDA recognized as a distinguishing attribute of medical foods is the statutory requirement that a medical food be "formulated to be consumed or administered enterally under the supervision of a physician." As a general requirement, the patient must be receiving short- or long-term "active and ongoing" medical supervision (e.g., in a health care facility or as

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<sup>20</sup>61 Fed. Reg. at 60667. The agency provided an example of a person possessing a special dietary need for a food that is in liquid form due to problems swallowing, noting that this special dietary need does not change his or her physiologic nutrient requirements. Along the same lines, a person allergic to gluten may need foods specially formulated, but the food would still provide the same amount of amino acids as needed by the general population because the quantitative and qualitative amount of overall protein required by the body is similar in both healthy and protein-sensitive individuals. *Id.*

<sup>21</sup>*Id.*

<sup>22</sup>J.M. Talbot, *Guidelines for the Scientific Review of Enteral Food Products for Special Medical Purposes*, Life Sciences Research Office, Federation of American Societies for Experimental Biology (1990).

<sup>23</sup>61 Fed. Reg. at 60668.

an outpatient).<sup>24</sup> Unlike foods for special dietary purposes, the FDA views medical foods as an integral component of the patient’s clinical management. Medical foods are not just simply recommended by a physician as a “part of an overall diet designed to reduce the risk of a disease or medical condition, to lose or maintain weight, or to ensure the consumption of a healthy diet.”<sup>25</sup>

The final fundamental element of the definition of medical food addressed in the 1996 ANPR is the statutory requirement that a medical food be intended for the “specific dietary management” of a disease or condition. The FDA advised that the term “specific dietary management. . . evidences that Congress intended [medical] foods to be an integral part of the clinical treatment of patients.”<sup>26</sup> The agency also cited the LSRO/FASEB Panel’s conclusion that the objective of incorporating the use of medical foods into patient management was, in part, to “ameliorate clinical manifestations of the disease,” “favorably influence the disease process,” and “positively influence morbidity and mortality (patient outcomes).”

Axona is an example of a medical food widely prescribed by physicians today. Axona, developed by Accera, is a medical food to provide the necessary nutrients for patients with Alzheimer’s disease (AD). It has been clinically shown to improve cognitive function in some patients with AD, the leading cause of dementia, and does not increase metabolism. AD is a neurodegenerative disease characterized by a decline in the ability of the brain to metabolize glucose, even in its early stages. Axona is made from caprylic triglyceride and other medium chain triglycerides, which are converted to ketone bodies by the liver, an alternative energy source for cerebral neurons.

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## 11.2 FDA guidance

In May 2007, the FDA published its first draft guidance (Draft Guidance) for the industry of medical foods.<sup>27</sup> This guidance reiterated the statutory and regulatory provisions addressing medical foods, as well as the FDA’s long-standing interpretations of those authorities. However, the guidance included no new statements of policy. Instead, the agency noted that the Draft Guidance was intended to be a convenient place for the industry to find answers to common medical food questions.

Just recently, in August 2013, the FDA released a revised version of its Draft Guidance (Revised Draft Guidance).<sup>28</sup> The Revised Draft Guidance was published the very same day the agency issued its second Warning Letter regarding medical

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<sup>24</sup>*Id.* (citing 56 Fed. Reg. 60377).

<sup>25</sup>*Id.*, at 60668.

<sup>26</sup>*Id.*

<sup>27</sup>FDA, Draft Guidance for Industry, Frequently Asked Questions About Medical Foods (May 2007).

<sup>28</sup>FDA, Draft Guidance for Industry: Frequently Asked Questions About Medical Foods (2d ed. August 13, 2013), <http://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocuments/RegulatoryInformation/MedicalFoods/UCM362995.pdf> (last visited September 17, 2013) (hereinafter, “Revised Draft Guidance”).



foods in 2013,<sup>29</sup> discussed in the enforcement section below. This Revised Draft Guidance both amended and expanded upon the original draft guidance published in 2007 by incorporating 15 new questions and answers. Specifically, the agency addressed medical food labeling, physician supervision, and the scope of permissible diseases or conditions that medical foods may be labeled or marketed to manage.

The Revised Draft Guidance first addressed the FDA's understanding of the medical food definition. The 2007 Draft Guidance described medical foods as foods that are "specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for the patient who is seriously ill or who requires the use of the product as a major treatment modality." The Revised Draft Guidance replaced the technical term "treatment modality" with the phrase "component of a disease or condition's specific dietary management," signifying the agency's growing emphasis on the idea that a medical food must be designed for dietary management of a disease condition, rather than generalized treatment.

The agency also reiterated that medical foods cannot be labeled or marketed for a disease or condition that can be *managed solely by a normal diet alone*. Such conditions or diseases discussed specifically in the Draft Guidance include inborn errors of metabolism (IEMs), pregnancy, diabetes mellitus (types 1 and 2), and nutrient deficiency diseases.

### 11.2.1 IEMs

IEMs, which include inherited biochemical disorders in which a specific enzyme defect interferes with the normal metabolism of protein, fat, or carbohydrate, are generally considered to be diseases or conditions that a medical food may be used to manage, according to the Revised Draft Guidance. Some IEMs can be managed solely with modification to the normal diet, but others cannot. For those IEMs that can be managed solely with modification to the normal diet (e.g., reduction of galactose and lactose for galactosemia), the FDA indicated that it would not be appropriate for a medical food to be labeled or marketed for that condition. For those IEMs that cannot be managed solely with modification to the normal diet, a medical food is required in addition to a specific dietary modification (e.g., reduced total protein/phenylalanine for PKU). A non-exclusive list of specific IEMs that medical foods could be used to manage is included in the 2013 Draft Guidance.

*Pregnancy.* The FDA does not consider pregnancy a disease, instead agreeing with the Institute of Medicine that it is a "life stage." The agency also does not consider pregnancy to be a condition for which a medical food could be labeled or marketed. The Revised Drafted Guidance explained that "generally the levels of micronutrients necessary for pregnancy can be achieved by the modification of the normal diet alone."

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<sup>29</sup>FDA, Warning Letter, Metagenics (August 13, 2013), <http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm367142.htm> (last visited September 17, 2013).

*Diabetes Mellitus (DM) Types 1 and 2.* The FDA does not generally consider a product labeled and marketed for DM to meet the regulatory criteria for a medical food, based on the theory that “diet therapy is the mainstay of diabetes treatment.” In the Revised Draft Guidance, the agency provided that a regular diet can be modified to meet the needs of a person with DM (along with appropriate drug therapy, if necessary).

*Nutrient Deficiency Diseases.* The agency explained in the Revised Draft Guidance that it does not consider classical nutrient deficiency disease, like scurvy or pellagra, to be diseases for which a medical food could be labeled and marketed. Excluding any permanent physical damage, such diseases can typically be corrected once foods (or dietary supplements) with these essential nutrients are consumed. In short, nutrient deficiency disease can be managed by normal diet alone.

The Revised Draft Guidance also emphasized that no written or oral prescription is necessary for medical foods. However, the FDA reiterated that it does not consider foods that are simply recommended by a physician or other health care professionals as part of an overall diet designed to reduce the risk of a disease or medical condition or to help support weight loss to be medical foods. Rather, the statutory requirements that a medical food be consumed or administered enterally “under the supervision of a physician” 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) of a physician who has determined that the medical food is necessary to the patient’s overall medical care.” The FDA stated it expects that the patient should generally see the physician on a recurring basis for, among other things, instructions on the use of the medical food.

With regard to labeling of medical foods, the guidance explained that medical foods are misbranded if their labeling bears the symbol “Rx only” and/or National Drug Code (NDC) numbers. However, the FDA does not object to the use of language communicating that the medical food may only be distributed enterally under the supervision of a physician. The FDA provided the following example of a permissible statement: “must be used under the supervision of a physician.”

The FDA is accepting comments on the Draft Guidance until October 15, 2013.

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## 11.3 Good manufacturing practices and import/export

Medical foods must comply with all applicable FDA requirements for foods. This includes the regulations pertaining to Current Good Manufacturing Practices (cGMPs),<sup>30</sup> Registration of Food Facilities,<sup>31</sup> and, if applicable, those specific to the

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<sup>30</sup>21 C.F.R. part 110.

<sup>31</sup>21 C.F.R. part 1, Subpart H.

product formulation and processing.<sup>32</sup> Examples of formula- and processing-specific regulations include those for thermally processed low-acid foods packaged in hermetically sealed containers,<sup>33</sup> acidified foods,<sup>34</sup> and emergency permit control.<sup>35</sup> Even though the level of industry experience in the cGMP and quality control procedures necessary to produce medical foods (i.e., products that contain nutrients within a narrow range of declared label values) increased in the decade directly following the establishment of the statutory definition of medical food, the agency felt it necessary to create compliance programs specifically designed for medical foods.

As noted in the 1996 ANPR, medical foods are complex formulated products requiring sophisticated and exacting technology comparable to that used in the manufacture of infant formulas and drugs.<sup>36</sup> Moreover, the populations that consume such foods are often extremely vulnerable, such as pediatric patients at periods of growth and development or the elderly. For these reasons, the FDA published its Medical Foods Compliance Program for domestic and imported products as part of the agency's Compliance Program Guidance Manual in 1996.<sup>37</sup> This program, which the FDA has explicitly stated is a "high priority" due to the "susceptible population for which the products are intended,"<sup>38</sup> remains in effect today.

The FDA's compliance program for medical foods provides FDA inspectors direction to (1) obtain information regarding the manufacturing/control processes and quality assurance programs employed by domestic manufacturers of medical foods through establishment inspections, (2) collect domestic and import surveillance samples of medical foods for nutrient and microbiological analyses; and (3) recommend action when significant violations of the FDCA and/or related regulations are detected.<sup>39</sup> During an inspection of a medical food facility, agency inspectors review labeling, promotional materials, brochures, and correspondence with physicians. They also collect samples of recent lots for microbiological and nutrient content analyses.<sup>40</sup>

Pursuant to its medical food compliance program, the FDA has also compiled a list of known non-U.S. medical food manufacturers and their products.<sup>41</sup> The inspection of these firms includes collection of medical food products intended for exportation to the United States, but they do not need to be routinely

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<sup>32</sup>See Revised Draft Guidance at 6.

<sup>33</sup>21 C.F.R. part 113.

<sup>34</sup>21 C.F.R. part 114.

<sup>35</sup>21 C.F.R. part 108.

<sup>36</sup>61 Fed. Reg. at 6066.

<sup>37</sup>FDA, Compliance Program Guidance Manual, Medical Foods Compliance Program § 7321.002 (1996), <http://www.fda.gov/downloads/Food/ComplianceEnforcement/ucm073339.pdf> (hereinafter, "Compliance Program") (last visited September 17, 2013).

<sup>38</sup>*Id.*, Introduction at 1.

<sup>39</sup>Revised Draft Guidance at 7.

<sup>40</sup>Compliance Program, Part III at 2.

<sup>41</sup>*Id.*, Part III at 3. This list, labeled Attachment A in the Compliance Program, is not for public distribution.

sampled under the compliance program when offered for import.<sup>42</sup> All imported and other shipments of medical foods not on the FDA's list "must be sampled and held" pending test results.<sup>43</sup>

In addition to the compliance program, the FDA has identified certain non-U.S. medical foods to be detained without physical examination under Import Alert #41-03.<sup>44</sup> According to the Alert, firms may be listed on the so-called "Red List" because the most recent FDA inspection conducted revealed that the facility was (1) not following cGMPs or was otherwise preparing, packing, or holding products under insanitary or other conditions that could render the products injurious to health and/or (2) one or more medical foods manufactured at the facility were analyzed by the FDA and classified as violating the FDCA (and/or its corresponding regulations).<sup>45</sup> Of note, a firm may also appear on the Red List if the product label misstates the active amount of an ingredient. An example is if a product is marketed as "low carbohydrate" contains 11 grams of carbohydrate based on agency testing when its label claims it only has 3 grams.<sup>46</sup> Two firms are currently on the Red List: Laboratorio Pisa Sa De Cv (Mexico) and Sunspray Food Ingredients Ltd. (South Africa).

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## 11.4 FDA enforcement of medical foods

To our knowledge, the FDA issued its first Warning Letter concentrating on medical foods in 2001.<sup>47</sup> Since then, 11 more Warning Letters have been distributed, the most recent of which was in August 2013,<sup>48</sup> the very same day as the release of the Revised Draft Guidance.

As in its other letters, the FDA stated in the August 2013 letter that it considers the statutory definition of medical food to "narrowly constrain" the types of products that fit within this category. Accordingly, the FDA told the company that:

*[A] medical food must be intended for a patient who has a 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. . . . [Y]our products do not meet these requirements and therefore do not qualify as medical foods under either the statute or FDA's regulations.*

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<sup>42</sup>*Id.*

<sup>43</sup>*Id.*

<sup>44</sup>FDA, Import Alert #41-03, *Detention Without Physical Examination of Adulterated and Misbranded Medical Foods* (Oct. 12, 2011), [http://www.accessdata.fda.gov/cms\\_ia/importalert\\_117.html](http://www.accessdata.fda.gov/cms_ia/importalert_117.html) (last visited September 17, 2013).

<sup>45</sup>*Id.*

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

<sup>47</sup>FDA, Warning Letter, Bristol-Myers Squibb Company (August 29, 2001), <http://www.fda.gov/iceci/enforcementactions/warningletters/2001/ucm178451.htm> (last visited September 17, 2013).

<sup>48</sup>FDA, Warning Letter, Metagenics (August 13, 2013), <http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm367142.htm> (last visited September 17, 2013).

Pursuant to this letter, the agency does not consider the following as diseases or conditions eligible for treatment and/or maintenance with medical foods: chronic fatigue syndrome; fibromyalgia; leaky gut syndrome; metabolic syndrome; cardiovascular disease; inflammatory bowel disease and/or conditions; type 2 diabetes, atopic disorders such as eczema, rhinitis, and allergy-responsive asthma; bariatric patients preoperatively and postoperatively; and peripheral artery disease.

Other conditions named within the last decade in Warning Letters as being inappropriate for medical foods include inflammatory conditions, migraines,<sup>49</sup> immune system deficiencies, AD<sup>50</sup>; arthritis; colitis; constipation; lactose intolerance; diarrhea<sup>51</sup>; chronic illnesses; failure to thrive; pre- and post-surgery conditions<sup>52</sup>; and vitamin deficiency throughout pregnancy, postnatal, and the lactating periods.<sup>53</sup> In each of these letters, the agency took one or more of the following positions: (1) there was inadequate evidence that the disease had distinct nutritional requirements, (2) there was inadequate evidence that the particular food at issue would meet the distinct nutritional requirements of the disease, and/or (3) there was no available evidence illustrating that the nutrient levels cannot be achieved by diet modification alone.

Aside from the Warning Letters, the FDA has not actively enforced the medical food regulations. However, the publication of the 2013 Revised Draft Guidance, combined with the issuance of the August 2013 Warning Letter, signals the FDA's heightened commitment in regulating this industry. Additional law enforcement efforts may soon follow in the coming year.

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## 11.5 Looking forward

The use of medical foods has grown steadily since the introduction of Lofenalac® over 40 years ago. Just within the last few years, however, the medical food market has prolifically expanded. In the United States and globally, there have been more than 100 new medical food product launches annually since 2009.<sup>54</sup> However, the actual size of the medical food market is unclear. In light of increasing use in long-term care and the aging baby boomer population,

<sup>49</sup>FDA, Warning Letter, Metagenics (October 1, 2003), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2003/ucm147751.htm> (last visited September 17, 2013).

<sup>50</sup>FDA, Warning Letter, Neuroscience, Inc. (December 19, 2011), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm284391.htm> (last visited September 17, 2013).

<sup>51</sup>FDA, Warning Letter, Ganeden Biotech Inc. (December 8, 2006), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076208.htm> (last visited September 17, 2013).

<sup>52</sup>FDA, Warning Letter, Nestle Healthcare Nutrition (December 3, 2009), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm194121.htm> (last visited September 17, 2013).

<sup>53</sup>FDA, Warning Letter, Pan American Laboratories, Inc. (November 20, 2009), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm191841.htm> (last visited September 17, 2013).

<sup>54</sup>Gregory Stephens, *Convergence of the Health Practitioner Channel & Medical Foods*, Nutraceuticals World (June 3, 2013), [http://www.nutraceuticalsworld.com/issues/2013-06/view\\_columns/convergence-of-the-health-practitioner-channel-medical-foods/](http://www.nutraceuticalsworld.com/issues/2013-06/view_columns/convergence-of-the-health-practitioner-channel-medical-foods/) (last visited September 17, 2013).

continued strong growth is likely. In 2011, global sales were projected at just less than \$9 billion,<sup>55</sup> but the lack of industry association and scarcity of public data have made it difficult to estimate medical food revenue in the United States. The best estimate is \$2.1 billion for 2011 with a growing rate of approximately 10%.<sup>56</sup>

The primary drivers identified for the medical food industry include (1) the aforementioned rise in the aging population, (2) a shift to enteral nutrition, and (3) the demand for personalized medicine. As life expectancy has steadily increased over the last few decades, the older population has, in turn, grown at a significantly higher rate than the total population. In fact, over the next half century, the proportion of older persons is projected to more than double.<sup>57</sup> Consequently, health care services are already strained, and surgical areas of cardiothoracic, ophthalmology, and urology are particularly expected to be overwhelmingly burdened in the near future.<sup>58</sup> This has prompted medical providers to ponder the question of how to keep people healthy for longer without abusing medical industry resources. Valuable solutions suggested have been medical foods and other nutritional substances, especially when long-term effects of medication are important.<sup>59</sup>

There has also been a shift to using enteral nutrition (i.e., absorption through the gastrointestinal (GI) tract) rather than total parenteral nutrition (i.e., absorption not through the GI tract, e.g., intravenous administration). Reasons for this change include the fact that enteral administration is safer since there is less risk of infection and it offers physiological benefits such as the maintenance of small intestine mass and pancreatic function. Moreover, technological advances have helped enteral administration become more cost-effective and led to improved feeding devices. For example, pumps are becoming lightweight, constructed from materials that alleviate cracking in high stress applications, and they are now easy to use and clean. In addition, nutrients can now be delivered in various formats, such as tablets and capsules, as opposed to sterile liquids and rehydratable powders.<sup>60</sup>

An outstanding issue of medical treatment continues to be that people respond differently. Medical foods, however, have the ability to cater to a person's individualized needs. Drugs often have severe side effects, thus developing nutritional

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<sup>55</sup>Dilip Ghosh, *Medical Foods: Opportunities In An Emerging Market*, Nutraceuticals World (April 1, 2013), [http://www.nutraceuticalsworld.com/issues/2013-04/view\\_features/medical-foods-opportunities-in-an-emerging-market/](http://www.nutraceuticalsworld.com/issues/2013-04/view_features/medical-foods-opportunities-in-an-emerging-market/) (last visited September 17, 2013).

<sup>56</sup>*Id.*

<sup>57</sup>United Nations, *World Population Aging 1950–2050* (May 23, 2013), [http://www.un.org/esa/population/publications/worldageing19502050/pdf/62executivesummary\\_english.pdf](http://www.un.org/esa/population/publications/worldageing19502050/pdf/62executivesummary_english.pdf) (last visited September 17, 2013).

<sup>58</sup>D.A. Etzioni, J.H. Liu, M.A. Maggard & C.Y. Ko, *The Aging Population and Its Impact on the Surgery Workforce*, 238 *Annals of Surgery* 170 (2003).

<sup>59</sup>I. Siro, E. Kopolna, B. Kopolna & A. Lugasi, *Functional Food Product Development, Marketing and Consumer Acceptance: A Review*, 51 *Appetite* 456 (2008).

<sup>60</sup>See Rebecca Pullon, *An Introduction to the Medical Foods Industry*, Healthcare Innovation Centre for Doctoral Training (May 24, 2013), <http://www.colleripmanagement.com/downloads/Medical%20Foods%20Report.pdf> (last visited September 17, 2013).

alternatives to treat the underlying cause of a condition or disease is an effective way to not only personalize medicine, but hopefully avoid risks associated with treatment and/or maintenance of the condition or disease.

Since medical foods are relatively lightly regulated, especially in comparison to drugs, the barriers to market entry are lower than for other medical products. The recent publication of the FDA's Revised Draft Guidance, coupled with the issuance of two Warning Letters in 2013 regarding the definition of medical food, indicates that the agency may be acknowledging the need for stricter enforcement of its medical food regulations. However, since Warning Letters appear to be the only real FDA enforcement efforts to date, only time will tell if the agency truly intends to intensify its regulation of medical foods.