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Food and Nutrition Policy

Medical Foods: Science, Regulation, and Practical Aspects. Summary of a Workshop

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ABSTRACT

On August 13–14, 2019, the Healthcare Nutrition Council and the ASN held the Medical Foods Workshop: Science, Regulation, and Practical Aspects. Medical food products help patients manage their disease and improve their quality of life. Yet many hurdles exist to getting patients new products. In this workshop, participants addressed some of these hurdles, with specific emphasis on topics like the statutory term *distinctive nutritional requirements*, the regulatory term *modification of the diet alone*, the role of clinical guidelines, the requirement that medical foods be used under medical supervision, and differentiation of foods for special dietary use from medical foods, as well as product innovation and future research. Real-world examples were discussed for intractable epilepsy, diabetes, end-stage renal disease, and inflammatory bowel disease. *Curr Dev Nutr* 2021;5:nzaa172.

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Summary of Medical Foods Workshop: Science, Regulation, and Practical Aspects, held in Washington, DC, August 13–14, 2019. The workshop was organized by the Healthcare Nutrition Council and the ASN and was sponsored by the Healthcare Nutrition Council. BS, Sarah Ohlhorst, JR, and AB served as the Workshop Planning Committee.

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Abbreviations used: ADS, arginine deficiency syndrome; ANPRM, Advance Notice of Proposed Rulemaking; ASPEN, American Society for Parenteral and Enteral Nutrition; CKD, chronic kidney disease; ESPEN, European Society for Clinical Nutrition and Metabolism; ESRD, end-stage renal disease; EU, European Union; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FSDU, food for special dietary use; FSMP, food for special medical purposes; IBD, inflammatory bowel disease; ICU, intensive care unit; MDSC, myeloid-derived suppressor cell; NASEM, National Academies of Sciences, Engineering, and Medicine; NLEA, Nutrition Labeling and Education Act of 1990; ONS, oral nutritional supplement; PKU, phenylketonuria.

Introduction

On August 13–14, 2019, the Healthcare Nutrition Council and the ASN held the Medical Foods Workshop: Science, Regulation, and Practical Aspects. Medical food products help patients manage their disease and improve their quality of life. Yet many hurdles exist to getting patients new products. In this 2-d workshop, participants addressed some of these hurdles, with specific emphasis on topics like the statutory term *distinctive nutritional requirements*, the regulatory term *modification of the diet alone*, the role of clinical guidelines, the requirement that medical foods be used under medical supervision, and differentiation of foods for special dietary use from medical foods, as well as product innovation and future research. Real-world examples were discussed for intractable epilepsy, diabetes, end-stage renal disease, and inflammatory bowel disease.

A core objective was to gather diverse stakeholders—patient groups, clinicians, government agencies, the medical foods industry, and scientific member organizations—to identify policy needs and public health initiatives and to identify practical ways to modernize the regulatory framework to promote nutritional approaches to improving patient care through innovation and research.

This publication summarizes the presentations of the 2-d workshop. The overall organization of the workshop is duplicated here.

The Regulatory Framework of Medical Foods

TM, Founder and President of Spectrum Nutrition, LLC, began the workshop with a brief history of the regulatory framework of medical foods. He noted that an understanding of this history is helpful because much of the regulatory framework has not changed. Some of the key dates outlined by Dr Morck as summarized in an Advance Notice of Proposed Rulemaking (ANPRM) from the FDA are as follows (1):

- Before 1972, medical foods were regulated as drugs by the FDA. One of the first products regulated as such was Lofenalac (Mead Johnson), which was used in the dietary management of patients with phenylketonuria (PKU), an inborn error of metabolism.
- In late 1972, Lofenalac was moved to the category of foods for special dietary use (FSDUs). As applied to food, *special dietary use* was defined to mean uses supplying particular dietary needs that exist by reason of age or uses supplementing or fortifying the ordinary or usual diet. This topic is addressed in more detail in the section "Differentiating Medical Foods and Foods for Special Dietary Uses."
- In 1988, the Orphan Drug Act was amended and created a *statutory definition* of medical food [21 USC 360ee(b)(3)] as shown in **Box A**.

BOX A

A **medical food** is "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**."

As defined in section 5(b)(3) of the Orphan Drug Act. 21 USC 360ee(b)(3) (emphasis added).

As highlighted in Box A, key points are that the medical food is administered enterally, under the supervision of a physician, and for the dietary management of a disease or condition, for which distinctive nutritional requirements are established by medical evaluation.

- In 1990, the Nutritional Labeling and Education Act (NLEA) exempted medical foods from the nutrition labeling requirements applicable to most other foods.
- In 1993, the final NLEA rule enumerated regulatory criteria that medical foods should meet for exemption from the nutritional labeling requirements of 21 CFR 101.9 (**Box B**) that further created a *regulatory definition* of medical foods.

BOX B

A medical food is exempt from the nutrition labeling requirements of 21 CFR 101.9 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**, meaning a tube or catheter that delivers nutrients beyond the oral cavity directly into the stomach or small intestine;

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.

As defined in 21 CFR 101.9(j)(8) (emphasis added).

Note that the statutory definition refers to the "specific dietary management of a disease or condition," whereas the NLEA regulatory criteria refer to the "dietary management of a patient with a specific disease or condition." This distinction is important because the FDA has clear delineation between drugs (to prevent, treat, mitigate, or cure disease) and medical foods (limited to addressing the dietary management of the patient with a disease, but not treating the disease itself). Furthermore, not all foods fed to patients with a disease are considered to be medical foods. Whereas the statutory definition (Box A) comes from the law (passed by Congress), the final NLEA rule enumerates regulatory criteria for medical foods for certain labeling exemptions (Box B).

- In 1996 the FDA recognized the need to re-examine the regulatory framework of medical foods and published an ANPRM announcing its intent to re-evaluate the medical food definition (1). Although many comments were received, in 2004 the Agency withdrew the ANPRM owing to limited resources, and it is no longer under active consideration. However, the FDA will "continue to refer to the basic principles described in the ANPRM" when evaluating medical foods (2).
- In 2016 the FDA published final guidance intended to help manufacturers better understand the regulations. The document *Guidance for Industry: Frequently Asked Questions About Medical Foods, Second Edition*, issued by the Office of Nutrition and Food Labeling, addresses common questions about the definition of, and regulations for, medical foods in a question-and-answer format (3).

Dr Morck described the key regulatory differences between the drug and food categories under the authority of the FDA. For example, drugs (which include brand-name and generic prescription drugs and over-the-counter nonprescription drugs) require premarket approval, safety and efficacy studies, premarket review of label claims, product registration, and mandatory adverse event reporting. Medical foods are not regulated under the drug provisions of the Federal Food Drug and Cosmetic Act, but under the food provisions (3). Dietary supplements, infant formula, and FSDUs are also regulated under the food provisions. As a consequence, medical foods do not require premarket approval, but as foods, must be safe. Except for NLEA-related requirements, medical foods must comply with overall food regulations. Medical foods must not be adulterated and must not be misbranded. The label claims and indications must be appropriately substantiated and must be truthful and not misleading. Medical foods are exempt from nutrient content label-

ing such as the Nutrition Facts panel, yet Dr Morck noted that many do use a "Nutrition Information" panel to list quantities of the various defined nutrients. For medical foods, the FDA's enforcement authority lies in postmarket surveillance, where it uses tools such as website monitoring, adverse event report monitoring, and facility inspection to evaluate both claims made for the product, and therefore, intent to market it for a specific purpose (nutritional support or dietary management of the disease). The FDA can issue warning letters if the product is misbranded as an unapproved new drug, when claims suggest the product can prevent, treat, mitigate, or cure a disease (3). The agency can also seize the product.

Key terms that remain without clear definitions 25–30 y after the first definition of medical foods include the following:

- What, exactly, are "distinctive nutritional requirements"?
- How are "recognized scientific principles" defined?
- What, exactly, does "established by medical evaluation" mean?
- How do "special medically determined nutrient requirements" differ from traditional DRIs?
- How is "dietary management cannot be achieved by modification of the normal diet alone" interpreted? What is a "normal diet"?
- What constitutes the "management of the unique nutrient needs that result from the specific disease or condition"?

Dr Morck closed by offering opportunities and challenges for stakeholders. He stressed having the mindset of the broader perspective of "nutrition," including physiological and biochemical processes at the organ and cellular level, when considering what effect a disease or condition might have on an individual. This goes beyond simply restating what is required by the general population to prevent nutritional deficiency diseases but encompasses "optimal nutrient needs" that foster good health and reduce chronic disease risk associated with inadequate nutrient levels. When designing, conducting, and reporting research, he urged stakeholders to specifically and directly focus their study design and outcomes on the nutritional consequences for the patient, not simply on a disease outcome. This approach will strengthen the proposition that the intervention is intending to directly address patient nutritional needs, not simply the pathology of the disease or symptoms related to it. In some instances, a disease might impose a "conditionally higher requirement" for a particular nutrient than seen in the generally healthy population. If the higher nutrient requirement cannot reasonably be met by modifying the normal diet (acknowledging deficits in the American population's achieving the recommended nutrient levels embodied by the *Dietary Guidelines for Americans*), a specially formulated medical food could be warranted to meet the distinctive nutritional needs of a patient.

Learnings from the 2018 National Academies of Sciences, Engineering, and Medicine Workshop on "Examining Special Nutritional Requirements in Disease States" and Looking Ahead

BS, Emeritus Professor of Nutrition at University of California, Davis, presented her interpretations of an April 2–3, 2018, National Academies of Sciences, Engineering, and Medicine (NASEM) workshop entitled Examining Special Nutritional Requirements in Disease States (4). According to Dr Schneeman, one of the key takeaways of that workshop was that the specific nutritional needs of clinical populations can differ from those of healthy persons. The workshop discussion of these nutritional requirements was framed within the context of the DRIs. DRIs include the concept of an estimated average requirement as well as an upper level of intake. The NASEM workshop was interested in looking at diseases for which the estimated average nutritional requirement is higher or lower than in the general population and diseases for which the nutrient distribution is completely shifted outside the DRIs estimated for the general population (i.e., the whole curve is shifted beyond the usual DRI curve).

Disease-related etiology (e.g., inflammation, trauma) leads to physiological impacts on nutrient requirements (e.g., gut absorption, metabolism, excretion) (4). Impaired absorption or metabolism of nutrients in turn affects human nutrition (e.g., whole-body deficiency, conditionally essential nutrients, and nutrient toxicities) or related biomarkers (4). The workshop examined examples of disease-induced deficiency that included genetic diseases (e.g., PKU, mitochondrial metabolic disorders), tissue dysfunction and regeneration [e.g., inflammatory bowel disease (IBD), chronic kidney disease (CKD)], and disease states that induce conditionally essential nutrients (e.g., arginine in sickle-cell anemia and trauma associated with surgery).

Dr Schneeman summarized that understanding the genetic or metabolic factors that result in a disease increases the ability to identify the special nutrient requirements of a disease. She explained that special nutrient requirements can be the cause of a disorder but can also be the consequence of a disorder. Thus, it is important to examine nutritional status in the context of the disease process and to recognize that certain patients might need special dietary requirements or patterns (as well as special nutrient requirements).

Special nutrient requirements can impact the management of disease in different ways. In the clear-cut case, said Dr Schneeman, the nature of the disease involves a special nutrient requirement, for example, an inborn error of metabolism. In other cases, a consequence of a disease can affect nutritional status, and managing the nutritional status of the patient can help to manage the episodes of disease. An example of this type of case discussed in the NASEM workshop was IBD. In addition, the disease process itself can result in an acute change in nutritional requirements, for example, after trauma. In this case, recognition of the changes in the nutritional requirement can be important in managing the disease and recovery.

From Essentiality to Quality of Life: Assessing "Distinctive Nutritional Requirements" in Different Clinical Contexts

The Healthcare Nutrition Council previously developed a proposed definition or interpretation of *distinctive nutritional requirements* that was distributed to workshop participants and used for reference (5):

> "Distinctive nutritional requirement" refers to the clinical need for a specific nutritional intake (compared with the intake of healthy populations) that can exist by reason of abnormal physiological manifestation or physical impairment associated with a disease or condition, the dietary management of which results in clinically meaningful improvements, including but not

limited to nutritional status, health outcomes, or quality of life.
"Abnormal physiological manifestation or physical impairment" includes the following conditions associated with acute and chronic diseases or health conditions:

(i) a limited, impaired, or disturbed capacity to ingest, digest, absorb, metabolize, or excrete ordinary food or certain nutrients or metabolites, or
(ii) other medically determined requirements for nutrients/other food substances of biological value.

Using case studies from clinical practice, the first session of the workshop explored different aspects of distinctive nutritional requirements associated with different limitations, impairments, or disturbances in a patient's ability to ingest, absorb, metabolize, or excrete ordinary food, certain nutrients, or metabolites.

Role of nutrition in managing disease

Sarah Ohlhorst, Chief Science Policy Officer of the ASN, reminded the audience that the United States no longer predominantly comprises a "healthy" population. She stated that more than half of Americans are living with some form of nutrition-related, preventable disease. In 2015, according to the CDC, almost 40% of US adults were obese (6). One in 10 Americans have type 2 diabetes (>1 in 3 have prediabetes) (7), and heart disease is responsible for 1 in 3 deaths (8).

The costs related to these diseases are equally high. Cardiovascular diseases cost an estimated $317 billion/y ($193 billion in direct health care costs and $124 billion in lost productivity) and type 2 diabetes costs reach $320 billion/y ($112 billion in direct health care costs and $208 billion in lost productivity) (8). The total cost of all obesity-related conditions makes up ~8% of the US gross domestic product (9).

Nutrition science is rapidly evolving to address these public health issues, as evidenced by the rise in nutrition-focused publications and research articles, such as the November 2018 special issue Diet and Health in *Science* (10). Ms Ohlhorst also shared how the number of scientific publications in PubMed (National Library of Medicine) on the topics of diet and cardiovascular health, diet and diabetes, and diet and obesity have likewise grown since 1960. She illustrated how federal agencies are taking note of this evidence of changing nutritional needs.

For example, the 2010 edition of the *Dietary Guidelines for Americans* was the first time the recommendations were no longer intended for "healthy Americans" but rather for "Americans ages 2 years and older, including those at increased risk of chronic disease" (11). The DRIs, which also were traditionally based on a healthy population, now recognize that the US population is predisposed to developing disease and moving forward will be developed taking into account chronic disease (12). Given the state of health of the US population, Ms Ohlhorst suggested that defining and identifying distinctive nutritional requirements on the basis of recognized scientific evidence could help more patients.

Distinctive nutritional requirements for single amino acids: arginine

Dr Juan B Ochoa Gautier, Medical Director of the Surgical Intensive Care Unit at Ochsner Medical Center, presented research on the delivery of supplemental arginine to manage arginine-deficient states. Arginine deficiency can cause clinical manifestations of disease, termed arginine deficiency syndrome (ADS) (13). Because ADS is not necessarily associated with protein-calorie malnutrition, it constitutes a distinct nutritional requirement. ADS cannot be resolved by increasing food (i.e., protein) intake; it is resolved by providing arginine supplementation at higher concentrations than in a normal diet. As such, arginine is a specific form of amino acid replacement and not a pharmacological therapy.

Dr Ochoa Gautier presented how arginine deficiency can occur through several mechanisms. Nonspecific causes, which include dietary deficiencies, can be treated by the provision of dietary protein of high biological value. Specific arginine destruction, by contrast, is the result of the pathological release of the enzyme arginase 1, which converts arginine to ornithine and urea (13). Arginase 1 is constitutively expressed in high concentrations in erythrocytes and hepatocytes (13). Therefore, pathologies associated with the release of arginase into the circulation include RBC damage (e.g., hemolysis, transfusions, mechanical injury) and liver insult (e.g., injury, inflammation, necrosis) (13).

Dr Ochoa Gautier further described how arginase 1 expression can be induced by certain inflammatory stimuli in myeloid immune cells, which can accumulate in sufficient quantities to deplete arginine. These constitute a heterogeneous group of cells now called myeloid-derived suppressor cells (MDSCs). Myeloid cells expressing arginase 1 are described in a growing number of illnesses such as trauma or after surgery (physical injury), cancer (e.g., renal cell carcinoma, breast cancer, colorectal cancer), and certain infections (13).

Arginase 1 inhibitors are being studied as possible adjuncts during cancer therapy. As early as 2004, a study showed that tumor-associated myeloid cells express high levels of arginase 1 and cause possible arginine depletion (14). That finding provided the theoretical basis for solutions aimed at restoring arginine availability.

Dr Ochoa Gautier presented several approaches to managing arginine-deficient states caused by MDSCs that are currently being researched. These include the use of pharmacological inhibitors of arginase, prevention of induction of MDSCs by blocking stimulatory cytokines (e.g., IL-13, PGE_2), depletion of MDSCs, and arginine replacement through dietary means, which has been referred to as *immunonutrition*.

The use of immunonutrition has gained clinical applicability in elective surgical patients, where multiple studies report evidence of efficacy in decreasing the risk of complications such as postoperative infection (15). Dr Ochoa Gautier noted that cancer patients might already be arginine-deficient before surgery. Although the half-life of arginine is short in plasma, it can accumulate in T cells, where it is protected from arginase activity (16). Thus, it makes sense to "preload" arginine to these patients. The most-used protocol is that of providing arginine-based immunonutrition perioperatively starting 5 d before surgery and continuing for 5–10 d postoperatively (17).

Dr Ochoa Gautier further reviewed the results of several clinical studies in surgical patients in which appropriate arginine-based immunonutrition was tested against a control diet containing an equivalent amount of calories and protein. In well-nourished patients undergoing cystectomy, arginine concentrations are maintained in patients who receive arginine-based immunonutrition (18). In malnourished patients (19), preoperative administration of immunonutrition decreases postoperative complication rates. Evidence of clinical

benefit is also observed in well-nourished patients. In addition to a decrease in the risk of surgical site infections, arginine-based immunonutrition is associated with improved tissue oxygenation and a decrease in anastomotic breakdown in gastrointestinal surgery. Clinical evidence of efficacy has been translated into real-world trials that demonstrate effectiveness and improved health care value. For example, a study showed that patients who consumed arginine-based immunonutrition exhibited a 50% reduction in readmission rates at 180 d (20). In trauma, evidence for the benefits of arginine-based immunonutrition is poor. As Dr Ochoa Gautier explained, like elective surgery, trauma is associated with increased arginase 1 activity and a decrease in arginine availability. Unlike in elective surgical patients, however, it is impossible to deliver arginine-based immunonutrition before a traumatic insult.

Meeting distinctive nutritional requirements with medical foods

Susan Lessar, Valley Health Director of the Clinical Nutrition Therapy Department of Winchester Medical Center in Virginia, presented the view of a clinical nutrition therapy department. She stated that for patients unable to maximize their oral intake, the most common routes of enteral access in critical care are nasogastric or orogastric tubes. The most common indications for enteral feeding include patients under mechanical ventilation support, patients post stroke, and patients with swallowing difficulties or intestinal failure. At Winchester Medical Center the registered dietitians, under the physician's guidance, have order-writing privileges. The enteral formulas that the registered dietitians commonly order include general-purpose formulas, nutrient-dense formulas (e.g., for patients with heart failure), oncology formulas, critical care formulas (e.g., for surgically stressed, trauma, and oncology patients), and formulas for conditions such as diabetes, hepatic disease, impaired gastrointestinal digestion or absorption, and renal disease.

Ms Lessar noted that when transitioning patients from enteral support, it is important to first establish that ≥65% of their estimated needs are being met orally. If feeding is needed long term, a nasogastric or orogastric tube is always switched to a surgically placed tube. Ms Lessar summarized that enteral nutrition can provide complete nutrition and improves quality of life in the management of patients with malnutrition.

Malnutrition and gastrointestinal impairment

A lack of consensus on how to best assess intolerance to feedings can result in unnecessary interruptions in enteral nutrition. Dr Mark DeLegge, Director of the Digestive Disease Center of the Medical University of South Carolina, proposed the need for a standardized tool for diagnosing intolerance to enteral feeding. Dr DeLegge noted that the average hospitalized patient receives ~50% of the calories prescribed enterally [where enteral nutrition includes oral nutritional supplements (ONSs) and nutrition administered by tube feeding]. In a survey of 1909 members of the American Association of Critical Care Nurses of methods to assess tolerance to gastric tube feedings (21), many critical care nurses reported reducing and stopping feedings in response to perceived intolerance. Dr DeLegge described the clinical reasons for interrupting enteral feeding as the following:

- Nausea and vomiting,
- High gastric residuals,
- Diarrhea,
- Abdominal pain,
- Bowel sounds,
- Bloating, and
- Abdominal distention.

Dr DeLegge suggested that how gastrointestinal intolerance is defined is subject to the interpretation of these clinical biomarkers. For example, no data exist on the efficacy of using nausea and vomiting as a measure for stopping feeding. The measure of diarrhea is also problematic. For example, ≥33 definitions of diarrhea can be found in the literature, which makes consistency in such measure difficult (22). Dr DeLegge also noted that it should be taken into account that some patients in the intensive care unit (ICU) might not have control over their external rectum sphincter; thus, having 4 to 6 small bowel movements in the ICU is considered normal.

Regarding other symptoms such as bowel sounds or bloating, 1 study in the literature showed no correlation of bowel sounds with oral tolerance (23), whereas bloating is a subjective sensation. Studies have examined, with mixed results, whether a sensation of bloating equals abdominal distention or whether bloating equates with more intestinal gas. Even without volume changes in the gut, Dr DeLegge described how subtle changes in body position can create new abdominal distention. Finally, Dr DeLegge commented on gastric residual volume, as the amount of fluid in stomach at any one time. No current data suggest that gastric residual volume has a significant impact on clinical outcomes such as frequency of gastrointestinal intolerance, frequency of regurgitation, or diet volume ratio (24).

Dr DeLegge offered the following clinical pearl to the participants concerning the rate of tube feeding, trying to contextualize what changes in volume velocity mean in practice:

- 10 cc/h = 1 cc every 6 min
- 20 cc/h = 1 cc every 3 min
- 30 cc/h = 1 cc every 2 min

(For illustration, he challenged the participants "not to swallow 1 cc of saliva in the next 6 minutes".)

Dr DeLegge concluded that people who are chronically ill do have gastrointestinal dysfunction. Although enteral nutrition formulas can be modified with alternative osmolarities, alternative fats, small peptides, low-carbohydrate content, and plant-based formulas, consistency in the assessment of gastrointestinal tolerance is needed. Dr DeLegge suggested that use of a standardized tool to diagnose enteral feeding intolerance could lead to more reasons to starting enteral nutrition than stopping it.

Role of clinical guidelines in distinctive nutritional requirements

In this session, Ainsley Malone, Clinical Practice Specialist with the American Society for Parenteral and Enteral Nutrition (ASPEN), provided the participants with an overview of the history and development of clinical practice guidelines in the context of nutrition therapy.

The Institute of Medicine provided the first formal definition and development process for clinical practice guidelines in 1992 (25). Ms Malone shared that compared with 374 practice guidelines in the MEDLINE index (National Library of Medicine) in 1992, >7500 clinical practice

guidelines were published by 2012. In 2011 the Institute of Medicine revised the definition of clinical practice guidelines with the publication of *Clinical Practice Guidelines We Can Trust* (26). The goal is for all health care decisions to be evidence-based by 2020. The revised standards also aimed to develop "trustworthy" guidelines based on a systematic review of existing evidence. Ms Malone noted the challenge of reviewing the evidence in the field of nutrition, because much of the existing evidence is not at the highest level in the hierarchy of evidence (i.e., randomized controlled trials). Different published approaches exist for rating the strength of evidence and clinical recommendations. For example, A: the recommendation is supported by GOOD evidence; B: the recommendation is supported by FAIR evidence; C: the recommendation is supported by EXPERT opinion (published); and I: evidence to make a recommendation is INSUFFICIENT (26).

ASPEN (27), the Academy of Nutrition and Dietetics (28), and the European Society for Clinical Nutrition and Metabolism (ESPEN; 29) regularly publish guidelines in the clinical nutrition space. Populations of study relevant to the discussion of distinctive nutritional requirements include unintended weight loss, oncology, HIV, cancer, geriatrics, liver disease, and critical care. Excerpts of selected guidelines relevant to the discussion of medical foods follow.

1. Academy of Nutrition and Dietetics: Unintended Weight Loss in Older Adults Guideline (2009) (30)
   - "The Registered Dietitian should recommend medical food supplements for older adults who are undernourished or at risk of undernutrition (those who are frail, those who have infection, impaired wound healing, pressure ulcers, depression, early to moderate dementia and/or after hip fracture and orthopedic surgery)" (Rating: strong)
   - Subpopulations included: frail adults, impaired wound healing, pressure ulcers, hip fracture, and orthopedic surgery
2. Academy of Nutrition and Dietetics: HIV/AIDS Guidelines (2010) (31)
   - "For people with HIV infection who have diarrhea/malabsorption, the registered dietitian (RD) should encourage the consumption of soluble fiber, electrolyte-repleting beverages and medium-chain triglycerides" (Rating: fair)
3. Academy of Nutrition and Dietetics: Oncology Guideline (2013) (32)
   - May consider use of medical food supplement containing fish oil in persons with cancer experiencing weight loss (Rating: strong)
   - 1.2–2.2 g EPA/d
4. ESPEN Guidelines on Nutrition in Cancer Patients (2016) (33)
   - Nutritional intervention, including offering ONSs, recommended to increase oral intake in cancer patients who are able to eat but are malnourished or at risk for malnutrition
   - Use of ONSs is advised when an "enriched" diet does not meet goals (Level of evidence: moderate)
5. ESPEN Guideline on Clinical Nutrition and Hydration in Geriatrics (34)
   - "After discharge from the hospital, older persons with malnutrition or at risk of malnutrition shall be offered ONS in order to improve dietary intake and body weight, and to lower the risk of functional decline." (Grade A recommendation)
   - "Older persons with malnutrition or at risk of malnutrition with chronic conditions shall be offered ONS when dietary counselling and food fortification are not sufficient to increase dietary intake and reach nutritional goals." [Grade GPP (good practice points/expert consensus)]
6. ESPEN Guideline on Clinical Nutrition in Liver Disease (2019) (35)
   - "ONS should be used when patients with severe ASH [alcoholic steatohepatitis] cannot meet their caloric requirements through normal food in order to improve survival" (Grade B recommendation)
7. ASPEN/Society of Critical Care Medicine Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient (2016) (36)
   - Immune-modulating formulations containing arginine and fish oil be considered in patients with severe trauma (Evidence quality: very low)
   - Routine use of an immune-modulating formula in the surgical ICU for the postoperative patient who requires enteral nutritional therapy (Evidence quality: moderate to low)
   - High-protein, hypocaloric feeding be implemented in obese ICU patients to preserve lean body mass, mobilize adipose stores, and minimize the metabolic complications of overfeeding (Evidence quality: expert consensus)

Key guideline recommendations support the use of enteral formulas and ONSs that might lead to improved clinical outcomes and support key tenets in the definition of distinctive nutritional requirements. (Note: Although a National Guideline Clearinghouse for disseminating clinical practice guidelines was previously available online through the Agency for Healthcare Research and Quality, the site was taken down July 16, 2018, because federal funding ended. Updates about the National Guideline Clearinghouse can be found at https://www.ahrq.gov/gam/updates/index.html.)

Practical Considerations for Meeting Distinctive Nutritional Requirements Through Modification of the Diet Alone

Modification of the diet alone

Dr David Cockram (Cockram Consulting, LLC), formerly Senior Director of Global Regulatory Science and Innovation at Abbott Nutrition, delved further into a specific phrase in the regulatory criteria for medical foods (Box B): "the dietary management of which cannot be achieved by the modification of the normal diet alone." (Dr Cockram also covered the regulatory history introduced by TM earlier in the workshop.) This additional language in the NLEA final rule is a key difference between the statutory definition and the regulatory definition's criteria of medical foods. Typically, regulatory language is interpreted by using the plain meaning of the words in the regulation, unless there is regulatory history that clarifies or provides context for Congress's intent when drafting the statute. In this case, little statutory history exists, so Dr Cockram first stepped the group through a dictionary definition of "modification of the diet alone":

- Modification: making a limited change in something.
- Diet: habitual food and drink, also a therapeutic diet.
- Alone: solely or exclusively.

Therefore, modification of the diet alone could be interpreted as a limited change in what one normally eats that can reasonably be accomplished just by modifying what one eats. The FDA, however, has interpreted *medical food* more narrowly than the plain reading of the words implies.

Dr Cockram then provided a brief historical context of the term "modification of the diet alone." In 1990, a Life Science Research Organization/Federation of American Societies for Experimental Biology report "Guidelines for the scientific review of enteral food products for special medical purposes" (37) solicited by the FDA to summarize the state of the art for medical foods used the term "modification of the normal diet alone" when defining medical food products. The ANPRM published by the FDA in 1996 included some references to modification of the diet alone (1), but the term was not clarified in the FDA's later 2016 guidance (3).

Questions to be discussed further include whether modification of the diet alone is a single definable standard (i.e., many factors determine whether an individual can successfully modify their diet, in addition to simple technical feasibility), whether the hurdle for modification of the diet alone is reasonable and fair, and whether the requirement impedes provision of optimal patient care.

Regulatory and legal context of "modification of the diet alone"

Jessica O'Connell, Partner, Covington & Burling, presented the regulatory and legal context for modification of the diet alone. She reminded the participants that the statutory definition (Box A) contains nothing on modification of the diet alone. Rather, the key concept in the statutory definition is the phrase "distinctive nutritional requirements." The criteria in the NLEA final rule were intended as exemptions to the NLEA labeling requirements rather than as a comprehensive definition. Ms O'Connell noted that these additional regulatory criteria (Box B) do not use the phrase *distinctive nutritional requirement* or even the word *nutrition* but rather *nutrient* (e.g., "special medically determined nutrient requirements" and "unique nutrient needs"). Ms O'Connell noted that the concept of modification of the diet alone did not come from Congress and did not come from the statute. She asked, what does the FDA mean by modification of the diet alone, and is there a way for the agency to tie this back to the statutory definition?

Table 1 summarizes the important distinctions in the statutory and regulatory language used to describe medical foods as defined in Boxes A and B.

Ms O'Connell noted that the FDA can send a warning letter to a company if it deems that a product does not meet a "distinctive nutritional requirement for the disease or condition" or a "distinctive nutritional requirement that cannot be met through dietary modification alone." The primary medical foods included in this second category since 2009 have been products for pregnancy, diabetes, and bariatric surgery recovery. Ms O'Connell noted that in the medical food draft guidance of 2013, the FDA addressed pregnancy, diabetes, and classical nutrient deficiency diseases and for each stated that individuals could meet their needs through modification of the diet alone. In the final guidance (2), the revised language adds that "there are no distinctive nutritional requirements" associated with pregnancy or with the management of diabetes. Ms O'Connell explained that the final guidance implies that a nutritional requirement is "distinct" only if it cannot be met through modification of the normal diet alone. She left the participants with 2 final points to consider: *1*) If a disease or condition has a broad patient population, can the diets of all patients always be modified? and *2*) Does the definition of distinctive nutritional requirements require an evaluation of whether the normal diet alone can meet those requirements?

Practicality of Using Medical Foods to Meet Nutritional Requirements

Intractable epilepsy

Dr Eric Kossoff, Professor of Neurology and Pediatrics and Director of the Child Neurology Residency Program at Johns Hopkins University, provided a perspective on the use of ketogenic diets in the dietary management of intractable epilepsy. Options besides drugs are often needed in epilepsy because not all patients respond to drug therapy. A study in 2000 reported that 47% of patients with epilepsy become seizure-free during therapy with the first drug prescribed, 14% with the second drug used, but only 1% with a third (38). An updated study conducted in 2018 reported similar findings despite many new antiseizure drugs (39). Four different therapies are used for epilepsy: medications, neurostimulation devices, surgery, and dietary therapy. Most epilepsy centers that take care of children have a ketogenic diet program.

At Johns Hopkins, the ketogenic diet for children is started in the hospital over 2–3 d, often after a 24-h fast, and consists of a 4:1 ratio of fats to carbohydrates in grams (sometimes 3:1 for infants and adolescents). The diet contains ~92% of calories from fat. Four ketogenic diets are used for epilepsy: the classic ketogenic diet, the medium-chain triglyceride diet, the modified Atkins diet (Simply Good Foods USA), and the low glycemic index treatment. Seven randomized controlled trials have studied the use of these ketogenic diets for refractory epilepsy. Updated guidelines of the International Ketogenic Diet Study Group were published in *Epilepsia Open* in 2018 (40). The publication contains a list of specific epilepsy syndromes and conditions for which the study group recommends that ketogenic diet therapy be used early in the course of epilepsy management (Table 1 in reference 40).

Dr Kossoff also shared the patient perspective. The ketogenic diet is strict, and the education provided (3 d in the hospital) is brief. These factors both affect compliance. Whereas epilepsy is a relatively private disorder, the diet is not. The diet also has side effects that can shorten its use. Addition of ketogenic formulas to a ketogenic diet can help improve compliance (41). However, for most families these products are not reimbursed by insurance. Families ask for prepared foods, preferably with texture (e.g., crunch), that are portable, savory (not just sweet), and inexpensive. As summarized by Dr Kossoff, neurological uses for ketogenic foods other than in epilepsy could include Alzheimer disease, autism, dementia, migraine, pain, and bipolar disorder. Studies of these conditions are underway.

Table 1 Summary of distinctions between the statutory and regulatory language describing medical foods

Language in the statute [21 USC 360ee(b)(3)]	Language in the NLEA regulation [21 CFR 101.9(j)(8)]
Refers to the "dietary management of a disease or condition"	Refers to the "dietary management of a patient"
Refers to "distinctive nutritional requirements" for the disease or condition that are "established by medical evaluation"	Refers to a patient who has other "special medically determined nutrient requirements" and "unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation"
Makes no mention of dietary modification	Refers to dietary management that cannot be achieved through "modification of the normal diet alone"

Diabetes

Dr Osama Hamdy, Director of the Inpatient Diabetes Program of the Joslin Diabetes Center at Harvard Medical School, reviewed the use of diabetes-specific nutritional formulas for managing diabetes and reducing costs. As summarized in a 2014 publication by Ley et al. (42), individual nutrients, foods, and dietary patterns play a role in the management of type 2 diabetes. For example, higher heme-iron intake and foods with a high glycemic index are associated with higher diabetes risk, whereas diets high in cereal fiber and magnesium lower the risk of diabetes (42). Intakes of green leafy vegetables are associated with lower risk, whereas intakes of processed meat and sugar-sweetened beverages are associated with higher risk (42). Thus, Dr Hamdy explained that choosing foods with low glycemic index carbohydrates and more protein, fiber, and MUFAs can help people with diabetes control their disease.

Diabetes-specific formulas are designed to improve glucose control (43, 44). The formulas contain slowly digested carbohydrates. Because the largest component of medical expenditures attributed to diabetes is in the hospital, a retrospective review of >500 hospitals studied whether the use of diabetes-specific enteral nutrition formulas affected cost (45). The study showed that tube-fed patients with diabetes who received a diabetes-specific formula had an average length of stay shorter by ~1 d compared with that in patients who received the standard nutritional formula. The shorter length of stay contributed to savings of ~$2500 per patient. The American Diabetes Association (46) has stated that diabetes-specific formulas appear to be superior to standard formula in controlling postprandial glucose, glycated hemoglobin, and insulin response, and an ESPEN expert group (47) endorses the use of diabetes-specific formulas for the nutritional support of people with obesity and diabetes.

In outpatients, use of a diabetes-specific nutritional formula can improve outcomes in patients with diabetes who are trying to lose weight (48). In patients with diabetes consuming these formulas, a mechanism for weight loss might be the stimulation of hormones such as peptide YY, or PYY (a strong satiety hormone), and amylin (49). Weight loss can significantly reduce diabetes-related medical costs, as shown in a study that abstracted administrative claims, electronic laboratory data, and medical chart information for adults with diabetes receiving antidiabetic therapy (50).

Finally Dr Hamdy reviewed the Nutrition Path Study, which tested nutrition therapy plus an individualized meal plan or a structured meal plan with the addition of diabetes-specific formulas. One group also received a weekly phone call. The 2019 Standards of Medical Care in Diabetes (51) state that medical nutrition therapy "throughout the course of a structured weight loss plan, is strongly recommended" and that "a variety of eating plans, varying in macronutrient composition, can be used effectively and safely in the short term (1–2 years) to achieve weight loss in people with diabetes. This includes structured low-calorie meal plans that include meal replacements."

End-stage renal disease

Dr Alison Steiber, Chief Science Officer of the Academy of Nutrition and Dietetics, discussed the use of medical foods in end-stage renal disease (ESRD). Diabetes, hypertension, and glomerulonephritis lead to CKD. Also, the rise in the prevalence of obesity and diabetes is leading to a greater prevalence of CKD. The global prevalence of CKD is estimated to be 1 in 5 men and 1 in 4 women aged 65 to 74 y (52). Dr Steiber explained that not all people with CKD will progress to ESRD; some will die before their disease progresses to ESRD, and in some, the disease will not progress to that stage. ESRD is one of the most expensive chronic disease states, and diet is a large part of the treatment.

Renal-friendly ONSs are the primary medical food product used for people with ESRD. Dr Steiber noted that by the time patients progress to ESRD, they are receiving mixed messages about diet. Previously they might have been told to increase their fruit and vegetable intake (high-potassium foods) but now in the later stages of disease they are told to lower their potassium intake because of the risk of developing hyperkalemia (53). This confusion can cause patients to become afraid to eat. As a result, she noted that patients with CKD tend to have monotonous intake, which contributes to inadequate diets.

Evidence suggests that the diet of many patients with ESRD is suboptimal to support adequacy of key nutrients. For example, a study of dialysis patients reported that 64% were deficient in vitamin K (as assessed by concentrations of protein induced by vitamin K absence II, a marker of functional vitamin K status with respect to the γ-carboxylation status of coagulation factor F11) (54). A second study showed that supplementation could increase vitamin K concentrations (using matrix Gla protein as a marker) (55). A study that examined dietary intake as percentages of the RDA showed that dialysis patients were deficient in every nutrient but vitamin B-12 (56). In a 2016 study, the only macronutrient for which >50% of patients met recommended targets was carbohydrate (57).

The Evidence Analysis Library of the National Academy of Nutrition and Dietetics (28) and the National Kidney Foundation recently conducted several systematic reviews of ONS interventions in patients with ESRD. (Dr Steiber noted that most intervention studies used albumin status as the criterion for malnutrition.) The analysis showed that

renal-specific ONSs result in statistically significant increases in protein intake in patients with ESRD. Results for the other 2 parameters studied (protein catabolic rate and energy intake) were nonsignificant. A more recent study showed a small but significant effect on serum albumin (58).

Patient perspective on modification of the diet alone

Laura Wingate, Senior Vice President of Education, Support, and Advocacy of the Crohn's and Colitis Foundation, addressed modification of the diet alone and distinctive nutritional requirements from the point of view of patients with IBD. A diagnosis of IBD, which includes Crohn disease and ulcerative colitis, can occur at any age but is most common at 7–18 y of age. The diseases are generally characterized by abdominal pain, ulcers throughout the gastrointestinal tract, rectal bleeding, fever, and extraintestinal manifestations. Crohn disease and ulcerative colitis also have a psychological impact due to the anxiety and stress associated with a relapsing-remitting and flaring disease state that can lead to incontinence and other isolating symptoms. Patients with IBD can end up with malnutrition both because of self-limiting their intake (e.g., fear of food causing disease flares) and because of the inflammation caused by the disease. Although many approved therapies are available, treatments can lose effectiveness over time or fail completely in some patients, leading to surgery and in some cases permanent ostomies. Treatment also changes over time, and the complexity of the disease makes treatment decisions difficult for the patient and their health care provider. Patients are looking for treatments that lead to positive health outcomes without life-threatening side effects.

Enteral therapy, especially in pediatric Crohn disease, has been shown to induce disease remission (59).

Patients are open to diet modifications, as evidenced by the popularity of diets such as the specific carbohydrate diet, low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, and gluten-free diet. However, patients report difficulty in managing and sustaining diets like the specific carbohydrate and low-FODMAP diet. The Crohn's and Colitis Foundation recently launched a precision nutrition in IBD research initiative to answer the question, "What should I eat?" The aim is to understand the mechanisms of response to food in patients with IBD and their correlation to disease outcome (60).

As many as one-third of patients with IBD are identified as malnourished. Vitamin and mineral deficiencies can include vitamin B-12, calcium, and vitamin D. Patients can also have iron-deficiency anemia. One-third of patients were found to be malnourished in a study conducted by the Crohn's and Colitis Foundation IBD Qorus, a national quality metrics initiative of the foundation. However, Ms Wingate noted that "distinctive nutritional requirements" has little meaning to a patient or caregiver. What matters is effective treatment and appropriate nutritional intake.

The Crohn's and Colitis Foundation provides patient information on diet and nutrition in a dedicated section of its website (61). The education is focused on nutrition and malnutrition and medical foods for dietary management, especially for the management of IBD in pediatric patients.

Challenges related to the use of medical foods faced by patients include insurance coverage of enteral therapies; most insurers will cover the cost of nasogastric tubes only, but patients report a preference for oral formulations. Ms Wingate shared that in a 2018 survey of Crohn's & Colitis Foundation members, 9.4% of patients reported lack of coverage for liquid or oral nutrition. Adherence to therapy is also a challenge; as Ms Wingate stated, patients desire feeding that is "more like a meal."

Ms Wingate suggested that research and policy need to advance to understand the role of modification of the diet alone as a therapeutic strategy in IBD, with an emphasis on understanding the role of the gut microbiome (62). She further urged the FDA to consider disease severity and the heterogeneity of the patient population with IBD in the definition of medical foods and to consider incorporating other forms of delivery of enteral nutrition.

International Perspective on Patient Foods Intended for the Dietary Management of a Disease or Condition

Two speakers provided a perspective on medical foods in the European Union (EU) and in Canada.

Foods for special medical purposes in Europe

Basil Mathioudakis, formerly a unit head with the European Commission, spoke on the EU experience. Mr Mathioudakis explained that in Europe, medical foods are termed foods for special medical purposes (FSMPs). In 1989, FSMPs were specified as a category in a revised EC directive on Foodstuffs Intended for Particular Nutritional Uses. A directive on FSMPs was adopted in 1999 (1999/21/EC). In 2013 the concept of foods for particular nutritional uses was abolished, and final specific rules on FSMPs were updated in regulations adopted in 2016 (2016/128). Mr Mathioudakis noted that in the EU regulations, the composition requirements are minimal owing to the wide range of products; the intention is to encourage innovation and research. Labeling requirements are extensive, however, including the mandatory labeling statement "For the dietary management of…." Nutrition and health claims are prohibited.

Mr Mathioudakis noted that FSMPs are considered critical for the health of an increasing number of patients. He also noted that inappropriate use of FSMPs can have serious consequences for patient health. Therefore, he emphasized that FSMPs should be placed on the market and controlled correctly. FSMPs are regulated as foods.

As defined in Commission Delegated Regulation (EU) 2016/128 (63) of September 25, 2015 and elaborated in European Commission 2017/C 401/01 (64), food for special medical purposes means (emphasis added):

> [F]ood *specially processed or formulated* and intended for the *dietary management of patients*, including infants, to be used *under medical supervision*; it is intended for the *exclusive or partial feeding* of patients with a *limited, impaired or disturbed capacity* to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients contained therein, or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved by *modification of the normal diet alone*.

Use under medical supervision.
Because certain FSMPs are not intended for persons not having the disease, "use under medical supervision" shall appear in the labeling of FSMPs. Although "use under medical supervision" is essential, Mr Mathioudakis explained that it is not the determining factor for classification of an FSMP.

Dietary management of disease.
To facilitate understanding of the definition, the guidance of the European Commission on the interpretation of the definition in the regulation provides examples of cases in which the dietary management of the disease cannot be managed by normal diet alone (64):

- inability to take in normal quantities of ordinary food (e.g., as a result of physical impairment from head and neck cancer or neurological impairment associated with stroke),
- inability to digest or absorb sufficient nutrients (e.g., impairment of the gastrointestinal tract, genetic disorders),
- inability to excrete certain nutrients or their metabolites (e.g., phosphate or potassium in kidney failure),
- medically determined requirements (e.g., healing of wounds or burns).

Mr Mathioudakis urged that the concept of dietary management be analyzed on a case-by-case basis. He also reminded the participants that any reference to therapeutic effect is prohibited for foods in the EU. FSMPs must be intended for the "dietary management" of a disease, condition, or medical disorder.

Modification of a normal diet.
In the EU, food supplements and fortified foods are considered part of the normal diet. "Modification of the normal diet," Mr Mathioudakis explained, should thus be interpreted broadly. When examining the issue of feasibility of modification of normal diet, Mr Mathioudakis cited the recurrence of the following controversial issues:

1. The potential for modification of the normal diet.
2. The nutritional needs of a patient "cannot be achieved by a modification of the normal diet alone."

He offered the following questions for consideration: Is it possible? If possible, is it realistic? Is it practical? Would use of the specific FSMP be safer and nutritionally advantageous for the patient? The European Commission guidance to manufacturers also considers stage of development or severity of the disease, impact on a patient's health, role and use of the FSMP compared with the normal diet, availability of other food products with similar composition, and the practical difficulties of fulfilling the patient's needs (64).

Canadian modernization of Division 24

Genevieve D'Annunzio, Manager, Regulatory Affairs, of Abbott Laboratories, briefed the participants on the Canadian modernization of Division 24, Foods for Special Dietary Use (FSDUs), of the Food and Drug Regulations (C.R.C., c. 870). In these regulations, *food for special dietary use* is defined as:

> food that has been specially processed or formulated to meet the particular requirements of a person (a) in whom a physical or physiological condition exists as a result of a disease, disorder or injury, or (b) for whom a particular effect, including but not limited to weight loss, is to be obtained by a controlled intake of foods.

Ms D'Annunzio noted that modernization of the division is needed. The category was promulgated in 1974. Although the category grew in the 1980s and 1990s, and meal replacements and other supplements have been added, the division has not been updated since. She described how minimal and maximal limits on nutrients overly limit manufacturing flexibility. The regulations are also not aligned with other jurisdictions; therefore, innovations cannot be imported to Canada. Patients see products that fit their condition available elsewhere but not in Canada.

Ms D'Annunzio presented an overview of previous modernization initiatives. In 1999 the Report on Health Canada policy on the addition of vitamins and minerals attempted to generate reviews of fortification regulations. In 2008 and 2012, initiatives were made to modernize the food regulatory framework in general. The Regulatory Roadmap for Health Products and Food was created to be responsive to new science and innovation. Although it did not result in changes to the regulations, it kept discussion alive and stakeholders engaged. In 2016 new labeling regulations were put in place; although reference values were updated, the regulatory limits of Division 24 were not.

In 2017 a multistakeholder workshop was held to assess the scientific basis of the Division 24 regulations and to determine the need and approach to modernizing with presentations from government, health care, industry, nongovernmental organizations, and academia (65). Ms D'Annunzio noted that the workshop format (preworkshop survey, presentations from stakeholders, and breakout roundtables) was deemed very successful.

Health Canada issued a call for data in 2019. Because there are no premarket notifications in Canada, Ms D'Annunzio explained that this is a way to learn which products are currently on the market and how patients are using them.

The formal objectives of modernizing Division 24 are to better meet the needs of FSDU users, provide more agile regulations that support scientific innovation, and ensure that FSDU products are safe and of high quality. Considerations for modernization include adding provisions for special populations, aligning with other jurisdictions, and determining whether to add a notification process before commercialization, whether to keep special nutritional labeling requirements, and whether to change advertising restrictions.

Q&A with the speakers

A question and answer session was held for the presentations on medical foods in the EU and Canada. One question addressed the EU's intent for the FSMP category. Mr Mathioudakis answered that the EU abolished the concept of foods for particular uses (which included FSMPs) and replaced it with regulations that have in their code foods for infants and young children, foods for very-low-calorie total diet replacement, and FSMPs. FSMP remains a special category. Questions on medical foods in Canada addressed the status of reimbursement of FSDUs and what patient advocacy looks like in Canada. Ms D'Annunzio explained that reimbursement is handled by public drug reimbursement programs or private insurance. FSDUs might be covered by reimbursement programs. A request for addition to the formularies must be submitted by the companies. Reimbursement is stable in Canada, although

the formularies might not be adding new products that do not add more value at a higher price than what is already listed. Most programs will reimburse products for sole source of nutrition; not all reimburse nutritional supplements. Concerning patient advocacy, patients ask individual companies about the availability of products in Canada and send letters to Health Canada. Companies also receive letters from health care professionals, often with testimonials about patients having to cross the border to obtain products.

The final topic of discussion was whether requirements existed for studies for acceptance of a product as an FSMP or FSDU. With respect to Canada, Ms D'Annunzio answered that there is no specific requirement for studies when determining the category of a product, but the right clinical studies would be needed for positioning a product and for any claims made about which population the product is intended for. Randomized controlled trials that have been replicated are the gold standard. Mr Mathioudakis answered that in the EU, the European Food Safety Authority issued guidance in 2017 as to what studies it would like to see for an opinion to be given on a certain product.

New Types of Evidence and Product Innovation

The ASPEN value project

Dr Peggi Guenter, Senior Director of Clinical Practice, Quality, and Advocacy for ASPEN, covered the ASPEN Value Project (66). Although it is recognized that many hospitalized patients are malnourished, evidence-based medicine supporting the health economic benefit of nutrition intervention is lacking. In 2017, ASPEN expanded its organizational goals to include articulating the value of nutrition support. The goal of the ASPEN Value Project is to describe the impact of nutrition care, particularly in relation to specific conditions, on health care costs and utilization. Findings on the value of nutrition support therapy have recently been published (67). For this work, a targeted literature review was first conducted to examine the impact of nutrition care on patient clinical and cost outcomes in 13 therapeutic areas. Raters then used a rubric to review and rank the studies collected and identified 8 therapeutic areas with the best-quality evidence for further analysis. The quality of the evidence was highly variable, and most end points focused on clinical outcomes. Few cost outcomes were presented and most of the literature was of grade 3 level. About 75% of the studies were of research conducted at a single site. Only 5 grade 1 studies were from the United States. From the 8 therapeutic areas, 5 therapeutic areas were chosen by the Value Project Scientific Advisory Council for an analysis of cost data using Medicare claims: pancreatitis, sepsis, gastrointestinal cancer, hospital-acquired conditions, and surgical complications.

The goal of the Medicare claims analysis was to understand the real-world cost impact of these data. That is, the goal was to identify the amount of savings if all patients with the selected diagnoses received the beneficial nutrition intervention. Savings were extrapolated on the basis of the outcomes of decreased length of stay and complications. The analysis started with 1100 individual studies; 8 were used to model. For 7 studies, the total cost reduction was $580 million (67). In the eighth study, the pancreatitis study, costs increased in association with survival/longevity, because multiorgan system failure was the study end point.

Limitations of the analysis include that the Medicare data cannot be extrapolated to the general population. Dr Guenter noted that, as for any nutritional intervention, more studies are needed, in homogeneous patient populations, reporting cost and savings, and collecting and reporting data on readmissions as well as length of stay. Nutrition intervention studies should explicitly capture information on the diagnosis of malnutrition to better characterize the value of nutritional treatment in patient subpopulations. In future steps of the Value Project, ASPEN will continue to update the literature for each therapeutic area.

Considerations in new product design and development

Dr Satya Jonnalagadda, Director of Global Nutrition Science, Innovation, and Education, Abbott Nutrition, explained that in product design, the patient is at the center of everything done in the field. On the one hand, proper nutrition is essential to address the health needs of patients and to ensure positive health outcomes. On the other hand, patients' health and nutritional needs are key considerations for product formulation.

Other considerations in product formulation include:

- Scientific evidence and clinical practice guidelines,
- Regulatory framework,
- Safety,
- Efficacy, and
- Cost.

New product development considers the goal of the product in terms of a patient's health condition and specific nutritional requirements and any impairments in normal nutrient intake, digestion, absorption, or tolerance. Patients are a heterogeneous population, Dr Jonnalagadda presented, and the nutritional requirements of different stages of disease are distinct. In the ICU, for example, many patients are not meeting their prescribed calorie or protein needs. Cahill et al. (68) reported that patients in the ICU meet only 59% of their prescribed calorie needs and 60% of their prescribed protein needs. Factors such as age and gender are also taken into consideration during product development, as is ensuring that products are culturally appropriate.

Selecting the right medical nutrition therapy for a patient is critical to ensure appropriate recovery. As defined by the Academy of Nutrition and Dietetics, medical nutrition therapy is a specific form of nutrition care that is focused on the management of disease (69). Medical nutrition therapy is a continuous cycle of assessment, diagnosis, intervention, and monitoring and evaluation. Assessment includes determining how the product can be consumed. If the patient has an intact gastrointestinal tract, then enteral feeding can begin. If not, then parenteral feeding is considered. The patient's condition is then considered to choose an appropriate therapy. Dr Jonnalagadda provided examples of how understanding a patient's condition leads to developing the right formula. In a patient with acute respiratory distress syndrome, for example, an inflammation-modulating formula (containing ω-3 fatty acids and antioxidants) could be used. Current guidelines and recommendations are also considered when formulating, especially when a specific recommendation is made, such as the administration of additional doses of glutamine to burn patients (70).

Product formulation is an iterative process to ensure that high-quality, evidence-based, science-driven formulations are developed to

meet the needs of patients. Dr Jonnalagadda noted that it takes >35 different functions to bring products to market: from market insights to procurement (access to ingredients) to nutrition science to regulatory operations. When considering ingredients and the formulation of a new product, existing scientific evidence is considered, and new evidence might need to be generated. Dr Jonnalagadda suggested that different forms of nutrition research should be considered to substantiate the nutritional benefits of product formulations, including health economics outcomes research, quality improvement studies, and "pragmatic randomized clinical trials" (as termed by ASPEN). A recent publication by Albert Barrocas (71) of the ASPEN Value Project reviews 4 decades of experience from nutrition support teams and offers recommendations for demonstrating the value of nutrition support. The process of bringing products to market moves from rapid prototyping in a laboratory to manufacturing, quality testing, and monitoring across product shelf-life. Depending on the product and key ingredients, the iterative process can take from 8 to 24 mo. The user experience is considered at each step.

Dr Jonnalagadda also stressed the importance of nutrition education and referred to a recent perspective in *JAMA Internal Medicine* (72). She suggested that continuing medical education could include education on the benefits of different product formulations to patients.

Evidence for medical nutrition therapy

Dr Krysmaru Araujo-Torres, Head of Medical Affairs, Nestlé Health Science, noted that a search of the terms *medical foods*, *medical nutrition*, *enteral nutrition*, *tube feeding*, and *oral nutritional support* in PubMed (National Library of Medicine) shows an increase in scientific publications and human clinical trials over the last 40 y.

Dr Araujo-Torres mentioned that a significant number of these studies focus on burden of disease, identifying populations at risk, and identifying gaps in clinical practice that could lead to quality improvement projects in all clinical settings. Significant research resources have also been invested in showing the consequences of inadequate nutritional support. In this regard, she highlighted the result of a longitudinal study conducted by Cansado et al. (73) in 2009 of 531 hospitalized older adults showing that the prevalence of patients with malnutrition is higher at discharge than at admission, demonstrating gaps in current patient care.

One key point made is that scientific evidence is incorporated at every step in the development of nutritional formulas, from patient insights to condition-specific nutritional recommendations and dietary guidelines during design, and finally to clinical and economic outcomes of nutritional interventions in real-world evidence of the benefits of nutritional interventions. In that regard, Dr Araujo-Torres reviewed some of the literature available on the benefits of ONSs for increasing total energy and protein intakes and evidence-based outcomes in specific settings and subsets of patients. A review of trials in the hospital setting showed the efficacy of ONSs for increasing total energy intake in patients with chronic obstructive pulmonary disease, postsurgical patients, orthopedic patients, patients with liver disease, and patients with cancer (74). Other studies show higher protein intake in malnourished patients who receive dietary advice with ONSs compared with dietary advice alone (75). In surgical populations, a meta-analysis of immunonutrition that evaluated preoperative, perioperative, and postoperative uses of arginine-supplemented diets showed a 41% reduction in infectious complications (the primary outcome) and a reduction in length of stay of 2.38 d (76). Finally, in critically ill patients with obesity in the ICU, hypocaloric high-protein and low-carbohydrate enteral nutrition has been shown to improve glucose management (77).

Although significant evidence exists for the burden of disease, which will help to elevate the role of medical nutrition therapy, patient populations and medical conditions remain for which additional relevant outcomes are needed to strengthen the body of evidence in clinical nutrition.

Panel discussion: new types of evidence and product innovation

During the time allowed for discussion, the speakers were asked whether the current definitions of medical foods and reimbursement are considered during product design and development. The speakers noted that complying with current regulations is non-negotiable, but further clarified that current regulations should also focus on fostering innovation rather than restricting it. Many larger companies think about the patient first when developing and formulating their specialized nutritional products and then look at the regulatory framework to determine the appropriate regulatory classification and related regulatory requirements. In the EU, for example, one product may be a general food in one member state but be in a different category in a different state. Regarding the issue of reimbursement for medical foods, there was a discussion about how to respond to denial of claims for reimbursement, which included recommendations to clearly document the medical justification for the product, resubmit the claim with all required documentation, and encourage patients to be proactive in advocating for coverage of these medically necessary products. One recent example of legislative action in this area mentioned at the workshop was the reintroduction of the federal Medical Nutrition Equity Act (in May 2019), which could provide for public and private insurance coverage for "medically necessary foods" (including vitamins) for specific conditions including certain digestive and inherited metabolic disorders.

Differentiating Medical Foods and Foods for Special Dietary Uses

As described in the section "The regulatory framework of medical foods," foods and food products are broken down into regulatory categories that include conventional foods, medical foods, dietary supplements, and FSDUs. The second day of the workshop devoted more time to distinguishing between medical foods and FSDUs.

Current regulation around foods for special dietary uses

Ms O'Connell provided a regulatory perspective on the distinction between medical foods and FSDUs. She explained that FSDU is an old category from 1938 that initially included dietary supplements and other products now regulated separately. The first regulation defining "special dietary uses" was promulgated in 1941 (1). In 1972, the FDA re-examined whether these products should be regulated as drugs and, as stated previously, concluded that Lofenalac (a low-phenylalanine product for use in patients with phenylketonuria) would instead be regulated

as a "food for special dietary use," which would minimize barriers to innovation and reduce consumer cost. Some FSDU products were exempted from nutrition labeling in 1973: foods that were the sole item of the diet and foods used solely under medical supervision for the dietary management of specific diseases and disorders.

The current regulatory status of FSDUs is shown in **Box C**. FSDUs cover a broad range of diseases and conditions.

BOX C

The term "special dietary use" includes but is not limited to the following uses:

- Supplying a special dietary need that exists by reason of a physical, physiological, pathological, or other condition, including but not limited to the conditions of disease, convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control the intake of sodium.
- Supplying a vitamin, mineral, or other ingredient for use by man to supplement his diet by increasing the total dietary intake.
- Supplying a special dietary need by reason of being a food for use as the sole item of the diet.

As defined in section 411(c)(3) of 21 U.S.C. 350(c)(3).

A key distinction between a medical food and an FSDU is the specific labeling exemptions for medical foods. Ms O'Connell suggested that the fact that exemptions were included for medical foods but not for FSDUs implies that Congress intended for these to be distinct categories. The regulations also include specific labeling requirements for certain categories of FSDUs, such as hypoallergenic foods and infant foods. Food for use in the diet of people with diabetes was revoked in 1996 as part of regulatory reform. Ms O'Connell noted that the FDA did not say there can never be an FSDU intended for people with diabetes but rather that a specific or dedicated regulation was not needed.

In the 1996 ANPRM for clarifying regulations of medical foods (mentioned earlier), "distinctive nutritional requirement" was considered to have 2 possible interpretations that could help to distinguish medical foods from FSDUs: physiological and alternative (1). In the physiological interpretation, a medical food would only be for nutritional requirements that differ from the nutritional requirements of healthy people. If the food is intended to meet typical nutritional requirements, it would be in the category of FSDUs. The alternative interpretation was broader and would also include limitations in the ability to ingest or digest conventional foods, even if nutritional requirements were no different from the general population. Although still representing key thinking on this topic by the FDA, these definitions were never finalized into regulations when the ANPRM was withdrawn from active consideration in 2004.

Thus, as explained in the Guidance for Industry, the FDA considers the statutory definition of medical food to "narrowly constrain the types of products that fit within this category of food [21 CFR 101.9(j)(8)]. Medical foods are distinguished from the broader category of foods for special dietary use by the requirement that medical foods be intended to meet distinctive nutritional requirements of a disease or condition, used under medical supervision, and intended for the specific dietary management of a disease or condition" (3). However, Ms O'Connell noted that the Guidance went on to provide a direct answer to Question #2, "Has FDA established by regulation any criteria that clarify the statutory definition of a medical food?" The affirmative answer was to restate the same 5 criteria shown in Box B (discussed above) as the regulatory definition of a medical food.

Differentiating medical foods and FSDUs: disease management compared with disease compatibility

In this presentation, JR, Director, Regulatory Affairs, Abbott Laboratories, presented further ideas on clarifying the differentiation between medical foods and FSDUs as well as modernized interpretations of the "distinctive nutritional needs" terminology. For both discussions, Ms Rostorfer stressed the importance of keeping patient needs at the forefront.

When considering patient needs in the dietary management of disease, whether the need is for a single nutrient or for total dietary management, Ms Rostorfer stressed that the overarching goal is to improve patient health. Patient compliance was a large part of the workshop discussion, and consideration of dietary management from the patient's perspective should consider practicality, feasibility, sustainability, and effects on quality of life. Therefore, how the regulatory framework should evolve to address safe, practical, and effective choices for dietary management must be considered.

Ms Rostorfer reviewed the current regulatory framework, noting that conventional foods are the mainstay of the diet and dietary supplements are intended to supplement the normal diet. The FDA has clearly defined labeling regulations for foods (NLEA) and dietary supplements (Dietary Supplement Health and Education Act). FSDU is a distinct category of foods that supply special dietary needs that can exist by reason of a physical, physiological, pathological, or other condition, but must also follow FDA food labeling regulations established for conventional foods (NLEA). Medical foods are intended for the dietary management of a patient with a particular disease or condition that results in a distinctive nutritional requirement and are exempt from NLEA labeling.

Ms Rostorfer noted that many active policy initiatives are focused on reducing the risk of disease through nutrition to improve public health. One example is the work of the National Academy of Sciences in incorporating chronic disease risk reduction end points into the DRIs. A second is the Nutrition Innovation Strategy (78) announced by the FDA in 2018, which acknowledges the rise in chronic diseases such as heart disease and cancer and the role of nutrition in reducing the burden of preventable chronic diseases. The Nutrition Innovation Strategy includes labeling reform, standards of identity renovation, and consumer education components. However, the focus of this workshop was on seeking a policy initiative that prioritizes nutrition for people already living with disease, and specifically, to ensure a patient-centric approach to therapeutic nutrition.

A potential path forward in clarifying the distinction between these 2 food categories (medical foods compared with FSDUs) as presented by Ms Rostorfer are the concepts of "management" and "compatibility." Medical foods are intended for the dietary management of a patient with disease for which distinctive nutritional requirements exist and must be used under medical supervision, hence playing a more central role in the management of the disease. On the other hand, FSDUs could be seen as

TABLE 2 Hurdles to patients getting new medical food products to manage their disease and improve their quality of life and steps to overcoming these barriers[1]

What is the biggest hurdle to getting patients new products?
Regulatory
• Interpretation of "modification of the diet alone"
• Lack of clarity in interpretation of the definition of distinctive nutritional requirements
• Focus on distinctive nutritional requirements instead of patients' clinical outcomes
• Narrow interpretation of what constitutes a medical food
• Need for a clearer differentiation between drugs and foods in the context of promoting optimal health
• How to make medical food regulations a priority focus at the FDA
Research and development
• Imprecise evidence framework used to substantiate a claim
• Challenges of randomized controlled trials to establish unique nutrient needs of patients
• Challenges for product development teams when regulatory definition, and therefore, commercial outcomes are unclear
Patient- and market-related
• Inconsistent policies of payers to reimburse for appropriate medical foods
• Lack of shared vision among stakeholders
• Lack of education on behalf of providers as to what nutritional options are available for patients
• Disconnect between what products can realistically be developed by industry and what is expected by patients and caregivers for therapeutic benefit
What steps can be taken to overcome these barriers?
Increase the frequency of dialogue between industry, patient advocacy groups, and FDA staff responsible for medical food regulatory policy
Develop a roadmap document outlining an integrated strategy to positively influence regulations
"Slice the salami" and discuss 1 topic at a time (e.g., at future conferences) following a logic sequence (i.e., not possible to discuss level of evidence before distinctive nutritional requirements definition is clarified; level of evidence might vary on case-by-case basis)
Make the case for why change is needed (e.g., for patient benefit)
Use health economic outcomes data to demonstrate cost-effectiveness of medical foods, particularly for reimbursement/market access discussions with payers
Use a multipronged approach that takes multiple stakeholders into account at the same time
Establish disease-specific patient registry to assess patient access
Work to rewrite the current regulatory definition for medical foods or create a new regulatory category (such as "therapeutic nutrition") that acknowledges scientific advances in nutrition science
Enlist the support of congressional committee members to advocate with the FDA for patient benefits
Study other pathways in the FDA for ideas (e.g., biosimilars)
Address reimbursement and what cost benefits can be achieved by nutritional approaches over drug prescriptions in certain disease conditions
Create working subgroups on some of the above topics that will report back to the larger group in a follow-up workshop
Include informed patients as stakeholders to bring reality to the discussions
Hold a listening session at the FDA on how nutritional products can effectively improve health outcomes for patients in ways that are different from drugs
Create CE and CME for health care providers as a way to encourage learning about nutritional therapies that benefit patients
Study European-supported initiatives to assess risk for malnutrition and action for guidance [e.g., ONCA (Optimal Nutritional Care for All)]

[1] CE, continuing education; CME, continuing medical education.

disease-compatible foods, that is, products for the everyday health of a person living with disease. One example could be a highly nutrient-dense ONS for a patient with malnutrition.

AB, Head of Regulatory Affairs US, Nestlé Health Science, reviewed the Healthcare Nutrition Council definition of distinctive nutritional requirements (5) (see the section "From essentiality to quality of life: assessing 'distinctive nutritional requirements' in different clinical contexts") and the 4 key pillars to ensuring a patient-centric approach to the medical foods category. These pillars are (5):

1. Focus on patients' complete nutritional requirements.
2. Consider feasibility (must consider patient perspective).
3. Keep positive health outcomes for patients as the core goal.
4. Recognize that disease severity can amplify a patient's need for medical food.

Reflections on medical food and FSDU concepts

In this panel discussion, Xin Tao, Senior Associate, Hogan Lovells, BS, TM, Ms O'Connell, AB, and JR held an open discussion on medical foods and FSDUs. Workshop participants also asked questions. Panelists first offered their reactions to the previous presentations on distinguishing medical foods and FSDUs. Panelists returned to the impact of disease severity on patient nutritional needs. Concerning distinguishing medical foods and FSDUs, 1 panelist suggested that another way to look at the distinction is to look at the types of claims allowed for conventional foods. For example, health claims for conventional foods are about reducing risk of disease, whereas medical foods and FSDUs are developed for people already managing a disease or condition. Discussion of how to change the current definitions offered multiple avenues: globally addressing the medical food definition through Congress; working to change the regulatory language, which is within the FDA's control; and working to expand the definition informally on

a case-by-case basis with the FDA through particular products with strong scientific evidence. Panelists discussed the need for a more pragmatic view about how to conduct clinical trials in nutrition.

Questions from the audience addressed nutrient content claims, the conduct of premarket research, and the availability of medical foods. Although medical foods, which are exempt from the labeling requirements for nutrient content claims, might carry a nutrient content claim, they would not necessarily be delivered in a single-serving size or would have a higher percentage daily value by design, which does not fit the purpose of those claims. As for any food, a medical food bearing a false or misleading claim would be considered misbranded under the Federal Food, Drug, and Cosmetic Act. When conducting premarket research for medical foods, the panelists advised specifying the disease, how it is defined, and the end points being measured and also to collect data in a healthy population. They suggested clearly specifying the goal of the research as the study of dietary management or the dietary status of the patient. Concerning availability, the panelists clarified for the audience that medical foods are not sold only to hospitals.

Summary

In the final discussion, panelists and participants discussed learnings from the workshop and proposed next steps. Panel moderator TM asked the panelists to list, from their perspective, one hurdle to patients getting new products to manage their disease and then to propose a step that could be taken either individually or collectively to overcome the barrier they listed. Panelists represented the perspectives of patients, industry, nutrition scientists, scientific societies, and dietitians. Audience members also joined in the discussion. **Table 2** summarizes the responses to these questions.

The final key issue discussed by the panel was the question, If regulatory outdatedness is a concern, what will it take for change? Panelists referenced the ASPEN Value Project (66). Panelists noted the importance of generating evidence on cost-effectiveness and characterizing the value proposition of effective nutritional care, although they acknowledged that it might not be the economic piece of the data that moves the FDA to action. The panelists noted that guideline groups should also include patient advocates. The group discussed whether different stakeholders could come together and, given the statutory language, put forward some very specific suggestions for regulatory change. Suggestions for working with the FDA included the following:

- Propose a workable solution to kickstart dialogue.
- Improve nutrition education among health care providers (little awareness of nutrition exists in certain specialties).
- Remember that the FDA medical food staff want to be part of the discussion (all stakeholders should have a seat at the table).
- Use existing ways of working with the FDA, such as:
    - in-person informational meetings with FDA staff,
    - official letters offering practical support (e.g., from ASPEN or Healthcare Nutrition Council),
    - political support (work with advocates and policymakers who have expressed interest in medical foods), and
    - citizen petitions.

A citizen petition is a means of requesting that the FDA "issue, amend, or revoke a regulation or order" of a statutory provision. The audience discussion noted that the first response from the FDA can be just acknowledgment of receipt (the FDA has 180 d to respond), but once a petition is posted, there is an opportunity for public comments. Thus, the participants noted that a citizen petition seems to be an expedient route to officially open a dialogue with the FDA.

The workshop ended with a short discussion of topics for future workshops. These included exploring the FDA's thinking related to investigational new drug applications for nutritional products, exploring incentives to start feeding rather than stop feeding in the hospital setting, developing guidance on generating scientific evidence to support the justification for a medical food, developing patient stories, addressing reimbursement, and developing a detailed work plan to move this agenda forward.

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