REGULATORY FOCUS

# Foods for special medical purposes/ medical foods: A global regulatory synopsis

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This two-part article covers the specific requirements for placing foods for special medical purposes (FSMPs) on the market in major jurisdictions – EU, UK, US, China, and other regions of the world – to improve the role of nutrition in support of optimal care for patients. Part 1 covers general principles governing FSMPs, use of FSMPs in community and hospital settings, common regulatory challenges, opportunities for category growth, and considers a multistakeholder initiative for optimal nutrition care for all. Part 2 presents a global overview of the regulatory framework for medical foods/FSMPs in the aforementioned countries and regions.

***Keywords*** **–** FSMP, global policy, medical foods, nutrition, patient care, regulatory synopsis

## Introduction

Foods for special medical purposes, or FSMPs, are known as medical foods in some non-EU countries (e.g., US, Argentina) or as enteral nutrition (e.g., Brazil), is also commonly used by healthcare professionals. FSMPs are specially

formulated and processed for the dietary management of patients with a disease, disorder, or medical condition, that is, intended for use under medical supervision for patients. FSMPs have a longstanding history of practical usage over the last decades, laying a foundation for nutritional patient care.[1] FSMPs may constitute a patient's sole source of nourishment over short or extended periods or may supplement his or her regular diet, administered via tube feeding or as an oral nutritional supplement (ONS). Gaining traction due to their potential support in health and disease management, FSMPs are subject in principle to general food legislation, including good manufacturing practice (GMP), and must be safe as labeled for their intended use, make truthful, not misleading claims and are subject to novel food, contaminants, additives, and packaging legislation, to name just a few.

FSMPs, as they are known in the EU, by Codex Alimentarius and most countries in the world, or medical foods in the US, are defined broadly as a category of foods that are specially processed or formulated and presented for patients' dietary management and used only under medical supervision. Overall FSMP or medical food regulations, their definitions, constraints, and opportunities, show remarkable similarities across multiple countries. This article presents an overview of the global medical food/FSMP regulatory framework, with a focus on Codex Alimentarius, the US, the EU (**Table 1**).

**Table 1. Regulatory synopsis for food for special medical purposes/medical food (noninfant)**

| | EU | US Medical Food | China | CODEX |
|---|---|---|---|---|
| **Governing Legal Definition** | Reg. 178/2002 | Section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3) | Food Safety Law | Codex Alimentarius Standard 180-1991 |
| **Medical Food Regulatory definition** | — | 21 CFR 101.9(j)(8) | — | |
| **FSMP definition** | Reg. 609/2013 | — | GB 25596-2010 | |
| **Micronutrient composition** | Reg. 2016/128, Annex I | None specifically addressed | GB 29922-2013 | |
| **Labeling** | Reg. 1169/2011<br>Reg. 2016/128 | 21 CFR 101.9(j)(8) | GB 7718-2010<br>GB 13432-2010 | Codex Stan. 146-1985<br>Codex Stan. 180-1991 |
| **Nutrients** | Reg. 609/2013<br>Reg. 2016/128 | None specifically addressed | GB14880-2012 | CAC/GL 10-1979 |
| **Additives** | Reg. 1333/2008 | None specifically addressed | GB2760-2010 | Codex Stan. 192-1995 for Food Additives. Food Category No. 13.3 |

## PART 1

**General principles of medical nutrition and its regulatory environment**

Originally, given the lack of an advanced regulatory framework since the 1960s, these specialized medical foods or FSMPs were traditionally governed by drug regulations.[2] Over the past several decades; however, they have increasingly been characterized under food laws worldwide. An FSMP is intended for the exclusive or partial feeding of patients with limited or impaired capacity to take, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients contained therein; or have other special medically determined nutrient requirements and whose dietary management cannot be achieved only by modifying the normal diet.

FSMPs are for enteral usage, including tube and sip feeding or oral nutritional supplementation (ONS). They are regulated as foods, not to be confused with parenteral nutrition (i.e., infusion of nutrients directly into the blood circulation), which is regulated under medicinal law.

Despite a growing body of evidence on the benefits of FSMPs, their usage is not reaching its full potential and facing challenges in regions worldwide. On the one hand, this may be due to the apparent "frontier situation" for foods for medical purposes with the need to build awareness and educate all vested stakeholders. On the other hand, regional differences in regulatory frameworks may contribute to this basic dilemma. US regulators and payers appear to apply a deliberately narrow interpretation to limit medical food usage largely to enteral tube feeds and for inborn errors of metabolism, yet seldom reimburse oral nutrition supplements. The EU has developed a pragmatic approach when revisiting the entire food for specific group (FSG) framework for vulnerable populations, abandoning the concept of foods for special dietary uses (FSDU), yet including a patient-oriented interpretation regarding FSMPs. In Asia, a slowly evolving FSMP framework in key countries faces issues such as lack of awareness and wide-spread healthcare reimbursement systems outside of hospitals, and a significant prevalence of parenteral nutrition usage over enteral nutrition.

The regulatory criteria that a medical food/FSMP be uniquely formulated to address distinctive nutritional requirements of patients with a disease or condition, outside normal dietary modification, is gaining evidence-based support as the nutritional science community reconsiders the meaning of "requirement" beyond avoidance of historical nutrient deficiency syndromes. Technological advances in analytical tests enable more sensitive diagnostics to characterize nutrient adequacy or impairment at the organ, tissue, and even cellular level. Accelerating innovation in medical food research, with willingness of regulatory bodies to adapt definitions as science advances, will enable healthcare professionals and funding agencies to administer and reimburse these safe, cost-effective, and necessary products that are increasingly shown to improve quality of life for patients while contributing better health economic

outcomes. Current challenges are given, along with practical opportunities to improve the role of nutrition in support of optimal care for patients.

**FSMPs in community and hospital settings**

FSMPs are used across various healthcare settings, in community and care homes and hospitals. Enteral nutrition can provide clinical benefits and lower healthcare costs by reducing hospital stays and maintaining patients' independence longer. Similar results were shown for specialized ONS in various settings.[3-5]

In the US, medical food coverage is state- and disease-dependent. Each state regulates products and diseases that must have coverage under state laws differently, including federal plans. Medicare covers some medical food products for inpatients in acute care and in long-term care facilities for the first 100 days. For outpatients, Medicare covers enteral nutrition for long-term use via tube feeding only after the initial 100 days in a long-term care facility; yet ONS are not covered. Commercial plans apply different coverage policies for medical foods in the US.

In the EU, reimbursement is based largely on diverse national, regional, or local coverage rules, which might include specific compositional criteria (e.g., protein, energy level, fiber). Beyond FSMPs for disease-related malnutrition (e.g., short bowel syndrome), reimbursement also may be possible for FSMPs for dietary disease management, such as infant allergies to cow's milk protein, inborn errors of metabolism (e.g., phenylketonuria, maple syrup urine disease).

**Common regulatory challenges**

There are common elements of medical food/FSMP regulations across the globe supporting the needs of multiple stakeholders. Healthcare professionals need clear, scientifically valid, detailed product information to support clinical judgment on which patients would benefit, and what medical conditions are addressed by specially formulated nutritional products. Manufacturers need well-defined regulations setting out patient/disease eligibility criteria, standards for GMP and any registration or approval processes to confidently produce and market the product. Regulatory bodies depend on research and medical scientists to characterize distinct nutritional requirements of various diseases requiring specially formulated FSMPs to compensate for the inability of simple diet manipulation to achieve. But, as already stated, a more integrated physiologic, metabolic, and cellular understanding is needed of how dietary "bio-active substances" contribute to health and even rebalance unhealthy situations resulting from disease. This should include previously defined nutrients, with daily requirements established for the general "healthy population" but advancing research evidence now suggests that dietary sources of enzymes, substrates, and metabolically active components should also be considered. Government or third-party healthcare payers must consider FSMPs as an essential component of disease management to justify reimbursement for the higher cost of specialized ingredients compared with typical "food." Together, when all have the patient's outcome as their primary focus, mutual benefits to larger integrated healthcare systems may be possible. Benefits

expected from targeted nutritional support include reduced costs associated with shorter hospital length of stay due to quicker recovery from acute illness or surgery; more effective therapeutic interventions due to better metabolic support from properly nourished patients; ample financial incentives to drive innovation for improved FSMPs addressing malnutrition or disease management more effectively, and ultimately, improved patient quality of life.[6]

There are certain challenges that will require multistakeholder attention in a coordinated way to overcome. A few examples of these challenges limiting a more rapid expansion of appropriate medical food/FSMP use are shown below, though this list is by no means exhaustive:

- Establishing with key opinion leaders, research scientists, clinicians, and patient groups whether specially formulated nutritional products are needed in specific diseases, when alteration of the normal diet is insufficient, including the recognition that the use of an FSMP can be of clinical benefit beyond just correcting a nutrient deficiency from inadequate dietary intake. This also includes possible benefits for patients with chronic diseases not traditionally considered for nutritional intervention (e.g., neurological disorders).
- Realigning priorities that consider nontraditional research designs (e.g., unethical randomization to placebo control; small patient populations with diseases, such as inborn errors of metabolism (IEM); and complexity of metabolic interactions with drugs and/or the microbiome) and place greater emphasis on medical determination of patient suitability for dietary management of their disease. Evidence of patient benefit from safe FSMP administration should drive regulatory acceptance, not be limited by it.
- Recognizing that there are cases in which it may be impossible, impractical, or unsafe for patients to exclusively consume foodstuffs that are not an FSMP, emphasized in official EU guidelines.[7]
- Redefining the role of the patient as a consumer and increasingly becoming an active participant in their own healthcare decisions that can influence compliance with FSMP medical recommendations.[8]
- Characterizing what aspect of nutritional support needs to be overcome/corrected to meet a patient's nutritional needs, such as higher nutrient levels to compensate for reduced digestion/absorption; enteral tube feeding when oral intake is contraindicated; hydrolyzed proteins or peptides when digestive enzymes are inadequate; lower levels of key nutrients if their metabolism is impaired, resulting in buildup of toxic wastes; or greater nutrient density when volume administered is of concern.
- Speeding up the process of validating "omic" biomarkers providing insight into metabolic and physiologic processing of nutrients, precursors, and active metabolites to more closely manage FSMP effectiveness in patients. It ultimately also may require redefining what constitutes a patient in the future, e.g., whether persons diagnosed with a genetic pre-disposition to a disease are considered (potential) patients.[9]

- Increasing nutrition research funding to validate the importance of FSMPs in disease management.
- Including impact on overall "cost of care" in prospective studies by capturing health economic outcome data in large clinical trials to prove cost-effectiveness and justify higher reimbursement rates not tied to calories as currently seen in some countries.

These are a sample of issues limiting growth of the medical food market, both in large and smaller countries. Importation of products from major countries into lesser-developed countries is common but meeting the criteria for registration with authoritative bodies requires similar data so the challenges are, essentially, global in nature.

**Opportunities for category growth**

New emerging developments in science will affect the practice of modern medicine and the nature of patient care, with a potential impact on regulatory frameworks at a faster pace than ever before. For instance, new tools using "omics" platforms to explore the interrelationships between genes, proteins, metabolism, environmental factors, and the intimate relationship with the microbiome are advancing the understanding of links between food, health, and disease.[10] It emphasizes the complexity of this relationship, making the evaluation of the impact on any one dimension more challenging. Further advances in diagnostics will influence how we define the future journey from health (consumers) to sickness (patient), leading to a more specific, personalized nutrition approach. Linking multiple observations together is the field of bioinformatics, applying big data technologies, including probability calculations and some level of uncertainty, that will influence our future approaches in how to launch new products for the individual, such as medical foods and FSMPs, with the benefit of science-based dietary disease management formulated, and intended to benefit each patient and improve overall healthcare outcomes. If key scientific, medical, and policymaking stakeholders can align on a patient-centric healthcare model, incentives to accelerate innovative medical nutrition formulations targeting nutritional management of patients with various diseases should follow.

While the challenges to reaching full potential of medical foods/FSMPs in advanced patient and disease management may appear to hinge on either the flexibility or constraints within the regulatory framework, progress is being made with a multistakeholder approach.

The nutritional science community consists of research experts working to establish and validate more sensitive biomarkers of nutrient adequacy, inadequacy, or even optimal ranges. Compared with past practices of establishing nutrient requirements based on epidemiologic models of healthy people, individualized nutrition, and personalized medicine fields are advancing rapidly. This is needed to satisfy medical food/FSMP criteria that patients who

are not healthy do, indeed, have requirements for certain nutrients, that differ from normal individuals.

There is a growing willingness to accept "n-of-1" study design, in which each research patient serves as their own control for a period of time, then is given the therapeutic test product, and outcome markers at the end of each period are compared. In this way, individual variation in metabolic, genetic, and dietary elements are better accounted for when compared with others in the study, which may have very different physiologic baselines.[11]

Medical practitioners will quickly adopt promising therapies when evidence of efficacy is demonstrated by clinical data. Together, and after collecting data on health economic outcomes for patients receiving FSMPs in addition to other medical treatments, the cost-effectiveness of safe, acceptable, specialized nutritional products will become evident. Providing market incentives to stimulate more innovative, food-based, specially formulated products that fall within the expanded definition of individualized nutritional support benefits all sectors. A current example of how this can work is shown below.

**Multistakeholder initiative to strive for optimal nutrition care for all[12]**
Disease related malnutrition is a significant, often still unrecognized issue in Europe as well as other parts of the world. The European Nutrition for Health Alliance (ENHA) driven Optimal Nutritional Care for All (ONCA) multistakeholder initiative is an ongoing concerted real-life example to overcome complexities in public health to ensure that "every patient who is malnourished, or at risk of undernutrition, is systematically screened and has access to appropriate, equitable, high-quality nutritional care."

Key to the ONCA campaign's progress is aligning diverse stakeholders, such as healthcare professionals, patients, industry associations, and public authorities in multiple focus countries behind a common goal to form a national alliance and develop a nutritional care plan to facilitate greater malnutrition screening and nutritional care implementation, which include FSMPs, and actively promote public awareness, appropriate reimbursement policies and medical education.

**Conclusion for Part 1**
A review of medical food and FSMP regulations, their constraints but opportunities, shows remarkable similarities across multiple countries. The opportunity for stakeholder engagement with improved quality of healthcare and patient-centered outcomes is growing. Each sector, be it medical, research, regulatory, patient, industry, or payers, benefits when communicating about the benefits of improved patient nutrition derived from specialized medical foods/ FSMPs.

## PART 2

### Global regulatory frameworks for medical foods/FSMPs

This section presents an overview of the regulatory frameworks for medical foods/FSMPs in the EU, US, China, Codex Alimentarius, as well as Brazil, Canada, South Africa, Australia/New Zealand, Japan, India, Turkey, the Middle East, and the Association of Southeast Asian Nations (ASEAN) member states.

It should be noted that the following sections provide a glimpse – with no expectation of completeness or coherence – of FSMP regulations (if present) in key countries or regions worldwide. It demonstrates that FSMPs are based on a food regulatory framework with some remarkable similarities, but that it is also complex and diverse. All FSMPs are required to be used under medical or healthcare supervision. That requirement is not surprising given that their intended role is to manage the dietary aspects of disease, which has become a new frontier for enhancing the role of nutrition.

Where possible in the References section of this article, links are provided to English documents. However, some regulations are available only in the original, regional languages, and in those cases, the links go to the original language documents.

### European Union

FSMPs have a long-standing history and practical usage in the EU. In 2013, the legal framework for FSMPs was revisited within the Foods for Specific Groups Regulation (EU) 609/2013,[13] harmonized across EU member states. Well anchored within food law (Regulation (EC) 178/2002),[14] the FSG regulation replaced the concept of dietetic foods established by the foods for particular nutritional uses (PARNUTs) framework directive in 1989. FSMPs are not subject to premarket approval. The legislation allows flexibility in formulating such products based on sound medical and nutritional principles (e.g., European Society for Clinical Nutrition and Metabolism [ESPEN] guidelines [15]) to meet their intended use for the dietary management of diseases, disorders, or medical conditions. FSMPs are to be used under medical supervision, intended for the exclusive or partial feeding of people whose nutritional requirements cannot be met by normal foods. Regulation (EU) 2016/128[16] has revised the specific compositional and information requirements for FSMPs. This framework allows the development and assessment of products positioned as FSMPs, recognizing the flexibility required in the regulations and their interpretations to accommodate the diversity of medical conditions for which FSMPs are currently used and should be used in the future.

#### *Framework regulation of FSGs*

Some individuals or population groups require specific nutritional support due to their physiological conditions or the specific diseases from which they suffer. The FSG Regulation is intended to strengthen provisions on foods for defined vulnerable population groups needing particular protection (Article 1):

- Infant and follow-on formulae,

- Processed cereal-based foods and other baby foods,
- Food for special medical purposes, and
- Total diet replacement for weight control.

A number of FSG Regulation articles are specifically relevant to FSMPs:

- Article 2(2)(g) contains the legal FSMP definition.
- Article 3 permits the European Commission (EC) to make interpretation decisions as to whether a product falls within the FSG Regulation's scope and, if so, in which category it belongs.
- Article 9 sets down general compositional and information requirements applicable to all FSG categories. It also clarifies the labeling, presentation, and advertising rules, particularly with reference to properties of preventing, treating, or curing a human disease and shall not prevent dissemination of useful information and recommendations intended for HCPs (i.e., persons with qualifications in medicine, pharmacy, or nutrition, or those responsible for maternal and child care).
- Article 11 sets down the areas in which the EC should adopt specific rules for food category composition and labeling within the regulation's scope.
- Articles 15 and 16 include the requirements for a Union list of substances that may be added to foods for specific groups. The annex contains the Union list of permitted substances, which includes sources of vitamins, minerals, amino acids, carnitine and taurine, nucleotides, choline, and inositol.

***EC notice on FSMP classification[17]***

Although harmonized, it has been recognized that the FSMP definition may be interpreted differently across the EU member states, and interpretative differences would impact the EU internal market's functioning and patient care, respectively. The EC hence issued a guidance document aimed at food business operators (FBOs) and member state national authorities, with the objective of striking a balance between ensuring the boundaries of the FSMP category are interpreted narrowly within the context of the total food and food supplement market while recognizing that nutritional science will continue to develop for use in the management of other disease areas. During development of the guidance and consultation with stakeholders, a number of key principles were established, critical to the concept of FSMPs:

- All elements of the FSMP definition must be taken into consideration, and no single element should be considered in isolation to include or exclude a product from the categories of special processing and/or formulation.
- Use in partial or exclusive feeding of patients and under medical supervision (i.e., recommendation of a qualified HCP) for the dietary management of patients, who as a result of their disease, disorder, or medical condition, have medically determined nutrient requirements,

and those medically determined nutrient requirements cannot be met by modification of the normal diet alone.
- The measure of whether it is possible to achieve the required nutritional intake by modification of the normal diet must be considered in the context of the patient and the challenges of their disease, disorder, or medical condition.
- FSMPs can also offer nutritional and clinical advantages to patients over and above modification of normal diet and this too must be considered. It can be impossible for some patients to meet their requirements via normal foods, but it also can be unsafe, impractical, or disadvantageous to modify patients' diets to meet the nutritional demands of their disease or medical condition, and FSMPs provide a pragmatic solution.

***EFSA guidance on Article 3 interpretation decisions[7,13]***

A provision in the FSG Regulation (Article 3) permits the EC to determine whether a food falls within the scope of FSG or one of its categories. Article 3 is intended for exceptional use and is not intended to replace the general rules at national level, which permit FBOs to market foods on the basis of their own determination as to compliance with the FSMP definition and leaves national authorities with the general responsibility for enforcing food law.

When there is uncertainty whether a product is considered an FSMP, a national competent authority may request the EC to interpret and decide, by means of implementing acts as defined in Article 3, Regulation (EU) 609/2013, to which specific category a given product belongs to ensure uniform implementation across the EU. In this context, the European Food Safety Authority's (EFSA's) panel on dietetic products, nutrition and allergies provided scientific and technical guidance on FSMPs. It presents a common format and outlines the data as well as the key issues to be addressed in the dossier to assess the extent to which a food product notified as an FSMP falls under the scope of the regulation, based on its proposed use.

The EC may ask EFSA to address the extent to which the specific food product and disease, disorder, or medical condition is characterized sufficiently for its classification as an FSMP. It considers the impossibility or difficulty of taking, digesting, absorbing, metabolizing, or excreting ordinary foodstuffs or certain nutrients, and specific medically determined nutrient requirements that cannot be satisfied reasonably or realistically by modifying the normal diet, that is, if it is impossible, impractical, or unsafe for patients to consume exclusively foodstuffs (including fortified foods and food supplements) that are not FSMPs or whether such patients would have nutritional or clinical disadvantages. The guidance will be updated, as appropriate, in the light of future experience gained.

EFSA's scientific and technical guidance aims to address key questions, which the EC may need to take into consideration to take decisions under Article 3. The questions address:

- Whether the specific food product is sufficiently characterized;

- The extent to which the disease/disorder/medical condition for which the specific product is intended is sufficiently characterized;
- The extent to which patients suffering from the specific disease, disorder, or condition
    - Are unable to (or have difficulty) taking, digesting, absorbing, metabolizing, or excreting ordinary foodstuffs, or certain nutrients contained therein, or metabolites; or
    - Have specific medically determined nutrient requirements, typical to the disease, disorder, or condition that cannot be reasonably or realistically satisfied by modifying the normal diet;
- The product's specific role in the dietary management of the disease, disorder, or intended condition, particularly the extent to which the specific product is different from or more suitable than non-FSMP foods (i.e., including food supplements and fortified foods), taking into account the product's composition, manufacturing process, physical form, mode of administration, pattern of consumption, intended use, and the proposed instructions of use;
- The extent to which the use of the specific food product is necessary or more practical or safer than the exclusive use of foodstuffs that are not FSMPs, and/or has a nutritional or clinical advantage for the patient, and the reasons why it needs to be administered under medical supervision; and
- Whether there are any potential restrictions of use.

***Notification***

An authorization is not required before placing the FSMP on the market. The FBO must notify the competent authority of each member state where the product is being marketed, by sending a model of the label used and any other information the Competent Authority reasonably may request to establish compliance with this regulation, unless a member state exempts the food business operator from that obligation under a national system that guarantees an efficient official monitoring of the product concerned (Article 9).[16]

***Labeling: Food and nutrition information, communication, claims***

Nutrition information is mandatory for FSMPs and should follow the general rules laid down in Regulation (EU) No. 1169/2011 on food information to consumers[18] for all foods, yet Article 6 of Regulation (EU) 2016/128 specifies that the mandatory nutrition declaration for FSMPs must consider additional information for the healthcare professional or patient using the product. The additional information includes:

- A statement that the product must be used under medical supervision;
- A statement whether the product is suitable for use as the sole source of nourishment;
- A statement that the product is intended for a specific age group, as appropriate;
- Where appropriate, a statement that the product poses a health hazard when consumed by persons who do not have the disease, disorder, or medical condition for which the product is intended;

- The statement “For the dietary management of ...” where the blank should be filled in with the disease, disorder, or medical condition for which the product is intended;
- Where appropriate, a statement concerning adequate precautions and contraindications;
- A description of the properties and/or characteristics making the product useful in relation to the disease, disorder, or medical condition, for the “dietary management” of which the product is intended, particularly, as the case may be, relating to the special processing and formulation, the nutrients that have been increased, reduced, eliminated, or otherwise modified and the rationale for the product’s use;
- Where appropriate, a warning that the product is not for parenteral use; and
- Instructions for appropriate product preparation, use, and storage after opening the container, as appropriate.

Whereas Article 3 of Regulation (EU) No. 2016/128 clarifies that “medical supervision” may be with the assistance of other competent healthcare professionals (e.g., with qualifications in medicine, dietetics, nutrition, nursing, pharmacy),

> Nutrition and health claims shall not be made on FSMP (*Art. 7*). 'Whereas Art. 14’ requires that all information on the properties and characteristics of the product (e.g., any special processing and formulation, nutritional composition and rationale of use of the product that make it useful for its intended purpose) is mandatory information and therefore not considered as nutrition and health claims within the meaning of Regulation (EC) 1924/2006.[19]

The FSG Regulation introduces additional provisions on pesticide levels as well as FSMP labeling, presentation, advertising and promotional, and commercial practices for infants (0-12 months), similar to those applicable to infant formula and follow-on formula. Regulation (EU) No. 2016/128 includes these specific provisions on labeling, presentation, and advertising of FSMPs intended for infants (Article 8). It states that any mandatory information intended for the consumer must appear in a language that is easily understood, and that it should not include pictures of infants and be designed to enable consumers to make a clear distinction between FSMPs and infant and follow-on formula. However, the necessity to communicate to healthcare professionals is recognized, allowing them to assess different products’ suitability for their intended use as well as provide appropriate information about the critical use and compositional information to patients and care providers (Article 8(4)).

**FSMP categories and flexibility of compositional requirements**

An FSMPs composition may differ substantially depending on its intended use, that is, the specific disease, disorder, or medical condition it is intended to manage; patient age; and where patients receive healthcare support. Because of FSMPs’ wide diversity, the rapidly evolving scientific knowledge on which

they are based, and the need to ensure adequate flexibility to develop innovative products, it seemed not appropriate to lay down detailed compositional rules for such products, rather than setting principles and requirements specific to them. Article 2(2) states that FSMPs' formulation should be based on sound medical and nutritional principles and should be safe, beneficial, and effective in meeting the specific nutritional requirements of the persons for whom they are intended. This means an FSMP's composition/ formulation should be supported by a strong nutritional and medical rationale, but specific clinical trials may not always be required if there are adequate data already available in the public domain to support their composition and use.

Regulation (EU) 2016/128 classifies FSMPs in three categories (Article 2) as nutritionally complete with a standard nutrient formulation, nutritionally complete with a nutrient-adapted formulation, or nutritionally incomplete (**Table 2**). FSMPs developed to satisfy infants' nutritional requirements should comply with the provisions relating to other nutrients applicable to infant formula and follow-on formula (Regulation (EU) 2016/127),[20] provided they are in line with the intended use.

**Table 2. EU FSMP subcategories and types of diseases[a]**

| Category defined in Regulation EU 2016/128 | Category description, required vitamin & mineral levels | Disease examples |
|---|---|---|
| a) *Nutritionally complete foods with a standard nutrient formulation* which may constitute sole source of nourishment for persons for whom they are intended | These 'standard' FSMP products are designed for use by a wide variety of patients who are malnourished or at risk while unable to consume adequate conventional foods to meet their nutrient requirements because of their disease or medical condition. Products should comply with minimum and maximum levels for vitamins and minerals (Annex I). | **Disease-related malnutrition**, e.g., energy/protein from poor intake, related to:<br>– Inflammatory bowel disease<br>– Dysphagic stroke or head & neck cancer<br>– Cystic fibrosis<br>– Cancer chemotherapy<br>– Severe multiple food allergy in infants |
| b) *Nutritionally complete foods with a nutrient-adapted formulation* which may constitute sole source of nourishment for the persons for whom they are intended | These FSMP products are suitable for use by patients with specific disease-related nutritional needs. There may be minimum and maximum compositional level deviations from (Annex I) with scientific justification. | **Malnourished patients** with specific needs (ICU stay, renal failure, hyperglycemia, pressure ulcer), related to:<br>– Renal disease on peritoneal dialysis<br>– Hereditary hypercalcemia in infants (low calcium/vit. D)<br>– Preterm infants |
| c) *Nutritionally incomplete foods* with a standard formulation or a nutrient – adapted formulation which are not suitable to be used as the sole source of nourishment | These FSMP products are diverse and should comply with the maximum compositional levels (Annex I) unless modifications for one or more of these nutrients are necessitated by the product's intended use. | – Inherited metabolic disorders, e.g., amino acid suppl. for phenylketonuria<br>– Dysphagia<br>– Renal disease |

[a]FSMPs referred to in (a) and (b) may also be used to supplement a patient's diet, e.g., oral nutritional supplements to increase energy/protein intake during gastrointestinal disease or chemotherapy owing to poor appetite or sore mouth.

***Plastic products***

The EU directive on the reduction of the impact of certain plastic products on the environment [21] attempts to prevent and reduce the significant negative environmental, health, and economic impact, respectively. Although, single-use plastic beverage containers for the administration of FSMPs in liquid form are exempted from product recycling and collection requirements.

***Market access, health economics, and reimbursement***

FSMPs are consumed across all healthcare settings, such as hospitals, clinics, and nursing homes and at home. They have been shown to result in lower healthcare costs by reducing hospital stays and maintaining a patient's independence longer.[22] While EU legislation on FSMP composition and labeling is harmonized across the member states, there is no harmonization of healthcare systems. Hence, reimbursement is based on national, regional, or local health organizations and budgets. Even within countries, rules could be applied differently by regions or provinces and public or private healthcare providers. The criteria for FSMP reimbursement approval vary according to local rules and may be based on composition or provision of scientific rationale and/or health economic evidence.

In most EU member states, many products notified as FSMPs are reimbursable as part of local healthcare systems (public or private payers). This typically includes nutritionally complete FSMPs that may serve as sole nutrition sources. Reimbursement levels also may be based on specific compositional criteria (e.g., protein, energy level [Kcal/KJ], fibre) per specific categories (e.g., infants/adults, hydrolyzed/nonhydrolyzed proteins) or according to national guidances.[6] Apart from products designed for disease-related malnutrition, reimbursement also may be possible for specific FSMPs that manage diseases or medical disorders such as:

- Infant allergy to cow's milk proteins or multiple food allergies;
- Malabsorption syndromes (e.g., short bowel syndrome) ;
- Hereditary inborn errors of metabolism of carbohydrate, fat or protein (e.g., phenylketonuria); and
- Epilepsy (ketogenic diet formulas).

***EU summary***

Health and disease management requires the development of appropriate, performing healthcare solutions, using all options from medicinal treatment, lifestyle changes, and nutrition. Patient perspectives on nutrition,[8] developed by patient associations the European Patients' Forum and European Genetic Alliances Network and the ENHA, demonstrates nutrition as a vital part of health and disease management. It examines the role of nutrition in relation to a variety of different health issues, including brain disorders, cancer, coeliac disease, diabetes, inflammatory bowel disease, and kidney disease.

This goes hand-in-hand with the principal notion of a regulatory framework that encourages innovation globally for the sake of determining the most suitable

pathways in health and disease management.[23] The EU FSMP Regulation – a result of expert input from all member states – provides a well-defined framework, including compositional criteria, specific and relevant provisions on labeling, information, and monitoring of products on the market. FSMPs are not subject to premarket approval. This framework recognizes the flexibility required to accommodate the diversity of medical conditions for which FSMPs are and should be used, based on sound medical and nutritional principles and supported by generally accepted scientific data (e.g., ESPEN guidelines) to meet their intended use for the dietary management of diseases, disorders, or medical conditions.

**United Kingdom**[24]

Following the UK's departure from the EU in 2020, referred to as "Brexit," new regulation is an autonomous matter for both the UK and EU as two separate legal and regulatory systems. After contributing significantly to EU legislation for around 40 years as an EU member state, the post-Brexit UK food, including medical food/FSMP-related requirements, still resemble their EU past. Processes are since solely dependent on UK governmental institutions, including the Department of Health and Social Care, the Advisory Committee on Borderline Substances, and National Health Service.[24]

**United States**

The US Food and Drug Administration (FDA) is charged with protecting the public health through oversight of drugs (human and veterinary), biological products, medical devices, cosmetics, and products that emit radiation. In addition, it oversees the nation's food supply, ensuring safety of ingredients and manufacturing processes, and helping the public get accurate, science-based information needed to use medicines and foods to maintain and improve health.[25]

Before 1972, any product labeled or promoted as an article intended for the prevention, mitigation, treatment, or cure of a disease was considered to be a drug, subject to pre-market approval through FDA's new drug application process. As a rare class of genetic diseases became recognized, so was it discovered that the only treatment for patients with IEM, such as phenylketonuria, was providing highly specialized formulas with nutrient ratios impossible to obtain from diet modification of normal food. The term "medical food" was first defined by the Orphan Drug Act, amended in 1988, which instructed the FDA to develop regulations permitting such specialized food formulations to be used under medical supervision for the nutritional management of a disease or condition with medically established distinctive nutritional requirements.[26]

Further expansion of this statutory mandate was incorporated into regulations for the food industry when the Nutrition Labeling and Education Act of 1990 (NLEA) was finalized in 1993.[27] The exact language is important to read verbatim, as summaries at times have created an imprecise picture of how strict the definition actually is. The full text, from 21 CFR 101.9(j)(8),[27] is as follows:

> Medical foods as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)). 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. A food is subject to this exemption only if:
>
> (i) 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;
> (ii) It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone;
> (iii) It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation;
> (iv) It is intended to be used under medical supervision; and
> (v) It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.

The FDA chose to narrowly interpret the statute, stating that even a specially formulated food could not be a medical food if the disease/condition for which it was intended could be managed "… by modification of the normal diet alone."[27] The need for ongoing medical supervision for patient appropriateness and progress was stressed; however, a definition of what constituted "special medically determined nutrient requirements" was lacking. While basic food information was required (manufacturer, net contents, ingredient statement), medical foods were exempt from other claims and nutrition facts format defined in the NLEA.

In an attempt to clarify terms such as "distinctive nutritional requirements" that must be associated with a disease, and "modification of the ordinary diet alone," FDA published an advance notice of proposed rulemaking (ANPR) in 1996, requesting public comments about the agency's expanded rationale at the time.[28] However, due to higher priorities for inadequately resourced staff, the ANPR was withdrawn from active consideration in 2004, after eight years of no regulatory action. To this day, however, it is referred to as "directional thinking" of the agency and is often quoted in warning letters to companies accused of marketing "unapproved drugs" under the false pretense as a medical food, when claims are made about its effect on the disease process.

Two approaches to determine if distinctive nutritional requirements exist for a disease were proposed in the ANPR. A "physiological interpretation" for when

dietary management of patients with specific diseases may require nutrients that differ significantly from the needs of healthy persons was compared with a second "alternative interpretation" for patients unable to ingest, digest, or metabolize conventional foods due to their disease or condition, outlined in a more in-depth analysis of these approaches.[29]

FDA issued draft, then final versions of nonbinding guidance to industry, giving answers to frequently asked questions about medical food. Extensive comments to the 2013 draft were submitted by companies, medical and patient societies, scientific and trade associations, congressional staff, and individuals, all of which challenged the agency's position that diabetes was not a disease suitable as a target for medical foods. The rationale that patients are able to modify their diet to meet nutritional needs remained in the final version, ignoring the extremely low compliance of patients asked to significantly change their diet.[30]

Another nonbinding guidance document that referenced medical foods was issued by the FDA in 2013, in final form without opportunity for public comment. Its purpose was to help investigators, sponsors, and institutional review boards (IRBs) determine whether human research studies could be conducted without filing an investigational new drug application (IND), typically required when studying a new drug or biologic. However, this guidance stated that even if the compound being studied was a food, medical food, or dietary supplement, if disease endpoints were being evaluated, it would be considered to be an investigational new drug. This dramatically impacts the academic research community, adding complexity, cost, and ambiguity when nutritional products were studied as potentially helpful in preventing chronic disease (topic of health claims) or in correcting nutrient imbalance related to disease. Some of these provisions were put on hold or "stayed" in a 2016 notice that reversed the IND requirement when studies were designed to determine the effect of structure or function of the body, and not expressly for disease management.[31]

There are encouraging signs that personalized nutrition, considering genetic, metabolic, environmental, lifestyle, and behavioral factors of each person, represents the most effective, and practical, approach to promoting health and wellness. After years of neglect, this aspect of nutrition is now gaining research priority within the National Institutes of Health (NIH), with the 2022 Budget allocating $170 million for research grants over 5 years,

> The Nutrition for Precision Health powered by the All of Us Research Program (NPH) will recruit a diverse pool of 10,000 participants who are part of the NIH's All of Us Research Program to inform more personalized nutrition recommendations.[32]

This builds upon progress made since the 2015 creation of the Precision Medicine Initiative, which states:

> The Precision Medicine Initiative (PMI), launched in 2015, is a nationwide initiative to move away from the "one-size-fits-all" approach to health care delivery and to instead tailor treatment and prevention

strategies to people's unique characteristics, including environment, lifestyle, and biology.[33]

***Enforcement actions in the US*** [34]

The objective of FDA regulatory programs is to assure compliance with the Federal Food, Drug, and Cosmetic (FD&C) Act. Adulteration or misbranding is usually the result of an individual failing to take steps to assure compliance with the law. Such an individual may be liable for a violation of FD&C Act and, if found guilty, be subject to the penalties specified by the law.

Although there is no pre-market approval required to introduce a medical food into the US market, FDA does exercise postmarket surveillance to insure that marketed products comply with all federal regulations, and that they do not pose a safety risk. With jurisdiction over food and drug labeling, FDA may examine product labels at the time of a manufacturing plant inspection, by collecting products through trade channels, or by reviewing sales/marketing materials posted on websites (which are considered to be "labeling"). The type of enforcement activity depends on the degree of violation. Specific enforcement activities include actions to correct and prevent violations, remove violative products or goods from the market, and punish offenders. These actions may range from issuing a letter notifying the individual or company of a violation and requesting correction, to criminal prosecution of the individual or company.

The Federal Trade Commission (FTC) has jurisdiction over advertising and verifying the truth in substantiation of any product claims made to consumers. Medical foods are intended to be used under medical supervision, not sold direct to consumers. However, if they are, FTC may coordinate with FDA if any violation in regulations governing labeling, or inappropriate health or disease claims, may be suspected.

***US summary***

The history of establishing a category of medical foods, separate from drugs but for the specific dietary management of patients with a disease or condition has been difficult. Both regulators and industry have struggled to bring innovative, safe, cost-effective nutritional products with evidence of clinical benefit to patients with altered ability to maintain a normal diet. The opportunity to increase the value of this category will depend on bringing together stakeholders representing nutritional science, medical practice, regulatory science, and clinical nutrition researchers as well as healthcare funding entities to leverage the potential clinical benefits of medical foods in the individualized nutritional management of patients with a diverse range of diseases and conditions. This would then need to be accommodated within a regulatory framework that adequately protects the consumer, while also allowing the timely scientific evaluation and progress of nutritional interventions. Globally, it is the same challenge, with some minor variations on the theme of foods intended to be used for special and unique medical purposes.

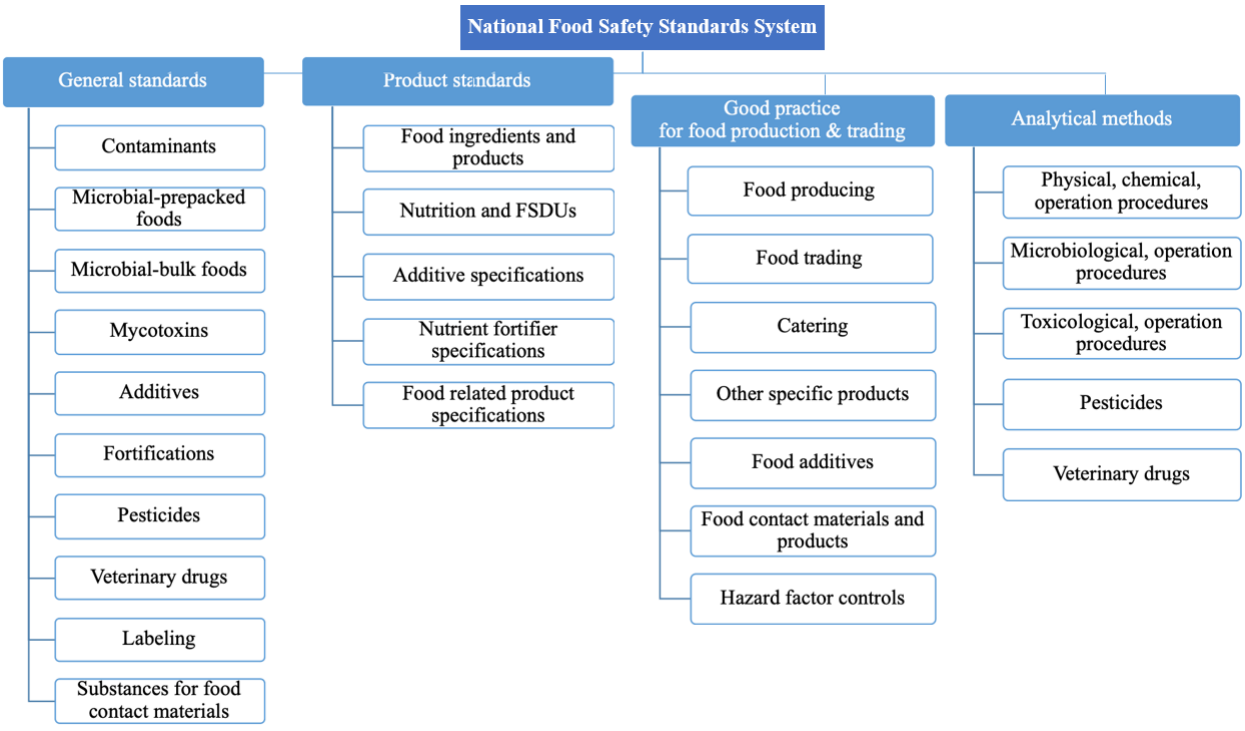
## China

The promulgation of the FSMP standards (**Figure 1**), as part of the national food safety standards, ended the long debate and confusion in China on whether FSMPs should be regulated as food or as medicine. FSMPs were now defined as specially formulated foods that were produced to meet the special requirements for nutrient or meals of people who suffered from eating limitation, disorder of digestion and absorption, metabolic disorders or special disease state and these products should be eaten individually or with other foods under the guidance of doctors or dietitians. FSMPs were categorized as food for special dietary uses, or FSDU. It is also stipulated in the Food Safety Law that FSDU products should be approved and registered under the specific regulations of State Administration for Market Regulation (SAMR).[35]

### *FSMPs and related food safety standards*

Currently, the FSMP standards included the FSMP standard for Infants (GB 25596-2010), General FSMP Standard for children older than 1 year (GB 29922-2013), and good manufacturing practice for FSMPs (GB 29923-2013). In general, they are in line with the Codex FSMP standards and regulations and standards in developed countries. The Chinese FSMP standards have more detail provisions, such as the subcategories of the FSMP products and range of nutrients contents. The FSMP products are further divided into three classes and five subcategories under the GB 25596 and 15 subcategories under the GB 29922 (**Figure 2**).

**Figure 1. National Food Safety Standards System of China[35]**




**FSDU,** foods for special dietary uses

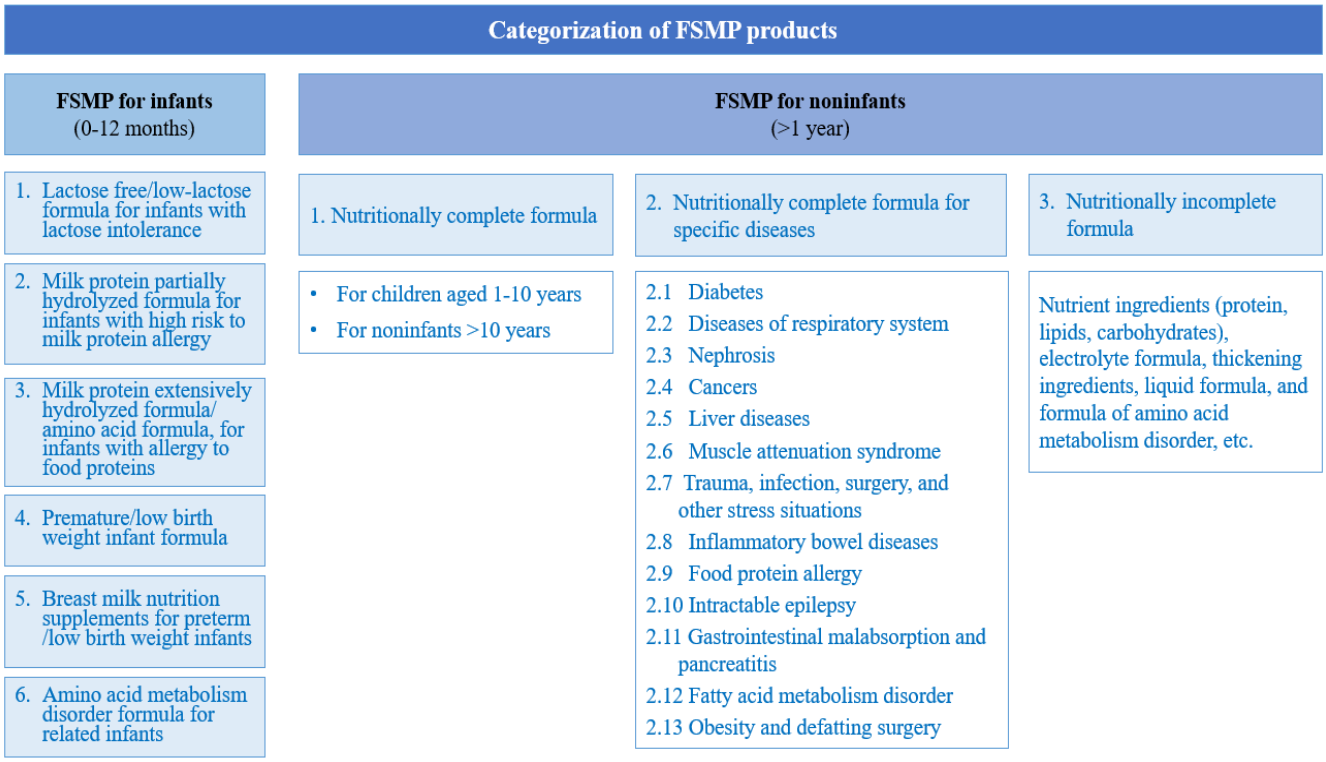
Compiled by Chen & Wu

To facilitate enforcement and inspection by the SAMR as well as product registration by the industry, an ongoing major revision of GB 29922 has been carried out, including the development of separate standards for individual subcategories of FSMPs for 2.1 to 2.8 and 2.10. In that case, there would be individual standards for each disease (e.g., cancer, diabetes, etc.) in the category of nutritionally complete formula for specific diseases. An overview of FSMPs and related applicable food safety standards is shown in **Table 3** (p. 21).[36]

***Product registration***

Corresponding regulations on the FSMP registration requirements had been promulgated by the SAMR since 2016, which were applicable to both domestic and imported FSMP products. The main regulations were the SAMR administrative regulation for registration of FSMPs. Its accompanied implementation regulations provided required information on the dossier content, the labeling, the stability testing, the clinical trial quality management practice, the on-site audit procedure, and the key requirements. Accordingly, the applicants are required to conduct three batches of production trials on the commercial production line, and to provide a comprehensive registration

**Figure 2. Categorization of FSMP products in China[35]**




**FSMP,** foods for special medical purposes

Compiled by Chen & Wu

**Table 3. Overview of FSMP and related food safety standards in China**[35]

| Product standards | FSMP for infants (GB 25596 -2010) | FSMP (GB 29922-2013) |
|---|---|---|
| Age range | 0-12 months | >1 year |
| Use of food additives | Use of food additives (GB 2760-2010) | |
| Use of nutritional substances | Use of nutritional fortifiers (GB 14880 -2012) | |
| Use of amino acids | GB 25596 -2010, Appendix B | GB 29922-2013, Appendix B |
| Labeling | Specific requirements in GB 25596 | Specific requirements in GB 29922 |
| | General standard for labeling of prepackaged food (GB 7718-2010) Standard for the labeling of prepackaged foods for special dietary uses (GB 13432-2013) | |
| Production | Good manufacturing practice for FSMP (GB 29923-2013) | |

**FSMP,** food for special medical purposes

Compiled by Chen & Wu

dossier including the product formula, the production techniques, the labeling, and the evidence of product safety, nutritional adequacy and clinical effects, and the stability test report. Mandatory on-site audits would be carried out if considered as necessary during application review by SAMR. For complete nutrition formula for specific diseases products, clinical trial report is required as part of registration dossier. The clinical trial should be conducted in China according to the SAMR's regulation on FSMP clinical trial quality management practice. For domestic FSMP products, in addition to product registration, the manufacturer needs to apply for a production license, which has been authorized by local administration for market regulation. The importation of FSMP products was supervised by the General Administration of Customs of the People's Republic of China (GACC). Before importing any FSMP products into the Chinese market, the foreign manufacturer needed to register its factory facility with the GACC and obtain product registration approval from the SAMR.

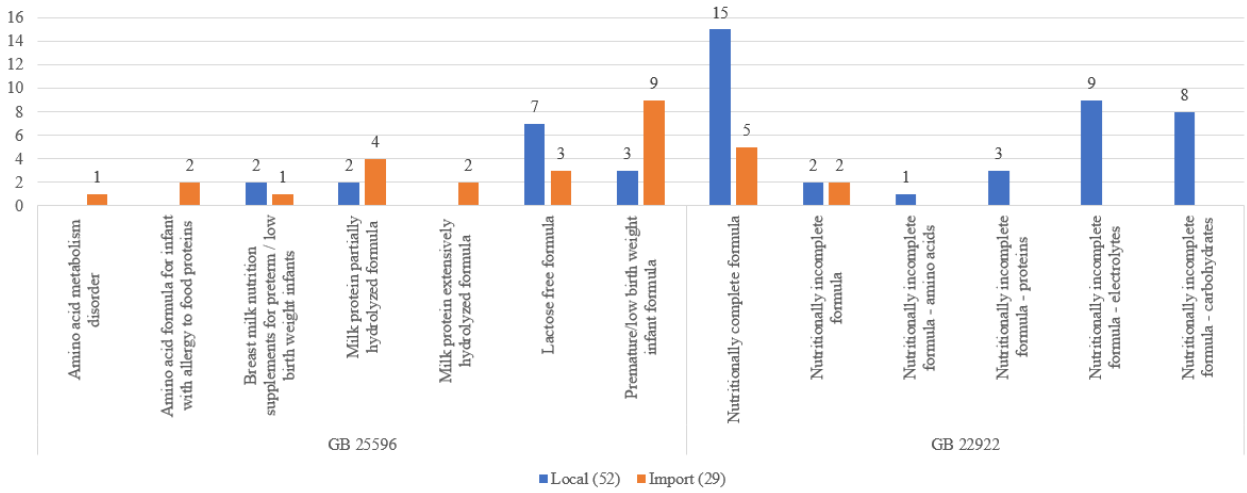
The time for the completion of a FSMP product registration is at least 2-3 years and could be much longer. As of February 2022, a total of 81 FSMP products were approved and registered under the SAMR. A summary of approved FSMP products by category is showed in **Figure 3** (p. 22).[37] It should be noted that no single complete nutrition FSMP product for specific diseases had been approved yet. A flowchart of FSMP regulatory control throughout the FSMP lifecycle is shown in **Figure 4** (p. 22).

***Challenges in the regulatory control of FSMP***

The decision to regulate FSMP products as food under the Food Safety Law was a significant progress, which was in line with Codex and most other countries in the world. The set of three FSMP standards were general and had considered

*Article continues on p. 23*

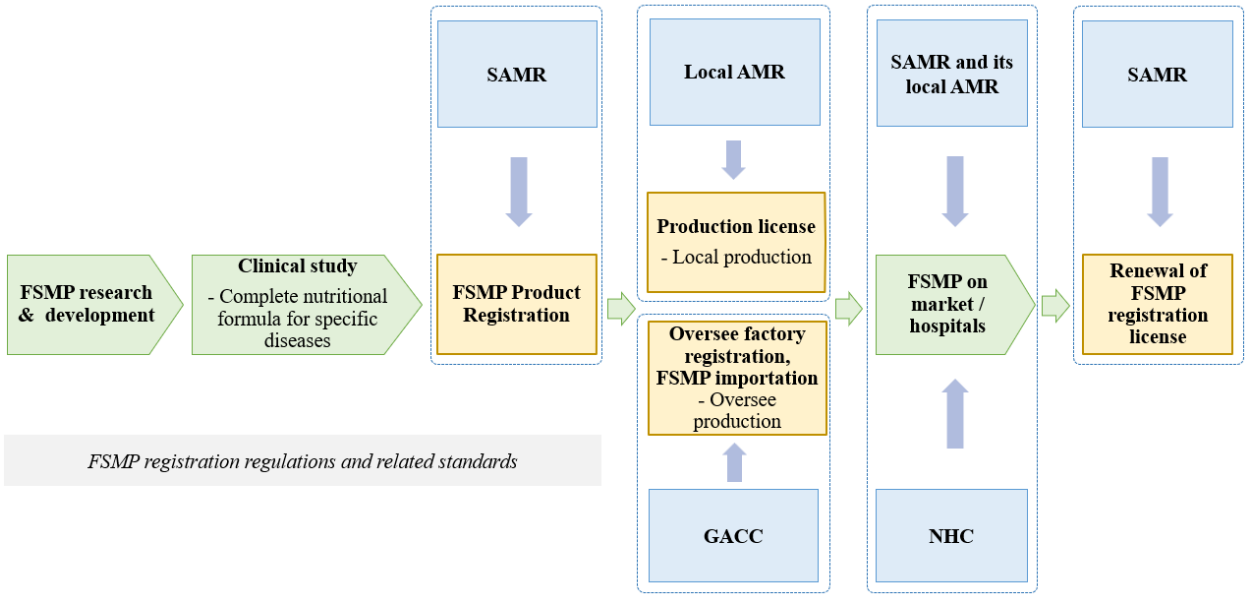
**Figure 3. Registered FSMP products in China by category to February 2022[35]**




**FSMP,** food for special medical purposes

Compiled by Chen & Wu; Source, SAMR

**Figure 4. A flowchart of FSMP regulatory control in China[35]**




**AMR,** Administration for Market Regulation; **FSMP,** foods for special medical purposes; **GACC,** General Administration of Customs; **MARA,** Ministry of Agriculture and Rural Affairs; **NHC,** National Health Commission; **SAMR,** State Administration of Market Regulation.

Source: Chen & Wu

the wide divergence of the FSMP products. However, the registration requirements for individual FSMP products were comprehensive in China.

Because the registration regulations are new, there are uncertainties in the requirements which presents challenges for the industry applicants. This was one of the major factors of the long application and review process (2-3 years or more). Clinical trials are mandatory for disease-specific complete nutrition formula application. It is expensive and time consuming, and some of the requirements are not feasible. Some nutritionists have questioned the rationale of a fixed-design clinical trial method and not allowing use of data from the real-world study from the FSMP industry.

On-site audit of FSMP facilities is another major challenge for international companies that have overseas production facilities. With travel restrictions due to the COVID-19 pandemic, no overseas audit was conducted since early 2020. The review process for these applications was not able to move forward without on-site audit when SAMR considers on-site audit is necessary. Another challenge is that FSMP products cannot be placed in most hospital pharmacies because they are considered to be food and not drugs. Recently, the SAMR has been exploring ways to improve the registration of FSMPs, formula for infant and health functional foods for young children. Given the divergent opinions among administrators, regulators, industry, and academia, the actual reformation would be a protracted process.

**Codex Alimentarius standards framework**

Codex Alimentarius is an international body whose mandate is to develop internationally harmonized food safety and quality standards to protect the health of consumers and ensure fair practices in the food trade. Although Codex Alimentarius standards and guidelines are, in principle, voluntary to follow, they have a significant impact on worldwide processes for setting and interpreting regulations, particularly in developing countries.[38]

The Codex Alimentarius Standard 180-1991[39] defines FSMPs as a category of foods for special dietary uses (FSDU; Codex Standard 146-1985),[40] which is specially processed or formulated and presented for the dietary management of patients and may be used only under medical supervision. It is intended for the exclusive or partial feeding of patients with limited or impaired capacity to take, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients contained therein; or who have other special medically determined nutrient requirements whose dietary management cannot be achieved only by modification of the normal diet, by other FSDUs, or by a combination of the two.

Under the standard, the formulation of FSMPs should be based on sound medical and nutritional principles. Their use should have been demonstrated, by scientific evidence, to be safe and beneficial in meeting the nutritional

requirements of the persons for whom they are intended. The labels, accompanying leaflets, and/or other labeling and advertising of all types of foods for special medical purposes should provide sufficient information on the nature and purpose of the food as well as detailed instructions and precautions for their use. In addition, the advertising of these products to the general public is prohibited. The format of the information given should be appropriate for the person for whom it is intended.

The FSMP definition is, in principle, equivalent to those in the US and EU. However, the standard – with the exception of FSMPs intended for infants (Codex Standard 72-1981)[41] – describes only specific labeling and claims aspects, and not compositional criteria, for patients older than 1 year.

Codex Alimentarius has also been instrumental in providing a platform for establishing an international guideline for the safe and efficacious use of ready-to-use therapeutic foods (RUTF), as part of the dietary management of severe acute malnutrition. The Codex Committee on Nutrition and Foods for Special Dietary Uses has established an electronic working group – chaired by South Africa and cochaired by Senegal and Uganda – which resulted in the finalization of the RUTF guideline in 2021, which is expected to be endorsed by the CODEX Alimentarius commission. It may be used as an appropriate reference for imported or locally produced products, to facilitate local regulation and encourage allocation of national budgets to these products.[42]

**Brazil**

Foods for controlled nutrients intake, such as formulas for enteral nutrition (RDC 21-2015),[43] are a defined category in Regulation for Food for Special Purpose (Portaria 29/1998),[44] which requires pre-market approval from the Brazilian Health Regulatory Agency, known as ANVISA. Enteral nutrition is classified into four subcategories:

- Standard formula for enteral nutrition,
- Modified formula for enteral nutrition,
- Pediatric Formula for Enteral Nutrition (for children younger than 10 years), and
- Modules of Nutrients for Enteral Nutrition.

ANVISA also determines compositional, stability study, sanitary registration, and labeling requirements. Nutrient compounds and other substances that can be added to formulas for enteral nutrition are defined in legislation (RDC 22-2015) that requires adoption of the requirements.[45] Regulation for specific food additives for formulas for enteral nutrition was published in 2017 (RDC 160-2017).[46] Nevertheless, ANVISA will review all legislation, which is expected to be published in 2024.

**Canada**

Health Canada is the primary federal government agency that sets the health and nutrition requirements for FSDUs, while the Canadian Food Inspection

Agency is responsible for the enforcement of Division 24 and other relevant food regulations that protect patients and consumers.
There are no regulatory provisions in Canada for medical foods or FSMPs. However, some foods regulated as such elsewhere are known in Canada as "foods for special dietary use," or FSDU. These foods are 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.[47]

FSDUs are regulated within Division 24 of the Food and Drug Regulations, which strictly prescribes the compositional requirements for the energy, macronutrient, and micronutrient profiles, as well as the requirements for labeling and any advertising or selling prohibitions. The foods included under the regulatory definition of FSDUs are formulated liquid diets, meal replacements for special dietary use, nutritional supplements, gluten-free foods, foods represented for protein-restricted diets, foods represented for low-[name of amino acid] diets, and foods represented for use in very low-energy diets. There is no notification process to bring an FSDU to market in Canada, with the exception of foods represented for use in very low-energy diets, in which case a 90-day premarket notification is required.

The current Canadian FSDU regulatory framework had its origins in the 1970s, with the publication in 1978 of the definition for FSDU. The most recent substantial changes to the framework were in 1995, with only minor changes since then.[47] With its early origins, the Canadian system influenced the development of the definition for FSDUs at Codex meeting in 1985.[40] However, the Canadian framework did not continue to evolve as the Codex standard for FSMPs was defined in 1991,[39] and international FSMP frameworks have since emerged.

From these origins, the Canadian FSDU framework is characterized by its closed categorical definitions, narrow and inflexible compositional requirements that do not align to current nutrition recommendations, and a divergence from international harmonization with other FSMP frameworks.[48] Canada has a significant opportunity to modernize its stringent and outdated FSDU regulations to bring them in line with the most current international FSMP systems[48] based on modernization goals and next steps proposed from a tripartite workshop.[49]

One area in which Health Canada is developing new FSDU regulations pertains to clinical trials that study the use of noncompliant foods intended as the sole or primary source of nutrition for infants, children, or adults. This modernization effort will cover previously nonpermitted infant formula, human milk fortifier, or formulated liquid diet FSDU to be considered for clinical study in Canada.[50]

**South Africa**

Currently, Codex Alimentarius is used as a reference for compositional requirements, claims, and labeling for all FSMPs in South Africa. In addition to this, the regulations related to the labeling and advertising of foodstuffs (No. R. 146-2010),[51] must also be followed similar to what is required for all foodstuffs. Infant or follow-up formulas for special dietary management for infants with specific medical conditions are also covered by the local infant regulations relating to foodstuffs for infants and young children (No. R. 991-2012).[52] This regulation covers all formulas from birth up to 36 months. FSMPs for young children and adults will be covered by the newly drafted general labeling regulations relating to the labeling and advertising of foods: amendment (No. R. 429).[53] This regulation has been in draft since 2014.

The industry is awaiting feedback from the Department of Health. However, it has been confirmed that the regulation will not be promulgated as is. It remains to be seen what impact the regulations will have on enteral foods as there is currently no certainty around whether the use of enteral foods for special medical purposes must be supported by data from clinical trials. Currently, FSMPs for adults can be launched without registering the product provided that it meets all relevant legislation.

**Australia and New Zealand[54]**

Standard 2.9.5 of the Food Standards Australia New Zealand (FSANZ) Code defines food for special medical purposes. Since most FSMPs are imported from overseas, compatibility with international regulations and standards is important to minimize the risk of imposing trade barriers on products imported into Australia and New Zealand. The purpose of the FSMP standard is to protect the health and safety of consumers, achieved through three major requirements:

- It requires that FSMPs, which are represented as being suitable for use as an individual's sole source for nutrition, complies with a set of compositional requirements of vitamins, minerals, and electrolytes. The standard allows for these requirements to be varied, depending on a particular medical condition.
- It contains mandatory labeling information, statements, and declarations (cf. Sections 2.9.5-9 and 2.9.5-10), [54] intended to ensure that healthcare professionals are provided with enough information to make appropriate decisions regarding patient use of the product. There is some flexibility in labeling of ingredients to adopt either Standard 1.2.4 of the Food Standard Code, or EU or US regulations.
- It imposes restrictions on where, and by whom, FSMPs may be sold directly to consumers. The restriction on sale is intended to promote consumers' incentive to seek medical and healthcare professional advice on appropriateness of the product for their condition, while restricting sale to vendors more interested in the commercial aspects of FSMP sale direct to consumers.

FSMPs do not include food formulated and represented as being for the dietary management of obesity or overweight; or an infant formula product as defined in Standard 2.9.1.

**Japan**

The FSMP standard within the Japanese food regulation was established before the Codex Alimentarius standard 180-1991, and therefore takes precedence over the international standard. FSMP products fall into a category of food for special dietary uses (FOSDU). To register a product as FOSDU, authority approval is needed, a process that takes around 2-3 years requiring scientific evidence to support the intended use. The registration fee varies according to the purpose of use. The FOSDU regulation contains disease specific criteria, such as rheological requirement of texture-modified products suitable for dysphagia.

**India**[55]

Codex Alimentarius Standard 180-1991 can be considered a pivotal source of reference for FSMPs. The Food Safety Authority of India has issued a direction for the operationalization of Food Safety and Standards (Health Supplements, Nutraceuticals, Foods for Special Dietary Use, Foods for Special Medical purpose and Probiotic and Prebiotic Food) Regulation, 2022, to be referred to as FSS (Nutra) Regulation, 2022. This is a revised overhaul regulation and would supersede the FSS (Nutra) Regulations, 2016.

**Turkey**

The Turkish Ministry of Health (MoH) is the responsible body for approving FSMPs and water. The Ministry of Agriculture and Forestry is responsible for other foods. The Turkish Food Codex Communiqué on Special Dietary Foods for Medical Purposes 2001/42[56,57] determines the composition and labeling conditions to ensure hygienic production, preparation, processing, preservation, storage, transportation and marketing. The communiqué provisions are executed by the MoH and the Ministry of Agriculture and Forestry.

The Communiqué on the Production Sites of Special Dietary Foods for Medical Purposes 13.09.2015/29474,[58] issued by the MoH, regulates the procedures and principles regarding the application, inspection and permission processes of production sites. Within the scope of the Draft Regulation on Licensing of Foods for Special Medical Purposes, the legislative studies, which are ongoing, and two draft guidelines have been circulated for feedback from third parties. The guidelines are:

- Draft Guideline on Application for Special Medical Purpose Foods License Application. This addresses the procedures and principles to be applied in the issuance of permission certificates and authorizing products to ensure the desired effectiveness and safety and required quality.
- Draft Guideline on the Stability Studies of Foods for Special Medical Purposes. This addresses the purpose of determining the requirements for stability studies to be included in the authorization application file.

The initial import permit application and import permit renewal application for special dietary foods for medical purposes are made to the MoH and Medical Devices Agency. For existing products, import permits, named control certificates, have to be renewed annually. For products registered for the first time, pricing and reimbursement are additional steps to the import permit approval process, which takes about 24 months from submission to approval. FSMPs may be sold only in pharmacies.

**Middle East**

The Gulf Cooperation Council (GCC) countries, including United Arab Emirates (UAE), Oman, Kuwait, Qatar, Kingdom of Saudi Arabia, and Bahrain, have recently published an FSMP standard (GSO 1366-2021)[59] and a new standard for food supplements (GSO 2571-2021).[60]

For infant formula, follow-up formula, and formula for special medical purposes for infants, the GCC issued a new standard (GSO 2106-2021),[61] based on the EU regulation and not CODEX, as previously. GCC countries have until the end of 2022 to put this standard into effect. FSMPs and infant formula are now required to be registered in all GCC countries and other Middle East countries. Registration is done through the following authorities in each country:

- The respective Food and Drug Authorities in Saudi Arabia, Kuwait, and Jordan; and
- The respective MoHs in Bahrain, UAE, Qatar, Oman, Iran, and Lebanon.

Iraq does not require registration.

In general, the following documents are required:

- Certificates of free sale, factory GMP, health, and analyses;
- Copies of the artworks of the product;
- Samples of the product (not required by all countries); and
- Product specifications.

**ASEAN member states**

The ASEAN comprises the founding members Indonesia, Malaysia, the Philippines, Singapore, Thailand, and the more recent members, Vietnam, Brunei Darussalam, Cambodia, Laos, and Myanmar. The FSMP category is not clearly defined yet in many of them, although some regulatory efforts have started in several. The Codex Alimentarius standard 180-1991 is an important and respected reference for all. [39]

**Indonesia** defines processed FSMPs, abbreviated as PKMK, as “processed food that is specially processed or formulated for dietary management for people with certain diseases/disorders” (Article 1 of Regulation 1-2018).[62] Infant formula for special medical needs is defined as “food for infants that is specially processed or formulated and serves as a dietary management of infant patients so that they can individually meet the nutritional needs of infants with disorders, diseases, or special medical conditions during the first few months of

life, until the introduction of breast milk, and should only be used under medical supervision" (Article 1, Regulation HK.03.1.52.08.11.07235-2011).[63]

Examples of FSMPs/PKMK for infants and children, as stipulated in Amendment Regulation 24-2020,[64] include patients with metabolic disorders (inborn errors of metabolism); child nutrition support risk of failure to thrive, malnutrition or malnutrition bad; premature babies; PKMK to complement breast milk nutrition (human milk); patients allergic to milk protein; ketogenic diet; malabsorption patients; patients with chronic liver disease; inflammatory bowel patients diseases; and lactose intolerant babies.

Examples of FSMPs/PKMK for adults include people with diabetes; patients with chronic kidney disease; patients with chronic liver disease; nutritional support for adult patients with malnutrition; patients with metabolic disorders (inborn errors of metabolism); and those on a ketogenic diet.

FSMP/PKMK distribution is limited to pharmacies, hospital pharmacies, and other public health centers (Article 16 of Regulation 1-2018). [62] FSMPs must be manufactured according to GMP and hazard analysis and critical control points, or HACCP. Regulations also provide guidance on composition and labeling for each type of PKMK.

**Vietnam** generally follows Codex standards and defines foods for special medical purposes or medical foods as "food administered orally or with feeding tubes which are designated to regulate the patient's diet and are only used under the supervision of health workers" (Article 2 of Circular No 43-2014).[65] It describes formulas with special medical purposes for infants as "products with liquid or powdered form processed from synthetic or natural ingredients with origin from animals or plants are produced to meet the special nutritional needs for infants up to 12 months suffering from illness, disorders, or in need of medical care. Formulas with special medical purposes for infants up to 12 months old can be used as a food source to replace breast milk" (Article 3 of Circular No 21-2012).[66]

FSMPs require premarketing approval. Human efficacy clinical studies are needed for FSMPs that have not been approved by competent authorities in the country of origin (Article 4 of Circular No 43-2014).[65]

**Thailand** refers to special purpose food as those foods that are processed or formulated or to specific ingredient foods for special purposes, suitable – due to their characteristics, appearances or categories and quantities of ingredients, clearly different from normal foods – for patients or persons who have a special purpose in food consumption, such as weight control or being elderly or pregnant (Thai Notification No. 238 and 357).[67,68]

**Malaysia's** special purpose food regulated by the MoH refers to food particularly suitable for consumption by persons with special nutrition needs, including standards for infant formula; follow-up formula; canned food for infants and children; processed cereal-based food for infants and young

children; low-energy food; special dietary foods with low-sodium content, including salt substitute; and formula dietary food. The latter is suitable as a complete diet when consumed in accordance with its intended use (Regulation 388).[69]

**Singapore's** special purpose food is suitable for consumption by persons requiring a special diet. It is composed of food ingredients modified or prepared to possess intended nutritional properties. It includes food for diabetics, low-sodium food, gluten-free food, low-protein food, carbohydrate-modified food, low-calorie food, energy food, infant formulas and formulated food (Regulation 247).[70]

**Brunei Darussalam's** food regulations are aligned with those of Malaysia and Singapore. Special purpose food should include diabetic food, low-sodium food, gluten-free food, low-protein food, carbohydrate-modified food, low-calorie food, energy food, low-protein food, infant formula food, and formulated food (Regulation 318).[71]

**Cambodia, Laos, and Myanmar** do not have specific regulation on FSMPs, but follow Codex standards.

**The Philippines** has no specific regulations for, or a definition of, FSMPs. It generally follows the Codex Alimentarius Standard 180-1991. FSMPs are regulated as "high-risk food."[72]

FSMPs must comply with the composition and quality standard and labeling stated in the reference guide to stakeholders to assess compliance of submitted documents as complete requirements for product registration (cf. Annex D of the regulation).

**Summary of Part 2**

A synopsis of the global regulatory frameworks for medical foods/FSMPs demonstrates the similarities as well as divergence amongst selected countries and regions worldwide. Ultimately, after decades of regulatory evolution concerning the dietary aspects of patient care, more harmonized, pragmatic approaches rather have prevailed for FSMPs, and although FSMPs are regulated under food law, they are required to be used under medical or healthcare supervision. This patient-focused pragmatism is gaining traction. Examples of this include the EU, where authorities were opting for non-disease specific FSMP regulations. There is recognition as well that FSMP product status recognizes cases (e.g., for dysphagia) when it is impossible, impractical, or unsafe for patients to exclusively consume foodstuffs that are not an FSMP. Likewise, Australia and New Zealand's position is noteworthy on importing FSMPs already legally marketed in other defined regions or countries, such as the EU or US.

FSMPs are consumed across all healthcare settings, such as hospitals, clinics, nursing homes, and in patients' homes. To further benefit patient and market access, it is prudent to recognize the essential value FSMPs bring to make

healthcare systems sustainable, that is, the link between regulatory and reimbursement and health economics. FSMPs lower healthcare costs by reducing hospital stays and maintaining patients' independence longer. Hence harmonizing reasonable reimbursement criteria by public or private healthcare providers across countries or regions will benefit FSMP product development to address the specific dietary needs for large an in particular sometimes very small patient populations.

**Acronyms and abbreviations**

**ANPR,** advance notice of proposed rulemaking; **ASEAN,** Association of Southeast Asian Nations; **ANVISA,** Agência Nacional de Vigilância Sanitária [Brazilian Health Regulatory Agency]; **EC,** European Commission; **EFSA,** European Food Safety Authority; **ENHA,** European Nutrition for Health Alliance; **ESPEN,** European Society for Clinical Nutrition and Metabolism; **EU,** European Union; **FBO,** food business operator; **FDA,** [US] Food and Drug Administration; **FSANZ,** Food Standards Australia New Zealand; **FSDU,** food for special dietary use; **FSG,** food for specific group; **FSMPs,** foods for special medical purposes; **FTC,** Federal Trade Commission; **GACC,** General Administration of Customs of the People's Republic of China; **GCC,** Gulf Cooperation Council; **GMP,** good manufacturing practice; **HACCP,** hazard analysis and critical control points; **HCP,** healthcare provider; **MoH,** Ministry of Health; **NLEA,** Nutrition Labeling and Education Act; **IND,** investigational new drug; **IRB,** institutional review board; **NIH,** National Institutes of Health; **ONCA,** optimal nutritional care for all; **ONS,** oral nutritional supplement; **PARNUT,** [food for] particular nutritional [uses]; **RUTF,** ready-to-use therapeutic food; **SAMR,** State Administration for Market Regulation; **UAE,** United Arab Emirates; **UK,** United Kingdom; **US,** United States.

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