Review

DOI: 10.5582/irdr.2025.01075

Foods for special medical purposes for the dietary therapy of rare diseases: Current status and future prospects

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SUMMARY: Foods for special medical purposes (FSMPs) is a type of products that provides targeted nutritional support for specific diseases or physiological conditions. Compared with conventional dietary therapy, FSMPs are more targeted, safer, and applicable in clinic. When FSMPs are used to treat rare diseases, their core principle is to bypass or alleviate metabolic disorders. With the increasing recognition of clinical treatment effectiveness and the growing demand from patients, the types and market scale of commercial rare disease FSMPs continue to expand. However, there are currently no article summarized and analyzed the characteristics of diverse commercial products. Based on this, this review collected and collated the vast majority of commercial rare disease FSMPs in the global market, and summarized the characteristics of these products by categorizing them into protein substitutes, nutritional modules, ketogenic diets (KDs), and special low protein foods (SLPFs). Following the comprehensive analysis of the global commercial rare disease FSMPs landscape, this review shifted focus to China and provided suggestions from product diversity, technological innovation, and policy optimization. It aims to offer available suggestions and references for the healthy development of rare disease FSMPs in China.

Keywords: rare disease, foods for special medical purposes (FSMPs), protein substitutes, nutritional modules, ketogenic diets (KDs), special low protein foods (SLPFs)

1. Introduction

Rare diseases are characterized by extremely low individual prevalence but a large global patient base. This feature presents a major challenge in diagnosis and treatment to the global public health system. Under the collective efforts of researchers and clinicians worldwide, treatment strategies for rare diseases have become increasingly diversified, including small molecule drug therapy, antibody therapy, oligonucleotide therapy, gene therapy, and cell therapy (*1,2*). Since the enactment of the "Orphan Drug Act" in 1983, over 7,000 orphan drugs have been developed, but only about 500 rare diseases have approved treatments (*3,4*). Narrow disease coverage, lack of specific therapeutic drugs, and low accessibility of some medications remain prominent issues for the management of rare diseases. Eighty percent of rare diseases are hereditary. A significant number of these hereditary conditions are inborn errors of metabolisms (IEMs), such as amino acid metabolic disorders, organic acid metabolic disorders, urea cycle disorders (UCDs), carbohydrate metabolism defects, and fatty acid oxidation disorders (*5,6*). The core of IEM treatment lies in correcting metabolic imbalances to prevent acute or chronic metabolic crises and support normal growth and development (*7*). Nevertheless, the vast majority of IEMs lack effective pharmacotherapeutic options.

In the 1950s, a low-phenylalanine diet was first used to prevent or alleviate clinical symptoms in patients with phenylketonuria (PKU). Since then, dietary therapy has gradually become the preferred and primary treatment for various IEMs (*8*). But it was soon to be found that dietary therapy achieved by adjusting the combination of natural foods may fail to meet the extreme nutrient needs of rare disease patients. Fortunately, FSMPs with precisely controllable formulas make up for the shortcoming of dietary therapy. In 1991, Codex Alimentarius Commission (CAC) provided the clear definition of FSMP in *CODEX STAN 180-199*, "Foods for special medical purposes are a category of foods for special dietary uses which are specially processed or formulated

and presented for the dietary management of patients and may be used only under medical supervision. They are 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 foods for special dietary uses, or by a combination of the two" (*9*). For non-IEM rare diseases, FSMPs can also be customized into easy-to-swallow and highly absorbable formulations according to patient needs. These formulations ensure patients' basic nutritional requirements and provide nutritional support for pharmaceutical treatment and rehabilitation training. According to market data, the global market size of rare disease FSMPs reached 1.33 billion US dollars in 2024, and it is expected to grow to 1.41 billion US dollars in 2025, with a projected compound annual growth rate of 6.1% (*10*). Modern medicine has been gradually recognized the important value of FSMPs in the clinical treatment of rare diseases. Therefore, the demand for rare disease FSMPs will continue to grow in the future.

Numerous articles have emphasized the importance and necessity of dietary therapy in IEMs. Some of them have elaborated on the mechanisms, applications, and therapeutic efficacy of dietary therapy for different rare diseases (*6,11-14*). For patients with rare diseases, commercial FSMPs are an indispensable component of their daily dietary therapy. However, after conducting literature searches on Web of Science, Google Scholar, China National Knowledge Infrastructure (CNKI), and Wanfang Data using the terms "rare disease", "foods for special medical purposes/medical foods", "dietary therapy", and "commercial product", we found that no any review has detailly summarized and analyzed the characteristics of commercial FSMPs. Based on this, we collated product information from nine global brands (Ajinomoto Cambrooke, Mead Johnson, Nutricia, Nestlé Health Science, Abbott, Prekulab, Eton Pharmaceuticals., PIAM Farmaceutici S.p.A., Orpharma) that market FSMPs. Then, products were categorized into four types (protein substitutes, nutritional modules, ketogenic diets and special low protein foods) to take the overviews of their characteristics and applicable patients. Finally, based on the comprehensive summary of currently commercial products, we provided insights into the future development of FSMPs in China. It aims to help researchers and companies identify current market gaps and promote the research and development of rare disease FSMPs.

2. Therapeutic strategies of rare diseases

The World Health Organization (WHO) defines rare diseases as specific health conditions with an incidence rate of less than 1 per 2,000 of the population (*15*). China proposed three criteria for judging rare diseases in 2021: *i*) the incidence rate of newborns is less than 1 per 10,000; *ii*) the prevalence rate is less than 1 per 10,000; *iii*) the affected population is less than 140,000. If one of them is met, it can be defined rare disease (*16*). In order to better manage rare diseases, China has released two batches of the "List of Rare Diseases" in 2018 and 2023, which included a total of 207 rare diseases. According to statistics, rare diseases affect hundreds of 300 million people worldwide, with over 20 million patients in China alone (*17*). However, the low incidence rate, clinical rarity, diverse types, and difficulty in diagnosis and treatment render rare diseases a public challenge for global healthcare. In recent years, through the collective efforts of researchers around the world, rare disease managements have witnessed significant breakthroughs. More potential and effective treatment strategies are emerging.

2.1. Small molecule drug therapy

Small molecule drug therapy is a therapeutic approaches that interferes with abnormal signaling pathways, inhibits enzyme activity, or blocks intermolecular interactions by binding small molecules to specific targets (*2*). Small molecule drugs typically have a relative molecular mass of less than 1,000 Da (*18*), featuring simple molecular structures and diverse chemical architectures. They have been successfully used in the treatment of rare diseases, like cystic fibrosis (*19*), lysosomal storage disorders (*20*), Duchenne muscular dystrophy (DMD) (*21*), and PKU (*22,23*). Small molecule drugs possess irreplaceable advantages compared to many advanced therapies, including convenient administration routes, a broad range of therapeutic targets, the ability to cross the blood-brain barrier and low production costs (*21*). However, identifying small molecules with favorable pharmacological effects, optimal pharmacokinetic profiles, and minimal off-target effects remains the primary challenge (*2*). With the advancement of artificial intelligence technologies, as well as progress in chemistry and biology, problems faced by small molecule drugs are being increasingly well addressed (*18,24*).

2.2. Antibody therapy

Antibody therapy is a therapeutic approach that confers specific immunity through the passive transfer of antibodies (*25*). Antibodies play a role by modulating signaling pathways, recruiting cells or proteins to specific sites, delivering cytotoxins, neutralizing or modulating circulating factors (*2*). Soliris, the first antibody drug for the treatment of paroxysmal nocturnal hemoglobinuria was approved by the U.S. Food and drug administration (FDA) in 2007 (*25*). Since that, antibodies have gained increasing attention in rare disease therapy.

Canakinumab, a monoclonal antibody targeting the key proinflammatory cytokine IL-1β has been used to treat cryopyrin-associated periodic syndromes (*26*). Emicizumab, a specific monoclonal antibody that binds both activated coagulation factors IX and X has been employed for the routine prophylaxis of hemophilia A (*27*). High specificity, high affinity, and low off-target toxicity are the advantages of antibody therapy. However, inconvenient administration routes, poor tissue and cellular penetration, and high costs have limited their application in rare disease treatments, which are critical issues requiring urgent resolution (*2*).

2.3. Enzyme replacement therapy

Given that the pathogenic mechanisms of numerous rare diseases are associated with enzyme deficiency or dysfunction, enzyme replacement therapy has long served as a critical therapeutic modality for rare diseases (*28*). Enzymes can be purified from human or animal tissues, or produced *via* recombinant technology (*29*). Enzyme replacement therapy restores normal metabolic function by exogenously supplementing the missing or abnormally functional enzymes. For example, Gaucher disease is caused by the deficiency of glucocerebrosidase, which leads to the accumulation of glucocerebroside in the body and causes the disease. Injecting recombinant glucocerebrosidase can replace the enzyme deficient in the body, catabolizes accumulated substrates, alleviates symptoms, and improves patient quality of life (*28*). Enzyme replacement therapy exhibits high target and favorable safety profiles in clinic. However, this therapeutic approach still faces several challenges, such as the high manufacturing and purification costs of recombinant enzymes and the long lead time required to establish manufacturing capacity for new products (*2*).

2.4. Oligonucleotide therapy

Oligonucleotide therapy regulates gene expression *via* synthetic nucleic acid sequences that bind to RNA targets through sequence-specific base pairing (*2*). Small molecule drug therapy, antibody therapy, and enzyme replacement therapy mentioned above are all interventions acting at the protein level. Oligonucleotide therapy acts at the RNA level, belonging to upstream regulation (*30*). In rare disease treatments, antisense oligonucleotide (ASO) and small interfering RNA (siRNA) have been the most extensively studied, and both of them have achieved significant efficacy in treating rare neuromuscular diseases. For example, Nusinersen acted as an ASO is used to treat spinal muscular atrophy (*31*). Eteplirsen is indicated for patients with DMD exon 51 skipping (*32*). Patisiran, the first FDA-approved siRNA drug, is applicable for the treatment of hereditary transthyretin amyloidosis (*33*). Oligonucleotide therapy can target molecules inaccessible to traditional therapies and reduces drug toxicity due to limited body's exposure. However, poor blood-brain barrier penetration remains a critical challenge to oligonucleotide therapy. In the future, this issue is expected to be better addressed with breakthroughs in chemical modification technologies and delivery systems (*2,30,34*).

2.5. Gene therapy

Gene therapy refers to a therapeutic approach that modifies or manipulates gene expression to alter the biological properties of living cells for therapeutic purposes (*35*). Adeno-associated virus is currently the most commonly used and successful vector for *in vivo* gene therapy, with proven therapeutic efficacy in rare diseases including spinal muscular atrophy, hemophilia A, hemophilia B, and hereditary retinal dystrophy caused by RPE65 gene mutations (*36-38*). Gene-editing represents the most cutting-edge gene therapy strategy, achieving in situ repair of genes at pathological sites by directly delivering gene-editing systems (such as CRISPR/Cas9) into the body. Casgevy is the first FDA-approved gene-editing therapy, used for treating sickle cell disease (*39*). Gene therapy exhibits high targeting specificity and precision, holding promise for achieving one-time cure of rare diseases. However, challenges such as the complexity of the technology itself, uncertainty in efficacy, safety risks, and high costs are issues that must be addressed in the development of gene therapy (*40*).

2.6. Cell therapy

Cell therapy involves transplanting autologous or allogeneic cellular materials into patients to replace, repair, or enhance the function of damaged tissues or cell (*41*). The most representative modalities in rare disease treatments are hematopoietic stem cell transplantation (HSCT) and chimeric antigen receptor T (CAR-T) cell therapy. Currently, multiple HSCT-based therapies are used to treat rare diseases such as childhood cerebral type of Adrenoleukodystrophy (*42*) and β-thalassemia (*43*). CAR-T cell therapy also shows great promise in treating autoimmune diseases like systemic lupus erythematosus (*44*) and multiple sclerosis (*45*). Cell therapy is a dynamic therapeutic strategy. Once viable cells are administered into the body, they can activate, proliferate, and establish immune memory, thereby providing long-term protection to patients. This dynamic action is unmatched by any chemical drugs. Furthermore, cell therapy also exhibits high targeting specificity and precision. However, like gene therapy, cell therapy faces many challenges including technological complexity, high safety risks, and substantial costs (*2*).

2.7. Dietary therapy

Dietary therapy plays a crucial role of saving lives and

maintaining health in the field of rare diseases. While distinct from pharmacotherapeutic interventions, gene therapy, and cell therapy, it remains an unshakable cornerstone in managing numerous rare diseases owing to its directness, relative accessibility, and safety. The core concept of dietary therapy is to bypass or alleviate metabolic disorders, thereby maintaining the stability of the body's internal environment through strict control of dietary composition. Of the 121 rare diseases showed in China's "First List of Rare Diseases", 32 rare diseases are amenable to dietary therapy, and 18 of them mentioned in Figure 1 require timely, lifelong, and adequate use of FSMPs (*46,47*).

2.8. The importance of FSMPs in rare disease treatment

FSMPs represent a pivotal dietary intervention for rare disease management. According to nutritional compositions, FSMPs are usually divided into three categories: *i*) nutritionally complete food with a standard nutrient formulation, which can serve as the sole source of nutrition; *ii*) nutritionally complete food with a disease-specific nutrient-adapted formulation that can serve as the sole source of nutrition; *iii*) nutritionally incomplete food with either a standard or disease-specific nutrient-adapted formulation intended for partial feeding or use as a dietary supplement (*48*). It should be noted that there are some different names for FSMPs in different countries, for instance, medical foods in the U.S. (*49*), foods for a special dietary use (FSDU) in Canada (*50*).

From the standpoint of rare disease treatment, FSMPs bypass specific metabolic defects by providing formulations devoid of the problematic components, rendering them potent etiological interventions that directly target the pathogenic mechanisms of disease. Furthermore, FSMPs can function as adjuvant therapeutic agents, acting in synergy with pharmacotherapy, gene therapy, and enzyme replacement therapy to prime a more favorable physiological milieu for these interventions.

From the standpoint of nutritional support, the stringent dietary restrictions imposed by treatment regimens for rare disease patients frequently predispose them to malnutrition. By eliminating or severely restricting problematic substrates while precisely fortifying all other essential nutrients, FSMPs ensure patients receive comprehensive and balanced nutrition. This is particularly critical for safeguarding the normal physical and intellectual development of infants and children with rare diseases. Additionally, FSMPs broaden the dietary repertoire of rare disease patients, alleviating dietary monotony. This not only enhances treatment compliance but also enables patients to experience a dietary pattern analogous to that of healthy individuals, thereby improving their quality of life.

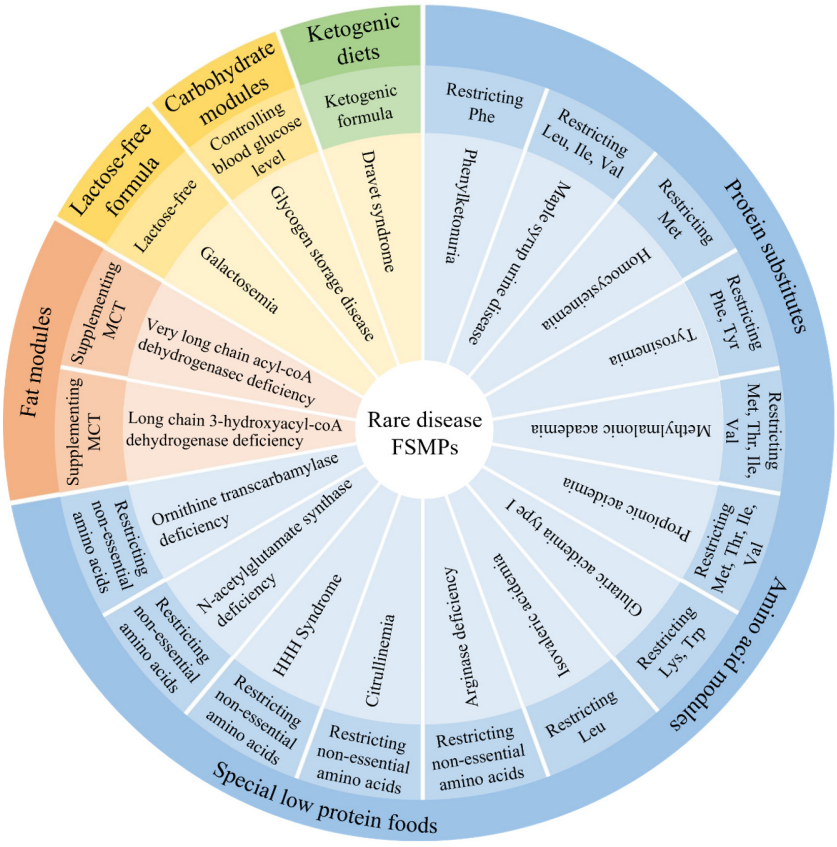

Figure 1. Eighteen rare diseases requiring long-term foods for special medical purposes (FSMPs) use and their product characteristics.

Within the integrated rare disease diagnosis and management framework, FSMPs constitute an indispensable pillar of the "screening-diagnosis-treatment" continuum. For many rare diseases for which no effective therapeutic interventions exist, FSMPs currently serve as the sole therapeutic modality capable of mitigating symptoms and extending survival. During the diagnostic phase, FSMPs function as life-saving emergency interventions. In the treatment phase, they act as core therapeutic tools for disease management, exerting a direct impact on patient prognosis. Throughout the long-term management phase, FSMPs provide a critical safeguard for sustaining lifelong health and quality of life.

3. Commercial product status of rare disease FSMPs

FSMPs are edible products designed for patients with special nutritional needs, and their therapeutic efficacy in rare disease management has been globally recognized. This rare disease management model that integrates clinic therapy with patients' daily dietary requirements has endowed FSMPs with substantial market potential. To cover a broader spectrum of rare diseases and provide more diverse options for patients, an increasing number of products have emerged. Protein substitutes, nutrient modules, KDs, and SLPFs are main four commercial rare disease FSMPs.

3.1. Protein substitutes

Protein substitutes, also termed amino acid metabolism disorder formulas, are a class of FSMPs tailored to the dietary management of amino acid or protein metabolism disorders. Protein substitutes are nutritionally incomplete FSMPs. They are specifically intended for target groups with specific nutritional needs and cannot act as the only protein source (*51*). Protein substitutes strictly restrict amino acid(s) that patients cannot consume while selectively providing other essential amino acid(s), non-essential amino acid(s), vitamins, minerals, and other nutrients (*52*). Thus, they need to be combined with natural proteins and other nutrients. This combination can support growth and development, maintains metabolic homeostasis, micronutrient balance, and normal neurological and psychosocial functions (*53,54*).

3.1.1. Design concepts of protein substitutes

Protein substitutes have been acted as treatment strategies for PKU, Tyrosinemia (TYR), Maple syrup urine disease (MSUD), Methylmalonic academia (MMA), Propionic acidemia (PA), Homocysteinemia (HCY), Glutaric acidemia type I (GA I), Isovaleric acidemia (IVA), and UCDs (Table 1). According to the composition of FSMPs, the design concept of protein substitutes can be divided into two types: *i*) totally without restricted amino acid(s) while containing other essential amino acid(s), non-essential amino acid(s), vitamins, minerals, and other nutrients; *ii*) totally without restricted amino acid(s) while containing large neutral amino acids (LNAAs), non-essential amino acid(s), vitamins, minerals, and other nutrients.

Protein substitutes adopting the first design concept dominate the commercial market of rare disease FSMPs. These formulations strictly control intake of the restricted amino acid(s) and have demonstrated efficacy in managing patients' health status. PKU infants treated with phenylalanine (Phe)-free FSMP (PKU Start, Nestlé Health Science) have been shown to maintain normal growth and satisfactory blood Phe control, with early gastrointestinal symptoms (constipation, colic, vomiting, and poor feeding) improving over time (*55*). A case report of a 29-year-old male with MSUD documented that his leucine (Leu) levels normalized (66 to 170 μmol/L) within 5 days when he ate a branched-chain amino acid (BCAA)-free FSMP named Ketonex-2 from Abbott and supplemented with 20 mg/kg L-isoleucine (L-Ile) and 20 mg/kg L-valine (L-Val) at the same time (*56*).

LNAAs mentioned in the second design concept refer to Phe, Tyr, Ile, Leu, Val, tryptophan (Try), threonine (Thr), methionine (Met), arginine (Arg), lysine (Lys), and histidine (His), sharing same transporter proteins in the brain and intestinal mucosae (*57*). LNAAs compete with and inhibit Phe transport across the intestinal mucosa and blood-brain barrier. Based on this mechanism, LNAAs have also become one of the methods for designing PKU FSMPs (*58*). Currently, only three LNAA-based products are approved for PKU, all three of which are manufactured by Prekulab. The first LNAAs product is PreKUnil® tablets. When six subjects aged 20-34 year were treated with it at 0.4 g/kg/day and consumed "relaxed" diets approaching to ordinary people, their blood Phe concentrations essentially unchanged, but brain Phe concentrations gradually decreased toward the carrier range (*59*). NeoPhe® tablets and NeoPhe® powder are two products modified from PreKUnil® by adjusting the concentrations of certain amino acid(s) and supplementing. NeoPhe® can reduce elevated blood Phe levels by 50% (*57*). Furthermore, NeoPhe® extends eligibility to pediatric patients. Notably, LNAA-based products enable PKU patients to obtain up to 80% of their protein intake from regular diets, making them particularly beneficial for patients with poor dietary adherence (*60*).

3.1.2. Dosage forms of protein substitutes

With the rapid development of the FSMP industry, the product formats of protein substitutes have expanded rapidly. Patients have more diversified choices, which is beneficial for improving compliance.

Powdered protein substitutes are currently the most prevalent FSMPs on the market, suitable for all age groups. These protein substitutes require reconstitution

Table 1. A part of common protein substitutes in global commercial market*

Rare disease	Product	Dosage form	Brand
Phenylketonuria (PKU)	Phenyl-Free® 1 Infant Formula & Medical Food, Phenyl-Free® 2 Medical Food, Phenyl-Free® 2HP Medical Food, PKU Anamix Infant, PKU Anamix Junior, PKU Lophlex LQ Powder, PKU Maxamum, PKU Synergy, PKU start™, PKU gel™, PKU explore™, PKU express™ plus, PKU express™ (newly renovated), PKU express®, PKU sphere®, Phenex-1®, Phenex-2®, Afenil 2, Afenil Gel, Afenil Medi 15, Afenil Buddy, Afenil Lime, NeoPhe Powder, PKU Go	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A., Prekulab, Orpharma
	PKU Anamix Junior LQ, PKU Lophlex LQ 10, PKU Lophlex LQ 20, PKU Lophlex Select 20, Easiphen, PKU cooler®, PKU air®, PKU Motion, PKU sphere® 20 liquid, PKU sphere™ NEXT15, Afenil 1, Afenil Squash 15, PKU Easy Shake & Go, PKU Easy Liquid, PKU Baby	Ready-to-drink	Nutricia, Nestlé Health Science, PIAM Farmaceutici S.p.A., Orpharma
	NeoPhe Tablets, PreKUnil Tablets, Afenil Micro 3H, Neutrafenil Micro R, PKU Microtabs, PKU Microtabs Plus, PKU Easy Tablets, PKU EASY Microtabs	Tablet	Prekulab, PIAM Farmaceutici S.p.A., Orpharma
	PKU Anamix First spoon, PKU Lophlex Sensation 20, PKU squeezie™	Semi-solid	Nutricia, Nestlé Health Science
	PKU GOLIKE PLUS®, PKU GOLIKE KRUNCH	Granules	Eton Pharmaceuticals
Tyrosinemia (TYR)	TYROS 1 Infant Formula & Medical Food, TYROS 2 Medical Food, TYR Anamix infant, TYR Anamix junior, TYR Lophlex LQ Powder, TYR Maxamum, XPHEN TYR Tyrosidon, TYR gel™, TYR explore5™, TYR express™, TYR express™ plus, TYR express™ newly renovated, TYR sphere®, Tyrex-1®, Tyrex-2®, TYR medi 2, TYR medigel, TYR medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	TYR Anamix junior LQ, TYR Lophlex LQ 10, TYR Lophlex LQ 20, TYR cooler™, TYR Easy Shake & Go Leaflet	Ready-to-drink	Nutricia, Nestlé Health Science, Orpharma
	TYR medimicro 3H, TYR Easy Tablets	Tablet	PIAM Farmaceutici S.p.A., Orpharma
Maple syrup urine disease (MSUD)	BCAD 1 Infant Formula & Medical Food, BCAD 2 Medical Food, MSUD Anamix infant, MSUD Anamix junior, MSUD Lophlex LQ Powder, MSUD Maxamum, MSUD gel™, MSUD explore5™, MSUD express™, MSUD express™ plus, MSUD express™ newly renovated, Ketonex-1®, Ketonex-2®, MSUD medi 2, MSUD medigel, MSUD medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	MSUD Anamix junior LQ, MSUD Lophlex LQ 10, MSUD Lophlex LQ 20, MSUD cooler®	Ready-to-drink	Nutricia, Nestlé Health Science
	MSUD medimicro 3H, MSUD Easy Tablets	Tablet	PIAM Farmaceutici S.p.A., Orpharma
Methylmalonic academia (MMA) / Propionic acidemia (PA)	OA 1 Infant Formula & Medical Food, OA 2 Medical Food, MMA/PA Anamix infant, MMA/PA Anamix junior, MMA/PA Maxamum, XMTVI Asadon, MMA/PA gel™, MMA/PA explore5™, MMA/PA express™, Propimex-1®, Propimex-2®, MMA/PA medi 2, MMA/PA medigel, MMA/PA medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	MMA/PA cooler™	Ready-to-drink	Nestlé Health Science

*Data were collected from: Mead Johnson (https://www.enfamil.com/products/metabolic-special-medical-needs/); Nutricia (https://www.nutricia.co.uk/hcp/products.html); Nestlé Health Science (https://www.nestlehealthscience.com/vitaflo); Abbott (https://www.abbottnutrition.com/our-products); Prekulab (https://www.prekulab.com/); Eton Pharmaceuticals (https://www.etonpharma.com/products/); PIAM Farmaceutici S.p.A. (https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/); Orpharma (https://www.orpharma.com/).

Table 1. A part of common protein substitutes in global commercial market* (continued)

Rare disease	Product	Dosage form	Brand
	MMA/PA medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
Homocysteinemia (HCY)	HCY 1 Infant Formula & Medical Food, HCY 2 Medical Food, HCU Anamix infant, HCU Anamix junior, HCU Lophlex LQ Powder, HCU LV, HCU Maxamum, HCU gel™, HCU explore5™, HCU express™ newly renovated, HCU express™, HCU express™ plus, Hominex-1®, Hominex-2®, HOM medi 2, HOM medigel, HOM medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	HCU Anamix Junior LQ, HCU Lophlex LQ 10, HCU Lophlex LQ 20, HCU cooler™	Ready-to-drink	Nutricia, Nestlé Health Science
	HCU Easy Tablets, HOM medimicro 3H	Tablet	PIAM Farmaceutici S.p.A., Orpharma
Glutaric acidemia type I (GA I)	GA Infant Formula & Medical Food, GA1 Anamix infant, GA1 Anamix junior, GA1 Maxamum, GA gel™, GA explore™ 5, GA express™, Glutarex-1®, Glutarex-2®, GA medi 2, GA medigel, GA medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	GA medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
Isovaleric acidemia (IVA)	LMD Infant Formula & Medical Food, IVA Anamix infant, IVA Anamix junior, I-Valex-1®, I-Valex-2®, IVA medi 2, IVA medigel, IVA medi 15	Powder	Mead Johnson, Nutricia, Abbott, PIAM Farmaceutici S.p.A.
	IVA cooler™	Ready-to-drink	Nestlé Health Science
	IVA medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
Urea cycle disorder (UCD)	WND® 1 Infant Formula & Medical Food, WND® 2 Medical Food, EAA supplement, UCD trio™, Cyclinex-1®, Cyclinex-2®, UCD medi 2, UCD medigel, UCD medi 15	Powder	Mead Johnson, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	UCD medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
long chain 3-hydroxyacyl-coA dehydrogenase deficiency (LCHADD)	Enfaport™ Infant Formula	Ready-to-drink	Mead Johnson

*Data were collected from: Mead Johnson (https://www.enfamil.com/products/metabolic-special-medical-needs/); Nutricia (https://www.nutricia.co.uk/hcp/products.html); Nestlé Health Science (https://www.nestlehealthscience.com/vitaflo); Abbott (https://www.abbottnutrition.com/our-products); Prekulab (https://www.prekulab.com/); Eton Pharmaceuticals (https://www.etonpharma.com/products/); PIAM Farmaceutici S.p.A. (https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/); Orpharma (https://www.orpharma.com/).

with water at an appropriate temperature, and detailed preparation guidelines must be provided in each product's instructions. Powdered protein substitutes typically have suboptimal palatability, which significantly impacts treatment adherence. To address this, many manufacturers have developed products with diverse flavors (such as vanilla, lemon, orange, raspberry, tropical, and chocolate) for patient selection.

Ready-to-drink protein substitutes are convenient ready-to-use formulations that require no reconstitution, allowing immediate consumption after opening and offering portability. These protein substitutes are suitable for patients aged over one year old. A study investigating adherence to protein substitutes among PKU patients demonstrated that liquid formulations reduced self-consciousness and facilitated out-of-home use. Additionally, they reduced product wastage (*61*). Notably, ready-to-drink protein substitutes typically have hyperosmolar concentrations in a small volume, which increases the risk of abdominal discomfort (*62*). Therefore, it is recommended that patients consume water or permitted beverages after ingesting liquid FSMPs.

Tablet protein substitutes are administered similarly to pharmaceutical tablets and are suitable for older children and adults. PKU patients received at least 40% of their protein requirements from amino acid tablets, and showed better compliance. 70% subjects preferred incorporating tablets into their usual protein substitute regimen (*63*). Tablet protein substitutes have good stability and long-shelf-life. This dosage form of protein substitutes can be carried by patients and is easy to consume when going out.

Semi-solid protein substitutes currently include two types: *i*) products supplied in a semi-solid state, which can be consumed with a spoon or directly sucked from a pouch; *ii*) Powdered products that can be easily reconstituted into a gel or paste with a small amount of water. These formulations are suitable for patients ranging from 6-month-old infants to adults. Importantly, semi-solid protein substitutes facilitate the transition of weaned infants from exclusive liquid diets to solid foods, as their consistency is analogous to weaning foods (*62,64,65*). Like liquid formulations, semi-solid protein substitutes are concentrated, so consumption of water or permitted beverages afterward is recommended.

Slow-release protein substitutes are novel FSMPs developed in recent years, typically formulated as granules or tablets. The core technology of these formulations involves embedding amino acid(s) within hydrophilic coatings. A novel slow-release protein substitute prepared using Physiomimic Technology™ extended the duration of amino acid elevation in plasma compared to free amino acid(s) (*66*). Patients consumed slow-release protein substitutes reported fewer gastrointestinal symptoms (diarrhoea, constipation, bloating, nausea or vomiting) compared to baseline (*67*). Furthermore, the coatings can mask the bitter taste and odor while reducing the osmolarity of free amino acid(s), which enhances product acceptability and patient adherence (*67,68*).

3.2. Nutrient modules

Nutrient modules are single-nutrient FSMPs that are usually used as supplements in the dietary management of rare diseases, providing nutritional support for patients (*5,69*). It is important to emphasize that nutrient modules are nutritionally incomplete products and cannot be used as the sole source of nutrition.

3.2.1. Amino acid modules

In addition to protein substitutes, amino acid modules can also be used in dietary therapy for patients with inborn errors of amino acid metabolism. Amino acid modules offer greater flexibility in application, as they can be used independently or in combination with other dietary therapeutic strategies (*70*). Commercial amino acid modules can be either single amino acid or amino acid mixtures, and present in powder. Patients usually supplement amino acid modules for two purposes, avoiding the intake of restricted amino acid(s) or supplementing specific amino acid(s).

When amino acid modules are used for avoiding the intake of restricted amino acid(s), their functions are similar to that of protein substitutes. Compared to protein substitutes which have more complex nutritional compositions and focus on fulfilling overall protein nutritional functions, amino acid modules can precisely adjust the types and contents of amino acids according to patients' specific conditions. This characteristic is particularly important for infants, toddlers, and children with rare diseases (*71,72*). On the one hand, amino acid modules can completely eliminate restricted amino acids while precisely provide other amino acids required for growth and development (*72*). On the other hand, younger rare disease patients may have weak digestive functions or prone to allergies in the gastrointestinal tract. Amino acid modules are carefully screened and designed for composition, without complete protein molecules and can be fully absorbed without digestion, which can reduce the burden on the gastrointestinal tract and have higher safety (*73,74*). Nestlé Health Science has already come up several amino acid modules without restricted amino acids, including UCD amino5™, MSUD amino5™, MMA/PA amino5™, and GA amino5™. Nutricia has launched XMTVI Asadon and XPHEN TYR Tyrosidon targeting MMA/PA and TYR, respectively.

Avoiding to intake of restricted amino acid(s) is the key strategy for dietary therapy of amino acid metabolism disorder, but attention should also be paid

to the disruption of metabolic pathways caused by the absolute deficiency or functional insufficiency of specific amino acids (*75*). For example, Arg and/or citrulline (Cit) impairs urea synthesis in UCDs. Supplementation of these amino acids is not only essential for correcting metabolic defects but also maximizes ammonia excretion during the acute phase of metabolic decompensation (*76*). Beyond supplementing specific amino acid(s) due to impaired synthesis, specific amino acid(s) can also be supplemented to compete with other amino acid(s). For instance, Arg can compete with Lys for the blood-brain barrier transporter *SLC7A1*. Compared with GA I patients on conventional Lys-restricted diets, those supplemented with Arg in their diets exhibit lower Lys concentrations in the plasma and reduced the urinary excretion of 3-hydroxyglutaric acid (*77*). There have been systematic reviews and meta-analyses summarized rare diseases that can be supplemented with one or several specific amino acid(s) (*75,78*). To meet the needs of rare disease patients for supplementation, Ajinomoto Cambrooke, Nutricia, and Nestlé Health Science have launched single amino acid powders.

3.2.2. Fat modules

Fat modules are FSMPs with fat (fatty acid) as the core functional ingredients, specifically designed to supplement or adjust fat (fatty acid) intake in specific populations. They primarily consist of long-chain fatty acid (LCT), medium chain fatty acid (MCT), and other permitted fatty acids. Fat modules deliver core nutritional support to rare disease patients by precisely supplementing fat sources, optimizing energy provision, and correcting metabolic imbalances, thereby helping alleviate symptoms, maintain physiological functions, and improve prognosis. Commercial fat modules include powdered product (MCTprocal™, Nestlé Health Science) and oil-based product (MCT Oil and Liquigen®, Nutricia).

Fatty acid metabolism disorders (such as long chain 3-hydroxyacyl-coA dehydrogenase deficiency (LCHADD) and very long chain acyl-coA dehydrogenase deficiency) urgently require fat modules to treat. Patients with these disorders cannot convert fatty acids into tricarboxylic acid cycle intermediates and subsequently into energy, due to disrupted fatty acid transport *via* the mitochondrial β-oxidation pathway or the carnitine transport pathway. In addition, fat modules can also apply in the dietary management of other rare diseases, including short bowel syndrome, cystic fibrosis, PKU, and refractory epilepsy. MCT is essentially pure trioctanoylglycerol, thereby its daily dose should be evenly distributed across all meals. Infants fed MCT-containing formula milk typically tolerate MCT without adverse symptoms. However, elderly patients supplementing MCT at the first time often experience gastrointestinal symptoms, including abdominal discomfort, cramping, flatulence, bloating, and diarrhea. Fat modules can be consumed alone or mixed into a variety of foods and beverages. To avoid gastrointestinal symptoms caused by the use of fa modules, patients are usually required to consume them on a non-fasting status.

3.2.3. Carbohydrate modules

Carbohydrate modules are classified as nutritionally incomplete FSMPs intended for patients with well-defined medical conditions that necessitate targeted carbohydrate supplementation to address specific nutritional requirements and provide energy. Carbohydrate sources encompass a broad range of compounds, including monosaccharides, disaccharides, oligosaccharides, polysaccharides, maltodextrin, glucose polymers, and other raw materials adhering to relevant regulatory guidelines. Commercial carbohydrate modules are currently in powder.

Glycogen storage disease type I (GSD I) is one of the rare diseases with the highest demand for specific carbohydrate supplementation. GSD Ia and GSD Ib are caused by mutations in the *G6PC* gene and *SLC37A4* gene, respectively, and both of them can lead to a deficiency of glucose-6-phosphatase translocase (*79*). Since GSD patients experience significant fasting hypoglycemia, the therapeutic principle is to maintain blood glucose within the normal range and maximize the duration of stable glycemia following carbohydrate supplementation (*80*). The clinical application of uncooked corn starch (UCCS) represents a key breakthrough in the foundational treatment regimen for GSD I. UCCS is slowly hydrolyzed into glucose by gastrointestinal amylases, with sustained glucose release over approximately 4 hours, thereby effectively preventing fasting hypoglycemia (*81*). Glycosade® is currently the most effective FSMP approved for the treatment of GSD I, and it has been validated to prolong the fasting tolerance of GSD I patients to more than 8 hours (*82-85*). Long-term follow-up studies have shown that the dosage of Glycosade® is lower than that of UCCS, but metabolic indicators are more stable. Furthermore, the average daily administration frequency of Glycosade® has decreased from 3.95 times to 3 times (*82*), which contributes to improve compliance. Recently, the *in vitro* dynamic small-intestine mode has demonstrated the therapeutic potential of sweet manioc starch (SMS) for GSD Ia (*86*). A randomized, triple-blind, Phase I/II cross-over study also confirmed that the duration of maintaining normal blood glucose with SMS (8.2 ± 2.0 h) is longer than that with UCCS (7.7 ± 2.3 h) (*87*). FSMPs targeting blood glucose maintenance in rare diseases are relatively scarce. In the future, more slow-release starch products with diverse carbohydrate sources and longer blood glucose stability durations should be developed.

3.3. Ketogenic diets

KDs are dietary therapies rather than FSMPs. Specific formula foods used to implement KDs are FSMPs and serve as critical interventions for certain rare diseases. KDs are characterized by high fat, low carbohydrate, and moderate protein and other nutrients, which have been utilized for epilepsy treatment since 1921 (*88*). KDs have been proven to be highly effective alternative therapies and are even considered the last resort for refractory epilepsy (*89*). Currently, KDs have been incorporated into the clinical management of various rare diseases, including Angelman syndrome, complex 1 mitochondrial disorder, Dravet syndrome, epilepsy with myoclonic-atonic seizures, febrile infection-related epilepsy syndrome, glucose transporter type 1 deficiency syndrome, infantile epilepsy spasms syndrome, Ohtahara syndrome, pyruvate dehydrogenase deficiency, super-refractory status epilepticus, tuberous sclerosis complex (*88*). These diseases are often accompanied by uncontrollable epileptic seizures. A range of FSMPs for KDs are commercially available (Table 2). To maximize tolerability, enhance palatability, achieve dietary diversification, and improve compliance, five distinct types of KDs have been developed (*88,89*).

3.3.1. Classic ketogenic diet

Classic ketogenic diet (CKD) is the most restrictive diet, typically maintaining the ketogenic ratio (the ratio of fats to carbohydrates and proteins combined) at 4:1 (*88*). CKD shows excellent clinic efficacy on refractory epilepsy, but is poorly tolerated in the gastrointestinal tract, particularly in infants and adolescents. For these populations, the ketogenic ratio of CKD can be adjusted to 3:1 (*90*), and even 2:1 (*91*). In a randomized controlled trial involving 76 children with refractory epilepsy, 30.5% of those on the 3:1 ratio achieved seizure freedom, compared with 55.0% of those on the 4:1 ratio (*92*). The 2:1 diet has a notably lower proportion of fat than 4:1 diet or 3:1 diet but nonetheless exhibits favorable efficacy in both short- and long-term follow-up (*91*).

3.3.2. Medium-chain triglyceride diet

Medium-chain triglyceride diet (MCTD) is an alternate version for CKD (*88*). The main source of fats in MCTD is saturated fatty acids with 6~12 carbons, mainly including octanoic acid (C8:0) and decanoic acid (C10:0). MCT is more readily hydrolyzed by gastrointestinal lipases and can rapidly and efficiently

Table 2. A part of common FSMPs implemented KDs in global commercial market*

Product	Ketogenic ratio	Dosage form	Brand
KetoCal 4:1, KetoVie Café Kwik Mix	4:1	Powder	Ajinomoto Cambrooke, Nutricia
K.Flo™, KetoCal 4:1 LQ, KetoVie 4:1, KetoVie Peptide 4:1, KetoVie 4:1 Plant-Based Protein	4:1	Ready-to-drink	Ajinomoto Cambrooke, Nutricia, Nestlé Health Science
K.Yo™	3:1	Semi-solid	Nestlé Health Science
KetoCal 3:1	3:1	Powder	Nutricia
KetoVie 3:1	3:1	Ready-to-drink	Ajinomoto Cambrooke
KetoCal 2.5:1 LQ	2.5:1	Ready-to-drink	Nutricia
KetoVie Café Cinnamon Donut Delights, KetoVie Café Pizza Petites	2.5:1	Solid	Ajinomoto Cambrooke
KetoVie Café Creamy Cereal, KetoVie Café Wholesome Bread	2:1	Solid	Ajinomoto Cambrooke
MCTprocal™	10 g MCT per 16 g	Powder	Nestlé Health Science
MCT oil	100% MCT	Oil	Nutricia
K.Quik™	20 g MCT and 1 g LCT per 100 mL	Ready-to-drink	Nestlé Health Science
KetoVie Café Raspberry Muffins	3.5:1	Solid	Ajinomoto Cambrooke
K.Vita	40 g MCT per 120 mL	Ready-to-drink	Nestlé Health Science
Liquigen	50% MCT	Ready-to-drink	Nutricia

*Data were collected from: Ajinomoto Cambrooke (https://www.cambrooke.com/); Nutricia (https://www.nutricia.co.uk/hcp/products.html); Nestlé Health Science (https://www.nestlehealthscience.com/vitaflo).

produce ketones (*93*). This property enables MCTD to have lower total fat content while incorporating higher amounts of carbohydrates and proteins (*89,94*). A study comparing CKD (n = 73) and MCTD (n = 72) for the treatment of childhood epilepsy found no significant differences between the two groups in terms of ≥ 50% and ≥ 90% reductions in seizure frequency or reduction in antiepileptic drug dosage after 3 months (*95*). MCT exhibits higher oxidative capacity than LCT, thereby enhancing thermogenesis and decreasing fatty acid accumulation in adipose tissue (*96,97*). Furthermore, studies have shown that adherence to MCTD leads to a significant reduction in the total cholesterol-to-high-density lipoprotein cholesterol ratio (*98*). An important consideration in the design of MCT-based FSMPs is using an appropriate ratio of C10 to C8. Most current products adopt a 60:40 (C10:C8) ratio, while K.Vita (Nestlé Health Science) utilizes an 80:20 (C10:C8) ratio. K.Vita significantly reduced seizure frequency and was associated with mild gastrointestinal adverse effects (*99*). Given that MCT is rapidly hydrolyzed, potential manifestations resulting from rapid ketogenesis (such as ketosis) require monitoring (*100*).

3.3.3. Low glycemic index treatment

The glucose stability during KD therapy is closely associated with seizure control (*101*). Low glycemic index treatment (LGIT) is a KD variant emphasizing low-glycemic foods, and has been validated for effective blood glucose regulation. LGIT imposes less stringent carbohydrate restriction, permitting 40–60 g of low glycemic index (GI) foods or limiting low-GI foods to no more than 10% of total caloric intake (*102,103*). A study involving 36 epilepsy patients with Lennox-Gastaut syndrome or Dravet syndrome undergoing LGIT demonstrated that 56% of patients achieved a ≥ 50% reduction in seizure frequency after 3 months. Only 6% of patients reported adverse events, and no patients developed symptoms such as vomiting, constipation, abdominal pain, or kidney stones (*104*). Maintaining an appropriate blood ketone level is critical for effective refractory epilepsy control. However, during LGIT for refractory epilepsy, researchers observed that seizure control could still be achieved even without strictly maintaining blood ketone levels (*105*). The underlying reason may be that the higher carbohydrate allowance under LGIT facilitates the maintenance of blood glucose within an optimal range, thereby enabling the production and functional efficacy of ketone bodies (*103,106*).

3.3.4. Modified Atkins diet

Modified Atkins diet (MAD) is a KD adapted from the Atkins diet (*107*), characterized by high fat, low carbohydrate, and minimal restrictions on protein intake (*88*). MAD does not require a fixed ketogenic ratio, though the typical ratio ranges from 1:1 to 2:1 (*88,108*). MAD can induce ketosis, thereby producing anti-epileptic effects. A study comparing MAD with anti-epileptic drug therapy found that 30% of patients in the MAD group had > 90% seizure reduction, 52% of patients had > 50% seizure reduction, while the drug group only had 7.7% and 11.5% (*109*). The MAD exhibits greater flexibility than other KD variants. Owing to the absence of a fasting period, faster initiation, and relative ease of implementation, it is convenient for clinicians to prescribe for outpatient emergency management (*107*). Its less restrictive nature also makes MAD the preferred dietary intervention for adult patients (*110*). A more recently developed alternative, the modified ketogenic diet, incorporates many design principles of MAD (*88*) and is regarded as the least restrictive KD variant (*111*).

3.4. Special low protein foods

For many rare diseases classified as inborn errors of intermediary protein metabolism, such as protein/amino acid metabolism disorders, organic acid metabolism disorders, UCDs, dietary management constitutes a pivotal therapeutic strategy (*112*). SLPFs are an integral component of such dietary therapy (*113,114*). SLPFs are considered indispensable for managing these disorders, which not only meet nutrients and energy requirements but also sustain anabolism and enhance dietary diversity. SLPFs are beneficial for maintaining metabolic parameters within target ranges.

One of the most special features of SLPFs is that they can be made into many different types. This feature renders them more similar to regular foods. Protein substitutes and amino acid supplements often have poor taste, which may affect patients' mood and autonomy in eating, thereby reducing compliance with products. SLPFs effectively address these challenges by offering greater dietary options, enabling patients to experience a sense of well-being analogous to that of healthy individuals during mealtimes (Table 3).

4. Prospects for China's rare disease FSMPs

The development of rare disease FSMPs in China is now in the stage of rapid growth. Since the registration of rare disease FSMPs was incorporated into the priority review and approval procedure in 2023, researchers and companies have invested greater efforts in rare disease FSMPs. Encouraged by this policy, two domestically developed rare disease FSMPs were launched in 2025. However, due to the relatively late start of China's rare disease FSMPs, there remain numerous gaps to be addressed and aspects to be optimized. Based on the statistical and analytical summary of commercial FSMPs status of rare diseases in the word, this part presents prospects for the development of China's rare disease

FSMPs from three aspects: product diversity, technology and process, and management policy.

4.1. Expanding the diversity of China's rare disease FSMPs

Insufficient product diversity remains a critical challenge in rare disease FSMPs industry. For instance, of the 32 rare diseases explicitly identified in China as requiring FSMPs to treat, only a subset have accessible products. And these products mainly target amino acid metabolic disorders, organic acid metabolic disorders, fatty acid oxidation disorders, carbohydrate metabolic disorders, and refractory epilepsy. A large number of patients who need FSMPs to treat still face the situation of no available products. For example, patients suffered from galactosemia need long-term use of lactose-free FSMPs, but there are no related products available. In the future, more FSMPs tailored to different rare diseases should be developed.

Expanding product diversity can be achieved not only by broadening the range of applicable diseases but also by exploring new raw materials. Currently, the use of raw materials still focuses on safety and compliance, so raw materials that meet the standards of various countries or organizations are prioritized in production. This has significantly constrained innovation in rare disease FSMPs. Going forwards, more sources of raw materials can be explored, such as plant-based ingredients (*48*), insect proteins (*115*), and marine bioactive compounds (*116*). In addition, rare diseases FSMPs have extremely strict restrictions on raw materials, requiring ingredients to be pure, effective, safe, and not induce metabolic disorders in patients. This poses a huge challenge to production technologies of raw materials. Synthetic biology offers a potential solution to this challenge (*117*). In the future, it should be used for the targeted synthesis of proteins/peptides with specific amino acid compositions, functional carbohydrates, and other substances required for rare disease FSMPs.

4.2. Accelerating innovation in technology and process

Regarding product manufacturing technology, innovations such as 3D/4D printing and targeted delivery systems have already been employed (*12*). Moving forward, these emerging technologies should be further leveraged to produce FSMPs with precisely designed modular dosage forms and enhanced slow or controlled-release profiles. FSMPs formulation imposes extremely stringent requirements on micronutrient content control. Thus, ensuring precise micronutrient dosing and uniform mixing at the industrial scale remains a major challenge. Future efforts should focus on advancing continuous production processes and developing more accurate real-time monitoring technologies.

In terms of product dosage forms, FSMPs in China's market are mainly in powder and liquid forms at present. More portable and edible dosage forms of rare disease FSMPs need to be designed to expand patients' choices in the future. SLPFs are an important product type for enriching patients' choices. A research group from China have developed steamed buns with a low protein content (0.50 g/100 g) for the potential nutritional treatment of abnormal amino acid and organic acid metabolism, urea cycle disorders, and chronic kidney disease (*118*). The design concept of SLPFs requires them to be more closely related to daily diets (*13,113*). Therefore, localized SLPFs can be developed by integrating traditional dietary cultures from different regions to enhance patients' appetite and happiness in the future.

Many ingredients used in rare disease FSMPs have bad tastes, which may greatly reduce the patient's acceptance of the product. Some rare disease FSMPs have been adjusted for flavor by using seasonings. In the future, it is recommended to use more advanced technologies to enhance the flavor of products, such as encapsulation technology (*119*), bio-enzymatic debittering technology (*120*) and odor-taste cross-modal interaction (*121*). Using advanced technologies is beneficial for accelerating the optimization process of rare disease FSMPs from functional priority to sensory pleasure.

4.3. Optimizing China's management policy

Due to variations in food production standards, healthcare systems, regulatory traditions, and risk perceptions, different countries or organizations have developed distinctly different management frameworks. The U.S., Canada, and Australia-New Zealand adopt relatively lenient regulations for FSMPs, with no pre-market registration or notification required. The U.K. and the E.U. implement a pre-market notification system for FSMPs. Japan employs a registration and approval system, though the process from application to approval takes at least six months (*122*). China implements a registration and approval system for FSMPs (*47*), establishing a comprehensive regulatory framework covering formula design, production, market access, and post-market supervision. In China, foods for special medical using are classified into two categories according to whether registration is required or not: *i*) foods with special medical using needed registration, including special medical purpose infant formula foods and FSMPs for one year onwards; *ii*) other foods for special medical purposes exempt from registration, including SLPFs, low glycemic index foods, nutrient supplements, easy-to-chew foods, and nutritionally formulated meals. Under this stringent registration policy framework, China has established the priority review and approval procedure to encourage the research and development and accelerate the market entry for rare disease FSMPs and urgently needed new FSMPs (*123*). Before the implementation of

Table 3. A part of common SLPFs in global commercial market*

Category	Product	Protein content/100 g	Brand
Pasta	Pierogi, Ravioli, Aproten Ditalini, Aproten Fusilli, Aproten Linguine, Aproten Penne, Aproten Pipe, Aproten Rigatoni, Aproten Sedani, Aproten Spaghetti, Pasta Duets, Pasta Solo - Elbows, Dital, Fusilli, Spaghetti, Penne, Loprofin Fusilli, Loprofin Penne, Loprofin Tagliatelle, Loprofin Macaroni, Loprofin Lasagne, Loprofin Spaghetti, Loprofin Animal Pasta, Promin Low Protein Lasagne, Promin Low Protein Pasta Spirals, Promin Low Protein Pasta in Sauce - Cheese & Broccoli, Promin Low Protein Pasta in Sauce – Tomato, Pepper & Herb, Promin Low Protein Cous Cous, Promin Low Protein Alphabets, Promin Low Protein MacPot - Macaroni Cheese, Promin Low Protein MacPot - Tomato Macaroni, Sineamin	0–3.03	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia, Orpharma, PIAM Farmaceutici S.p.A.
Mix (baking, cake, cookie, sugar, bread, soup)	Baking Mix, Blueberry Scone Mix, Chewy Fudgy Brownie Mix, Chocolate Chip Cookie Mix, Gingerbread Mix, MixQuick, Sugar Cookie Mix, Wel-Made Baking Mix, Blueberry Scone Mix, Chewy Fudgy Brownie Mix, Chocolate Chip Cookie Mix, Gingerbread Mix, Sugar Cookie Mix, Alfredo Sauce Mix, Bread Mix, Loprofin Mix, Loprofin Chocolate Cake Mix, Promin Low Protein Hot Breakfast, Promin Low Protein Chocolate Hot Breakfast, Promin LowProtein Scrambled Egg & Omelette Mix, Promin Low Protein XPot - All Day Scramble, Promin Low Protein Burger Mix – Original Flavour, Promin Low Protein Sausage Mix - Original, Promin Low Protein All Purpose Baking Mix, Promin Low Protein Potato Cake Mix, NEC	0–4	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia, Orpharma, PIAM Farmaceutici S.p.A.
Bread	Bagel Bars French Toast, Bagels, Brookelyn Dog Buns, Camburger Buns, Cinnamon Raisin Swirl Bread, Focaccia Sticks - Italian Style, HomeStyle Bread, Pita Pockets, Toaster Topz - Banana Chip, Tuscan Pizza Crusts, The Bigger Bagel, GO! Pockets, Ciabattine, Pane Casereccio	0.34–1.9	Ajinomoto Cambrooke, Nestlé Health Science
Biscuit	Cookies, Mini Crackers, Vitabite, Cookies, Frollini, Loprofin Crackers, Loprofin Herb Crackers	0.22–0.7	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia
Cereal	Loprofin Flakes, Loprofin Loops, Creamy Hot Cereal, Malt-O-Meal	0.32–4	Ajinomoto Cambrooke, Nutricia
Cheese	Cheddar Shreds, Cheddar Wizard, Cheese Singles, Cream Cheese Plain, Mozzarella Shreds	1.8–2.14	Ajinomoto Cambrooke
Bar	Fruit Bar, Apple Breakfast Bars, Blueberry Breakfast Bars	0.32–0.6	Ajinomoto Cambrooke, Nestlé Health Science
Rice	Rice, Loprofin Rice, Short Grain Rice	0.4–0.6	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia
Pizza	Pizza Base, Pizza	0.9–1.45	Ajinomoto Cambrooke, Nestlé Health Science
Chocolate	Chocotino, Chocolate Cha-Cha's	0.4–1.25	Ajinomoto Cambrooke, Nestlé Health Science
Flour	Wheat Starch	0.3	Ajinomoto Cambrooke
Snacks	Yuca Tater Home Fries, Wise Onion Rings, Promin Low Protein Potato Pot – Onion and Croutons, Promin Low Protein XPot - Beef & Tomato	0.2–2.14	Ajinomoto Cambrooke, Orpharma
Sauces	Marinara Minis	1.41	Ajinomoto Cambrooke
Spread	Pea-Not Butter	3.57	Ajinomoto Cambrooke
Meat replacer	Tweekz	1.15–3.44	Ajinomoto Cambrooke

*Data were collected from: Ajinomoto Cambrooke (*https://www.cambrooke.com/*); Nutricia (*https://www.nutricia.co.uk/hcp/products.html*); Nestlé Health Science (*https://www.nestlehealthscience.com/vitaflo*); PIAM Farmaceutici S.p.A. (*https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/*); Orpharma (*https://www.orpharma.com/*).

Table 3. A part of common SLPFs in global commercial market* (continued)

Category	Product	Protein content/100 g	Brand
Egg replacer	Loprofin Egg Replacer, Loprofin Egg White Replacer, Eggz	0–1.88	Ajinomoto Cambrooke, Nutricia
Milk replacer	ProZero, Loprofin Sno-Pro, Loprofin Drink LQ, Milco	0–0.4	Nestlé Health Science, Nutricia, PIAM Farmaceutici S.p.A.

*Data were collected from: Ajinomoto Cambrooke (*https://www.cambrooke.com/*); Nutricia (*https://www.nutricia.co.uk/hcp/products.html*); Nestlé Health Science (*https://www.nestlehealthscience.com/vitaflo*); PIAM Farmaceutici S.p.A. (*https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/*); Orpharma (*https://www.orpharma.com/*).

Table 4. Fourteen rare disease FSMPs entered the priority review and approval procedure*

Announcement time	Acceptance number	Product	Applicant for registration
May 15, 2024	TY20240024	Kairuntai® Special Medical Purpose Intant Amino Acid Metabolism Disorder Food PKU Formula	Jiangsu Daisy Special Medical Food Co., Ltd.
Oct. 18, 2024	TY20240076	Teaibingjia Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	Qingdao Sainte Nutritional Food Co., Ltd.
Oct. 18, 2024	TY20240077	Teaibenjia Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	Qingdao Sainte Nutritional Food Co., Ltd.
Mar. 13, 2025	TY20250032	Enruiyoute Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	SINOFN (Tianjin) Pharmaceutical Technology Co., Ltd.
Mar. 21, 2025	TY20250033	Enzhuoyoute Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	SINOFN (Tianjin) Pharmaceutical Technology Co., Ltd.
Mar. 21, 2025	TY20250034	Enboyoute Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	SINOFN (Tianjin) Pharmaceutical Technology Co., Ltd.
Jun. 11, 2025	TY20250054	Aizhizun Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	Chifeng Sunrise Pharmaceutical Co., Ltd.
Jun. 11, 2025	TY20250055	Aizhixi Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	Chifeng Sunrise Pharmaceutical Co., Ltd.
Jun. 11, 2025	TY20250060	Aifuxi Special Medical Purpose PKU Amino Acid Module Formula Food	Heilongjiang Bright Songhe Dairy Co., Ltd.
Jun. 20, 2025	TY20250062	Ruibaoan® Amino Acid Metabolism Disorder PKU Infant Formula Food	Inner Mongolia Tekangrui Nutritional Food Co., Ltd.
Nov. 15, 2025	TY20250120	Nuobaowei® PKU Formula Food	Hebei Aisheng Technology Co., Ltd.
Nov. 25, 2025	TY20250130	Nuobaorui® PKU Formula Food	Hebei Aisheng Technology Co., Ltd.
Dec. 31, 2025	TY20250155	Kairuntai® Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	Jiangsu Daisy Special Medical Food Co., Ltd.
Jan. 8, 2026	TY20250151	Teyiwei Special Medical Purpose PKU Formula Powder	Shandong Ruoyao Special Medical Food Co., Ltd.

*Data were collected from: Center for Food Evaluation, State Administration for Market Regulation (*https://www.cfe-samr.org.cn/*).

the priority review and approval procedure, there were only three rare disease FSMPs from Nutricia that applied for registration. Fortunately, since the implementation of this procedure, 14 rare disease FSMPs have been included (Table 4), and two of them from Qingdao Sainte Nutritional Food Co., Ltd. have been approved (*124*). It is expected that more high-quality, reasonably priced domestic FSMPs will enter the market in the future.

While the priority review and approval procedure has significantly facilitated the development of China's FSMP industry, the types and quantities of FSMPs still fails to meet patient needs and problems such as complex registration processes, lengthy approval cycles, and insufficient corporate innovation incentives persist still exist. These indicate that the regulatory policy framework of FSMPs requires optimization. Going forward, under guaranteeing high standards for product safety, it will be necessary to establish clear and flexible technical standards for different FSMP categories to reduce approval uncertainties and accelerate market access. For overseas FSMPs that have been marketed but not registered, it is recommended to implement different

approval criteria based on their overseas safety record and clinical research data. This approach would not only ensure the safety of products but also accelerate the entry of overseas products into the China's market.

5. Conclusion

In summary, FSMPs play a crucial role in rare disease management. This review focuses on the commercial rare disease FSMPs around the word. By analyzing the design of products, applicable diseases, and treatment effects, we proposed suggestions for the development of China's rare disease FSMPs in terms of product diversity, technology and process, and management policy.

It should be pointed out that this review only collected commercial rare disease FSMPs. Although this can help researchers and companies understand current market gaps and promptly fill in the shortage of product types, it fails to fully cover and track products that have been studied but not yet marketed. Future studies may consider using systematic review and meta-analysis to comprehensively evaluate rare disease FSMPs that have been launched and are currently under developing. This can provide a more detailed understanding of product development trends and scientific basis for clinical decision-making.

Funding: This work was supported by Shanghai Municipal Three Year Action Plan for Strengthening the Construction of Public Health System (2023–2025) Discipline Leader Project (GWVI-11.2-XD19), Registration Requirements of Food for Special Medical Purposes for Rare Diseases (2023) commissioned by State Administration for Market Regulation.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received November 17, 2025; Revised January 10, 2026; Accepted January 13, 2026.

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Released online in J-STAGE as advance publication January 15, 2026.