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ORIGINAL ARTICLE

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Food or medicine? A European regulatory perspective on nutritional therapy products to treat inborn errors of metabolism

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Abstract

Dietary or nutritional management strategies are the cornerstone of treatment for many inborn errors of metabolism (IEMs). Though a vital part of standard of care, the products prescribed for this are often not formally registered as medication. Instead, they are regulated as food or as food supplements, impacting the level of oversight as well as reimbursed policies. This scoping literature review explores the European regulatory framework relevant to these products and its implications for current clinical practice. Searches of electronic databases (PubMed, InfoCuria) were carried out, supplemented by articles identified by experts, from reference lists, relevant guidelines and case-law by the European Court of Justice. In the European Union (EU), nutritional therapy products are regulated as food supplements, food for special medical purposes (FSMPs) or medication. The requirements and level of oversight increase for each of these categories. Relying on lesser-regulated food products to treat IEMs raises concerns regarding product quality, safety, reimbursement and patient access. In order to ascertain whether a nutritional therapy product

functions as medication and thus could be classified as such, we developed a flowchart to assess treatment characteristics (benefit, pharmacological attributes, and safety) with a case-based approach. Evaluating nutritional therapy products might reveal a justifiable need for a pharmaceutical product. A flowchart can facilitate systematically distinguishing products that function medication-like in the management of IEMs. Subsequently, finding and implementing appropriate solutions for these products might help improve the quality, safety and accessibility including reimbursement of treatment for IEMs.

KEYWORDS

European Union, food supplements, foods for special medical purposes, inborn errors of metabolism, medical food, nutritional therapy

1 | INTRODUCTION

Inborn errors of metabolism (IEMs) are a heterogeneous group of genetic conditions in which metabolic pathways are disrupted. In the treatment of these disorders, striving for metabolic stability is key. One important strategy to achieve this goal is the dietary management of the disorder, also known as nutritional therapy.[1,2] This can involve complex dietary plans, restricting the intake of certain nutrients or foods, or the addition of mixed or single nutrients to the diet. It is therefore not surprising that the supplementation of nutrients is a key element in the standard of care treatment guidelines for many IEMs and often the only currently available therapy.[3] Examples include vitamins as the mainstay of therapy in vitamin-responsive IEMs, such as pyridoxine for the treatment of pyridoxine-dependent epilepsy (PDE-ALDH7A1, OMIM: #266100) or biotin for biotinidase deficiency (OMIM: #253260).[4–6] Other examples include single amino acid supplementation in amino-acidopathies, such as the supplementation of valine and isoleucine in the management of maple syrup urine disease (OMIM: #248600), as well as the often critical dependence on medical foods like phenylalanine (Phe)-free foods in phenylketonuria (PKU, OMIM: #261600).[7,8]

Although nutritional therapy is a well-established strategy for the management IEMs, the terminology used for the nutrients prescribed for this is not. Different (legislative) terms are used interchangeably and the regulatory implications of these varying categorizations are often overlooked.[3] Their functioning straddles the border between food and medicine and they may be regulated as either, a distinction that is however not systematically made and mainly driven by manufacturers. Single nutrients, like the aforementioned vitamins and single amino acids or co-enzymes, are available in the form of supplements.[9] A limited number of nutritional therapy products is formally authorized as medication.[3,10] Additionally, specifically designed amino acid mixtures are available as special medical foods to supply patients with sufficient amounts of amino acids without the amino acid of which the metabolism is affected (e.g., Phe-free amino acid mixtures for PKU).[8,11] The lack of consistent terminology and clear delineation within the regulatory landscape hinders the discourse pertaining to the availability and accessibility of suitable nutritional therapy products required for the management of IEMs in current clinical practice.

As a result, issues related to the reliance on food-grade nutritional therapy products, regulated less stringently than medication, may remain obscured. Because patients with IEMs can be critically dependent on the administration of these nutrients, concerns regarding the quality of the product or issues with patient access, including reimbursement, can create an undesirable and unsafe situation.[9,12–14] This scoping review therefore aims to analyze the European regulatory framework governing these nutritional therapy products, as well as its implications for the treatment of IEMs. Furthermore, our objective is to develop a systematic, case-based approach to assessing the alignment between a product's regulatory classification and its practical functioning, with the ultimate goal of identifying and addressing unmet medical needs that undermine the essential quality and accessibility needed for successful treatment of IEMs.

2 | METHODS

2.1 | Regulatory exploration: resources and analytical approach

The regulatory framework applicable to food and medicine in the European Union (EU) was studied by

analyzing pertinent EU legislation, assisted by a legal expert, and their interpretation and implementation was evaluated further by studying court decisions by the Court of Justice of the European Union (CJEU), identified through searches in the InfoCuria database, as well as relevant guidelines published by the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA). Since this review is focused on the European perspective, EU legislative terms are used whenever possible. In the absence of a legal term combining all food-related products used in the treatment of IEMs, we will use the umbrella term 'nutritional therapy products' as a comprehensive descriptor for all manufactured nutrient substances that may be used in the management of IEMs.

2.2 | Clinical search strategy and study selection

To explore the impact of the regulatory framework on clinical practice, a literature search was performed in August 2021 using the PubMed database by combining the key words: 'inborn errors of metabolism' or 'inherited metabolic disease' and their variations with the terms 'dietary supplements', 'medical foods' and 'nutritional therapy' and their alternatives. On the 15 December 2022, an additional search was performed to identify possible newly added articles (published in 2021 or 2022). These searches yielded 1174 hits (see Figure S1). Titles and abstracts were screened for research regarding nutritional therapy products for the treatment of IEMs, which led to exclusion of 916 publications and an additional 9 that were not available in English or Dutch. Full-text of 243 of the remaining 249 publications were available and upon review, 21 of these reported findings relevant to (an aspect of) the regulatory framework on nutritional therapy and were included. This set was supplemented by articles identified by examining reference lists from full-read articles (7 articles) and relevant literature known to the authors and other experts (4 articles), resulting in the inclusion of a total of 32 articles.

3 | RESULTS

3.1 | EU regulatory framework: food versus medication

This section provides a concise overview of the relevant provisions regulating nutritional therapy products for the treatment of IEMs in the EU. Before analyzing these, it is important to note that the terminology used to describe these products can be diverse and interchangeable (see Table 1. for an overview). There is no global or even academic consensus on the nomenclature for these products as a group and the same is true for defining the varying subcategories, including food supplements and medical foods.[3,23,24] Additionally, the designations "food-grade" and "pharma-grade" are commonly used to describe products manufactured in compliance with the respective food or medication regulatory frameworks, but have no legal basis in the EU.

In general, nutritional therapy products are regulated as either food or medication (see Table 2 for an overview and Table S1 for a synopsis of relevant provisions). These product classifications form a generalized, overarching framework of harmonized rules applicable to all EU member states. At the national level, this can be expanded upon with more detailed legislation, especially in areas not (yet) included in EU legislative acts.[i] Enforcement and implementation of the framework relating to food and medicine involves coordination and collaboration between EU regulatory agencies, that is, the EMA and the EFSA, and national competent bodies.

3.1.1 | Nutritional therapy products regulated as food

For many nutritional therapy products, no authorized medicinal products exist and clinicians prescribe food-grade alternatives. Like all foods, these must firstly comply with General Food Law, which is primarily aimed at guaranteeing food safety.[25] To monitor food safety, the EU mainly relies on self-reporting by manufacturers, overseen by the EFSA as well as national authoritative bodies The EFSA also publishes guidelines to assist food manufacturers in complying with food safety regulations. On top of the General Food Law, two specific EU provisions regulate food supplements and foods for special medical purposes (FSMPs).[15,17]

Food supplements

Food supplements are regulated by the Food Supplement Directive (FSD), which defines food supplements as "nutrients" (specified as vitamins or minerals) or "other substances" (without additional specification).[15] Furthermore, the FSD outlines that the aim of food supplements is complementing the normal diet, they are available in dose form and are meant to be taken in small unit quantities. It should be noted that this definition does not align with the way nutritional therapy products are utilized in the treatment of IEMs, as their aim in this context is the correction of metabolic dysfunction and supra-

TABLE 1 Overview of terminology used to describe nutritional therapy products.

Product category[a]	Alternative terms (i.e., terms describing similar product category)	Description	Legislative basis
Food supplements	-	Concentrated sources of vitamins/minerals with a nutritional or physiological effect, in small-quantity dose form meant to supplement the normal diet	Yes (EU)[15,b]
	Dietary supplements	Same	Yes (US)[16,c]
	Nutritional supplements	Same	No
Food for special medical purposes (FSMPs)	-	Foods specifically manufactured for the (partial) feeding of patients who cannot metabolize certain foods or nutrients, to be used under medical supervision	Yes (EU)[17,d]
	Medical foods	Same	Yes (US)[18,e]
	Specialized food	Same	No
Medicinal product	-	A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.	Yes (EU)[19,f]
	Drug	Same	Yes (US)[20,g]
	Medication	Same	No
Nutritional therapy products[3]		Food supplements, FSMPs and other food-related products (for example single amino acids) used in the treatment of IEMs	No
	Nutraceutical[21] (nutri-pharmaceutical, nutra-pharmaceutical[22])	Combines the words "nutrition" and "pharmaceutical", to describe foods that provide medical benefits, including the treatment of disease.	No
	Functional food	Same	No

[a]The terminology used to describe categories in this review.
[b]Directive 2002/46/EC art 2(a,b).
[c]Dietary Supplement Health and Education Act of 1994 sect.3(a).
[d]Regulation (EU) No 609/2013 art 2(g).
[e]Orphan Drug Act of 1983 sect 5(b)(3).
[f]Directive 2001/83/EC art 2 para 1, 2.
[g]Federal Food, Drug, and Cosmetic Act sect 201(g).

physiological dosing is common. The compositional requirements for food supplements are limited to a list of permitted chemical formulations of vitamins and minerals.[15]

Furthermore, daily reference values and upper limits have been defined by EFSA guidelines for 27 vitamins and minerals.[29] Requirements can be more detailed at the national level, although these must be in line with existing EFSA guidelines.[30] Non-vitamin, non-mineral food supplements, such as single amino acids, lack additional guidelines. Therefore, they are only required to be safe for human consumption and labeled correctly under the general food safety provisions.[31]

Foods for special medical purposes

In the EU, FSMPs are included as a subcategory in the Regulation for Food for Special Groups, which defines FSMPs as foods specifically manufactured for the (partial) feeding of patients who cannot metabolize certain foods or nutrients.[17] This product category especially applies to amino acid mixtures that aim to (partially) substitute a patient's nutritional intake, such as the aforementioned Phe-free amino acid mixtures in the management of PKU.[8] FSMPs must be "suitable" and "appropriately satisfy the nutritional needs" of the intended recipient, in accordance with "generally accepted scientific data", but there is no agency actively monitoring this in the same way medications are

TABLE 2 Outline of European regulatory framework on food and medication.

	Food	Medication
Relevant legislative acts[a]	General food law regarding food safety,[25] Food Supplement Directive,[15] Food for Special Groups (including FSMPs)[17]	Community code for medicinal products,[19] Directive for medication, orphan medicinal products regulation (outlining incentives)[26]
Primary aim of regulations	Guaranteeing food safety	Guaranteeing safety, quality, efficacy and availability of medicinal products
Guidelines	EFSA guidelines assist manufacturers in adhering to regulations (national regulations required to respect these), non-obligatory GMP guidelines exist	Obligatory compliance with EU Good Manufacturing Practice (GMP) guidelines[27] for manufacturing of medicinal products and active substances used as starting materials, European Pharmacopoeia outlining official quality standards for specific medicines and their ingredients, ICH guidelines[28]
Authority	EFSA, national competent bodies	EMA, national competent bodies

[a]EU legal acts include regulations (directly applicable in all EU Member states) and directives (applicable only after transposition into national law).

monitored. Maximum levels for 13 vitamins and 15 minerals (for infants and adults) have been codified into law.[32] FSMPs are thus regulated more stringently than food supplements.

3.1.2 | Nutritional therapy products regulated as medication

A limited number of nutrients has a marketing authorization as medicinal products. Pyridoxine, for instance, is registered for the treatment of inborn errors of the vitamin B6 metabolism, including PDE-ALDH7A1, in most European countries.[33] Several other nutrients exist in the form of medicinal products, but are not formally registered for the treatment of an IEM. Intramuscular hydroxocobalamin, for example, is registered for the treatment of megaloblastic anemia, but is also prescribed to improve metabolic homeostasis in methylmalonic acidaemia (OMIM: # 251000).[33,34] These products must comply with the stringent provisions governing medicinal products, which dictate specific instructions regarding a product's composition, manufacturing, safety and availability. Requirements for authorized medicinal products are outlined in the Community code for medicinal products as well as in the EU Good Manufacturing Practice (GMP) guidelines.[19,27]

Before a medicinal product is allowed to enter the market, it must obtain a marketing authorization, which can be done at either the EU or the national level. Once market access has been granted, marketing authorization holders carry the responsibility for the availability of the product within the applicable market. To ensure that registered medicinal products are manufactured as standardized, high quality products, mandatory compliance with the EU-GMP guidelines and the European Pharmacopoeia is enforced.[27] To monitor medication safety after a product enters the market, the European Medicines Agency (EMA) and national authoritative bodies have so-called pharmacovigilance systems in place and safety data is reviewed in the dossier required for authorization.[35] One relevant exemption to the overarching legislation for medication is provided for pharmacy compounding, as pharmacists are permitted to prepare small-batch formulations for their own patients.[36]

3.1.3 | Nutritional therapy products as food or medication: who decides?

The responsibility for classifying a product as a medicinal product or as a food is placed with the manufacturer or importer and ultimately with the courts, which have to decide on the status of a product whenever asked to do so.[19,36–39] In order to manufacture and obtain a marketing authorization to sell a nutritional therapy product as medication, the product must either *function* or be *presented* as a medicinal product.[19ii] European case-law further dictates this should be interpreted restrictively, applying only to products with scientifically studied pharmacological effects.[39] The implications of categorization as a food supplement, FSMP or medicinal products are summarized in Figure 1.

3.2 | Challenges related to nutritional therapy in clinical practice

IEMs are routinely treated with food supplements or FSMPs, since the majority of nutritional therapy products

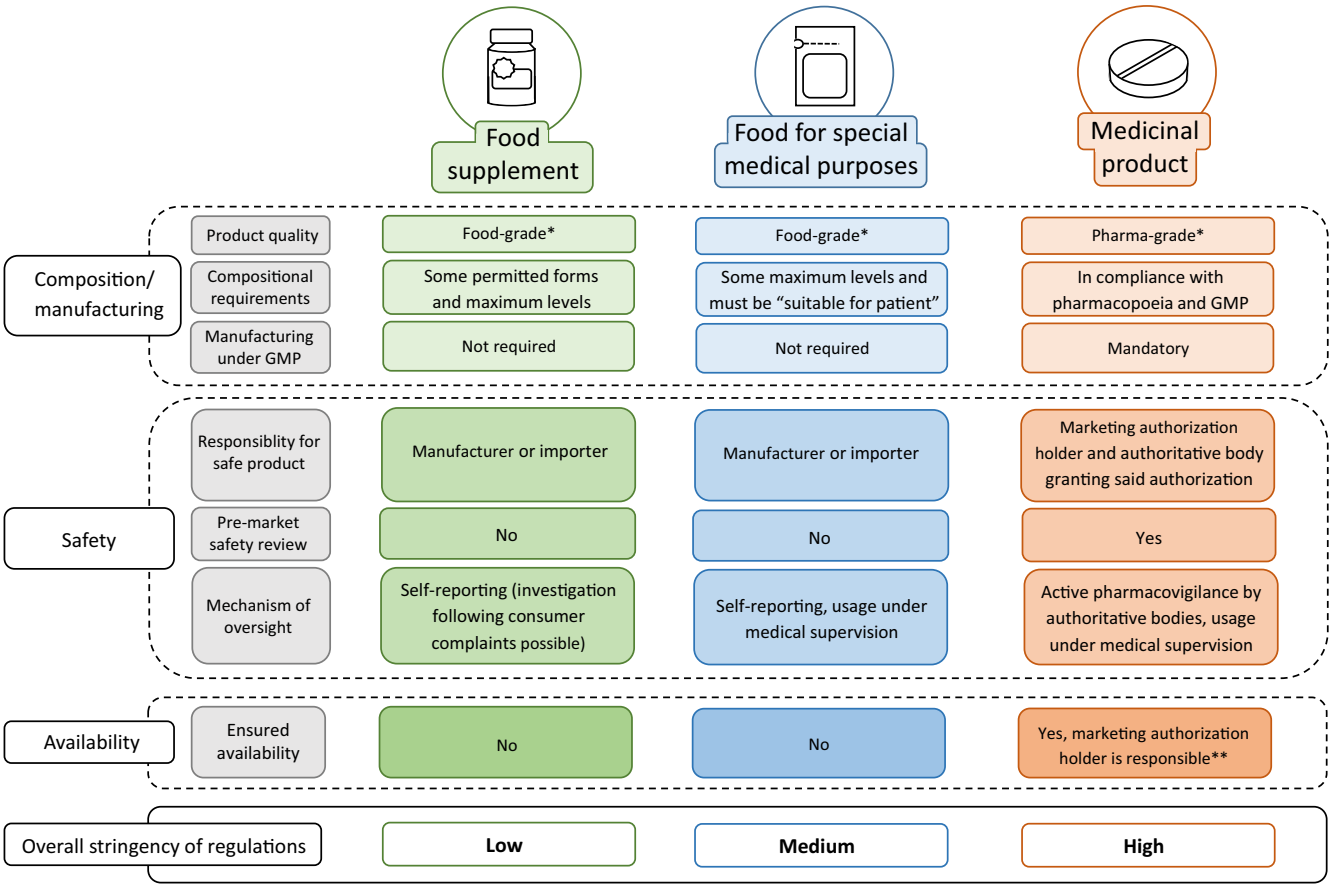

FIGURE 1 Relevant implications of regulatory frameworks for food supplements, FSMPs and medicinal products. *Food-grade and pharma-grade are non-legislative terms used to describe products manufactured in compliance with the respective food or medication regulatory frameworks. **Despite marketing authorization holder responsibility, availability issues can still occur.

do not exist as authorized medicinal products. Although food-grade products can be sufficient for some therapeutic purposes, there are uncertainties regarding their quality, safety and availability that complicate their use in the treatment of IEMs.

3.2.1 | Product quality and safety challenges

Product composition

As Figure 1 outlines, FSMPs and food supplements especially are subjected to far fewer compositional requirements than medication. Consequently, there is less certainty about dose accuracy, which can have a major impact on the efficacy of nutritional therapy and may have life-threatening consequences. A well-documented example is the treatment of pyridox(am)ine-5′-phosphate oxidase (PNPO) deficiency (OMIM: #610090), an ultra-rare inborn error of vitamin B6 metabolism presenting with neonatal seizures.[40] Oral, high-dosed pyridoxal-5′-phosphate (PLP, the active form of vitamin B6) can be used as the sole treatment to achieve and maintain seizure control in PNPO deficiency.[40,41] However, since no medicinal PLP product exists, patients are relegated to treatment with food supplements—despite inaccuracies of substantial differences between the concentration described and the PLP concentration actually present in the product found in PLP supplements.[9] PNPO deficient patients have suffered complications related to the insufficient quality of the food supplements, including seizures and PLP intoxication.[13]

In the US, where a similar legislative framework applies to nutritional therapy products[3] another case of extreme dose inaccuracy was reported for a food supplement concerning a newborn with carbamoyl phosphate synthetase I deficiency (CPS I, OMIM: # 237300), a urea cycle disorder.[12] This patient was stable on a low-protein enteral diet and continuous IV infusion of arginine hydrochloride. After replacing IV arginine by oral L-citrulline, there was an immediate steep rise in plasma ammonia level. Further investigation and laboratory testing of the product revealed that while the label stated "99.88% pure L-citrulline", the substance in fact did not contain any L-citrulline.[12]

Concerns regarding the effect of product composition on effective treatment also exist for FSMPs.

Micronutrient deficiencies in PKU patients have been linked to the bioavailability of these nutrients in FSMPs as well as suboptimal composition of these foods.[42–45] On the other end of the spectrum, excessive dosing of certain nutrients like zinc and folate in FSMPs aimed at PKU patients is worrisome too, especially when exceeding tolerable upper levels set out by the EFSA.[46,47] Excessive supplementation has also been reported in the treatment of organic acidurias, where FSMPs with disproportionately high levels of leucine have been scrutinized for inducing iatrogenic amino acid deficiencies.[48–51]

Third-party oversight

For FSMPs and food supplements used in the treatment of IEMs, pre-market assessment of their efficacy, weighed against potential adverse effects by an authoritative body is currently not required. Additionally, side effects associated with the use of these products are not routinely monitored and descriptions are often limited to case reports, if captured at all. This can result in insufficient monitoring of their potential occurrence and subsequent necessary precautions.

Third-party oversight is also not mandated in the dispensing of food-grade nutritional therapy products, since this is not reserved to pharmacies. This means these products can be acquired without a pharmacist' oversight and usage advice for their utilization in clinical treatment. Even if nutritional therapy products are distributed through a pharmacy, their legislative status as food can mean they are exempt from the controls required for dispensing prescription medicinal products. Additionally, knowledge of these products may be limited due to a lack of information resources for nutritional products. This has resulted in mix-ups in their dispensing by pharmacies and although the frequency of dispensing errors occurring remains unknown, one study into routes of dispensing these products reported a total of 12 errors experienced by nine patients who collected their prescriptions from pharmacies in a 9-month period.[52] The errors in this study did not result in hospital admissions, but similar errors have precipitated serious complications in patients with IEMs, including metabolic decompensation, hospitalization, feed intolerance and parental and patient distress.[52,53]

3.2.2 | Challenges in patient access

Availability

While authorized medicinal products have the responsibility for their guaranteed availability placed with the company holding their marketing authorization, food supplements and FSMPs lack such safeguards (see Figure 1). Production can be reduced or ceased at any time and the dependence of patients with an IEM on these products is thus concerning for both patients and clinicians. The reduced availability of higher-dosed PLP supplements in the Netherlands, for instance, precipitated many brand switches in the search for an acceptable alternative for PNPO deficient patients.[13]

Costs

Differences exist in patients expenditure on nutritional therapy products in EU countries, stemming from dissimilarities in the actual cost of these products, as well as the level of reimbursement.[54] In the Czech Republic, for instance, the economic burden for patients requiring amino acid mixtures for the management of IEMs is high.[55] For food supplements, reimbursement may be even more limited, with 30% of participants in a recent survey examining the medical needs of metabolic patients in Europe reporting that supplements and dietary integrators were not covered by insurance.[56] This is problematic, since costs can negatively influence dietary adherence and may therefore seriously impact health outcomes.[57,58]

Pharmaceutical enclosing

The absence of medicinal nutritional therapy products can result in a process that has been called the "enclosing" of these substances by private pharmaceutical companies.[59] Common nutritional therapy products can be repurposed as orphan medicinal products (OMPs). OMPs are medication for rare diseases, defined as a prevalence less than 5:10 000, a cut-off most IEMs meet.[26] OMPs are granted special incentives, including a 10-year market exclusivity.[26] Manufacturing of an OMP might alleviate unmet medical needs in nutritional therapy, but this does not guarantee improved patient access, especially since OMP's can be extremely expensive. National policies and reimbursement negotiations vary and therefore access to specific OMPs can differ between countries.[60,61]

4 | DISTINGUISHING FOOD FROM MEDICINAL PRODUCTS: AN EVALUATION FLOWCHART

As the previous sections illustrate, the efficacious treatment of IEMs can be improved by increased safeguarding of the quality, safety and patient access to nutritional therapy products. The research on this topic is limited and at present, no clear avenues for improvement have been proposed. It is our belief that the first step towards this goal is discerning if a nutritional therapy product could be categorized as a medicinal product within the

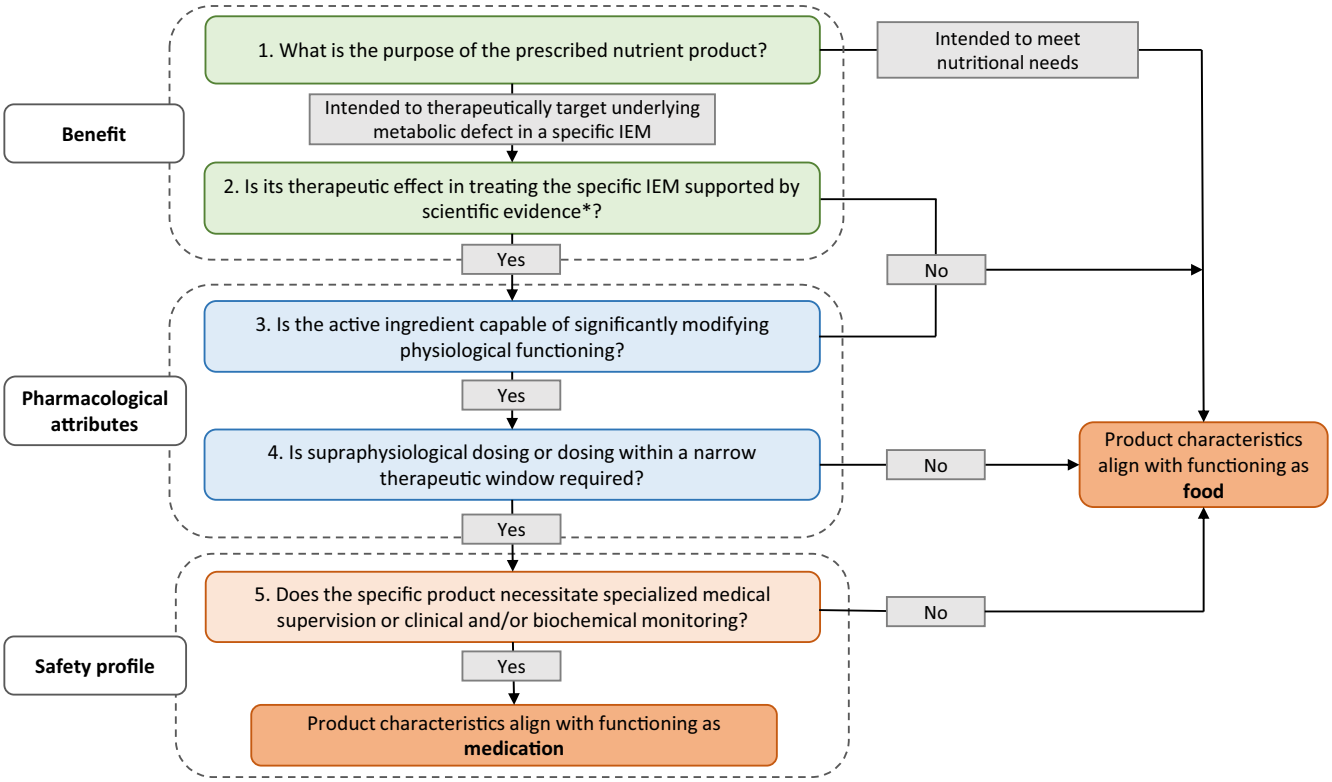

FIGURE 2 Proposed flowchart for distinguishing between food and medication-like functioning of nutritional therapy products. *Please note that this flowchart does not address the quality of scientific evidence supporting the therapeutic effect of the product. Nevertheless, it is important to acknowledge that that consideration of the level of evidence may be relevant and examined in potential subsequent stages, such as during an application for marketing authorization.

current regulatory framework. To this end, we designed a flowchart that facilitates making this distinction by reviewing the relevant functional characteristics of a specific product within the context of treating an IEM (see Figure 2). The flowchart assess a product's benefit by differentiating products prescribed with the purpose of treating an IEM, that is, targeting a specific metabolic defect or pathways in a specific disorder, from those aimed at meeting nutritional needs, as well as the scientific evidence for this distinction. This differentiation aligns with the separate categorizations for food supplements, FSMPs and medicinal products in the EU regulations, as well as relevant case-law.[15,17,19,36–39] Further deriving from this framework, a product's pharmacological attributes (ability to modify physiological functioning and dosage) and its safety profile (as expressed by supervision requirements) are reviewed.[36–39] In this manner, it is possible to establish if a product's functioning can be regarded as akin to a medicinal product to the extent that it could be considered as such.

If this is the case, there may be a justifiable need for an authorized medicinal alternative, as well as sufficient basis to support this argument within the EU regulatory framework. If, for instance, the features of PLP as a treatment for PNPO deficiency are evaluated, its benefit (administered to restore insufficient PLP concentration due to dysfunctional PNPO; scientific publications support its functioning as anticonvulsive monotherapy), the pharmacological attributes (suppresses convulsions by restoring PLP; prescribed in supra-physiological dosages of 30 mg/kg/day, far exceeding the age-dependent vitamin B6 limit of 5–25 mg/day per EFSA advice) as well as the safety profile (its anticonvulsive purpose and the potential for liver toxicity require clinical biochemical monitoring) all underline its functioning as medication and thereby the need for a registered medicinal form of PLP.[9,13,40,62] In other cases, a product might have some medicinal properties but can still be considered food and regulation as such should likely suffice. An example of a nutritional therapy product that does not meet the threshold for medication-like functioning would be Phe-free amino acid mixtures prescribed in PKU. These mixtures do not target but rather circumvent a metabolic defect (i.e., the patient's inability to metabolize phenylalanine) and although their stimulatory effect on protein synthesis does reduce phenylalanine levels, their primary purpose is to ensure patients meet their nutritional needs

(namely their protein requirement).[8] These mixtures thus align best with the definition set out for FMSPs.[17]

5 | DISCUSSION

Dietary management strategies are often the only available and critically important treatments for IEMs. Yet both the quality of and the access to the required nutritional therapy products can be limited, with sometimes life-threatening consequences.[9,12,13,53] The regulatory framework governing these products in the EU distinguishes between food supplements, FSMPs and medicinal products, with varying levels of oversight.[15,17,19] This directly impacts the treatment of IEMs, since treatment routinely includes the prescription of food supplements or FSMPs. For food supplements especially, concerns exist regarding their quality and the level of third-party oversight. Additionally, inadequate availability, costs and the risk of pharmaceutical enclosing jeopardize patient access to these products. Despite these challenges, clinicians and patients often have no other choice but using food grade products, since few nutritional therapy products are available as authorized medicinal products.

Addressing these concerns necessitates a comprehensive understanding of which nutritional therapy products effectively function as medicinal products and which serve primarily as food. To facilitate this differentiation, we propose here a systematic approach in the form of a flowchart to assess relevant treatment characteristics. These include a product's benefit, its pharmacological attributes and the safety profile. By utilizing the proposed flowchart, researchers and clinicians can analyze nutritional therapy products in a structured manner, enabling a clearer distinction between those that align with the functional definitions reserved for medicinal products and those functioning as food. If a product's functioning as a medicinal product can be substantiated—like the case of PLP in the treatment of PNPO deficiency—it is not only plausible but arguably even imperative to formally recognize and authorize these products as medication.[9,13]

The next hurdle, however, is realizing this. When a product's therapeutic features justify authorization, obtaining the required marketing authorization can be a lengthy and expensive process, even with the discounts available to OMPs. Another alternative might be the compounding of such substances by pharmacists, as is already done in some cases.[63] This route bypasses the intensive authorization process while still yielding pharmaceutical preparations, although they are regulated less stringently than authorized medicinal products. Perhaps specific (national) policies could even protect common and often compounded food-related substances with a well-established use in rare diseases like IEMs as so-called "pharmaceutical commons", safeguarding them from pharmaceutical enclosing.[59]

It is also important to acknowledge that while some nutritional therapy products fail to meet the threshold for functioning as medication, the current regulatory framework might still be insufficient to safeguard necessary product aspects. Amino-acid mixtures, for instance, are, in our opinion, usually rightly classified as food (for special medical purposes); as an integral part of management, however, their quality might still warrant more stringent monitoring and fairer reimbursement policies than those provided for FSMPs. Low-protein foods adhere to the regulatory definition of conventional foods even more closely, placing them beyond this review's scope. Even so, due to their significance to the dietary intervention in certain IEMs, it is noteworthy that patient access to these products can be impacted by similar disparities in reimbursement and availability.[64] In any case, discovering appropriate solutions for the challenges facing nutritional therapy products is imperative—for without them, patients and clinicians remain depended on prescribing unsuitably regulated products, despite long-standing quality and safety concerns and potential threats to patient access. Continuation of the current situation critically endangers the efficacious treatment of IEMs in clinical practice.

AUTHOR CONTRIBUTIONS

N. N. Stolwijk and C. E. M. Hollak conceptualized the review. N. N. Stolwijk collected the data, wrote the manuscript and created the tables and figures. A. M. Bosch and M. Langeveld helped conceptualize and refine Figure 2. A. M. Bosch, N. Bouwhuis, J. Häber, F.J. van Spronsen, C. van Karnebeek and M. Langeveld were involved in data interpretation. C. E. M. Hollak oversaw the general direction of the article and critically reviewed the manuscript. All authors reviewed, edited, and approved the manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

Outside of submitted work, M. Langeveld and C. E. M. Hollak report to be involved in pre-marketing studies with Genzyme, Protalix, and Idorsia. Financial arrangements are made through AMC Research BV. F. J. van

Spronsen has consulted for Applied Pharma Research, is involved in studies with BioMarin and Nutricia and has served on advisory boards for Nutricia and Arla Foods International. C. van Karnebeek serves as PI for clinical trials sponsored by Vitaflo. N. N. Stolwijk, A. M. Bosch, N. Bouwhuis, J. Häber and C. E. M. Hollak have no conflicts of interest to disclose.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, C. E. M. Hollak, upon reasonable request.

ETHICS APPROVAL

As this is a narrative review, ethics board review was not required by our institution.

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ENDNOTES

[i] EU legal acts include regulations (directly applicable in all EU Member states) and directives (applicable only after transposition into national law).

[ii] Directive 2002/46/EC art 2(a,b).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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