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ARTICLE

Could Pharmacopoeial Reference Standards Serve as a Platform to Enhance the Quality and Safety Control Systems of European Food Supplement Businesses?

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Abstract

Previous research has highlighted several quality-related concerns regarding food supplements available on the market, which compromise their safe consumption. This study evaluates whether the adoption of the European Pharmacopoeia (Ph. Eur.) as a framework for improving supplement quality could enhance quality and safety control practices. The findings are derived from a comparative legal analysis of the Canadian and U.S. legal systems. The results suggest that its application in the Canadian market may serve as an illustration of the Brussels effect in practice. Simultaneously, the European Food Safety Authority (EFSA) already encourages EU Food Business Operators (FBOs) to utilise the Ph. Eur. when assessing food supplement ingredients. Nevertheless, careful consideration is necessary regarding the extent of regulatory compliance by FBOs to mitigate potential conflicts with existing EU legislation and to prevent delays in innovative developments within the supplement market.

Keywords: food law; food quality; food safety; food supplements; pharmacopoeia

I. Introduction

Even though they may often resemble pharmaceutical products in appearance, under European Union (EU) law food supplements are classified as foodstuffs.[1] While legally defined as food products intended to supplement the normal diet, research shows that consumers often perceive these products as a low-risk means of maintaining or enhancing their health, rather than merely as sources of nutritional value.[2] This divergence gives rise to questions as to whether the existing regulatory framework is suitably designed to ensure effective oversight of the food supplement market,

[1] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements (2002) OJ L 183/51. Member States, however, are free to categorise food supplements as pharmaceutical products in their country in case they meet the respective criteria of EU law.

[2] V Catalani and others, "The Market of Sport Supplement in the Digital Era: A Netnographic Analysis of Perceived Risks, Side-effects and Other Safety Issues" (2021) 1 Emerging Trends in Drugs, Addictions, and Health 100014.

particularly with respect to market surveillance.[3] Given the credence nature of these products, consumers cannot independently ascertain whether food supplements possess the claimed nutritional and health-related properties, nor whether they are affected by potential deficiencies. One way of dealing with such shortcomings may be the introduction of more robust market surveillance mechanisms with the aim of empowering consumers to make informed choices and to realise the free movement provisions under EU primary law.

In EU food law, food quality and safety are distinct but interdependent concepts. Its horizontal legal framework constitutes a risk-based regulatory system, which defines the conditions for food safety under Article 14 of Regulation (EC) No 178/2002 (General Food Law), whereas the marketing of food which is injurious to human health or otherwise unfit for consumption is prohibited.[4] The General Food Law imposes an obligation on food business operators (FBOs) to ensure and verify that their products comply with the requirements of food law.[5] This regulatory framework applies by definition also to food supplements.[6] Several European food safety acts also relevant to food supplements, such as Regulation (EC) No 852/2004 (Food Hygiene Regulation), Regulation (EC) No 396/2005 (Food Pesticides Regulation), and Commission Regulation (EU) 2023/915 (Food Contamination Regulation), establish specific manufacturing standards and permissible limits.[7]

The term of food quality is not uniformly defined by EU law, instead it is indirectly addressed through sectoral legislation, such as Directive 2002/46/EC (Food Supplements Directive), consumer information rules, or voluntary quality schemes. However, as quality defects may evolve into relevant safety aspects, such as contaminations or compositional inconsistency, establishing food quality serves a pivotal role in maintaining food safety and food supply chain integrity.

Implementing an effective quality control system is critical for performing robust product analyses and for the periodic assessment of results to identify and address quality defects, such as galenic inconsistencies or contamination.[8] However, the EU's legal framework does not prescribe detailed quality control measures specific to the food supplement sector, leaving the development and implementation of such measures to individual FBOs. Since regulatory authorities typically evaluate the efficacy of quality control methods during inspections, this dynamic may, willingly or unwillingly, allow lower-quality products to enter the market.[9] This significance of this dynamic is further underscored by FBOs facing significant methodological challenges in developing effective quality control methods, particularly for complex products such as multi-herbal ingredient supplements.

Additionally, the range of enterprise sizes within the EU supplement market, from small and medium-sized enterprises (SMEs) to globally operating corporations, results in

[3] R Warda, K Purnhagen and M Molitorisová, "Has Mutual Recognition in the EU Failed?—A Legal-Empirical Analysis on the Example of Food Supplements Containing Botanicals and Other Bioactive Substances" (2024) 47(3) Journal of Consumer Policy 425.

[4] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (2002) OJ L 31/1.

[5] Ibid.

[6] Directive 2002/46/EC (n 1).

[7] A Vettorazzi and others, "European Regulatory Framework and Safety Assessment of Food-Related Bioactive Compounds" (2020) 12(3) Nutrients 613.

[8] R Owusu-Apenten and E Vieira, "Food Safety Management, GMP & HACCP" in R Owusu-Apenten and ER Vieira (eds), *Elementary Food Science* (Berlin, Springer International Publishing 2023).

[9] CAF Oliveira and others, "Food Safety: Good Manufacturing Practices (GMP), Sanitation Standard Operating Procedures (SSOP), Hazard Analysis and Critical Control Point (HACCP)" in J Barros-Velázquez (ed), *Antimicrobial Food Packaging* (Amsterdam, Elsevier 2016).

considerable disparities in financial and human resources. Although product quality is regarded as a key competitive factor among FBOs, the substantial effort required to develop and implement adequate quality control measures may place SMEs at a disadvantage compared to larger companies.[10] These variations affect FBOs' ability to establish robust quality control systems, whether independently or through third-party contractors.[11,12] Addressing the resource allocation discrepancies between SMEs and larger enterprises in ensuring effective quality control could enhance consumer access to high-quality supplements across the EU, benefiting both public health and informed decision making.[13]

The United States of America (USA) and Canada have adopted a more nuanced approach to regulating food supplements by explicitly considering their pharmaceutical properties. Both countries have updated their pharmacopoeial compendia for supplements, aiming to enhance their quality and safety. Building on these developments, this article explores whether utilising the European Pharmacopoeia (Ph. Eur.) as a platform for improving food supplement quality could strengthen quality control practices among FBOs and regulatory authorities.

This study seeks to examine the potential benefits and risks associated with introducing pharmacopoeial reference standards in the EU supplement market by comparing the EU's legal framework, designed to support the production and sale of high-quality supplement products, with alternative regulatory approaches.

1. State of the art of the EU food supplements market regarding safety and quality control

The EU food supplements market has expanded from approximately €26 billion to nearly €32 billion between 2018 and 2020 and is projected to reach €48 billion by 2026.[14] This rapid growth highlights an increasing relevance of enhancing consumer access to safe and high-quality supplements.

Previous research has identified a range of persisting quality defects compromising the safe consumption of food supplements in the EU, with contamination being a primary concern. Among the most significant toxicological risks are the presence of heavy metals such as lead, arsenic, and chromium.[15,16] Pesticide residues and metabolites have also been detected in botanical food supplements, likely originating from the agricultural treatment of plants and raw materials.[17] Notably, substances such as piperonyl butoxide, cyromazine and chlorate, whose use is either strictly limited or prohibited in the EU due to safety

[10] NZ Noor Hasnan and others, "Analysis of the Most Frequent Nonconformance Aspects Related to Good Manufacturing Practices (GMP) Among Small and Medium Enterprises (SMEs) in the Food Industry and Their Main Factors" (2022) 141 Food Control 109205.

[11] K Sato, K Kodama and S Sengoku, "Optimizing the Relationship Between Regulation and Innovation in Dietary Supplements: A Case Study of Food with Function Claims in Japan" (2023) 15(2) Nutrients 476.

[12] N Hasnan and others (n 10).

[13] IB Murimi-Worstell and others, "Association Between US Pharmacopeia (USP) Monograph Standards, Generic Entry and Prescription Drug Costs" (2019) 14(11) PloS One e0225109.

[14] Statista, "Value of the Dietary Supplements Market Worldwide in 2018 and 2020 With a Forecast to 2026, by Region (in Billion U.S. dollars)" (20 September 2021) <https://www.statista.com/statistics/1264459/region-global-dietary-supplement-market/> (accessed 8 November 2024).

[15] P Rzymski and others, "Essential and Toxic Elements in Commercial Microalgal Food Supplements" (2019) 31(6) Journal of Applied Phycology 3567.

[16] B Poniedziałek and others, "Monitoring of Essential and Toxic Elements in Multi-Ingredient Food Supplements Produced in European Union" (2018) 13(1) Journal of Consumer Protection and Food Safety 41.

[17] JG Costa and others, "Contaminants: A Dark Side of Food Supplements?" (2019) 53(sup1) Free Radical Research 1113.

concerns, have been found.[18,19]Microbiological contamination poses an additional threat, with potentially human-pathogenic bacteria such as *Enterobacter* spp., *Salmonella* spp., and *Escherichia coli* confirmed in food supplements.[20] Identification of harmful mycotoxins produced by fungi, including ochratoxins, aflatoxins, and fumonisins, further exacerbate microbiological risks.[21] Moreover, frequent consumption of herbal supplements containing naturally occurring toxic compounds such as hepatotoxic pyrrolizidine alkaloids may lead to acute or short-term toxicity, as highlighted by the European Food Safety Agency (EFSA) in 2016.[22]

While the contamination issues documented in research may fall within the range of permitted daily doses and may not cause immediate toxic symptoms, the potential for frequent exposure to toxic substances and associated long-term health risks must be taken into account.[23] Beyond contamination, research has highlighted significant variability in ingredient quantities across supplements containing similar components, illustrating the broader problem of inconsistent galenic quality in EU food supplements.[24] Reflecting the prevalence of quality defects and their impact on product safety, food supplements have consistently ranked among the most frequently reported product categories in the European Commission's (EC) annual Alert and Cooperation Network (ACN) reports, which track food product-related issues in the EU.[25,26]

The increasing complexity and diversity of food supplements' compositions present a major challenge for developing laboratory methods capable of verifying the purity, identity, and quality of new ingredients or individual substances in mixtures.[27] Accurate identification and labelling of ingredients are especially critical for botanical supplements due to their potential toxicological impacts.[28,29] However, developing effective quality control measures for singular ingredients within complex botanical mixtures is widely

[18] RD Alves and others, "Fast Determination of Four Polar Contaminants in Soy Nutraceutical Products by Liquid Chromatography Coupled to Tandem Mass Spectrometry" (2016) 408(28) Analytical and Bioanalytical Chemistry 8089.

[19] Y Chen and others, "Determination of Multiresidue Pesticides in Botanical Dietary Supplements Using Gas Chromatography-Triple-Quadrupole Mass Spectrometry (GC-MS/MS)" (2016) 64(31) Journal of Agricultural and Food Chemistry 6125.

[20] M Ratajczak and others, "Quality of Dietary Supplements Containing Plant-Derived Ingredients Reconsidered by Microbiological Approach" (2020) 17(18) International Journal of Environmental Research and Public Health 6837.

[21] Ibid.

[22] HK Knutsen and others, "Risks for Human Health Related to the Presence of Pyrrolizidine Alkaloids in Honey, Tea, Herbal Infusions and Food Supplements" (2017) 15(7) EFS2 e04908.

[23] Poniedziałek and others (n 16).

[24] A Stellavato and others, "Comparative Analyses of Pharmaceuticals or Food Supplements Containing Chondroitin Sulfate: Are Their Bioactivities Equivalent?" (2019) 36(11) Advances in Therapy 3221.

[25] European Commission, "Alert and Cooperation Network: 2022 Annual Report" (2022) <https://food.ec.europa.eu/document/download/499ffcf1-6c99-43ec-8905-5ff3e812eeb2_en?filename=acn_annual-report_2022.pdf> (accessed 11 November 2024).

[26] European Commission, "Alert and Cooperation Network: 2023 Annual Report" (2023) <https://food.ec.europa.eu/document/download/911d49f2-b3ef-4752-8ea3-5f20dbbe9945_en?filename=acn_annual-report_2023.pdf> (accessed 11 November 2024).

[27] G Indrayanto, "Regulation and Standardization of Herbal drugs: Current Status, Limitation, Challenge's and Future Prospective" (2024) 49 Profiles of Drug Substances, Excipients, and Related Methodology 153.

[28] AR Bilia and MDC Costa, "Medicinal Plants and Their Preparations in the European Market: Why Has the Harmonization Failed? The Cases of St. John's Wort, Valerian, Ginkgo, Ginseng, and Green Tea" (2021) 81 Phytomedicine: International Journal of Phytotherapy and Phytopharmacology 153421.

[29] H You and others, "Analytical Strategies to Determine the Labelling Accuracy and Economically-Motivated Adulteration of 'Natural' Dietary Supplements in the Marketplace: Turmeric Case Study" (2022) 370 Food Chemistry 131007.

recognised as a difficult task.[30,31] Furthermore, these quality control measures are often not publicly disclosed, as they remain proprietary to FBOs or third-party contractors, limiting transparency and collaboration in addressing these challenges.[32]

2. Consideration of pharmacopoeias as a remedy?

The current regulatory framework for food supplements in the EU places primary responsibility on FBOs, with a more limited role for competent authorities, to design and implement appropriate production and quality control procedures.[33] In contrast, jurisdictions outside the EU have adopted an alternative approach to enhancing the quality and safety of food supplements by providing the industry with scientifically validated production and quality control standards through pharmacopoeial codification.[34] In the USA, following debates over the regulatory status of certain botanical supplements and the subsequent enactment of the Dietary Supplements Health and Education Act (DSHEA) in 1994, the United States Pharmacopoeia (USP) was revised to incorporate supplement ingredients and preparations.[35] Additionally, the American Herbal Pharmacopoeia (AHP), which specialises in botanical supplements and ingredients, is accessible to supplement manufacturers.[36]

In Canada, food supplements have been regulated as natural health products (NHPs), a category of over-the-counter (OTC) drugs, since 2004.[37] However, there is no specific Canadian pharmacopoeia dedicated to natural health products.[38] Instead, authorities actively encourage FBOs to utilise validated production and laboratory quality control methods outlined in recognised pharmacopoeias, such as the Ph. Eur. or the USP.[39,40]

Traditionally associated with the pharmaceutical industry, pharmacopoeias constitute public collections of monographs containing standardised guidelines for defining, identifying, preparing, and storing ingredients, raw materials, and formulations. They also include suitable methods for determining the quantity, purity, and quality of listed ingredients or galenic preparations.[41] With contributions from stakeholders, including academics, regulatory authorities, and industry representatives, the development of pharmacopoeial monographs often achieves a high level of methodological validation.[42] In this context, the Ph. Eur. has long been established as a common reference standard for

[30] Indrayanto (n 27).

[31] H Wang and others, "Advancing Herbal Medicine: Enhancing Product Quality and Safety Through Robust Quality Control Practices" (2023) 14 Frontiers in Pharmacology 1265178.

[32] N Sarma and others, "Pharmacopeial Standards for the Quality Control of Botanical Dietary Supplements in the United States" (2023) 20(3) Journal of Dietary Supplements 485.

[33] KP Purnhagen and A Molitorisová, "Public and Private Enforcement in European Union Food Law" (2022) 13(3) European Journal of Risk Regulation 464.

[34] Sarma and others (n 32).

[35] DD O'Dwyer and S Vegiraju, "Navigating the Maze of Dietary Supplements" (2020) 35(3) Topics in Clinical Nutrition 248.

[36] American Herbal Pharmacopoeia, "About AHP Monographs" <https://herbal-ahp.org/about-ahp-monographs/> (accessed 22 January 2025).

[37] Natural Health Products Regulations, SOR 2003/196 (Can, 2003)

[38] Natural and Non-prescription Health Products Directorate, "Compendium of Monographs: Version 3.0" (13 June 2014) <https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/consultation/natur/2013-08-compendium-eng.pdf> (accessed 12 August 2024).

[39] Natural and Non-prescription Health Products Directorate, "Quality of Natural Health Products Guide" (1 May 2015) <https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodnatur/legislation/docs/eq-paq-eng.pdf> (accessed 12 August 2024).

[40] Sarma and others (n 32).

[41] O'Dwyer and Vegiraju (n 35).

[42] Sarma and others (n 32).

quality assurance programs across the European pharmaceutical market.[43] Given the challenges FBOs face in implementing effective quality control, pharmacopoeial standards applicable to supplements could offer a low-threshold solution by providing uniform, validated reference standards for FBOs in the EU.

II. Methodology

Through employing the functional method of comparative law, this study will examine the potential of the Ph. Eur. to serve as a platform for accelerating the development of quality control methods within the EU food supplement sector using the regulatory frameworks of the USA and Canada as case studies. The USA and Canada were selected as case studies as they already integrated pharmacopoeial standards into their regulatory systems, albeit to varying degrees, providing a broader perspective on the application of such standards in supplement regulation.[44] Moreover, the United States hosts the world's largest supplement market, whereas Canada has adopted a distinct regulatory approach to supplements. As EU food law must balance progressing the EU's internal market freedoms with ensuring a high level of consumer protection, this study also examines the legally binding nature of pharmacopoeias within these regulatory frameworks.[45,46]

The functional method of comparative law provides an effective approach for identifying similarities and differences between legal frameworks governing a specific sector across different jurisdictions.[47] As described by previous research, comparative law can provide deep understanding and accelerate improvements of a legal system.[48] The functional method does not solely investigate the theoretical background of the studied legal frameworks provided by comprehensive law texts.[49] Instead, it also considers the effects created by these frameworks, thereby investigating different approaches to dealing with a comparable socio-legal problem.[50] Although there is no uniform definition of conducting functional legal comparison, it has been recognised as a suitable research method in the context of European law development.[51] In this study, we first examined and compared the corresponding legal frameworks defining and regulating the quality of food supplements in the observed countries. Second, we comparatively assessed the relevance of pharmacopoeial standards within the respective supplement markets. European legal texts were retrieved from N-Lex, US–American legal texts from the Federal Register. Canadian legislation was retrieved from the public Justice Laws Website maintained by the Canadian Department of Justice. To enhance the context of the studied legal texts, we included relevant grey literature, such as institutional statements, in the functional comparison.[52]

[43] AS Bouin and M Wierer, "Quality Standards of the European Pharmacopoeia" (2014) 158 Pt B Journal of Ethnopharmacology 454.

[44] Sarma and others (n 32).

[45] F Ronchetti, L Springer and KP Purnhagen, "Pre-Market Authorisation" in F Ronchetti, L Springer and KP Purnhagen (eds), *The Regulatory Landscape in the EU for Dairy Products Derived from Precision Fermentation* (Berlin, Springer Nature Switzerland 2024)

[46] Purnhagen and Molitorisová (n 33).

[47] M van Hoecke, "Methodology of Comparative Legal Research" (2015) Law and Method 1–35.

[48] Ibid.

[49] R Michaels, "The Functional Method of Comparative Law" in M Reimann, R Zimmermann and R Michaels (eds), *The Oxford Handbook of Comparative Law* (Oxford, Oxford University Press 2006).

[50] Ibid.

[51] J Husa, "Methodology of Comparative Law Today: From Paradoxes to Flexibility?" (2006) 58(4) Revue internationale de droit comparé 1095.

[52] van Hoecke (n 47).

The comparison between the European Roman law-based legal culture against the Anglo-Saxon legal cultures of the USA and Canada is not subject of this research as the assessment of different legal cultures primarily focuses on broad societal patterns and would exceed the scope of this study.[53,54]

III. Results

1. Food supplement quality and safety framework conditions

a. Classification: Food or medicine

In the EU, supplements are regulated as foodstuff intended to supplement the regular diet with concentrates of vitamins, minerals and other micronutrients such as botanicals, amino acids, and other bioactive substances via the Food Supplements Directive.[55] Food supplements must also be marketed in pharmaceutical-like single-dosed forms intended for oral ingestion, such as capsules, tablets, powders or liquids.[56]

In the USA, the Federal Food, Drug and Cosmetics Act (FD&C Act) stipulates comprehensive legal framework conditions for several product categories derived from the food and pharmaceuticals sector, defining basic terms and responsibilities.[57] In 1994, the FD&C Act was amended by the Supplements Act DSHEA.[58] Similarly to EU legislation, DSHEA Article 3 (21 United States Code (U.S.C.) Article 321(ff)) defines food supplements as foodstuff intended to supplement the diet, containing minerals, vitamins, botanicals, amino acids or other dietary ingredients and does not include a substance considered as a drug, antibiotic, biological or a substance under clinical investigation.[59]

In Canada, food supplements are categorised as NHPs, a type of OTC self-care products containing naturally occurring substances designed for personal health maintenance.[60] Since 2004, around 120,000 products have been licensed, of which around half have been placed on the Canadian market.[61] Substantiated in a generally assumed level of risk derived from their consumption, although lesser than other pharmaceutical preparations, the corresponding regulatory framework provided by the Natural Health Products Regulation (NHPR) was adopted in 2004.[62] NHPR Article 1 defines NHPs as preparations containing Schedule 1 ingredients, meaning botanicals or their parts, algae, bacteria, fungi, animal materials or extracts and isolates derived from them.[63] NHPR Schedule 1 lists minerals, probiotics, enzymes, and certain vitamins as permitted ingredients.[64] Homoeopathic and traditional medicines, such as traditional Chinese medicine or ayurvedic medicines, and

[53] D Nelken, "Comparative Legal Research and Legal Culture: Facts, Approaches, and Values" (2016) 12(1) Annual Review of Law and Social Science 45.

[54] J Ivančík, "Roman Principles – Foundations of the European Legal Culture and Their Position in the Changing World" (2021) Vilnius University Open Series 58.

[55] Directive 2002/46/EC (n 1).

[56] Ibid.

[57] JA Brinckmann and others, "25 Years of DSHEA: Impact on Supply, Conservation and Sustainability, GACPs and Regulatory Compliance of Botanical Ingredients" in Á Máthé (ed), *Medicinal and Aromatic Plants of North America* (Berlin, Springer International Publishing 2020).

[58] "Dietary Supplement Health and Education Act of 1994, Pub L No 103-417, 108 Stat 4325 (US 1994)."

[59] Ibid.

[60] Health Canada, "Self-Care Products and Health Canada" (30 January 2017) <https://www.canada.ca/content/dam/hc-sc/documents/services/publications/drugs-health-products/fs-eng.pdf> (accessed 12 August 2024).

[61] Health Canada, "Proposed Fees for Natural Health Products (for Consultation)" (1 May 2023) <https://www.canada.ca/content/dam/hc-sc/documents/programs/consultation-proposed-fees-natural-health-products/overview/overview.pdf> (accessed 11 November 2024).

[62] Natural Health Products Regulations SOR 2003/196 (n 37).

[63] Ibid.

[64] Ibid.

some cosmetics, such as certain sunscreens or toothpastes, also fall in the category of NHPs.[65] As of 2023, following the enactment of the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law), the definition of therapeutic products in the Canadian Food and Drug Act (F&D Act) was revised to include NHPs.[66]

b. Baseline prerequisites for lawful market access

The eligibility of food supplements being placed on the market in the EU is generally regulated by the General Food Law and the Food Supplements Directive, stipulating that all foodstuff must be safe for human consumption, for which the FBO is responsible, and cannot be a medicinal product, cosmetic or medical device.[67,68] In the USA, by stating that food is considered adulterated if it is injurious to human health, FD&C Act Section 402(a)(1) (21 U.S.C. Article 342(a)(1)) also places the responsibility of ensuring food safety upon the FBO.[69] Section 402(g)(1) (21 U.S.C. Article 342(g)(1)) further requires FBO to manufacture their products in accordance with the applicable Good Manufacturing Practices (GMP) regulations.[70] DSHEA Article 4 (21 U.S.C. Article 343) requires supplements to be safe for consumption.[71] However, it places the burden of proof that a product or ingredient is unsafe for it being considered injurious upon the responsible authority, meaning the Food and Drug Administration (FDA).[72]

Although NHPs are considered therapeutic products, the Canadian F&D Act only applies to them if specifically mentioned, as the NHPR is the primary legal act providing framework conditions.[73] However, the F&D Act stipulates that therapeutic products and foodstuffs must be safe for humans to consume (compare Section B.01.001, B.01.002., and C.01.016).

c. Technical regulations

While not directly aimed at supplements, horizontal technical specifications laid down in EU legislation concerning food quality and safety also apply to supplements as they fall under the definition of foodstuff.[74] Commission Regulation (EU) 2023/915 specifies maximum levels for food contaminants such as heavy metals, mycotoxins, pyrrolizidine alkaloids, polycyclic aromatic hydrocarbons (PAHs), dioxins or polychlorinated biphenyls (PCBs).[75] Regulation (EC) No 396/2005 further regulates maximum pesticide residue levels,

[65] Ibid.

[66] Health Canada, "Guide to Authorities Under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)" (1 August 2023) <https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/medical-devices/application-information/guidance-documents/clinical-evidence-requirements-medical-devices/guide-authorities-protecting-canadians-unsafe-drugs-act-vanessas-law-eng.pdf> (accessed 11 November 2024).

[67] Regulation (EC) No 178/2002 (n 4).

[68] E Breitweg-Lehmann, B Liebscher and C Bendadani, "Food Supplements: Definition and Classification" in FJ Hock and MR Gralinski (eds), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology* (Berlin, Springer International Publishing 2020).

[69] Federal Food, Drug, and Cosmetics Act, Pub L No 75-717, 52 Stat 1040 (US, 1938).

[70] Ibid.

[71] (n 58).

[72] Ibid.

[73] Natural Health Products Regulations SOR 2003/196 (n 37).

[74] P Noble, "Nahrungsergänzungsmittel: Rechtliche Grundlagen, Abgrenzung zu Arzneimitteln, sonstige Fragestellungen" [Food Supplements: Legal Foundations, Distinction from Medicinal Products, Other Issues] (2017) 60(3) Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 260.

[75] Commission Regulation (EU) 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006 (2023) OJ L 119/103.

while Regulation (EC) No 2073/2005 specifies microbiological criteria for foodstuff.[76,77] General requirements concerning product labelling, allergen declarations and advertisement claims are laid down by Regulation (EU) No 1169/2011 (Food Information Regulation) and Regulation (EC) No 1924/2006 (Health Claims Regulation).

Pursuant to Regulation (EC) No 1925/2006, the general use of ingredients or substances in food may be prohibited or limited in the EU if placed in the annexes of the regulation, such as ephedra or red yeast rice extracts.[78] Positive Union lists on ingredients approved for use in supplements exist only for vitamins and minerals, which are placed in the annexes of the Food Supplements Directive.[79] The creation of a list of approved ingredients other than nutrients, namely botanicals or other bioactive substances, was abolished by the EC in 2008.[80] Instead, it was anticipated that the principle of mutual recognition, where a product lawfully sold in a Member State cannot be restricted from entering the market in another Member State, would contribute to harmonising this supplement category.[81] As this particular mode of governance has not been widely established in the supplement sector, the use of botanicals in the EU remains mostly regulated at the national level.[82] While the applicable legal framework sets technical conditions that food supplement production has to meet, it remains the responsibility of the FBO to develop quality control methods suitable for process monitoring.[83] Since no uniform codex containing validated methods is available, FBOs must develop and implement these themselves or commission a third-party contractor.[84] The appropriateness of the implemented measures is regularly inspected by food safety authorities, as the assessment of production and quality control systems is mandated by Article 9(1) of the Official Controls Regulation (Regulation (EU) 2017/625).[85]

Contrary, the quality of food supplements on the US market is further regulated by Chapter I, Subchapter B, Part 111 of Title 21 of the Code of Federal Regulation (21 CFR 111), which codifies current GMP (cGMP) rules applicable to manufacturing, packaging, labelling, and holding operations.[86] It contains detailed requirements that FBOs must meet regarding personnel and staff training, documentation, sanitary conditions, facility specifications and equipment.[87] Subpart E specifically mandates steps quality control systems should incorporate, emphasising the need for scientifically valid methods to continuously ensure defined identity, purity, composition and contamination limits.[88]

[76] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC (2005) OJ L 70/1.

[77] Commission Regulation (EC) No 2073/2005 of 15 November 2005 on microbiological criteria for foodstuffs (2005) OJ L 338/1.

[78] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods (2006) OJ L 404/26.

[79] Directive 2002/46/EC (n 1).

[80] European Commission, "Report from the Commission to the Council and the European Parliament on the use of substances other than vitamins and minerals in food supplements" (2008) COM(2008) 824.

[81] P van Cleynenbreugel, "Maximum Vitamin Amounts in Food Supplements: Towards Science-Based and Streamlined EU Mutual Recognition and Risk Assessment Procedures?" (2018) 9(1) European Journal of Risk Regulation 162.

[82] Ibid.

[83] Regulation (EC) No 178/2002 (n 4).

[84] Sarma and others (n 32).

[85] Regulation (EU) 2017/625 of the European Parliament and of the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products (2017) OJ L 95/1.

[86] 21 CFR 111 - Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling or Holding Operations for Dietary Supplements (US, 2025).

[87] Ibid.

[88] Ibid.

However, manufacturers must only implement measures to identify reasonably expected contaminations and may rely on quality certificates provided by suppliers or third parties.[89]

In Canada, the NHPR sets out a comprehensive framework governing the manufacturing, distribution and sale of NHPs. cGMP requirements are laid down in Part 3, and Article 43(1) makes compliance with them mandatory for selling, manufacturing and distribution. While cGMP requirements are more generally described, stipulating the need for business operators to implement sufficient measures to assess purity, identity, quantity and potency, describe testing methods and define their tolerance levels, emphasis is placed upon the responsibility of quality assurance staff Article 47 requires staff to be qualified for functional roles through sufficient training, education, or experience. Article 51 requires businesses to employ a trained quality assurance person responsible for approving every specification, material, method, procedure or activity before manufacturing and selling NHPs. To assist manufacturers in their legal obligations, the Natural and Non-prescription Health Products Directorate (NNHPD) has published a GMP guidance document, laying down specific steps ranging from sanitary conditions and formulation of standard operating procedures to effectively performing quality assurance activities.[90]

d. The role of food safety authorities

EFSA, on behalf of the EC, is the EU's authority responsible for safety assessments of food ingredients and providing guidance for FBOs. Following the adoption of the Food Supplements Directive, EFSA developed the list of minerals and vitamins and their chemical forms permitted for use in supplements.[91] Additionally, in the absence of respective legal statutes, EFSA published an overview of tolerable upper intake levels for nutrients.[92] Per Regulation (EC) No 1925/2006, EFSA carried out safety assessments for substances for which safety concerns were raised by Member States or the EC and subsequently banned or restricted, such as monacolins, ephedra or yohimbe.[93] However, following a decentralised approach, enforcing compliance of FBOs with EU food law to ensure safety and quality through inspections or sanctions remains the responsibility of national competent authorities.[94]

Health Canada, being the Canadian Ministry of Health, and its subordinate NNHPD are the responsible authorities for regulating the use and sale of NHPs.[95] Via the introduction of Vanessa's Law, Health Canada is entitled to order recalls, enclose confidential business information, or mandate healthcare institutions to report adverse reactions.[96] The act aims to strengthen regulatory oversight of NHPs in response to an audit by the Commissioner of the Environment and Sustainable Development in 2021.[97,98] Its report identified, among other issues, an inability of Health Canada to comprehensively enforce

[89] Ibid.

[90] Natural and Non-prescription Health Products Directorate, "Good Manufacturing Practices Guidance Document: Version 3.0" (11 June 2014) <https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/consultation/natur/gmp-bpf-eng.pdf> (accessed 12 August 2024).

[91] Directive 2002/46/EC (n 1).

[92] D Turck and others, "Guidance for Establishing and Applying Tolerable Upper Intake Levels for Vitamins and Essential Minerals: Draft for Internal Testing" (2022) 20(1) EFSA Journal e200102.

[93] Regulation (EC) No 1925/2006 (n 78).

[94] Purnhagen and Molitorisová (n 33).

[95] Sarma and others (n 32).

[96] Health Canada, "Guide to Authorities Under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)" (n 6).

[97] Ibid.

[98] Office of the Auditor General of Canada, "Reports of the Commissioner of the Environment and Sustainable Development to the Parliament of Canada. Report 2: Natural Health Products – Health Canada" (2021)

NHP safety and quality under the NHPR, e.g., successfully removing adulterated and contaminated products from the market.[99]

In the USA, the FDA's authority to regulate the sale and manufacturing of food supplements is limited by DSHEA to sole post-market enforcement.[100] Therefore, unlawfully marketed products can only be removed from the market upon individually establishing that they are misbranded, adulterated or hazardous.[101] In response to monitoring the sale of unlawfully sold or insufficiently produced supplements, the FDA has repeatedly issued warning letters to manufacturers.[102]

e. *Notification procedures*

As NHPs are considered therapeutic products under Canadian law, the NHPR prohibits their manufacturing, sale and importing without a respective license.[103] Business operators are mandated by NHPR Part 1 to apply with the NNHPD for a product license prior to selling (compare Article 4(1)). Application requirements are also specified, whereas the names of ingredients and excipients and their potency, quantity, and purpose must be stated. After issuing a license, every NHP is assigned a number, which must be presented on the label. Amendments or changes to the permit needs approval from the authority or must be notified 60 days prior. NNHPD retains the authority to remove a product from the market upon the reasonable belief of unsafety and the business operator's inability to prove its safety sufficiently.[104] As of 2023, Canadian authorities receive around 10,000 product applications annually.[105] NHPR Part 2 also mandates that every production site or storage site, in the case of imported NHPs, must be licensed by the NNHPD before manufacturing, packaging, labelling, or storing NHPs.[106] Site licence applications further require the statement of an assigned quality assurance person that all used buildings, equipment, practices and procedures comply with cGMP requirements. If a licence is obtained by an FBO, it must be renewed periodically.

In the EU, FBOs intending to place a new product on the market are required by the Food Supplements Directive to notify the responsible national authority.[107] However, the design of the notification procedures is left to the individual European Member States and may range from a simple notification form to authorisation-like procedures.[108] As many botanical ingredients, extracts or preparations may be found in food or medicine, EU legislation allows the marketing of a majority of them as herbal medicinal products (HMPs) or food supplements.[109,110] HMPs are defined as pharmaceuticals containing a botanical

<https://open.canada.ca/data/dataset/4bfc8fde-63bf-4096-83f0-2a3daddbd372/resource/7b72ead3-75ee-40d3-81a4-c0b1bb8b34a3/download/parl_cesd_202104_02_e.pdf> (accessed 11 November 2024).

[99] Ibid.

[100] A Nieto, "Supplementing DSHEA One Step at a Time: The FDA's Modernization Plan" (2022) 70(1) DePaul Law Review 115.

[101] Ibid.

[102] J Tucker and others, "Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated with US Food and Drug Administration Warnings" (2018) 1(6) JAMA Network Open e183337.

[103] Natural Health Products Regulations SOR 2003/196 (n 37).

[104] Ibid.

[105] Health Canada, "Proposed Fees for Natural Health Products (for Consultation)" (n 61).

[106] Natural Health Products Regulations SOR 2003/196 (n 37).

[107] Directive 2002/46/EC (n 1).

[108] European Commission, "Report from the Commission to the Council and the European Parliament on the use of substances other than vitamins and minerals in food supplements" (n 80).

[109] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (2001) OJ L 311/67.

[110] V Silano and others, "Regulations Applicable to Plant Food Supplements and Related Products in the European Union" (2011) 2(12) Food & Function 710.

active ingredient by Directive 2001/83/EC (Medicinal Products Directive), thereby being regulated by medicinal products law in terms of efficacy, quality and safety.[111] Botanical ingredients used in medical indications for at least 30 years can also be registered as Traditional Herbal Medicinal Products (THMPs) under the provisions of Article 16(a)(1) of the Medicinal Products Directive, which includes a simplified authorisation procedure, requiring proof of quality and safety, but not of efficacy.[112] Depending on commercial interests, such as authorisation procedures, development costs or permitted advertisement claims, FBO may choose under which legal framework they register their product.[113,114] The European Court of Justice (ECJ) established in its case *Commission v Germany* (C-319/05) that supplements containing botanical ingredients, which may be found in both food or pharmaceuticals, should be considered a supplement if their physiological effect and dosage are comparable to regular dietary consumption of this ingredient.[115]

f. New dietary ingredients

Following a debate on the legal status of botanical supplement ingredients, comparable to the EU borderline product issue, all supplement ingredients legally marketed in the USA before 1994 are considered safe without the need for pre-marketing approval from the FDA since the adoption of DSHEA.[116] Since then, only so-called new dietary ingredients (NDI), which were placed on the market after DSHEA was adopted, require pre-market approval from the FDA.[117] FBO intending to sell NDI supplements must notify the authority 75 days before market entry, during which the agency shall issue a decision based upon an individual safety assessment.[118] However, as stated by the FDA, the growing number of available supplements and FBOs pose a great regulatory challenge.[119] As estimated by the authority, several thousand NDI were not notified correctly prior to market entry, circumventing pre-market authorisation procedures.[120]

Comparable to the US-American regulation of NDI, the EU Regulation (EU) 2015/2283 (Novel Food Regulation) defines substances which have not significantly been consumed in the EU before 1997, are newly developed and innovative food products, or are foodstuff produced by using new technologies as novel foods.[121] Regarding supplements, these mainly concern new botanicals, certain bioactive micronutrients or new analogues of permitted nutrients. Comparable to the USA, novel foods in the EU also require pre-market authorisation by the EC, contingent upon individual safety assessments by EFSA.[122] FBOs must detail scalable and reliable production procedures and provide a proof of safety in their application file.[123] EFSA published several guidance documents aimed at FBOs,

[111] Directive 2001/83/EC (n 109).
[112] Ibid.
[113] Bilia and Costa (n 28).
[114] Silano and others (n 110).
[115] Case C-319/05 *Commission of the European Communities v Federal Republic of Germany* (2007) ECR I-09811 (Court of Justice of the European Union).
[116] Brinckmann and others (n 57).
[117] (n 58).
[118] Ibid.
[119] Food and Drug Administration, "Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-Market Notification: Guidance for Industry" (2022) <https://www.fda.gov/media/158369/download?attachment> (accessed 12 August 2024)
[120] Ibid.
[121] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods 11 December (2015) OJ L 327/1.
[122] Ibid.
[123] Ibid.

detailing the required product information necessary for a sufficient safety assessment. Besides toxicological data, emphasis is placed on the description of production procedures and the provision of compositional data and stability. In its Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 from 2024, EFSA explicitly states a preference for internationally recognised and validated methods such as provided by the Ph. Eur.[124] Another example of the use of Ph. Eur. quality control methods relevant to novel food safety assessment is the mention of Ph. Eur. methods for conducting dissociation studies.[125] Further, in its scientific opinion on assessing the safety of botanical ingredients in food supplements, EFSA advises FBOs to follow the Ph. Eur. nomenclature for the identification of botanicals.[126] To standardise manufacturing procedures of botanical supplements and set analytical specifications for characterising one or multiple ingredients, EFSA also recommends leveraging on validated Ph. Eur. methods.[127] However, the use of these methods is focused on the proof of safety of an ingredient or product, albeit there might be an overlap in determining a product's quality to demonstrate its safety. Therefore, supervising production procedures and quality control methods for food supplements containing novel food ingredients remain with the responsible national food safety authorities.

2. *Pharmacopoeias: Ph. Eur., USP-NF, AHP, compendium of monographs*

a. Pharmacopoeial compendia

The Ph. Eur. is the EU pharmacopoeia, codifying definitions of active pharmaceutical ingredients (APIs) and preparations thereof and validated analytical or production methods.[128] The European Directorate for the Quality of Medicines & Health Care (EDQM), a directorate of the Council of Europe, is the responsible agency for developing the Ph. Eur. and its monographs. In cooperation with the European Medicines Agency (EMA), national safety authorities, academic experts, and stakeholders from the pharmaceutical industries, the EDQM's Ph. Eur. Commission aims to continuously update and revise the Ph. Eur. monographs and general chapters.

In the USA, USP develops and publishes standards for ensuring the identity, purity and strength of APIs, pharmaceutical preparations, excipients and food supplements, published as monographs in the USP-National Formulary (USP-NF).[129] Unlike EDQM, USP is a scientific non-profit organisation aiming to improve the quality of pharmaceuticals and food supplements and strengthen its supply chains by developing public reference standards.[130] It is governed by the USP Convention, which consists of 455 primarily US–American member organisations, ranging from healthcare professional associations, consumer organisations, manufacturer and trade associations, and academic or governmental entities.[131] The

[124] D Turck and others, "Guidance on the Scientific Requirements for an Application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283" (2024) 22(9) EFSA Journal e8961.

[125] Ibid.

[126] D Turck and others, "Guidance on the Preparation and Presentation of an Application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283" (2016) 14(11) EFSA Journal e04594.

[127] Ibid.

[128] Bouin and Wierer (n 43).

[129] United States Pharmacopoeia, "An Overview of USP Monographs" (2019) <https://www.usp.org/sites/default/files/usp/document/about/public-policy/monograph-basics.pdf> (accessed 12 August 2024).

[130] United States Pharmacopoeia, "Annual Report 2022" (2023) <https://www.usp.org/sites/default/files/usp/document/about/annual-report/usp-annual-report-2022.pdf> (accessed 12 August 2024).

[131] United States Pharmacopoeia, "USP Convention Members by Membership Category" (3 January 2023) <https://www.usp.org/sites/default/files/usp/document/convention/2024_Members-by-region.pdf> (accessed 28 November 2024).

development of monographs is conducted by voluntary USP Expert Committees working together with FDA experts representing governmental liaisons.[132] The life cycle of monographs is also continuously updated by incorporating public comments from academia, industry, healthcare professionals or governmental entities.[133] Additionally, the AHP non-profit organisation was founded in 1995, shortly after DSHEA was adopted. AHP provides several public monographs on botanical ingredients intended for use in herbal medicines or food supplements.

Unlike the EU and the USA, the quality of NHPs and other types of therapeutic products are not defined by a national pharmacopoeia in Canada.[134] Instead, the NNHPD provides the Compendium of Monographs, explicitly pertaining to single or multiple NHP ingredients and specific so-called product monographs.[135] Compendial monographs set out the proper common and scientific name, administration route, recommended use, dosage, preparation method, current risk information and duration of use.[136] However, unlike the Ph. Eur. or USP, they do not detail methods for verification of quality, purity or identity. All monographs are publicly available through the Natural Health Products Ingredient Database and may function as references for which efficacy, quality and safety have been demonstrated during licence application procedures.[137,138,139]

b. Monographs

The Ph. Eur.'s general part contains detailed information on analytical methods for physicochemical and microbiological testing, standard procedures for assays involving biological materials, and descriptions of preparing, using and calibrating reference standards for these methods.[140] An additional list of reagents for use in analytical methods and assays, detailing their preparation and standardisation, is also provided.[141] A chapter on pharmaceutical technology describes preparation and testing methods, including guidelines on their respective performance and specifications for primary contact materials and dosage forms such as tablets, capsules or injections.[142] The specific part contains a collection of monographs which define and characterise natural, synthetic, semi-synthetic, biological or microbiological API.[143] Each API monograph contains information and reference values for analytical identification, purity and stability methods.[144] Monographs on excipients and bulking agents for pharmaceutical use can be found in the general part.[145]

Like the Ph. Eur. monographs, USP–NF monographs define quality aspects of a substance or preparation, such as identity, purity, strength, composition or

[132] United States Pharmacopoeia, "An Overview of USP Monographs" (n 129).
[133] Ibid.
[134] Sarma and others (n 32).
[135] Natural and Non-prescription Health Products Directorate, "Compendium of Monographs" (n 38).
[136] Ibid.
[137] Natural and Non-prescription Health Products Directorate, "Natural Health Products Ingredients Database: Listing of Single Ingredient Monographs" (2024) <https://webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq?monotype=single> (accessed 12 August 2024).
[138] Natural and Non-prescription Health Products Directorate, "Natural Health Products Ingredients Database: Listing of Product Monographs" (2024) <https://webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq?monotype=product> (accessed 12 August 2024).
[139] Natural and Non-prescription Health Products Directorate, "Compendium of Monographs" (n 38).
[140] European Directorate for the Quality of Medicines & Healthcare, "European Pharmacopoeia" (2020).
[141] Ibid.
[142] Ibid.
[143] Ibid.
[144] Ibid.
[145] Ibid.

pharmacodynamic aspects and provide validated testing methods and acceptance levels for these criteria.[146] Besides monographs, the USP–NF also contains general chapters, which provide manufacturers with information on validated production and testing procedures.[147] Additionally, USP–NF provides material references as standards for reagents and apparatus to be used in conjunction with the general chapters and monographs.[148] AHP monographs outline quality control methods required to assess the identity, purity and quality solely of botanical preparations and raw ingredients. Additionally, they also encompass reviews on traditional use and current scientific-based knowledge.

As quality assurance methods are not described by NHP monographs, the NNHPD provides an additional quality control guideline to FBOs, detailing validated control procedures, analytical methods and corresponding specifications.[149] Moreover, the NNHPD specifically references methods and procedures described by other international pharmacopoeias such as USP–NF or Ph. Eur.[150] Against the background of a Canadian national pharmacopoeia being unavailable, the NNHPD generally accepts and supports FBOs in leveraging specifications and methods published in certain other international pharmacopoeias to effectively ensure the quality of NHPs and food supplements.[151]

c. Compendial legal character

As the legal framework conditions for pharmaceuticals are more restrictive, based on a generally higher assumed risk for consumers arising from consumption thereof, Article 8(3)(h) of the European Medicinal Products Directive stipulates that APIs and preparations thereof must comply with specifications laid down in the Ph. Eur. to obtain a marketing authorisation.[152,153,154] Mandating the summary of product characteristics and the production process to comply with the pharmacopoeia, the legally binding character of the Ph. Eur. in the EU pharmaceutical sector is further strengthened by Article 11 and 23.[155] Although pharmacopoeial monographs may concern ingredients or formulations identically used in food supplements, such as minerals, vitamins, botanical preparations, or essential oils, the Ph. Eur. exclusively applies to medicinal products.[156,157] FBOs manufacturing supplements containing ingredients also referenced in the Ph. Eur. could choose to adhere to pharmacopoeial reference standards voluntarily. However, previous research has identified great differences in quality between herbal medicinal products and food supplements containing similar ingredients on the EU market.[158]

The USP–NF is legally recognised as the official compendium of the USA by Section 201(j) of the FD&C Act (21 U.S.C. Article 321(j)).[159] Section 501(b) FD&C Act (21 U.S.C. Article

[146] United States Pharmacopoeia, "Combined Index to USP 43 and NF 38, Volume 1–5" <https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-commentary/usp-43-nf-38-index.pdf> (accessed 12 August 2024).

[147] Ibid.

[148] Ibid.

[149] Natural and Non-prescription Health Products Directorate, "Quality of Natural Health Products Guide" (n 39).

[150] Ibid.

[151] Ibid.

[152] Bilia and Costa (n 28).

[153] Directive 2001/83/EC (n 109).

[154] Ibid.

[155] Ibid.

[156] European Directorate for the Quality of Medicines & Healthcare (n 140).

[157] Bilia and Costa (n 28).

[158] Ibid.

[159] Federal Food, Drug, and Cosmetics Act (n 69).

351(b)) stipulates that pharmaceuticals which do not comply with USP standards are deemed to be adulterated, thereby making adherence mandatory for business operators.[160] Regarding food supplements, the USP–NF is also recognised by Section 403(s) FD&C Act (21 U.S.C. Article 343(s)) as an official compendium, but only deeming them misbranded if they state to comply with a compendial standard but fail to do so.[161,162] Therefore, compliance with the USP–NF remains voluntary in the supplement sector.[163] However, cGMP rules applicable to food supplement production laid down in 21 CFR 111 emphasise the implementation of scientifically valid methods.[164] To clarify the term of validation, the FDA stated in their final rule on the cGMP code in 2007 that while the authority recognises the significance of compendial standards such as USP or AHP, a specific compendium shall not be listed as a source of validated methods.[165] Instead, it should remain the responsibility of the FBO to validate applied production and quality control methods, regardless of whether they are compendial or not.[166]

d. Limitations of pharmacopoeial methods in quality assurance

Despite methods and procedures described by the Ph. Eur. are considered validated and sufficient for meeting their analytical purposes, previous research identified cases in which they could not deliver desired analytical results compared to other non-pharmacopoeial methods.[167] This was partly attributed to Ph. Eur. materials not always corresponding with the latest materials practically in use. Additionally, research has identified a shortcoming of Ph. Eur. development regarding the adoption of innovative laboratory methods, such as the characterisation of different nanoparticles or DNA-based analytical methods pertaining to identifying herbal ingredients individually or in multi-ingredient compositions.[168,169]

In the USA, where FBOs are voluntarily subjected to USP standards, only few seek official USP verification. Compared to around 80,000 supplements available on the US market, as of 2024, only a small number of around 100 products are certified with the USP label.[170,171] Additionally, despite issuing warning letters from the FDA to FBOs regarding the detection of insufficient food supplement quality, research has identified an increasing trend of supplements adulterated with pharmaceuticals sold in the USA.[172] In Canada, the

[160] Ibid.

[161] Ibid.

[162] Brinckmann and others (n 57).

[163] Ibid.

[164] 21 CFR 111 – Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements (n 86).

[165] Food and Drug Administration, "Current Good Manufacturing Practice – Dietary Supplements; Manufacturing, Packaging, Labelling, or Holding Operations; Final Rule: Federal Register 72, Volume 121" (25 June 2007) <https://www.govinfo.gov/content/pkg/FR-2007-06-25/pdf/FR-2007-06-25.pdf> (accessed 10 August 2024).

[166] Ibid.

[167] A Bogni and others, "Tetrabutylammonium HPLC Analysis: Shortcomings in the Ph. Eur. Method" (2020) 63(4) Journal of Labelled Compounds and Radiopharmaceuticals 203.

[168] A Pallotta and others, "Quality Control of Gold Nanoparticles as Pharmaceutical Ingredients" (2019) 569 International Journal of Pharmaceutics 118583.

[169] K Mahima and others, "Advancements and Future Prospective of DNA Barcodes in the Herbal Drug Industry" (2022) 13 Frontiers in Pharmacology 947512.

[170] United States Pharmacopoeia, "USP Verified Products" <https://www.quality-supplements.org/usp_verified_products> (accessed 14 August 2024).

[171] Food and Drug Administration, "Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-Market Notification: Guidance for Industry" (n 119).

[172] PA Cohen and others, "Nine Prohibited Stimulants Found in Sports and Weight Loss Supplements: Deterenol, Phenpromethamine (Vonedrine), Oxilofrine, Octodrine, Beta-Methylphenylethylamine (BMPEA),

regulatory requirements to manufacture and sell food supplements are higher than in the EU and USA due to them being considered a subset of therapeutic products. However, in the 2021 audit report, the Commissioner of the Environment and Sustainable Development also emphasised that Health Canada failed to enforce compliance with NHPR and GMP regulations due to a lack of routine inspections of production sites between 2017 and 2020.[173] The limited monitoring of license holders led to non-compliance of FBOs, e.g., selling of unlicensed products, unauthorised manufacturing activities, or product mislabeling.[174] This was partly found to be due to the high numbers of registered products on the market and pending licence applications affecting Health Canada's ability to enforce NHP regulations.[175]

IV. Discussion

The EU's regulatory framework governing food supplements faces multiple challenges to ensure access to products of sufficient quality and safety.[176] Previous research has identified a wide range of quality issues impairing the safe consumption of food supplements available in the EU.[177] Additionally, the extent to which they are present in food supplements remains uncertain, and it has been estimated that only 1 % of adverse effects are reported.[178] Consumers cannot generally assess and differentiate the quality of supplements nominally containing the same ingredients.[179] Instead, they have to rely on efficacy and quality claims made by FBOs and trust that the stated quality complies with technical specifications in EU regulations.[180,181] However, as product quality can be considered a factor driving competition in a free market, the lack of opportunity for consumers to independently assess supplement quality could represent a distorting factor for the EU internal market.[182] Furthermore, against the background of the continuously expanding supplement market, it could be considered an incentive to reduce adequate quality assurance due to financial or other interests despite the risk of punitive actions or sanctions from regulatory authorities.[183]

The regulation of the EU supplement market has been described as fragmented by previous research due to missing harmonisation in certain aspects, such as permission of herbal and bioactive ingredients or dosages, resulting in differing national regulatory approaches.[184] Additionally, the enforcement practices of responsible safety authorities vary greatly between Member States. These have not been fully mitigated despite certain

1,3-Dimethylamylamine (1,3-DMAA), 1,4-Dimethylamylamine (1,4-DMAA), 1,3-Dimethylbutylamine (1,3-DMBA) and Higenamine" (2021) 59(11) Clinical Toxicology 975.

[173] Office of the Auditor General of Canada (n 98).

[174] Ibid.

[175] Ibid.

[176] M Abdel-Tawab, "Do We Need Plant Food Supplements? A Critical Examination of Quality, Safety, Efficacy, and Necessity for a New Regulatory Framework" (2018) 84(6-07) Planta Medica 372.

[177] Costa and others (n 17).

[178] CW Binns, MK Lee and AH Lee, "Problems and Prospects: Public Health Regulation of Dietary Supplements" (2018) 39 Annual Review of Public Health 403.

[179] H Boon and N Bozinovski, "A Systematic Narrative Review of the Evidence for Labeling of Natural Health Products and Dietary Supplements" (2019) 25(8) Journal of Alternative and Complementary Medicine 777.

[180] Ibid.

[181] C Muela-Molina, S Perelló-Oliver and A García-Arranz, "Health-Related Claims in Food Supplements Endorsements: A Content Analysis from the Perspective of EU regulation" (2021) 190 Public Health 168.

[182] A Ezrachi and ME Stucke, "The Curious Case of Competition and Quality" (2015) 3(2) Journal of Antitrust Enforcement 227.

[183] J Toropilová and P Bystrický, "Why HACCP Might Sometimes Become Weak or Even Fail" (2015) 5 Procedia Food Science 296.

[184] Warda, Purnhagen and Molitorisová (n 3).

Union-level governance efforts, e.g., via mutual recognition procedures.[185,186] Since harmonisation efforts in the EU aim to strengthen consumer protection and establish the internal market, a single set of quality rules generally recognised for reference purposes may reduce regulatory fragmentation. The Ph. Eur. has long been established in the pharmaceutical sector, and its uniform quality standards benefit the industry and consumers alike. Manufacturers and third-party contractors gained public access to effective, validated methods for analytical testing to ensure reliable product quality management in accordance with the requirements set by the applicable legislation. Despite singular incidents, patients generally benefit from the exclusion of low-quality therapeutic products from the EU market via the mandatory adherence to Ph. Eur. standards. As food supplements and pharmaceuticals share galenic forms and properties, the Ph. Eur. could potentially offer comparable opportunities for the supplement market.[187,188]

The American and Canadian regulatory systems illustrate that it is possible to include pharmacopoeial compendia in food supplement regulation to improve the quality and safety by strengthening quality control practices.[189,190] Additionally, the factual implementation of the Ph. Eur. in the Canadian NHP sector could be considered as an example of the Brussels effect, whereas EU legislation is adopted or impacts comparable legal frameworks in third countries outside the EU.[191] Despite not being recognised as an official supplement compendium in the EU, EFSA already references the Ph. Eur. in its ingredient safety assessments and encourages FBOs to leverage validated pharmacopoeial methods.[192]

However, the results of this study demonstrate obstacles encountered by Canadian and USA authorities in implementing pharmacopoeial reference standards in the respective supplement markets, illustrated by the emergence of quality issues comparable to those identified in the EU.[193,194] In the USA, the adulteration of supplements with APIs, usually found in prescription drugs or doping substances, remains a persisting issue in particular.[195,196] This has primarily been attributed to DSHEA placing the burden of proof of a product hazard or manufacturing sites and procedures not being cGMP-compliant upon the FDA.[197,198] Regarding NDI, for which pre-market approval is required, the FDA has stated that thousands of unapproved supplements containing such ingredients are

[185] Ibid.

[186] S Weatherill, "The Principle of Mutual Recognition: It Doesn't Work Because It Doesn't Exist" (2018) 43 European Law Review 224.

[187] Bouin and Wierer (n 43).

[188] L Righetti, C Dall'Asta and R Bruni, "Risk Assessment of RYR Food Supplements: Perception vs. Reality" (2021) 8 Frontiers in Nutrition 792529.

[189] Sarma and others (n 32).

[190] Wang and others (n 31).

[191] A Bradford, "Exporting Standards: The Externalization of the EU's Regulatory Power via Markets" (2015) 42 International Review of Law and Economics 158.

[192] D Turck and others, "Guidance on Scientific principles and Data Requirements for the Safety and Relative Bioavailability Assessment of New Micronutrient Sources" (2024) 22(9) EFSA Journal e8946.

[193] G Schwalfenberg, I Rodushkin and SJ Genuis, "Heavy Metal Contamination of Prenatal Vitamins" (2018) 5 Toxicology Reports 390.

[194] AM Abe, DJ Hein and PJ Gregory, "Regulatory Alerts for Dietary Supplements in Canada and the United States, 2005–13" (2015) 72(11) American Journal of Health-System Pharmacy 966.

[195] RS Pawar and E Grundel, "Overview of Regulation of Dietary Supplements in the USA and Issues of Adulteration with Phenethylamines (PEAs)" (2017) 9(3) Drug Testing and Analysis 500.

[196] Tucker and others (n 102).

[197] JP Swann, "The History of Efforts to Regulate Dietary Supplements in the USA" (2016) 8(3–4) Drug Testing and Analysis 271.

[198] RR Starr, "Too Little, Too Late: Ineffective Regulation of Dietary Supplements in the United States" (2015) 105(3) American Journal of Public Health 478.

available on the market.[199] This, further illustrated by the FDA repeatedly issuing warning letters to manufacturers, could highlight that manufacturers tend not to comply with the applicable legal provisions of DSHEA.[200,201] Against the background of a legal framework considered to shield the private sector from extensive regulatory oversight, FBOs manufacturing supplements generally seem to refrain from adopting pharmacopoeial standards.[202] Although the low number of USP-verified food supplements does not necessarily indicate that FBOs do not apply these standards, there appears to be little incentive to seek compliance with the USP–NF officially.[203]

In contrast, the Canadian legal framework conditions governing supplements impose a stricter regime on FBOs for manufacturing and selling NHPs.[204] However, authorities allow for a flexible approach while keeping high-quality validated reference standards, whereas FBOs may choose their preferred pharmacopoeia or develop a comparable method or procedure by themselves.[205,206] Previous research found that the Canadian NHP industry has welcomed the approach, as although some FBOs followed this approach before the introduction of the NHPR in 2004, its introduction advanced equal conditions in the NHP market regarding efforts for implementing comprehensive quality assurance programs.[207] The acceptance of the introduction of higher quality and safety requirements via NHPR has been described as being promoted through close communication of Canadian authorities with stakeholders such as industry associations or healthcare professionals during its development.[208] Despite its introduction is generally being considered an improvement of food supplement regulation in Canada, it also increased the regulatory and financial burden on FBOs.[209,210] Aligning with observations from other food categories such as the EU novel food sector, streamlining the NHP regulatory conditions has been found to increase the risk of lowering innovation in this sector.[211,212] SMEs could be especially affected, as they require more resources to market innovative or niche products lawfully.[213] For Canadian authorities, the regulatory burden to enforce safety and quality provisions of the NHPR has also increased.[214] In this regard, previous research has identified a lack of regulatory oversight by provincial health ministries due to unmet personnel requirements.[215] Additionally, the

[199] Food and Drug Administration, "Current Good Manufacturing Practice – Dietary supplements; Manufacturing, Packaging, Labelling, or Holding Operations; Final Rule" (n 165).

[200] Starr (n 198).

[201] HA Oketch-Rabah and others, "Challenges and Opportunities for Improving the Safety Assessment of Botanical Dietary Supplements: A United States Pharmacopeia Perspective" (2018) 104(3) Clinical Pharmacology and Therapeutics 426.

[202] Ibid.

[203] Sarma and others (n 32).

[204] JY Ng, M Kim and A Suri, "Exploration of Facilitators and Barriers to the Regulatory Frameworks of Dietary and Herbal Supplements: A Scoping Review" (2022) 15(1) Journal of Pharmaceutical Policy and Practice 55.

[205] Natural and Non-prescription Health Products Directorate, "Quality of Natural Health Products Guide" (n 39).

[206] A Smith, S Jogalekar and A Gibson, "Regulation of Natural Health Products in Canada" (2014) 158 Pt B Journal of Ethnopharmacology 507.

[207] R Walji and M Wiktorowicz, "Governance of Natural Health Products Regulation: An Iterative Process" (2013) 111(1) Health Policy 86.

[208] Ibid.

[209] Ibid.

[210] Smith, Jogalekar and Gibson (n 206).

[211] Walji and Wiktorowicz (n 207).

[212] A Monaco and K Purnhagen, "Risk Triggers as Innovation Triggers? Risk Analysis and Innovation´s Promotion under the Novel Food Regulation" (2022) 17(3) European Food and Feed Law Review 219.

[213] Ibid.

[214] Walji and Wiktorowicz (n 207).

[215] KT Ganson, E Sinicropi and JM Nagata, "Assessing Canadian Regulation of Muscle-Building Supplements: Identifying Gaps and Recommendations for Improvement to Protect the Health and Well-Being of Young People" (2023) 11(3) Performance Enhancement & Health 100255.

reliance on the NHP industry to provide correct testing methods and results for products and manufacturing sites has also been found to be a potential weak point of the Canadian NHP regulation.[216] This seems to be acknowledged by Canadian authorities, as Health Canada's ability to supervise and enforce applicable NHP regulations appears to be challenged by a high number of products, licence applications and manufacturing sites.[217] Additionally, while Canadian sellers, importers and distributors are obligated to comply with the NHPR, selling and importing non-compliant supplements via internet trade has been identified as a possibility to circumvent implemented higher regulatory requirements.[218] Therefore, amending the Ph. Eur. to include food supplements and the extent of its legally binding character in this sector must be considered carefully.

EU primary law mandates that interventions with the EU's free movement of goods, including foodstuff, should not be more restrictive than necessary and justified in balancing other fundamental rights such as the protection of consumer health. Within the EU's risk-based legal framework governing products intended for use in humans, food supplements being considered as food nominally constitute a lower risk as compared to pharmaceuticals. Mandating FBOs and adherence to Ph. Eur. quality standards, originally intended to ensure safety and quality of a product category for which a higher risk has been established, could conflict with EU law. However, leaving it to the FBOs' discretion to adhere to pharmacopoeial standards could lead to a comparable situation like in the USA, where FBOs are reluctant to apply them to their manufacturing operations to decrease production costs and increase profit margins.[219,220] Contrary, as discussed by previous research and observed from our study on the Canadian NHP regulatory framework, mandatory compliance to augmented safety legislation could increase the regulatory burden of administrative procedures for authorities and industry in the EU.[221] As the adoption of Vanessa's Law in Canada demonstrated, food safety authorities require sufficient resources and a robust legal mandate to enforce such regulations. The decentralised enforcement landscape across the Union may form another obstacle to effectively implementing this approach.

Another aspect that should be considered is the development of pharmacopoeial validated methods, as the development of analytical methods suitable for ingredient or product quality control is rapidly advancing. Although pharmacopoeias such as the Ph. Eur. or USP–NF are constantly reevaluated by the responsible committees, concerns have been raised by research whether new and innovative methods, e.g., genetic fingerprinting of herbal ingredients or identification of nano-particles, are insufficiently integrated.[222,223] Missing suitable reference standards despite a potential mandatory adherence could lead to a regulatory gap, creating legal uncertainty, especially in the field of innovative products, underscoring the effect of additional regulatory burden on consumers' access to new products. However, in this regard, the Canadian NHP framework, providing the opportunity for FBO to leverage non-pharmacopoeial methods if they are considered a suitable quality control method nonetheless, could be considered.

In conclusion, the Ph. Eur. could serve as a platform to generally improve quality control practices of food supplement FBOs, based on its already existing overlap with this product category. Additionally, while EFSA promotes the use of pharmacopoeial validated

[216] Ibid.

[217] Office of the Auditor General of Canada (n 98).

[218] Ganson, Sinicropi and Nagata (n 215).

[219] DP Carter, TA Scott and N Mahallati, "Balancing Barriers to Entry and Administrative Burden in Voluntary Regulation" (2018) 1(3) Perspectives on Public Management and Governance 207.

[220] Brinckmann and others (n 57).

[221] Monaco and Purnhagen (n 212).

[222] Pallotta and others (n 168).

[223] Mahima and others (n 169).

methods in the supplement and novel food sector, Canada has officially encouraged the use of the Ph. Eur. for supplement quality standards. However, if considered in the EU, careful considerations such as the extent of legal adherence by FBO, an increased need for resources for both industry and authorities, and the potential effects on innovations on the market must be made.

This study is subject to several limitations considering the methodological approach of functional comparative legal analysis. While extensive literature research was performed, insights derived from empirical research, such as expert interviews, are missing. As empirical methods can contribute to support findings derived from comparative legal analysis, data on stakeholders, such as FBOs or authorities illustrating their perception of pharmacopoeial references to supplements, could have been a valuable addition. However, it would have exceeded the scope of this research. Additionally, the studied legal systems differ significantly, as the EU is governed by a multi-leveled structure consisting of horizontal technical regulations and different food law enforcement structures on national levels. Canada and the USA have implemented national regulatory systems, independent from an additional comparable supra-national legal framework. Further, while supplements are considered foodstuff in the EU and the USA, they are regulated as therapeutic products in Canada. This has major implications for legal quality and safety requirements, which cannot necessarily be met by EU and US food law.

V. Conclusion

Pharmacopoeial reference standards and monographs offer considerable potential to strengthen food supplement quality control practices. Although traditionally applied in the pharmaceutical sector, pharmacopoeial standards have long been extended to food supplements in major markets outside the EU. This study demonstrates, however, that both the scope of their application and the degree of industry adherence vary substantially.

Integrating food supplements into the Ph. Eur. could enhance consumer access to high-quality products while reducing barriers for SMEs to implement effective product quality control measures. Nonetheless, legislators should appropriately calibrate the extent to which the use of pharmacopoeial references is mandated. Minimal mandatory requirements risk discouraging the private sector from adoption for economic reasons. Conversely, overly stringent requirements could impose additional regulatory burdens on both the industry and authorities, potentially hindering the entry of innovative food products into the EU market.

Future research should therefore focus on empirical research to highlight the perspectives of the EU industry on proportionate strategies, that enhance the safety and quality control practices in the food supplement sector without impeding innovation or market access.

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