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The Regulatory Framework Across International Jurisdictions for Risks Associated with Consumption of Botanical Food Supplements

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Abstract: Dietary supplements, including those containing botanical ingredients and botanical-derived compounds, have been marketed to consumers globally for many decades. However, the legislative framework for such products remains inconsistent across jurisdictions internationally. This study aims to compare the regulatory framework of botanical food supplements in the EU, USA, Canada, Australia, New Zealand, India, Japan, and China. The study also aims to investigate and describe safety assessment criteria for botanical food supplements where they are present in the above said jurisdictions, and attempts to analyze whether these criteria are suitable for addressing the toxicological risks associated with the use of botanical food supplement products, based on the evaluation of reported adverse effects related to botanical food supplement use as examples. Finally, this study discusses some future issues that need further attention, such as the consideration of less than lifetime exposures, potential for misidentification, and adulteration of botanical supplements by pharmacologically active substances. It is concluded that the regulatory approaches towards botanical food supplements differ significantly across jurisdictions. In addition, national authorities are increasingly considering having more regulatory oversight for such products. Further consideration of the actual impact of adverse events arising from botanical food supplement usage will be helpful in guiding such decisions.

Keywords: botanicals, botanical food supplements, regulatory framework, regulatory challenges, risk assessment

Introduction

Although dietary supplements containing botanical ingredients and botanical derived compounds have been available to consumers for several decades, the approach towards the regulation of these botanical food supplements differs greatly across jurisdictions internationally. While some countries regard such products as food, others regulate them as health products or medicines (Aschwanden 2001). In 1997, the Codex Alimentarius Commission (CAC) considered work on the establishment of international standards for these products, aiming particularly at discussing the use of potentially harmful herbs and botanicals as food, but ultimately decided not to proceed. The CAC noted that this was a matter for national authorities to decide as regulations and practices in this area greatly differed from one country to another (Codex Alimentarius Commission 1997).

In contrast, the World Health Organization (WHO) has recognized the role that botanicals play in traditional herbal medicines, and a series of monographs on selected medicinal plants have been published by the WHO (World Health Organization 1999, 2004, 2007, 2009, 2010). These monographs present technical reviews of the quality, safety, and efficacy of commonly used herbal medicines, with the intention of harmonizing the use of herbal medicines internationally (Mahady 2001).

Despite the differences in the regulation of botanical food supplements, consumer demand for these products continues to grow. The global dietary supplement market has been valued at USD 109.8 billion in 2013 and is expected to grow to an estimated value of approximately USD 180 billion by 2020 (Persistence Market Research 2015b). Botanical supplements form the largest segment of this market, with the estimated market worth of USD 54.6 billion in 2013 (Persistence Market Research 2015a). These figures are suggestive of the increasing availability of botanical food supplements. For example, dietary supplements that were previously traditionally sold in health food shops are now increasingly being found in major supermarkets.

At the same time, reported cases of adverse events have shown that real risks to public health can arise from the consumption of such products. Adverse effects arising from issues such as adulteration with pharmaceutical substances (Rocha and others 2016), as well as accidental replacement of botanicals with toxic plants (Stegelmeier and others 2015), have been reported in the literature. Furthermore, some botanicals contain naturally

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occurring substances that can result in long-term adverse effects, such as the alkenylbenzenes estragole and methyleugenol, which have been found to be genotoxic and hepatocarcinogenic in experimental animals (SCF 2001a, b), although for methyleugenol, DNA adducts have also been detected in liver samples from human subjects (Herrmann and others 2013; Tremmel and others 2017). The severity of reported adverse effects associated with the consumption of botanicals range from transient elevation in blood pressure to acute liver failure requiring liver transplantation, tumors of the urinary tract, and even death (Shaw and others 1997; Lord and others 1999; Fujita and others 2007; Nortier and others 2009).

In a systematic review of adverse effects of plant food supplements and botanical preparations, Di Lorenzo and others (2015) concluded that, although numerous cases of adverse effects of botanicals have been cited in literature, the number of citations with adequate evidence for causal relationships based on the WHO's Causality Assessment Criteria was significantly less. Nonetheless, due to the possibility of severe and even fatal adverse effects, as well as the possibility that the number of adverse effects reported may be underestimated, a close study of the regulatory oversight and safety assessment and quality control of dietary supplements containing botanical ingredients and botanical derived compounds remains pertinent to the scientific community's efforts in protecting public health.

This study, therefore, aims to provide clarity on the current state-of-the-art in regulations of botanical food supplement products in jurisdictions where such products have been available for many years, including the European Union (EU), the USA, Canada, Australia, New Zealand, India, Japan, and China. Several of these jurisdictions were chosen as they were considered to possess advanced regulatory frameworks for these products. In addition, an effort to include jurisdictions, with both Western and Asian cultures was made in order to identify any differences in approach. Although several authors have described and commented on the regulatory frameworks of food supplements in the EU and the USA (Silano and others 2011; Avigan and others 2016; Rocha and others 2016; Swann 2016), there have been few published works comparing the regulatory frameworks in other countries where food supplements are marketed. Shao (2017) described market entry requirements for functional foods and dietary supplements in several jurisdictions including those reviewed in this paper, classifying the jurisdictions by their use of mandatory notifications or registrations, as well as the utilization of positive or negative ingredient lists.

In addition, this study aims to provide a comparison between the safety assessment criteria among different jurisdictions; such a comparison currently does not exist in published literature. Finally, the inventory to be made will also elucidate and discuss current bottlenecks and issues in the risk assessment and regulation of botanical supplement products that should be considered in the future.

The outcome of the study is expected to be of relevance to regulatory policy decision makers who need to make decisions regarding the regulation of botanical supplements, and also will serve as a preliminary quick guide to industry members who wish to better understand the related current regulatory frameworks in the jurisdictions covered. Members of the general public may also gain knowledge from the study on some of the possible risks arising from the consumption of botanical supplement products, and perhaps reconsider the perception that "natural" equates to "safe" (Ernst 1998).

Regulation of Botanical Food Supplements

Consumers can be exposed to botanicals and botanical derived compounds through the consumption of various product categories. These range from the culinary use of botanicals and botanical-derived substances as ingredients or flavoring substances, dietary or food supplements, herbal teas, traditional herbal medicines, and botanical drug products. Except for culinary usage, the definitions of the categories described above vary from jurisdiction to jurisdiction, with seemingly no international harmonization and coherence.

In this study, the term "botanical food supplement" has been used to describe food supplements containing botanicals and botanical-derived substances. Considering that the terms used to describe botanical food supplements differ in the jurisdictions reviewed, for the purposes of comparing across jurisdictions, the definition for "plant food supplements" or PFS as utilized by the EU PlantLIBRA project has been considered in this study to be equal to "botanical food supplements."

PFS are "foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of botanical preparations that have nutritional or physiological effect, alone or in combination with vitamins, minerals, and other substances which are not plant-based. PFS are marketed in dose form, such as capsules, pastilles, tablets, pills, and other similar forms, sachets of powder, ampoules of liquids, drop-dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities"(Garcia-Alvarez and others 2014).

Table 1 presents an overview of the possible product categories used to classify products containing botanicals or botanical ingredients in the different jurisdictions. From this overview it follows that although in the EU, India, New Zealand, and the USA, botanical food supplements are regarded as food, in Canada and Australia they are considered in the medicine/drug category. In addition, in Japan and China botanical food supplements are not specifically defined as such, but such products are considered to fall under categories of "health food" that are permitted to carry various health claims.

It was interesting to note that differences in regulatory approaches may have stemmed from cultural differences. For example, the categorization of botanical food supplements as "health food" in China potentially reflected the consideration of the concepts of Traditional Chinese Medicine where the nature, tastes, and functions of foods and their effects on human constitutions are considered to result in therapeutic effects of foods (Shen and others 2010).

Regulations in the EU

In the EU, "food supplements" are defined and regulated as a specific category of foodstuffs under Directive 2002/46/EC (European Commission 2002a). However, this directive currently only establishes rules applicable for the use of vitamins and minerals in food supplements, and does not include rules on the use of botanicals.

Although the EU currently does not have a centralized authorization procedure for the use of botanicals and derived preparations in food supplements, the European Commission has noted that the use of botanicals in food supplements is required to comply with the broader requirements for food as established by the EU General Food Law (Regulation [EC] No 178/2002) as well as requirements for novel food (Regulation [EC] No 258/97 and Regulation [EU] 2015/2283; European Commission 2008). In particular, the EU General Food Law establishes the prohibition

Table 1–Classification of products containing botanical ingredients within various jurisdictions.

Country	Food				Medicine /drugs
EU	Culinary use (flavorings, ingredients)	Food supplements			Traditional herbal medicinal products
USA	Culinary use (flavorings, ingredients)	Dietary supplements			Botanical drug products
New Zealand	Culinary use (flavorings, ingredients)	Supplemented food		Dietary supplements	Herbal remedies
Canada	Culinary use (flavorings, ingredients)				Natural Health Products (includes herbal remedies and Traditional medicines such as traditional Chinese medicines)
Australia	Culinary use (flavorings, ingredients)				Complementary medicines (herbs, vitamins, minerals, nutritional supplements, homeopathic and certain aromatherapy preparations)
Japan	Culinary use (flavorings, ingredients)	Foods with health claims (FNFC, FOSHU, FFC)			Pharmaceuticals and quasi-pharmaceuticals
China	Culinary use (flavorings, ingredients)	Health food			Traditional herbal medicines
India	Culinary use (flavorings, ingredients)	Speciality food containing botanical ingredients with safe history of use	Health supplements	Nutraceuticals	Traditional herbal medicines

of products that are injurious to health or unfit for consumption, obligations for food business operators to ensure compliance with food law, and the concept for mutual recognition in ensuring the free movement of foodstuff on the European Community market (European Commission 2002b).

At the same time, requirements under the novel food regulation ensure that foods and food ingredients that fall under the definition of "novel food" (that is, not used for human consumption to a significant degree within the EU before 15 May 1997), would be required to undergo an authorization procedure that includes a safety assessment, before they may be placed on the market (European Commission 1997, 2015).

Botanical extracts may often be used in both food supplements as well as herbal medicinal products (HMPs). In contrast to the ambiguity in definitions for botanical food supplements, HMPs are regulated in the EU as a category of medicinal products, and definitions for both "HMPs" and "Traditional Herbal Medicinal Products (THMPs)" have been introduced under Directive 2004/24/EC (European Commission 2004). The European Medicines Agency (EMA) is responsible for assessing the safety and efficacy of these products, and has established pre-market regulatory pathways for such assessments (EMA n.d.).

The difference between EU regulatory frameworks for botanical food supplements and THMPs, as well as the lack of a centralized authorization procedure for botanical food supplements, has led to situations where some products are marketed as food in some EU Member States, although the same product is considered to be a medicinal product in other Member States (European Commission 2016). This has been seen in European Case law. For example, in Case C-319/05, the Court of Justice of the European Union (CJEU) was of the opinion that the German authority had overstepped its discretion in classifying a garlic preparation in capsule form as a medicinal product instead of as a foodstuff (van der Meulen and Szajkowska 2014). Some EU authorities have published nonlegislative guidance documents to help industry decide on the appropriate classification of its products. Such guidance documents by national authorities may not always have consistent messages. For instance, although both the German BfR and Czech SUKL describe food supplements as foodstuffs, the BfR notes that food supplements with pharmacological effects should be regarded as medicinal products, while the SUKL advises that food supplements should not declare preventive, therapeutic, or healing properties (BfR [German Federal Institute for Risk Assessment] 2008; SUKL [Czech State Inst. for Drug Control] 2010).

In addition to the above issues on product classification, a situation has arisen where inconsistencies exist when specific limits for certain substances related to the use of botanicals have been established in order to protect public health. An example that illustrates this last aspect can be found in the different limits for pyrrolizidine alkaloids (PAs) that have been implemented by various EU Member States. PAs are naturally occurring toxins found in a wide variety of plant species, and have been associated with potentially fatal acute and chronic liver damage (EFSA Panel on Contaminants in the Food Chain [CONTAM] 2011). Table 2 presents a comparison of regulations related to PAs previously described (Merz and Schrenk 2016), and shows that although some European countries such as Austria and Belgium have utilized a "zero tolerance" approach towards PAs, others such as Germany and the Netherlands have adopted approaches utilizing maximum limits. In addition, differences exist between these approaches utilizing maximum limits. Although Germany's limits are established based on daily intakes, those by the Netherlands are based on the concentration of PAs as found in the product. Assuming that the herbal preparations containing PAs are consumed in small dosage forms, exposure to PAs from products complying with Dutch maximum limits could potentially be much lower than those complying with German maximum limits. It is important to stress that these regulatory limits are generally not based on health based guidance values defined through risk assessment using a suitable toxicological database, but rather reflect the outcome of risk management actions taken to prevent or limit high-level human exposure.

These inconsistencies in regulatory approaches for botanical food supplements within the European Union have drawn the

Table 2–Regulatory status in some EU countries regarding the presence of pyrrolizidine alkaloids (PAs) in food (Adapted from Merz and Schrenk 2016).

Country	Regulatory status
Austria	Use of plants containing PAs only allowed if analyzed and found to not contain PAs.
Belgium	Borage (*Borago officinalis*) prohibited from food use but borage oil allowed for food supplement use if can be proven to not contain PAs.
Germany	Maximum limits exist for presence of PAs in herbal medicines: • For products with customary oral intake, the total PA content should not exceed 1 μg per day. • For products intended to be consumed for periods >6 months, the limit is 0.1 μg per day. A labeling warning notice informing pregnant or lactating women not consume the product is also required.
Netherlands	Maximum limits exist for presence of PAs in herbal preparations and herbal extracts. Total PA content must not exceed 1 μg /kg or 1 μg /L.

attention of food safety policy makers. In a recent speech to the European Parliament, Dr. Vytenis Andriukaitis, the European Commissioner for Health and Food Safety, lauded the "BELFRIT" project as an example of EU Member States voluntarily cooperating to develop a common approach for the safety evaluation of botanicals (European Commission 2016). The "BELFRIT" project involved the Belgian, French, and Italian authorities, integrating their respective national lists of botanicals into a single common positive list (Cousyn and others 2013). The European Commission has also announced preparatory work for a "Regulatory Fitness Evaluation (also known as REFIT)" in health claims regulation, and also includes investigations on whether the safety, quality and free circulation of botanical food supplements in the EU should be further examined (European Commission 2016).

In addition to these efforts in regulatory approaches, the European Food Safety Authority (EFSA) had made the safety of botanicals in food supplements a focus for risk assessment already in 2004, when a discussion paper expressing concerns about quality and safety issues of botanicals and botanical preparations was published (EFSA Scientific Committee 2004). EFSA subsequently published a toolkit intended for both risk assessors and food manufacturers, comprised of: a guidance document for the safety assessment of botanicals and botanical preparations (EFSA Scientific Committee 2009), a report with example case studies of selected botanicals (EFSA Scientific Cooperation [ESCO] Working Group on Botanicals and Botanical Preparations 2009), and also a compendium of botanicals that are reported to contain toxic, addictive, psychotropic, or other substances of concern (EFSA 2009). Parts of this toolkit have also been further enhanced over time, with the guidance document complemented by an opinion discussing the suitability of the Qualified Presumption of Safety approach (EFSA Scientific Committee 2014), and ongoing updates to the compendium of botanicals (EFSA 2016).

Regulations in other jurisdictions

In the other countries reviewed, botanical supplements may be regulated either as a special category of food (USA, New Zealand, Japan, China, and India), or as medicinal products (Canada, Australia). Table 3 provides a summary of the relevant legislative instruments and information on whether pre-market authorization of botanical food supplements is required in these jurisdictions.

In the USA, dietary supplements, which include botanical food supplements, are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994. The DSHEA prohibits the marketing of dietary supplements that are adulterated or misbranded, and places the responsibility of ensuring safety of products and compliance to labeling requirements on the manufacturers and distributors of the products (U.S. Food and Drug Administration [FDA] 2016a). In addition, the FDA also monitors the marketplace for dietary supplements that may be unsafe or advertising misleading claims. Enforcement actions are taken when products are found to be unsafe, fraudulent, or in violation of the law (FDA 2016c).

Although the FDA is responsible for taking action against adulterated dietary supplements on the market, approval from the FDA is not required before marketing dietary supplements (FDA 2008), and only "new dietary ingredients (NDIs)" or ingredients used in dietary supplements that have not been marketed in the USA before 1994 are required to be notified to the FDA with information on the identity and safety of the ingredient before being marketed (FDA 2016b).

In New Zealand, although dietary supplements are regulated and defined under the Dietary Supplements Regulations of 1985 (which falls under the Food Act 2014), there is no premarket approval process for dietary supplements, and it is the responsibility of the person placing the product on the market to ensure product safety (New Zealand Medicines and Medical Devices Safety Authority n.d.). Information relating to manufacturer's guidelines for ensuring safety of dietary supplements was neither found on the website of the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE), nor in the Dietary Supplements Regulations of 1985.

In India, regulations establishing definitions for "health supplements" and "nutraceuticals," as well as listing the ingredients that may be used in these products, have been recently introduced (Food Safety and Standards Authority of India [FSSAI] 2016). Interestingly, botanical food supplements could potentially be fitted into either of these product categories, with one of the key differences between them being that health supplements are intended to supplement the diet with nutrients, whereas "nutraceuticals" are expected to be able to provide physiological benefits and help in maintaining good health (FSSAI 2016). Based on the same regulations, premarket approval of these product categories does not seem to be required. However, the use of ingredients that are not currently listed would require prior approval from the FSSAI (2016).

In Japan, there is no legal definition for dietary supplements, although such products are regulated as foods (Japan External Trade Organization [JETRO] 2011). Most dietary supplements, including botanical food supplements can fall within the areas of either "Foods in General" or "Foods with Health Claims" with the difference being the presence of health claims on products (Consumer Affairs Agency 2015). Products classified as "Foods in general" are not subject to pre-market authorizations or notifications. However, "Foods with Health Claims," which could be further defined as either "Foods for Specified Health Uses" (FOSHU), "Foods with Nutrient Function Claims" (FNFC), or "Foods with Function Claims" (FFC), are regulated with different pathways ranging from a rigorous and lengthy approval process for FOSHU, to shorter pre-market notifications for FFC (Mangino and Hayashi 2015).

Table 3–Summary of relevant legislative instruments and requirement for premarketing authorization of botanical supplements in Australia, Canada, China, India, the European Union, New Zealand, Japan, and the USA.

Jurisdiction	Legislative instrument	Pre-marketing authorization required
Australia	Therapeutic Goods Act	Yes
Canada	Natural Health Products Regulations	Yes
China	Food Safety Law of the People's Republic of China and Measures for the Administration of Registration and Recording of Health Food	Yes
India	Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016	No
European Union	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	No Botanical ingredients meeting the definition of "novel food" must be first authorized
Japan	Food Sanitation Act (Act No. 233, 1947)	No – "Foods in general" Yes – "Foods with health claims"
New Zealand	Dietary Supplements Regulations 1985 Food Act 2014	No
USA	Dietary Supplement Health Education Act (DSHEA) 1994	No

Similarly in China, dietary supplements, including botanical food supplements, are regulated as "health foods" or "保健食品." Chinese market entry regulations have been recently revised, replacing a lengthy registration procedure with a notification based approach for basic vitamin-and mineral-containing products (China Food and Drug Administration [CFDA] 2016b). However, other health food products are still required to undergo extensive testing and premarket approval (Shao 2017). In detailed rules published by the CFDA, new ingredients used in health food are required to be supported by a package of toxicological data, including an acute oral toxicity study, 3 genotoxicity assays, and a 28-d oral toxicity study. Based on the outcome of these studies, additional studies such as 90-d oral toxicity studies, teratogenic, and reproductive toxicity studies may also be required (CFDA 2016a). In addition to these rules, a national standard for health food (GB 16740-2014) covering requirements for heavy metals and microbiological criteria has been in place since 2014 (National Health and Family Planning Commission of the People's Republic of China 2014).

On the other hand, botanical food supplements are regulated as medicinal products in Canada and Australia. However, even when considered as medicinal products, the regulatory requirements for botanical supplements vary between these countries. In Canada, botanical food supplements are regulated as "natural health products (NHPs)" (Health Canada 2013). Premarket authorization of NHPs is required, during which detailed information on the product's medicinal ingredients, source, dose, potency, non-medicinal ingredients, and recommended use has to be submitted (Health Canada 2016).

In Australia, botanical food supplements are considered as "complementary medicines," and a risk-based tiered approach is taken with regard to the regulation of complementary medicines (Therapeutic Goods Administration [TGA] 2013b). Although lower-risk medicines are merely listed on the Australian Register of Therapeutic Goods (ARTG), higher-risk medicines must be registered on the ARTG (TGA 2013a, c). The therapeutic indications on listed medicines are not evaluated by the Australian TGA whereas registered medicines are evaluated for quality, safety, and efficacy before they are accepted (TGA 2013c). Most complementary medicines marketed are listed medicines, and only fewer than 40 registered complementary medicines on the ARTG have been evaluated by the TGA for safety, quality, and efficacy thus far (TGA 2016c).

The variety in regulatory approaches in the jurisdictions as seen above, reflect the complex difficulties dietary supplement manufacturers face when attempting international trade. In a striking example, Australia and New Zealand have established a Trans-Tasman regulatory system which harmonizes much of the food standards between these countries (Food Standards Australia New Zealand [FSANZ] 2016). Conspicuously, however, the regulatory framework for food supplements has not been harmonized, reflecting the difficulty faced by New Zealand companies, which currently follow food law, in conforming to Australian requirements for complementary medicine (European Advisory Services 2007).

Botanical Ingredient Safety Assessment Criteria

Given the variety in regulatory approaches in the jurisdictions reviewed, it was surmised that the criteria for assessment of botanical ingredients used in botanical food supplements could differ substantially as well. Indeed, among the jurisdictions reviewed, guidance documents on assessment criteria for the safety evaluation of ingredients used in food or dietary supplements were found only for the EU, USA, Australia, and China. Of these, only the EU, Australia, and the USA have established specific criteria for the safety assessment of botanical ingredients.

EU

As indicated above, within the EU, EFSA has published a guidance document on the safety assessment of botanicals and botanical preparations in 2009, as well as an opinion on the use of the Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations in 2014.

EFSA's guidance document proposes a 2-tiered general framework. At the 1st tier (Level A), safety assessment is based on available knowledge, including the botanical ingredient's history of food use (EFSA Scientific Committee 2009), where the intended uses of the botanical ingredient do not result in significant increases of intake as compared to historical food use, a presumption of safety may be applied, and no additional data would be necessary for safety evaluation (EFSA Scientific Committee 2009). However, where botanical ingredients lack a history of food use, or where the intended uses of the ingredient would result in exposures exceeding historical levels, a 2nd tier (Level B) of safety assessment is applied, which is based on additional experimental toxicological studies (EFSA Scientific Committee 2009).

In addition to the information in EFSA's guidance document, EFSA has noted that prior guidance documents established by the French Agency for Food Safety (Agence Française de Sécurité Sanitaire des Aliments [Afssa] 2003), the Council of Europe (Council of Europe 2005), and the European Branch of the International Life Sciences Institute (ILSI; Schilter and others 2003) should be taken into account when conducting safety assessments of botanicals. It is interesting to note that each of these prior guidance documents provide details on the information requirements in making safety assessments of botanicals that are in some ways more comprehensive as compared to EFSA's own guidance document. However, as these documents are only referred to by EFSA, is may be unclear for companies preparing such safety assessment dossiers as to which of them would be considered the "gold standard" reference.

Australia

In Australia, the TGA has published several guidance documents related to complementary medicines. Because of Australia's classification of botanical supplements as complementary medicines, the TGA has also adopted EU guidance documents on HMPs published by the European Agency for the Evaluation of Medicinal Products (currently known as the EMA; TGA 2006). In addition, the TGA has also established guidance documents on establishing equivalence of herbal extracts in complementary medicines, as well as the use of modified unprocessed herbal materials (TGA 2016b).

USA

The FDA recently introduced a revised draft guidance on NDI notifications for the industry that replaced the previous version issued in July 2011. Although the draft guidance is legally nonbinding, it provides a useful insight on the FDA's approach towards the subject. In this guidance, the FDA clarified on situations warranting the need for an NDI notification, as well as the type of data required for substantiating safety. In addition to information that applies to all forms of dietary supplements, the draft guidance also addresses information requirements specific to botanical supplements such as requirements on identity information and information on production methods (FDA 2016b).

Uniquely, the FDA has recommended the provision of a curated voucher of the botanical source material as part of the information package on identity. Botanical vouchers typically consist of pressed and dried samples of individual herbarium specimens, including leaves, stems, flowers, fruits, and roots (Culley 2013). They are of particular importance when the identity of a botanical is limited to locally known common plant names (Culley 2013). Cheung and others (2006) identified 7 different botanicals containing the common Chinese plant name "Mu Tong" from the Encyclopaedia of Chinese Materia Medica, including *Aristolochia manshuriensis* Kom. or "Guan Mu Tong," a botanical containing aristolochic acids. This confusion in plants named "Mu Tong" has been suspected to have resulted in several cases of aristolochic acid nephropathy reported globally (Lord and others 1999; Debelle and others 2008; FDA 2011; Jadot and others 2017).

Differences in assessment criteria

A comparison of the assessment criteria mentioned in the different guidance documents available in Australia, the EU, and the USA was conducted. Much of the criteria, particularly information requirements related to the basic identification of the botanical substance and description of its manufacturing process, were largely similar. However, some differences between the jurisdictions regarding the specifics of toxicological data required, and consideration of clinical trial data, adverse reaction reports, and historical use of botanicals as medicines were observed (Table 4).

In terms of requirements on toxicological data, EFSA's (EU) guidelines were noted to have been comparatively brief on the specific toxicological studies that would be considered necessary for the safety assessment of a botanical ingredient. Readers are however, directed to EFSA's guidance on submissions for food additive evaluations for additional information on which toxicological studies would be expected (EFSA Panel on Food Additives and Nutrient Sources added to Food [ANS] 2012). In contrast, the guidance documents by the TGA (Australia) and the FDA (USA) have described the necessary toxicity studies in more detail. In particular, the FDA's draft guidance contains a "Safety Testing Recommendation Matrix," where different combinations of toxicological data are recommended for various scenarios based on whether the proposed exposure to the NDI would be more or less than the exposure through historical usage, as well as the proposed duration of use of the NDI (FDA 2016b). Based on this matrix, business operators considering toxicity studies for their botanical food supplements can avoid conducting excessive studies, thereby potentially saving costs.

In terms of consideration of clinical trial data, EFSA's guidelines have not mentioned such information. In comparison, the TGA noted that data relating to safety issues in clinical trials should be submitted (TGA 2016a). Similarly, the FDA noted that although human clinical studies are not legally necessary for an NDI notification, short-term tolerability studies, and adsorption, distribution, metabolism, and excretion (ADME) studies may be useful in considering adjustments to safety factors used for the calculation of margins of safety, as well as to relieve specific safety concerns arising from animal studies (FDA 2016b). In addition, data from clinical trials and other human studies may also be useful in determining the nutritional implications and allergenic potential of the botanical ingredient (Advisory Committee on Novel Foods and Processes [ACNFP] 2002; Howlett and others 2009).

In terms of consideration of previously reported adverse reaction reports during the safety assessment of botanical ingredients, such requirements were not as apparent in the EFSA and FDA guidance documents as in the guidance provided by the TGA. The TGA's guidance explicitly states that all adverse reaction reports (published and unpublished) that are relevant to the assessed substance should be submitted (TGA 2016a). Adverse reaction reports are traditionally more closely associated to pharmaco-vigilance rather than the monitoring of safety for food products (Edwards and Aronson 2000). The difference in requirements in this aspect may thus potentially be explained by the fact that the TGA regulates botanical food supplements as complementary medicines rather than foods.

Hepburn and others (2008) have previously compared the monitoring of adverse effects for medicines and novel foods, noting that while physicians and pharmacies would be the main sources of information for the post-market surveillance of medicines, adverse reports arising from novel food consumption are likely to occur through direct contact between the consumer and marketing company. In view of this, investigations on the causality of adverse effects attributed to food ingredients are likely to be less precise than those for medicines.

Finally, although all 3 jurisdictions took the history of use of botanical ingredients into consideration, the utilization of

Table 4–Differences in information required for assessment of the safety of botanicals in botanical supplements based on official guidance documents in the EU, Australia, and the USA.

Risk assessment criteria	EU	Australia	USA
Toxicological data	(EFSA Scientific Committee 2009) No specific information on toxicological studies required. Reference made to EFSA's Guidance for submission for food additive evaluations.	(TGA 2016a) In the absence of evidence on traditional use to demonstrate safety, relevant toxicological studies are required including: • Single dose toxicity • Repeat dose toxicity (study length dependent on duration of proposed used of substance). • Genotoxicity studies • Carcinogenicity studies • Reproductive and developmental toxicity studies	(FDA 2016b) Matrix of toxicological tests required for various scenarios. Scenarios are based on whether the anticipated exposure of the substance exceeds historical consumption.
Clinical trial data considered	No	Yes	Yes
Summary of reported adverse reactions/poisonings	No	Yes	No
Historical use as medicine	No	Yes	Yes

information on the history of use of botanicals in traditional medicines differed. Due to consumer-driven demands for food innovation, businesses have been interested in bringing botanical ingredients typically used in traditional medicines into the field of food supplements. It was intriguing to note that EFSA's guidance has explicitly stated that information on the history of use of botanical ingredients should be restricted to history of food use only (EFSA Scientific Committee 2009). This has also been demonstrated in the case studies conducted by the ESCO Working Group on Botanicals and Botanical Preparations (2009), where, although the traditional medicinal use of some botanical ingredients such as dried bitter orange peel and holy basil were noted, such information was not taken into consideration and did not seem to influence the outcome of the safety assessments on the respective food supplements. It is also interesting to note that in its more recent guidance document on the preparation and application for authorization of a novel food, EFSA has raised the possibility of non-food historical uses being considered in the safety assessment of the novel food (EFSA NDA Panel [EFSA Panel on Dietetic Products, Nutrition, and Allergies] 2016).

In contrast, the FDA draft guidance has acknowledged the possibility of inclusion of history of use of botanicals as traditional medicines in the consideration for safety of botanical food supplements. In such instances however, the FDA considers that additional safety information is almost always required due to differences in composition, conditions of use, and target populations (U.S. Food and Drug Administration [FDA] 2016b).

In Australia, because supplements are considered as complementary medicines, the situation is reversed, and the TGA has recognized that well established medicinal or food use of botanical substances may be used to support the substances' safety. Nonetheless, the TGA has also noted that the same substance where used in therapeutic goods may present a different risk profile as compared to food due to the factors such as the presence of other components in the food matrix, dosage, and dosage forms, as well as administration routes and frequency. An example has been seen in the tea polyphenol (-) epigallocatechin-3-gallate (EGCG). Chen and others (1997) showed that intragastric administered pure EGCG was absorbed and excreted at a faster rate in rats as compared to EGCG occurring in decaffeinated green tea. In another example, the flavonoid nevadensin found in basil has been seen to inhibit the sulfotransferase-mediated bioactivation of estragole and methyleugenol (also present in basil) to their ultimate carcinogenic metabolites (Alhusainy and others 2010; Alhusainy and others 2012; Alhusainy and others 2014). It should be noted, however, that while these inhibitory effects of nevadensin have been observed at high dose levels necessary for animal bioassays, physiologically based kinetic modelling outcomes suggest that the same inhibitory effects may not be present at more realistic exposure levels arising from dietary intake of basil (Alhusainy and others 2012; Alhusainy and others 2014). Additional examples of food matrix-derived combination effects influencing the ADME characteristics of food-borne toxic compounds in the literature have been studied by Rietjens and others (2015), who noted that such interactions may result in decreased or increased bioavailability and/or toxicity of compounds. These authors further concluded that matrix-derived combination effects should be considered on a case-by-case basis, taking into account the mode of action of individual interactions, as well as dose-dependency, since effects observed at the high doses used in *in vivo* studies may be absent at more realistic lower intake levels (Rietjens and others 2015).

Given the above-mentioned differences in approaching history of use, it is also vital to keep in mind that, although most of the assessment criteria in the jurisdictions above took into account the history of use of botanicals, a number of these guidance documents have explicitly noted that the absence of evidence for adverse effects cannot be interpreted as evidence for the absence of adverse effects (Schilter and others 2003; EFSA Scientific Committee 2009; ESCO Working Group on Botanicals and Botanical Preparations 2009). This is particularly true considering that typically, unless specific investigations are conducted, only acute and severe adverse effects are likely to be reported and thus associated with specific botanicals (Schilter and others 2003).

Nonetheless, information on the history of use of botanicals may be useful for safety assessment for 2 reasons. First, botanicals that have indeed been reported to cause adverse effects may be immediately flagged during the assessment, so that further detailed toxicological investigations may be conducted. Second, information on history of use provides necessary information for estimating the resulting additional exposure to a specific botanical after it has been introduced to wider use.

Current Bottlenecks and Issues for Risk Assessment and Regulation

Considering the outcome of the review on regulatory frameworks among various jurisdictions, it becomes clear that much work remains to be done, in order to reach a harmonized approach

towards the risk assessment and regulation of botanical food supplements. In addition, new risks related to botanicals continue to arise, due to developments in extraction technologies, as well as through the dynamics of economically motivated fraud. Furthermore, some items have so far not been considered in the guidance documents for risk and safety assessment of botanical food supplements that may need further attention. For example, the use of synthetic copies of naturally occurring compounds in botanicals has not been mentioned in any of the guidance documents reviewed other than the USA, where the FDA has ruled out such compounds as dietary ingredients (FDA 2016b). In the next sections some of these topics that need future efforts in the framework of harmonizing and improving guidelines for risk and safety assessment as a basis for regulation of botanical food supplements are discussed in more detail.

Less-than-lifetime exposure

Although current guidelines include the evaluation of the safety of long-term exposure to botanicals and botanical ingredients using chronic studies, many consumers use botanical supplements with the aim of alleviating short-term symptoms. In a PLANTLIBRA consumer survey covering the usage of plant food supplements in 6 European countries, 22.2% of respondents reported using PFS products when experiencing a ''flare-up or worsening of a condition'' (Garcia-Alvarez and others 2014). In addition, some supplements may contain statements warning consumers not to consume products for longer than certain periods arising from issues identified in a safety assessment. For example, the EMA's community herbal monograph on bitter fennel notes that the botanical should not be taken for periods exceeding 2 wk (EMA 2007b). This limit of 2 weeks was established considering the lack of available safety data on long term use of fennel preparations at the time of evaluation by the EMA, as well as the traditional short term use of such products in self-medication (EMA 2007a).

Despite these trends indicating the existence of less-than-lifetime exposure to botanical supplements, such considerations and their effects on the outcome of safety assessments of botanical supplements has not been well elucidated in the official guidance documents of the reviewed jurisdictions. Indeed, the current methods for quantitative risk assessment are designed to generate risk values that are protective for the worst case assumption of daily exposure over an entire lifetime. Although these conservative estimates are deemed protective, disadvantages may also occur, such as the prevention of any additional uses of botanicals containing substances that are deemed to be near or exceeding their respective health-based guidance values. For example, the ESCO Working Group on Botanicals and Botanical Preparations (2009) conducted a risk assessment exercise on the risks of exposure to estragole from the consumption of bitter fennel tea using the ''Margin of Exposure (MOE)'' approach, and estimated a MOE of about 34 to 1000. The MOE approach is a tool used by risk assessors to prioritize the risk from exposure to genotoxic and carcinogenic substances. The MOE is defined as the ratio between a dose level inducing a certain increase in tumor incidence and the estimated daily intake of the compound under consideration (EFSA 2005). Smaller MOE values represent larger risks as compared to larger values, with MOE values above 10000 considered by EFSA to be of low concern from a public health point of view with respect to the carcinogenic effect (EFSA 2005). MOE values of 34 to 1000 would thus be considered to be of high priority for risk management, and could possibly result in the prevention of any additional use of bitter fennel in new botanical supplement products. One could argue, however, that for shorter than life-time exposures an MOE value based on life-time exposure may be unnecessarily conservative.

At present there is no generally agreed method or guidance in any of the guidance documents on how to take such short-term exposure conditions into account when considering short-term use of a botanical food supplement. Although a staged threshold of toxicological concern (TTC) concept to address short-term exposure to genotoxic impurities with unknown carcinogenic potential in pharmaceuticals has been developed (Muller and others 2006; FDA 2008; EMA 2010; Schilter and others 2014), a similar approach has not been extended to botanical ingredients.

In the case of exposure to botanical ingredients that are both genotoxic and carcinogenic, some examples exist where authors have applied extrapolation of the exposure using Haber's rule to illustrate the impact of less-than-lifetime exposure in botanical supplement risk assessment (Felter and others 2011; van den Berg and others 2014; Abdullah and others 2016). Haber's rule states that the product of exposure concentration and time would result in a constant toxic response of a substance ($C \times T = k$, where C is concentration or dose, T is time, and k is a constant toxic response for the specific substance; Rozman and others 2010). Its application in cancer risk assessment thus assumes that the carcinogenic potential of a substance is related to the lifetime cumulative dose received (Felter and others 2011).

Through the application of Haber's rule, van den Berg and others (2014) for example, have reported that the consideration of less-than-lifetime exposure to estragole from use of fennel teas could result in margins of exposure (MOEs) that are 3 orders of magnitude higher than those derived based on assumptions of lifetime exposure. Assuming that all other factors are constant, such differences in MOEs due to the consideration of less-than-lifetime exposure could shift the outcome of the risk assessment of estragole in fennel tea from being a high priority for risk management to a low priority for risk management.

However, recent estimations by Abdullah and others (2016) have suggested that even after taking into consideration less-than-lifetime exposures in the risk assessment of aristolochic acid levels in plant food supplements and herbal preparations reported in the literature, more than 50% of the samples considered would still present MOE values below 10000. These 2 examples represent the nascent stage of applying Haber's rule in the MOE approach in risk assessment in the published literature. Further development in this application of Haber's rule should be made cautiously, considering actual consumption patterns of botanical food supplements, as well as the need for detailed insight into the mode of action of the carcinogens of concern, an area where data gaps are common (Felter and others 2011).

Deliberate or accidental misidentification of botanicals and adulteration with pharmacologically active substances

Recent papers and news reports have unveiled risks associated to economically motivated fraud in botanical food supplements, and cases of botanical supplements containing misidentified components, or adulterated with illegal drugs (Colombo 2016; Curry and others 2016; Rocha and others 2016).

Misidentification of botanicals in herbal supplements in the past has resulted in severe and even fatal outcomes. Vanherweghem (1998) described the occurrence of at least 100 cases of extensive interstitial fibrosis of the kidneys observed in Belgian women who had followed a weight loss program which included the use of Chinese herbs. Investigations following these cases suggested that

the prescribed herb *Stephania tetrandra* (*Han Fang Ji "漢防己"*) was in fact mistakenly replaced with another Chinese herb *Aristolochia fangchi* (*Guang Fang Ji* "广防己"), as evident from the absence of tetrandrine, a characteristic alkaloid in *Stephania tetrandra,* in the capsules taken by patients. In addition, it was noted that the Chinese characters and pinyin name of the 2 herbs were similar with the exception of the prefix, and hence could have been easily confused for each other (Vanherweghem 1998).

An investigation by the New York State Office of the Attorney General (2015) on store brand herbal supplements sold by 4 major retailers, found that only 21% of herbal supplement products analyzed using DNA-barcoding methods, were positive for the products' respective labeled botanicals. The remaining 79% of store-brand herbal supplements either could not be verified to contain the labeled botanical, or were found to contain ingredients that were not listed on the labels. These findings echoed those that had been previously reported by Newmaster and others (2013), who found that 59% of herbal products tested using DNA-barcoding methods, contained DNA-barcodes from plant species that were not listed on the labels.

When considering the above, it is also important to note that DNA-barcoding methods for the authentication of botanicals in herbal supplements have not been validated, and the use of these methods in regulatory frameworks is currently being debated (United States Pharmacopeial Convention [USP] 2015; Tims 2016). In particular, DNA-barcoding methods utilizing universal barcode sequences have been found to be unsuitable for the authentication of botanical extracts and finished botanical supplement products (Wohlmuth and others 2016).

In addition to risks arising from the misidentification of botanicals in supplements, multiple reports of botanical supplements marketed for use in weight loss, body building or athletic performance, and sexual performance, being adulterated with active pharmaceutical compounds have been reported (Avigan and others 2016). Based on a compilation by Rocha and others (2016) of studies performed on the analysis of adulterants in weight loss dietary supplements, body building and athletic performance supplements, and sexual performance enhancement supplements, the percentages of total adulterated samples in each of these categories were 33.9% (195 out of 575 samples), 19.4% (140 out of 721 samples), and 43.7% (419 out of 957 samples), respectively. In one of these studies, an investigation of botanical food supplements for weight loss, sampled on the Dutch market, reported that 24 out of 50 samples contained active pharmaceutical substances such as sibutramine, desmethylsibutramine, didesmethylsibutramine, rimonabant, sildenafil, and/or the laxative phenolphthalein (Reeuwijk and others 2014). In addition, the authors noted that 20 out of these 24 samples contained sufficiently high levels of these active pharmaceutical substances to potentially result in pharmacological effects if consumed.

In an earlier study that sampled botanical food supplements claiming sexual potency from the Dutch market, Reeuwijk and others (2013) identified phosphodiesterase type 5 (PDE-5) inhibitors, such as sildenafil and analogous PDE-5 inhibitors in 23 out of 71 samples. Levels of adulterants in 18 of these 23 samples were sufficiently high enough to conceivably result in pharmacological effects if consumed.

The risks in botanical food supplements associated with economically motivated fraud, misidentified ingredients, or adulteration with illegal drugs are unlikely to be mitigated by national authorities at the stage of safety assessment of botanicals and botanical ingredients. Although mandatory pre-market approval is necessary in some of the jurisdictions reviewed, this alone is not able to prevent the occurrence of the above issues once market access has been granted. Rather, continuous monitoring by both national authorities, and careful adherence to good manufacturing practices by industry members will be necessary.

The large number of botanicals makes it tedious and expensive to generate toxicological data and safety assessments

Despite the large amount of published literature investigating the beneficial effects of botanicals, relatively few botanicals have been subject to rigorous safety assessments. Often investigations of botanical ingredients begin with the aim of verifying efficacy of traditional or folklore medicinal usage, rather than of assessing safety. Even when safety assessments are conducted, issues such as differences in purity or extraction methods of botanical materials mean that the outcomes of these safety assessments cannot be easily used to assess the safety of the same botanical extracted using other processes. This has been seen in the assessments conducted by the U.S. National Toxicology Program (NTP) Botanical Dietary Supplements Program, which has conducted 2-y carcinogenicity studies for 10 botanical substances thus far, and is in the process of conducting studies for 8 further botanical substances (NTP 2016). Despite the considerable resources put into such studies, a past NTP study, concluding that *Ginkgo biloba* leaf extract caused cancers of the thyroid gland in male and female rats and male mice and cancers of the liver in male and female mice (NTP 2013), received criticisms that the study had used an extract of inappropriate purity as study material, and that doses administered were too high to be of relevance for humans (Intertek Cantox 2012; Rider 2016). Such issues undermine the utility of scientific studies in the literature on toxicological data, which is already scarce.

To overcome such difficulties, some authorities have attempted to design new methods in safety assessment that would be able to facilitate the consideration of large numbers of botanical substances. A prominent example of such innovation has been EFSA's attempt to develop a "QPS" approach, which is currently in use for the safety assessment of microorganisms added to the food chain, for the assessment of botanicals (EFSA Scientific Committee 2014). A key concept in such a QPS approach would be for botanicals for which an adequate body of information exists to benefit from a "presumption of safety" and thus be considered safe for human consumption without having to undergo additional toxicological testing (EFSA Scientific Committee 2014).

One of the benefits of the use of the QPS approach in microorganisms lies in that safety considerations could often be applied to high taxonomic levels. Unfortunately, however, it has been challenging to apply this benefit for botanicals. This is due to the wide variability in morphology and chemical composition in the same botanical species, being affected by geographical and environmental factors (Stegelmeier and others 2015). For example, using chromatographic fingerprint and chemometric approaches, Sun and Chen (2011) demonstrated that differences in ginsenoside compositions existed between *Panax quinquefolius* samples cultivated in the USA and those grown in China.

Another tool implemented by EFSA is the compendium of botanicals that are reported to contain toxic, addictive, psychotropic, or other substances of concern. Rather than being simply a legal negative list, the compendium provides a uniform platform and reference that facilitates hazard identification when the various Member States of the EU carry out risk assessments of new botanical ingredients (EFSA 2009). Although the EFSA

compendium identifies possible hazards without providing further information needed for subsequent risk assessment, it is a useful common overview for botanicals and botanical ingredients of possible concern. In addition, when considering the quality control of botanical preparations, one important challenge is the complex nature of the respective mixtures and the difficulty in their analysis. Efforts to date focus mostly on targeted analyses in order to quantify chemical constituents of concern that are known to be present in specific botanicals. This is where lists such as the EFSA compendium may be of use. However such a targeted analytical strategy would not facilitate detection of unknown chemical constituents of concern. To that end, one may consider use of bioassays. This would also allow for detection of effects that result from multiple target interactions (Prinsloo and others 2017).

The utilization of positive and negative lists for ingredients that may or may not be used in botanical food supplements has already been used in the regulatory frameworks of various countries. Positive lists specify botanical ingredients that may be used in the country, whereas negative lists specify those that are not allowed (Shao 2017). In a review of market requirements for supplements, Shao (2017) found more countries utilizing positive lists as compared to those utilizing negative lists. Countries noted to utilize positive lists include Australia, Brazil, China, India, Mexico, Russia, Venezuela, Italy Denmark, and the Czech Republic (Shao 2017). The level of similarity between the positive ingredient lists in these countries, however, is currently not known. The "BELFRIT" project mentioned in this paper is an example of countries working together to harmonize recognized botanicals so as to facilitate trade of botanical food supplements. Such collaborative efforts may also be useful for regulatory authorities in managing scarce resources by avoiding duplicate risk assessment work across jurisdictions for the same botanical ingredients.

Conclusions

The popularity of botanical food supplements and increasing innovation in the use of previously unutilized plant species, provide impetus towards the further understanding on the risks of consuming such products. Although current research suggests that adverse effects related to the consumption of botanical food supplements remains relatively rare, new trends such as the increasing prevalence of economically motivated fraud and adulteration of products with active pharmaceutical substances require attention from regulators in order to ensure public safety.

Furthermore, the world currently appears to have a fragmented approach towards the regulation of botanical food supplements, with some countries regarding these as foods, whereas others consider them as medicines. The birth of internet sales of botanical food supplements has further complicated matters as consumers can now easily purchase products from across the world.

To address these issues and ensure public health, increasing regulatory oversight for botanical food supplements seems inevitable. However, the regulatory burden of increased regulation cannot be ignored. Harmonization of risk assessment criteria as well as the creation of internationally recognized compendia of botanicals should be emphasized as a way forward. The international regulatory community may also wish to create a list of botanicals with known safety concerns akin to the botanical compendium as established by EFSA as a start.

Although some authors, such as Zakaryan and Martin (2012), have advocated mandatory pre-market approval of botanical supplements as a means towards ensuring product safety, our review of the current regulatory frameworks and the vast number of existing and new products on the market suggest that such an approach would be unrealistic, not least because of the additional regulatory burden on both national authorities and businesses, but also due to technical challenges posed by the natural variation in the composition of botanicals, difficulties in technical analysis of specific chemical constituents of concern, as well as differences in extraction methods for various extracts. Furthermore, checks at only the point of market access does not prevent risks occurring from subsequent misidentification of botanicals used, or the deliberate adulteration of products with pharmaceutically active compounds, issues which require continuous monitoring by both national authorities, as well as careful adherence to good manufacturing practices by industry members.

Finally, national authorities and industry should attempt to shift consumers' mind-sets towards botanical food supplements. Rather than expecting "natural" supplements to be "safe," consumers should be educated to expect that toxins can enter the botanical food supplement chain even through "natural" ingredients, and consume such products with discretion and also to consult qualified healthcare practitioners before making decisions on chronic consumption of any specific botanical food supplement.

Abbreviations

ARTG	Australian Register of Therapeutic Goods
BfR	German Federal Institute for Risk Assessment
CAC	Codex Alimentarius Commission
CFDA	China Food and Drug Administration
CJEU	Court of Justice of the European Union
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
FFC	Foods with Function Claims
FNFC	Foods with Nutrient Function Claims
FOSHU	Foods for Specified Health Uses
FSSAI	Food Safety and Standards Authority of India
HMP	Herbal Medicinal Products
MOE	Margin of Exposure
NDI	New Dietary Ingredient
NHP	Natural health products
NTP	U.S. National Toxicology Program
PA	Pyrrolizidine alkaloid
PDE-5	Phosphodiesterase type 5
PFS	Plant food supplement
SUKL	Czech State Institute for Drug Control
TGA	Therapeutic Goods Administration, Australia
THMP	Traditional herbal medicinal products
USA	United States of America
WHO	World Health Organization

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Authors' Contributions

T. Y. Low collected the data and wrote the manuscript. K. O. Wong and A. L. L. Yap conceptualized and critically reviewed the part on regulatory frameworks. I. M. C. M. Rietjens conceptualized and planned the parts on comparison of assessment criteria and future issues and critically reviewed the manuscript. Laura H. J. De Haan critically reviewed the manuscript.

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