Regulatory Toxicology and Pharmacology 114 (2020) 104647

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Regulatory landscape of dietary supplements and herbal medicines from a global perspective

Shraddha Thakkar[a], Elke Anklam[b], Alex Xu[c], Franz Ulberth[b], Jing Li[d], Bo Li[e], Marta Hugas[f], Nandakumara Sarma[g], Scott Crerar[h], Sibyl Swift[i], Takashi Hakamatsuka[j], Valeriu Curtui[f], William Yan[k], Xingchao Geng[e], William Slikker[a,**], Weida Tong[a,*]

[a] National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA), USA
[b] European Commission, Joint Research Centre (JRC), Belgium
[c] Center of Drug Evaluation (CDE), National Medical Products Administration (NMPA), China
[d] Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), USA
[e] National Institutes for Food and Drug Control (NIFDC), National Medical Products Administration (NMPA), China
[f] European Food Safety Authority (EFSA), EU, Italy
[g] US Pharmacopeia (USP), USA
[h] Food Standards Australia New Zealand (FSANZ), Australia
[i] Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA), USA
[j] National Institute of Health Sciences (NIHS), Japan
[k] Health Canada (HC), Canada

ARTICLE INFO

Keywords:
Dietary supplements
Herbal medicine
GSRS
Regulatory science
Emerging technology
Harmonization

ABSTRACT

The number of Individuals that use dietary supplements and herbal medicine products are continuous to increase in many countries. The context of usage of a dietary supplement varies widely from country-to-country; in some countries supplement use is just limited to general health and well-being while others permit use for medicinal purposes. To date, there is little consensus from country to country on the scope, requirements, definition, or even the terminology in which dietary supplement and herbal medicines categories could be classified. Transparent science-based quality standards for the ingredients across these regulatory frameworks/definitions becomes even more important given the international supply chain. Meanwhile, there has been a rapid advancement in emerging technologies and data science applied to the field. This review was conceived at the Global Summit on Regulatory Sciences that took place in Beijing on September 2018 (GSRS2018) which is organized by Global Coalition for Regulatory Science Research (GCRSR) that consists of the global regulatory agencies from over ten countries including the European Union. This review summarizes a significant portion of discussions relating to a longitudinal comparison of the status for dietary supplements and herbal medicines among the different national jurisdictions and to the extent of how new tools and methodologies can improve the regulatory application.

1. Introduction

The use of dietary supplements and herbal medicines derived from natural substances for improved quality of life or their purported benefits has increased worldwide (Eisenberg et al., 1993, 1998; Mahady, 2001). Even though, herbal medicines have been present for centuries, the chronology of regulation of herbal medicines varies across jurisdictions, where in some countries, it has been in existence for long time, whereas some countries started regulating recently. Additionally, sometimes the emotion is also attached with remedies that may be within a family or practiced among a population for centuries. The use of many dietary supplements and herbal medicine could be based on the knowledge from traditional medicine practices. Products that contain this type of ingredients are often marketed to the consumer by highlighting specific “health claims”. Without proper education or context pertaining to “health claims”, it may lead to the improper substitution of these products for drugs which could be potentially dangerous for the consumer (Ernst, 1998; Moreira et al., 2014; Zhu

* Corresponding author.
** Corresponding author.
E-mail addresses: william.slikker@fda.hhs.gov (W. Slikker), weida.tong@fda.hhs.gov (W. Tong).

https://doi.org/10.1016/j.yrtph.2020.104647
Received 7 January 2020; Received in revised form 19 March 2020; Accepted 23 March 2020
Available online 16 April 2020

et al., 2019). As serious adverse effects of these products, including hepatotoxicity, renal failure, and carcinogenicity have been reported, their safety has become an essential issue for regulatory authorities (Avigan et al., 2016; Geller et al., 2015; Stickel et al., 2005; Vanherweghem, 1998; Zhu et al., 2019). Due to the gap between increased usage of these products and lack of knowledge about their risks and benefits, it is of importance to global regulatory agencies to discuss their respective regulatory principles and understand the potential utility of emerging technologies and big data for an improved and harmonized regulatory framework to guide the safe application of dietary supplements and herbal medicines.

In a common use, natural substances can be treated as either “supplements” to improve health or “medicines” for illness. However, the line between the two varies significantly across countries depends on how they are regulated. Therefore, the primary challenge to initiate any conversation related to regulations in this field is the lack of global consensus on the definition and categorization of a product (Borins, 1998; Kayne, 2010). This is likely due to the fact that there are multiple independent decisions to treat these products differently in different jurisdiction regulatory schemes and thus the independent driver towards drawing consensus is a challenge.

While It is not uncommon for dietary supplements and herbal medicines to be considered as two entirely different regulatory categories (Avigan et al., 2016; Rocha et al., 2016; Silano et al., 2011; Swann, 2016), for each category, however, the consensus for regulation is also lacking across countries (Low et al., 2017). In one aspect, such a variability reflected in the way quality standards are regulated in different countries (Commission et al., 2007; Sahoo et al., 2010). Most agencies follow risk-based approaches (Avigan et al., 2016; Low et al., 2017) where consistent standards, particularly in quality, should be applied to achieve some degree of harmonization across regulatory frameworks in different countries. It is important to point out that a significant challenge faced by regulatory agencies is that many of the herbal medicine and dietary supplement products are mixtures or blends of same product produced by different sites and little is known about the supply chain. To better address the quality issues, for example, pharmacopeias around the world such as the United States Pharmacopeia, the European Pharmacopeia, and the Pharmacopeia of the People's Republic of China, to name a few, are setting quality standards for an increasing number of herbal medicine and dietary supplement ingredients and finished dosage forms. In addition, there have been several efforts from the World Health Organization to discuss how it may be feasible for dietary supplements ((WHO), 1999; (WHO), 2003; (WHO), 2010).

Clearly, there exists the variability in distinguishing between dietary supplements for health and herbal medicine for illness and to the extension of regulatory oversight for each category across countries (Boullata et al., 2000; Sahoo et al., 2010). In addition, when health claims are made on the product labeling, which could also pose additional variability (Low et al., 2017; Mahady, 2001; Rocha et al., 2016). Thus, there is an unmet need for the development of a comprehensive approach to evaluating the safety and quality of dietary supplements and herbal medicine. The rapid advancement in emerging technologies such as big data analytics and next-generation sequencing could play a role, which is centered in discussion among the participants in the 8th annual conference of Global Summit on Regulatory Science (GSRS).

The Global Coalition for Regulatory Science Research (GCRSR) was established in 2013, under the leadership of the US Food and Drug Administration (FDA). Its membership is comprised of regulatory bodies from ten countries including the European Union (EU). GCRSR has forged international partnerships and collaborations that focus on adopting emerging technologies and big data science to improved regulatory science research on the safety and efficacy of foods and drugs. To the end, it facilitates and promotes the development of regulatory science research as a tool for advancing regulatory science in a manner that is directly applicable to the public health goal of safe food and therapeutic products. GCRSR has hosted the annual GSRS conference since 2013 as a platform for improved communication among international regulators (Healy et al., 2016; Pettitt et al., 2016; Slikker et al., 2018; Tong et al., 2015). The 2018 GSRS (GSRS2018) was the 8th consecutive annual summit was held September 26–27 in Beijing, China at the National Institutes for Food and Drug Control. The topics discussed this occurrence of the meeting covered some of the risk and benefit associated with dietary supplements and herbal medicines. The presenters represented 10 countries including China, Korea, Japan, and India), EU, USA, Canada, and Australia. The summit began with a discussion on the global regulatory structure for dietary supplements and herbal medicine. It was estimated that, over 80% of the world's population uses dietary supplements or herbal medicine. Based upon the magnitude of that figure, there was a dedicated session for discussion of their safe use (Low et al., 2017). The summit concluded with discussions that focused on the challenges and opportunities of using new tools and methodologies in this area.

This paper summarizes some of the key topics discussed in GSRS2018. The conference surveyed and compared the regulatory structure for dietary supplements and herbal medicines across several nations, with a specific emphasis on how the existing structure in each country responds to emerging products in these categories. Manuscript is focused on the regulatory framework of seven regulatory bodies and its comparative. Additionally, this manuscript also discusses that way new tools and methodologies like next-generation sequencing (NGS) and data analytics may play a role in the future regulatory application were emphasized.

2. Definitions, terminologies and classifications

Several terms were discussed during the conference; however, while many of the terms can be used interchangeably, some of them have very specific definitions that would prevent this from occurring. Table 1 summarizes the primary terms used by some of the regulatory agencies that participated at GSRS2018, including those from the USA, Canada, Japan, China, EU, and Australia. Differences in terminologies could result in a product being categorized in a completely dissimilar manner, this causing wide variations in regulatory decisions that vary significantly from country to country. For example, if a product is regulated under the food-related regulation, in most cases, a therapeutic claim cannot be made. If a product is regulated under the medicine category in a particular jurisdiction, therapeutic claims can be made, but every jurisdiction has different pre-approval requirements.

For the convenience of discussion in this manuscript, natural products used in this context were divided into two categories, “Classified as Supplements” and “Classified as Medicines”. The former is used as supplements for health benefits with no or limited claim on therapeutic effects while the latter is used for the treatment of illness with announced health claims. Table 2 summarized some critical aspects of both categories across countries. However, these claims are usually varied by the jurisdiction.

3. Regulatory landscape

3.1. Regulation in the United States of America

The US-FDA regulates products marketed as dietary supplements under the Federal Food, Drug and Cosmetic Act (the FD&C Act) as amended by the Dietary Supplement Health and Education Act (DSHEA) of 1994 (FDA, 2019a,b; Denham, 2011; Hathcock, 2001; Ross, 2000). The FD&C Act defines dietary supplement as a product, other than tobacco that are intended to supplement the diet and that contain one or more of the following dietary ingredients: a vitamin; a mineral; a herb or other botanical; an amino acid; a dietary substance, for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any

Table 1
Main terminologies and definitions for dietary supplements and herbal medicine presented in GSRS2018

Terminology	Official terminology of Country	Definition
Dietary supplements	United States	In the USA, the term dietary supplements are legally defined for the product "The Federal Food, Drug, and Cosmetic Act defines a dietary ingredient as a vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of the preceding substances Unlike drugs, supplements are not intended to treat, diagnose, prevent, or cure diseases. That means supplements should not make claims, such as "reduces pain" or "treats heart disease." Claims like these can only legitimately be made for drugs, not dietary supplements. Dietary supplements include such ingredients as vitamins, minerals, herbs, amino acids, and enzymes. Dietary supplements are marketed in forms such as tablets, capsules, softgels, gelcaps, powders, and liquids".
Herbal medicines		Herbal medicine interpreted differently in a different jurisdiction. To bring the harmonization for the international efforts, WHO considers herbal medicine that includes herbs, herbal materials, herbal preparations. The herbal preparation could have the active ingredients that are either part of one plant or derived from the combination of the multiple plants. However, some herbal medicine preparations at some countries contain the active ingredients from non-plant source as well, such as minerals or animal parts. In the USA, herbal medicine would come under botanicals, some of which are included under dietary supplements. In New Zealand, known as Herbal Remedies while in EU known as Herbal Medicinal Products. Different jurisdictions have a difference in regulation.
Functional food		There is no defined and legal terminology, however, it is used as an alternative term for the 'nutraceutical,' with the concept that foods can have some health benefits. Functional food can be an extract, powder, or other processed forms originated from normal food such as gapes and peanuts that contain resveratrol with antioxidant properties. Health Canada has the definition of 'nutraceutical,' and is considered as the product originated from the food. In the EU legislation, "functional foods" or "nutraceuticals" are not recognized categories.
Health food	Japan and China	Japan and China mainly use the term health food, but with different regulatory processes. The general concept of health food is that the food contains nutrient as well as health benefits. Thus, some permitted health-related claims can be made. In Japan, health and nutrition claims handled separately, processing via different regulatory route while, in China, the claims are restricted to the pre-defined twenty-seven health claims.
Natural Health Products	Canada	Natural Health Products (NHP) is the category created for a variety of products that are naturally sourced products intended for improving human health. This is well defined in Canada and contains a variety of products like vitamins, minerals, herbal and homeopathic medicine and traditional medicines (e.g., Traditional Chinese Medicine).
Food supplement		These foods are packed with nutrients or other substances with a nutritional or physiological effect, and mainly contained in the concentrated form and available in specific dosage form to supplement the normal diet. Food supplements can bear approved nutritional and health claims, but medical claims are not permitted. Food supplements are defined in EU as food and monitored through centralized legislation.
Novel food	EU, Canada, Australia	Novel food is mainly defined in EU and Canada and Australia, to deal with the category of the food that was not consumed as food historically in that region. Certain alterations to the regular food could be considered as novel food such as using new technologies or production processes (e.g., bioengineering, nanotechnology, or UV treated food, etc.), or upgraded with the addition of nutrients, or used the new sources for known products.
Complementary medicine	Australia	It is mainly used in Australia as a regulatory term. It denotes to all the health care practices that are not conventional part of a country's health care practices. Health care system from those countries is not integrated with these practices.
Alternative medicine		It is commonly used to cover the health care practices which were not considered the part of the conventional healthcare system and practices. These practices sometimes considered to have not enough scientific evidence to prove their efficacy and used in substitution of conventional practices.
Traditional medicine		These are practices that have a long history of usage in particular jurisdiction. The practice could be a combination of beliefs, knowledge, and skills in addition to medicine. It could be used for preventative, diagnosis, or treatment of physical and mental health.
Traditional Chinese medicine (TCM)	China	It is part of ancient Chinese healthcare system. This system includes medicines, practices, acupuncture, massage and have preventative health as well as restoring the health. The medicines can be single herb, complex combination from plant or animal origin. Some of the cases prescribed by the health care practitioner. TCM are still integral part of Chinese healthcare system with hospitals and health care practitioners are there to monitor as well as prescribe the medicine or combination of therapy to the patients.
Kampo medicine	Japan	It is popular in Japan and derived from the ancient version of Traditional Chinese Medicine. Although Kampo medicine and TCM share a similar philosophy, the ingredients are different. Specifically, Kampo medicine has evolved and modified to incorporate materials from Japanese origin.

Table 2
Natural products "Classified as Supplements" or "Classified as Medicines" in different jurisdiction.

Country	Regulatory Agency	Classified as Supplements	Classified as Medicines
USA	Food and Drug Administration (FDA)	**Dietary Supplement - Center for Food Safety and Applied Nutrition (CFASN)/FDA** • Herbs/Botanicals • Vitamin • Minerals • Amino Acids • Dietary substance for use by man to supplement the diet by increasing the total intake • Concentrate, metabolite, constituent, extract or combination of the preceding substances.	**Botanical drugs - Center for Drug Evaluation and Research (CDER)/FDA**
Australia	Therapeutic Goods Administration (TGA)		**Complementary Medicines - Complementary and OTC Medicines Branch/TGA** • Herbs • Vitamin • Minerals • Nutritional supplements • Homeopathy • Microorganism (whole extracted) etc.
Australia	Food Standards Australia New Zealand (FSANZ)	**Novel Food** • Foods and extracts from plants, animals, etc., • Foods and their extracts resulting from production processes and practices, and new technologies.	
New Zealand	New Zealand Ministry for Primary Industries (MPI)	**Supplemented food** • Foods modified or with added substances so that they perform a physiological role	
New Zealand	New Zealand Medicines and Medical Devices Safety Authority (Medsafe)	**Dietary supplements**	**Herbal Remedies**
New Zealand	Food Standards Australia New Zealand (FSANZ)	**Novel Food** • foods and extracts from plants, animals, etc., • Foods and their extracts resulting from production processes and practices, and new technologies.	
Canada	Health Canada (HC)		**Natural Health Products** • Traditional medicine • Herbal Medicine • Homeopathy
China	China Food and Drug Administration (CFDA)	Health foods	Traditional Chinese Medicine
Japan	Ministry of Health, Labor and Welfare (MHLW) for Medicines Consumer Affairs Agency (CAA) for Supplements	Health foods	**Kampo Medicine**
EU	European Medicines Agency (EMA)		**Herbal Medicinal Products** National competent authorities of EU Member States
EU Member States	National competent authorities European Food Safety Authority (EFSA) if centralized procedures apply	Substances with a nutritional or physiological effect (vitamins, minerals, botanicals, etc.)	

ingredient described previously (FDA, 2019). Dietary supplements must be intended for ingestion; therefore, they cannot be indicated for use though any other means (e.g., sub-lingual, injected, inhaled, etc.). They also cannot contain ingredients that were previously approved or studied as drugs (unless they were marketed as a dietary supplement prior to being approved as a drug). Unlike FDA's regulation of drugs, where safety and efficacy need to be proven before approval, dietary supplements are primarily regulated through post-market surveillance and are not approved at all (FDA, 2017). Generally speaking, new dietary ingredients that are introduced after 1994 should undergo a safety review through the New Dietary Ingredient Notification (NDIN) process, although there are exceptions to that requirement (FDA, 2016). In order to market dietary supplements in the United States, pre-marketing approval is not required; however, the responsibility is on the manufacturer ensure that their product is safe for the population and conditions of use is specified on the label. Under U. S. law, dietary supplements may not be marketed to diagnose, cure, mitigate, treat, or prevent disease (FDA, 2016).

FDA regulates drugs that contain botanical ingredients in a different manner; there products are intended to diagnose, cure, mitigate, treat or prevent disease. Products in this category must follow the appropriate pre-market approval process (FDA, 2016). Currently, there are only two FDA-approved botanical drugs, Veregen® (sinecatechins ointment) (FDA, 2006; Abramovits and Gupta, 2010) that is indicated for the topical treatment of external genital and perianal warts and Mytesi® (crofelemer)that is used for symptomatic relief of non-infectious diarrhea in patients with HIV/AIDS on anti-retroviral therapy (Klein et al., 2013; Zhang et al., 2013).

3.2. Regulation in Australia

In Australia, most natural products such as herbal, vitamin, mineral, and nutritional supplements are treated as "complementary medicines" with the mission of better health in mind and termed as the "therapeutic goods," regardless of whether they are "Classified as Supplements" or "Classified as Medicines" (TGA, 2013). These products are regulated under the Therapeutic Goods Act (TGA), which was established in 1989, which also regulates the medicinal products. Some products could be in both "Classified as Supplements" and "Classified as Medicines" categories. The Australian government provides the Food-Medicine Interface Guidance Tool to characterize a product. The products that is classified as therapeutic goods (including medicine) are

regulated by TGA at federal level, however, the food (food with health claim) are mainly regulated by state authority and regulatory bodies that controls territory food. The products are divided into two categories, "low-risk medicines" and "high-risk medicines," which are available from the Australian Register of Therapeutic Goods (ARGT) (TGA, 2013). The regulatory guidance is provided at the Australian Regulatory Guidance for complimentary Medicine (ARGCM), that provides the details on requirements to be low risk or high-risk medicine. Low-risk medicines are "listed" (TGA, 2018a) whereas the higher risk medicines must be "registered" (TGA, 2013); the products that are "registered" must be evaluated for their quality, safety and efficacy. While products that are "listed" are not subjected to that requirement. . Some of the “listed” complementary medicine also assessed by TGA which tend to make slightly riskier health claims comparatively. However, “registered” complementary medicines are those that either contain ingredients with higher risk or make health claims with serious condition. Currently, not many complementary medicines have gone through the "registered" route, and most are just "listed". Specifically, only ~40 complimentary medications are registered (TGA, 2018a) and evaluated at ARGT, while > 11,000 medicines are listed on the register (TGA, 2011). For "Classified as Supplements," some therapeutic claims could be made but must contain a label that states that TGA does not evaluate such a claim.

3.3. Regulation in New Zealand

New Zealand has two categories of products (i.e., Classified as Supplements or Medicines). In the New Zealand's framework, dietary supplements are regulated by the Dietary Supplements Regulations of 1985. Dietary supplements in New Zealand are not required to submit for premarket approval, are supposed to be taken orally with a specific dosage found of the drug label and should not be intended for therapeutic purposes (Medsafe, 2019). The category of dietary supplements also contains animal-derived products, when the products contain ingredients from animal or animal product origin. This subcategory is required to follow either the Animal Product Act 1999 or Food Act of 2014. New Zealand also has a Supplemented Food Standard that sets out requirements for products that are represented as foods but have been modified in some way or had substances added to them (i.e., certain vitamins, minerals, herbals and bioactive) so that they perform a physiological role as defined in the New Zealand Food Safety (2016) as “Supplemented Food” (NZFS, 2016). Of note, New Zealand legislation is working on a Natural Health Product Bill that will supersede the Dietary Supplements Regulations, (1985) once approved (New Zealand Parliament, 2011). The new bill encourages the use of new tools and methodologies, such as an electronic database Where manufacturers will be required to register their product and provide evidence in the report format to support any health claims that they make about the product effects (NewZealandParliament, 2019).

3.4. Regulation in Canada

Like Australia, in Canada, most natural products, if not all of them are classified as a subclass of medicine “Classified as Medicines,” are called natural health products (NHPs) and are regulated by Health Canada (HC). NHPs are regulated under the Natural Health Products Regulations (NHPR), which were enacted in2004 (HC, 2016a). The regulations set out in the NHPR provide for product and site licensing requirements (e.g., manufacturing, importing, distributing), good manufacturing practices, adverse reaction reporting, clinical trials, as well as labeling, including warnings and recall features. Evidence for the health claims that are made on product labels is required for ensuring both safety and efficacy (HC, 2019b) and could be in the form of a clinical trial, published literature, and pharmacopeia. Health Canada also has published a compendium of monographs of NHPs to which an applicant can attest as their sole source of evidence for safety and efficacy. For quality, applicants must comply fully with the specifications set out in one of the major international pharmacopeias specified in Schedule B of the Canadian Food and Drugs Act (i.e., “Compendium of Monographs”) (HC, 2009). NHPs are required to apply for premarket authorization and submit all material for evaluation by Health Canada before entering the market. This provides Health Canada with the ability to monitor both the manufacturing as well as the post-marketing processes (HC, 2016b). Manufacturers must procure a license for a product to be sold in Canada by providing information that indicates; dose, potency, ingredients, source, and the recommended use. The manufacturer also must meet labeling requirements and adverse reaction reporting requirements established by Health Canada (HC, 2018).

There exists a huge overlap between the herbs and food. Furthermore, clearly defining these products’ regulatory classification is challenging because it is based on intended use of the product (product representation), product format, and public perception and history of use. Herbal medicines can be sold with prevention and therapeutic claims, with the exception of those that overlap with a specific list of serious diseases and disorders. Finally, the manufacturer must adhere to strict labeling guidelines.

Canada is also developing a framework for supplemented foods. An example of a supplemented food would be a pre-packaged product that is manufactured, sold or represented as a food, which contains added vitamins, minerals, amino acids, herbal or bioactive ingredients. Bioactive ingredients are defined as those that may potentially perform a physiological role beyond the provision of nutritive requirements. The current Temporary Marketing Authorization framework for supplemented foods (HC, 2016c) is being used to gather information for the development of evidence-based regulations for this category of foods on an ongoing basis (HC, 2019a).

3.5. Regulation in China

The Chinese Food Safety Law was enacted in 2015. It established a new centralized system under the National Medical Products Administration (NMPA) (Robinson, 2006). Their improved legislation has enhanced the mechanism for record-keeping and registration mechanism (Jiang, 2005). Under the Chinese Food Safety Law, the natural products fall under either “Classified as Supplements” or “Classified as Medicines.” The “Classified as Medicines” products have a strong presence in China and commonly referred to Traditional Chinese Medicine (TCM) (Normile, 2003). The category of TCM includes products that have an extensive history of use by the Chinese population and influenced the traditional medicine around that area such as Kampo medicine in Japan (Jiang, 2005). Therefore, the structure for manufacturing, healthcare system, hospital, and regulation are well established and streamlined for TCM (Jiang, 2005; Xu and Yang, 2009).

The category identified as “Classified as Supplements” is called Health Foods including products that are treated in conjunction with the functional foods under the Chinese Food Safety Law. Manufacturers in China are allowed to market Health Foods that make therapeutic claims out of a list of predefined therapeutic claims (a total of 27 claims at present) (Dobos et al., 2005). Therefore, before these products are approved, they must demonstrate compliance with an extensive testing and premarket approval process, including requirements of toxicity testing when a product contains a new ingredient.

3.6. Regulation in Japan

Japan's recent legislation (2015) is largely adopted from the United States with a few exceptions. Foods in Japan are either regulated as "Foods in General" or "Food with Health Claims” (Tanaka et al., 2004). Under the "Food with Health Claims," there are three distinct categories (Shimizu, 2003): (1) "Food with Nutrient Function Claims" (FNFC) that are mainly vitamins and minerals, (2) "Food for Specified Health Uses" (FOSHU) for other functions, and (3) "Foods with Function Claims"

Table 3
Differences in requirement for natural products "Classified as Supplements" or "Classified as Medicine".

		US	Australia	New Zealand	China	Japan	Canada	EU
"Classified as Supplements"	Agency	FDA	TGA	MEDSAFE	CFDA	MHLW for Medicine CAA for Supplements	HC	EC and National Authorities
	Product	Dietary supplement	NA	Supplemented food Dietary supplements	Health Food	Health food with claims	Supplemented Food	Food Supplements
	Allowed route of admin	Oral only	NA	Oral only	Oral only	Oral only	Oral only	Oral only
	Pre-market approval	no	NA	no	yes	no	yes	Only if considered as "novel foods" safety assessment by EFSA
	Therapeutic claims	no	NA	no	Only from one of 27 predefined	FOHU and FFC can have health claim	no	no
	Recommended dosing	yes	NA	If supplemented food, no If Dietary supplements, yes	yes	yes	yes	yes
	Addition of new compound	Via NDI Notification*	NA	Active ingredient must be listed on website	Apply for registration and show tox data	Needs to go through the registration process	Needs to go through novel food process	Apply for registration
"Classified as Medicine"	Product	Botanical Drugs	Complimentary Medicine	Herbal Remedies	Traditional Chinese Medicine	Kampo Medicine	Natural Health Products	(EMA) Herbal Medicinal Product
	Pre-market approval	yes	yes	yes	yes	yes	yes	Yes
	Clinical trial data	yes	yes	yes	yes	yes	yes	No/yes
	Therapies	Medicine only	Medicines Homeopathy Aromatherapy	Medicine Only	Medicine and Procedure	Medicine and Procedure	Medicine only	Medicine Homeopathy
	Reported adverse reactions/poisonings	yes	yes	yes	yes	yes	yes	Yes
	Historical usage	yes	yes	yes	yes	yes	no	Yes

* This is not an absolute requirement, there are significant exceptions present for this requirement.

(FFC). These categories are regulated under different pathways, that range from rigorous for FOSHU to the short pathways for FFC (Ohama et al., 2008). Consumer Affairs Agency will only allow Health Foods to be marketed as FOSHU if the claims on the product labels have been submitted for examination. FOSHU should contain information about dietary usage and health advantages. Manufacturers should provide evidence on products safety and efficacy-related evidence for approval (e.g. clinical trials). New labeling guidance for FFC was approved in 2015, which includes a simplified marketing process of submission of premarket notification and less rigorous requirements than FOSHU products (Martirosyan et al., 2015).

Products that fall into the practice of Kampo Medicine are "Classified as Medicines" in Japan. Kampo originated in ancient China and later developed distinctively in Japan (Saito, 2000). It is widely used in daily practice by physicians. Products in this category are considered to be the same as a government-regulated prescription drug. Currently, there are 148 kinds of prescription Kampo medicines covered by Japan's national health insurance. In short Japanese law does not distinguish between Kampo medicine and chemically synthesized medicine (Terasawa and Medicine, 2004; Yu et al., 2006). Kampo medicines normally appears on the market in the form of granules but can sometimes be formulated into capsules or tablets. Japan also has over-the-counter (OTC) Kampo medicines. The approval standards for marketing OTC Kampo medicines consist of 294 different formulas.

3.7. Regulation in EU

In the EU, products fall into one of the two categories: “Classified as Supplements” or “Classified as Medicines.” Under the category of “Classified as Supplements,” there are Food Supplements which are regulated as food under the Directive 2002/46/EC (European Commission) (EU, 2002; Gulati and Ottaway, 2006). There is no centralized pre-market authorization for food supplements in the EU. EU Member States may request to be notified when a particular food supplement is placed on the market in their territory so that the competent authority of the Member State may monitor its use in the territory. The harmonized legislation in the EU regulates the vitamins and minerals, and the substances used as their sources, which can be used in the manufacturing of food supplements (EU, 2006; EU, 2015b). For ingredients other than vitamins and minerals, the European Commission has established harmonized rules to protect consumers against potential health risk and maintains a list of substances which are known or suspected to have adverse effect on health and the use of which is therefore controlled (Annex III of Regulation (EC) No 1925/2006) (EC, 2015a). If a product intended to be used in food supplements does not have a history of safe use in the EU prior to 1997, a new production process has been applied, or it contains or consists of engineered nanomaterials, then the product is classified as a novel food. That triggers a request for a safety assessment by the European Food Safety Authority (EFSA) according to Regulation (EC) No 2015/2283 on novel foods (EC, 2015a). Even if the non-harmonized substances are under national legislation, the “principle of mutual recognition” also applies also to food supplements, meaning that Member States are not allowed to prohibit or restrict the import of products from another Member State if such a product is lawfully manufactured or marketed in the exporting Member State. A number of exceptions apply to this principle, among them the protection of health and life of humans, animals or plants (EU, 2015a). Regulation (EC) No 1925/2006 offers the possibility to exclude or restrict the use of substances other than vitamins and minerals in food supplements in case this would represent a potential risk to consumers (EC, 2015a, EU, 2006).

For Novel Foods, the EU has established a harmonized and centralized pre-market authorization. Specifically, one centralized list has been established for the novel foods across the EU (EC, 2015b) and the safety evaluation is also be carried out in a centralized fashion by EFSA. The European Commission consults with EU member states to determine if a novel food should receive authorization. On the other hand, Herbal Medicinal Products are “Classified as Medicines” and regulated under EU medicinal law Directive 2004/24/EC (European Commission 2004) (Fisher and Ward, 1994). The safety, efficacy, and premarket authorization of these products is handled by the European Medicines Agency (EMA) (Benzi and Ceci, 1997; Blumenthal et al., 2000; Calapai, 2008).

4. Comparison of regulatory requirements

Table 3 provides a horizontal comparison across different countries that regulate natural products as either “Classified as Supplements” or “Classified as Medicines”; two primary types of differences were observed.

First, a product could be placed into more than once category, depending upon in which jurisdiction it is marketed and the claims that were associated with it. In countries such as the US, EU, Japan and China, products can be “Classified as Supplements” as well as “Classified as Medicines” depending upon a product and its claims made. Consequently, the regulatory requirements and type of safety assessment vary, and manufacturers must follow and adhere to the guidance provided by the regulatory agencies for each respective market. There are some differences observed between various regulatory bodies regarding the specifics of toxicological data required, and how each utilized clinical trial data, adverse event reports, and historical use of botanicals as medicines and food in their review. Therefore, one must carefully consider how each product is categorized based upon the jurisdiction in which it is manufactured and marketed.

Second, even if a product is classified into the same category, the regulatory requirements across countries could still vary. Regulations are usually consistent for the products that are “Classified as Medicines” across jurisdictions. However, when we consider the products “Classified as Supplements,” the regulatory requirements vary significantly between countries. Despite some inconsistencies between regulatory requirements across various jurisdictions, the one commonality between every county is that the prime focus is the safety of consumer.

5. Green tea extracts and vitamin E as examples

Both green tea extracts and Vitamin E were used as examples by several speakers at GSRS2018 to illustrate the regulatory applications and considerations for natural products.

Green tea is made from the unfermented leaves of *Camellia sinensis* (L.) Kuntze and is frequently used without fermentation. For example, Green tea has been extensively consumed as an infusion in a beverage in Asian countries for centuries. Many people consume green tea as an extract but do so with the perception that it is just as beneficial as the beverage. It is known that green tea extract has a very different chemical composition compared to green tea itself. Moreover, different manufacturing process might produce green tea extracts with different chemical composition. Consumers are often unaware of the critical differences that the type of extraction may yield on an ingredient's effects. Some forms of green tea extract have been linked to reports of liver injury, which led to a warning being issued by several government agencies (Mazzanti et al., 2009; Molinari et al., 2006; Sarma et al., 2008). As shown in Table 4, green tea extract is “Classified as Medicines” in Canada and Australia while “Classified as Supplements” in Japan, China, New Zealand, and the EU. However, it is treated as both a botanical drug for topical use and as a supplement in the US.

Vitamin E is the common term used for a group of fat-soluble antioxidants, which are reported to act to protect against cell damage (Brigelius-Flohe and Traber, 1999; Esterbauer et al., 1989). It is widely used worldwide as a product in the category of “Classified as Supplements.” Vitamin E exists in eight different forms with varying degrees of antioxidant potential. These eight forms can be grouped into two

Table 4
Examples from green tea extract and vitamin E.

Country	Green Tea Extract	Vitamin E
USA	• "Classified as Supplements" ◦ Dietary Supplement ◦ Issued warning Letters for liver damages; Medwatch reports in publications • "Classified as Medicines" ◦ Veregen – ointment containing green tree extract	• "Classified as Supplements"
Canada	• "Classified as Medicines": Natural Health Products (Medicine) ◦ Adverse Drug Reaction monitoring agency reports published	• "Classified as Medicine" ◦ Natural Health Products (Medicine) sold OTC
EU	• "Classified as Supplements" ◦ Food Supplement (food) ◦ Investigated by EFSA and published the report in 2018	• "Classified as Supplements" ◦ Food Supplement (food)
China	• "Classified as Supplements" ◦ Health food and can have claim (food)	• "Classified as Supplements" ◦ Health food and can have claim (food)
Japan	• "Classified as Supplements" ◦ Functional food and can have claim (food)	• "Classified as Supplements" ◦ Functional food and can have claim (food)
Australia	• "Classified as Medicines" ◦ Complimentary Medicine – Registered (high risk) ◦ Issued safety advisory	• "Classified as Supplements" ◦ Complimentary Medicine - listed
New Zealand	• "Classified as Supplements" ◦ Dietary supplements ◦ cited warning from USP	• "Classified as Supplements" ◦ Dietary supplements

categories, tocopherols, and tocotrienols (collectively called "tocols"), where the latter has stronger antioxidant potential than the former (Hosomi et al., 1997; Nukala et al., 2018; Traber et al., 2007). Alpha-tocopherol (belonging to the tocopherol group) is one of the most abundant forms in humans and plants (Burton, 1994; Hosomi et al., 1997). Thus, in most cases, alpha-tocopherol is referred to as "Vitamin E," but which can also be a mixture of tocopherols. In many counties (e.g., US, Australia, Canada, and New Zealand), tocopherols and tocotrienols are treated as separate entities for regulatory purposes. In accordance with this approach, EFSA published in 2015 a scientific opinion on Dietary Reference Values for vitamin E as alpha-tocopherol (EFSA, 2015). In that Opinion, EFSA considers vitamin E as alpha-tocopherol only (EFSA, 2015).

There is a significant variation across countries for the recommended dosage for Vitamin E in the world-wide markets. In the US (Institute of Medicine) (FNB, 2011) and Canada (HC) the recommended dietary allowance (RDA) and the tolerable upper intakes (UL) for the alpha-tocopherol form of Vitamin E is defined as 15 mg/day and 1000 mg/day respectively for adults (both male and female). For females, this dose remains the same during pregnancy and lactation. However, the EU (EFSA), Australia and New Zealand (National health and medical council) recommended that UL should be much lower (i.e., 300 mg/day). Meanwhile, the UL in Japan is different for males (900 mg/day) compared to females (700 mg/day). Significant overages (e.g., above the UL) raises concern about the potential risks associated with excessive intakes of vitamins and minerals (Andrews et al., 2018). Therefore, the recommended level should be harmonized.

The difference in how these products are regulated and the recommendations that are made about them across different countries raises the question of whether and how harmonization could be implementable since there exists a substantial difference in diet, historical knowledge and the consumer, across these countries.

6. The role of emerging technologies

Many countries have acknowledged the role that emerging technologies could play in regulatory function. Therefore, the on-going efforts to incorporate these new methodologies in both quality control and safety assessment was discussed at GSRS2018. Despite of the different nuances between various agencies' regulatory and quality standards there are some global similarities across the globe, serving the basis for global harmonization. It was also recognized that a harmonized approach for improved guidelines is essential to incorporate these new methodologies. One significant challenge that every agency face is how to assess complex ingredients, which gives rise to uncertainty and variability in safety assessments and insufficient data to thoroughly evaluate the claims. The inherent complexities with botanicals demand the use of orthogonal methods that are fit-for-purpose and can discriminate closely related species. Emerging technologies may play an essential role in ensuring the safety and quality of botanical products. Some of the new tool could also be helpful to lead a more transparent system (regardless of whatever regulation is followed). For example, a global surveillance system should be established to track the origins of these products so that characteristics of the products can be accurately communicated. Such a global system may be based on emerging analytical methods to ensure high standards of quality control. In addition, it would be helpful to develop a more transparent system so that this information could be made available to consumers.

Science-based pharmacopeial standards, such as the up-to-date standards, can play a critical role in this regard by providing a common understanding of appropriate quality attributes for botanical products and their ingredients to the benefit of manufacturers, regulators and all other stakeholders across the supply chain. These publicly available specifications incorporating appropriate emerging technologies, combined with recognized principles of GMPs, represent a vital element of the quality assurance of dietary supplements and herbal medicines. Transparent public quality standards (monographs, general chapters and Reference Standards) for herbal medicines and botanical dietary supplements are developed through collaboration with global stakeholders and expert volunteers. To define all attributes of quality, USP monograph contains the specification for the article, which includes tests, procedures, and acceptance criteria. In addition, USP monographs include several components, including definition, description, packaging, storage, and labeling statements.

As depicted in Fig. 1, there are numerous emerging tools, technologies, and methodologies that could be relevant to quality control and/or safety assessment, all of which have been presented and actively discussed during GSRS2018, and their potential application for both quality control and safety assessment was appreciated by attendees. (Table 5).

7. Challenges

It appears the lack of global consensus mainly due to the fact that there is a difference in the regulatory definition and categorization of products between countries. Generally, when a product is "Classified as

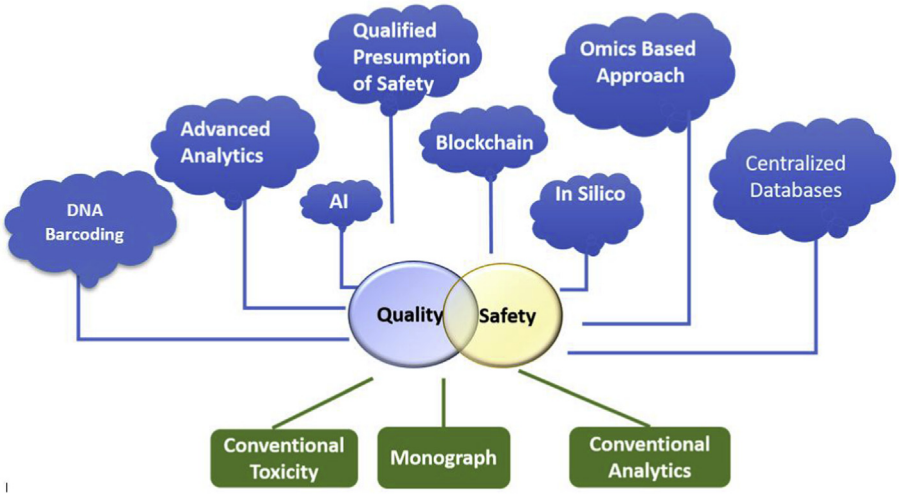

Fig. 1. Conventional and emerging safety and quality assessment methods presented at GSRS18.

a Supplements" nutritional claims and/or health claims may be made, though the specifics of the claims that are allowed vary based on the regulatory framework in the country in which they are made. However, when a product is "Classified as Medicines" some countries' regulations allow medical claims in addition to the health claims. For a harmonized approach towards the risk assessment of dietary supplements and herbal medicine, guidance documents need to be updated to account for evolving scientific advances. Furthermore, some areas within the guidance documents that have not yet received consideration in particular those related to risk and safety assessment, should receive attention. Although guidelines in some countries may include a safety evaluation of the long-term exposure based on chronic studies, many consumers may use botanical supplements for a short duration and therefore, guidelines should reflect the short-term exposure as well. Moreover, there is no harmonization in the recommendations for intake levels by various regulatory bodies, and different agencies may set drastically different levels for the same botanical product. Toxicological information that can be shared among the various agencies would be a useful resource. Considering the international commerce of botanicals across traditional systems, global public standards and the verification program can help manufacturers in meeting regulatory requirements through science-based specifications and can facilitate label uniformity

Table 5
Emerging technologies discussed at GSRS18.

Technologies	Description
Advanced analytical techniques	Several advanced methodologies such as next-generation sequencing and microarrays were presented. The emerging technologies are now high-sensitive and high-throughput in nature. Thus, developing a strategy of measuring origin of the products and ensuring reproducible results with standards and reference samples are crucial. This is an area of importance to recognize common reference standard and information sharing across the agencies.
In silico tools	Combination of in-silico tools using chemoinformatics and toxicogenomics in conjunction with conventional toxicological methodologies can improve the understanding of toxicological effects of the dietary supplements and botanical drugs.
Qualified Presumption of Safety (QPS) approach	EFSA has developed a Qualified Presumption of Safety (QPS) approach, which is currently in use for the safety assessment of microorganisms added to the food chain, for the assessment of botanicals. 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. Similar regulation is in existence at FDA under that manufacturer must give only premarket notification to FDA.
Toxicologicalassessments	EFSA compendium identifies possible hazards without providing further information needed for subsequent risk assessment; it is a useful standard overview for botanicals and botanical ingredients of possible concern.
Up-to-date quality standards	US Pharmacopeia (USP) contains quality standards for dietary supplements and herbal medicines based on current and emerging technologies. It partners with the global stakeholder and expert contributors to develop transparent public standards such as monographs, general chapters, and reference standards, which provide scientifically-valid specifications for identity, strength, and purity.
DNA Barcoding	To catch the fraud in the food and dietary supplement, DNA barcoding methods are used and need to be validated and made it reproducible. However, to fight against the fraudulent manipulations of ingredients for the food products as well as food supplements requires global corporation from various regulatory agencies.
Blockchain	Blockchain approach could be utilized to monitor the herbal medicine and dietary supplement ingredients from its source to destination so only the finest quality ingredients can be reached to the consumers.
Omics based approach	The development of quality control methodology to ensure the safety and effectiveness of the drug is essential. Since the botanical and herbal supplements use a different part of the same plant differently, the computational and analytical approach can be effectively used to distinguish the different part of the same plant as the different parts tend to have a different effect sometimes. Computational methods can be effectively employed for performing network pharmacology and ingredient content to identify bioactive chemical markers

of quality herbal medicine and dietary supplements.

Of note, in most countries, manufacturers are expected to maintain the safety of product by following Good Agricultural and Collection Practice (GACP) and Good Manufacture Practices (GMP) for herbal medicine and dietary supplements to ensure the quality of product. The requirements and specification for authenticity of the plant and plant parts are more rigid for herbal medicine than those for dietary supplements. It is essential to have proper tracking on herbal origins, information on cultivation conditions, harvesting, handling, processing, labeling, packaging, and distribution. The newly developed DNA barcoding or other DNA-based system, in combination with omics-based analytical approaches will help to increase the reliability of the techniques for herbal authentication (Clark et al., 2018; Newmaster et al., 2013) as a comprehensive database is developed. Barcoding should be web-based and should be accessible across the globe in a non-proprietary platform to maintain transparency. Because the properties of botanicals vary through different harvesting environments, conditions, and time, the combination barcoding and chemistry-based omics approach can account for these inherent variabilities and might be useful additions to GAP/GMP documentation to include the details of herbal origins, cultivation conditions, harvesting, handling, and processing of each herbal batch studied.

8. Future Directions

New efforts have already taken place towards harmonization. For example, EFSA published guidelines on safety assessment of botanical products and preparations in 2009 ((EFSA), 2009). Additionally, Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations was published by EFSA in 2014 (EFSA, 2014). Compendium of botanicals reports naturally occurring substances of possible concern for human health when used in food and food supplement in most countries. In 2012, EFSA released Database of Compendium of botanicals that is available on the EU Open Data Portal (http://data.europa.eu/euodp/data/dataset/efsa-botanical-compendium). Having the database, many emerging technologies and methodologies can be effectively incorporated to enhance the quality or safety of the product. For example, with the use of advanced computational methods and bioinformatics, systems of decentralized data storage built on a net of users where “blocks” of data are bound together in a “chain” and secured using cryptography (blockchain). This approach enables to trace the dietary supplements and herbal medicine material from its origin to the final product. Current existing surveillance systems implemented in various countries provide useful information resources on the adverse events of herbal products, including the ADR reporting system in China, the FDA MedWatch program, Medsafe in New Zealand and, in the EU, the Pharmacovigilance (EMA) and Rapid Alert System for Food and Feed (European Commission). Informatic approaches can be used to mine the post-marketing surveillance information. However, some countries still lack such surveillance programs. Establishing transparent analytical approaches with emerging technology will ensure the worldwide quality and safety of dietary supplements and herbal products. Establishing centralized information on botanical standards not only ensures a quality product but makes it easier to identify contamination. Moreover, emerging technologies and computational methodologies can now be used to increase the benefits and decrease the safety concerns of dietary supplements and herbal medicines that were previously only used for conventional drugs. Data analytics methods may play a significant role in the development of robust quality evaluation methodologies to enhance the quality evaluations for natural products that either “Classified as Supplements” or “Classified as Medicines”.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors acknowledge the outstanding contributions of all the speakers, panelists and session chairs of GSRS2018. We also acknowledge the colleagues and staffs from China National Institutes for Food and Drug Control to support the conference.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2020.104647.

References

HC, 2019b. Natural health products regulations. 2019 (SOR/2003-196).
Abramovits, W., Gupta, A.J.S., 2010. Veregen (sinecatechins ointment) 15%. 8, 46.
Andrews, K.W., et al., 2018. Dietary supplement ingredient database (DSID) and the application of analytically based estimates of ingredient amount to intake calculations. 148, 1413S–1421S.
Avigan, M., et al., 2016. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States. 17, 331.
Benzi, G., Ceci, A.J.P.R., 1997. Herbal medicines in European regulation. 35, 355–362.
Blumenthal, M., et al., 2000. Herbal Medicine. Expanded Commission E monographs. Integrative Medicine Communications.
Borins, M.J. P.m., 1998. The dangers of using herbs: what your patients need to know. 104, 91–100.
Boullata, J.I., Nace, A.M., 2000. Safety issues with herbal medicine. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 20 (3), 257–269.
Brigelius-Flohe, R., Traber, M.G., 1999. Vitamin E: function and metabolism. FASEB J. 13 (10), 1145–1155.
Burton, G.W., 1994. Vitamin E: molecular and biological function. Proc. Nutr. Soc. 53 (2), 251–262.
Calapai, G.J.D.S., 2008. European legislation on herbal medicines. 31, 428–431.
Clark, A.M., et al., 2018. Developing Next Generation Tools for Computational Toxicology. pp. 363–387.
Commission, C.A., et al., 2007. Codex alimentarius Commission: procedural manual. Food Agric. Org.
Denham, B.E.J.J., 2011. Dietary supplements—regulatory issues and implications for public health. 306, 428–429.
Dietary Supplements Regulations http://www.legislation.govt.nz/regulation/public/1985/0208/latest/DLM102109.html.
Dobos, G., et al., 2005. Are national quality standards for traditional Chinese herbal medicine sufficient? In: Current Governmental Regulations for Traditional Chinese Herbal Medicine in Certain Western Countries and China as the Eastern Origin Country. 13. pp. 183–190.
EC, 2015a. Annex III of regulation. 2019 (EC) No 1925/2006.
EC, 2015b. Novel food catalogue 2019.
EFSA, 2009. Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. 7, 1249.
EFSA, 2014. Scientific Opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations. 12, 3593.
EFSA, 2015. Scientific opinion on dietary reference values for vitamin e as α-tocopherol. 13, 4149.
Eisenberg, D.M., et al., 1993. Unconventional medicine in the United States–prevalence, costs, and patterns of use. 328, 246–252.
Eisenberg, D.M., et al., 1998. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. 280, 1569–1575.
Ernst, E., 1998. Harmless herbs? A review of the recent literature. Am. J. Med. 104, 170–178.
Esterbauer, H., et al., 1989. Vitamin E and other lipophilic antioxidants protect LDL against oxidation. 91, 316–324.
EU, 2002. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the aApproximation of the Laws of the Member States Relating to Food Supplements. vol. 45. pp. 51–57.
EU, 2006. 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. vol. 50. pp. 26–38.
EU, 2015a. 2283 of the European parliament and of the Council of 25 November 2015 on

Novel Foods, Amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and Repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. vol. 327. pp. 1–27.
EU, 2015b. Regulation (Eu) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on Novel Foods, Amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and Repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001, vol. 2019 The European Parliament and The Council of The European Union.
European Parliament and the Council of the European Union, 2004. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004, amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union 136, 85–90.
FDA, 2006. Approval Letter Veregen™ Ointment, 15%. NDA, 021902.
FDA, 2016. Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. Guidance for Industry April 1.
FDA, 2019a. New Dietary Ingredients (NDI) Notification Process. 2017. https://www.fda.gov/food/dietary-supplements/new-dietary-ingredients-ndi-notification-process.
FDA, 2019b. Dietary Supplements. https://www.fda.gov/food/dietary-supplements.
FDA https://www.fda.gov/food/dietary-supplements/new-dietary-ingredients-ndi-notification-process.
FDA https://www.fda.gov/food/dietary-supplements.
Fisher, P., Ward, A.J.B., 1994. Medicine in Europe: complementary medicine in Europe. 309. pp. 107–111.
FNB, 2011. Dietary Reference Intakes (DRIs): Vitamins. In: Institute of Medicine, N. A. pp. 14 USA.
Geller, A.I., et al., 2015. Emergency department visits for adverse events related to dietary supplements. 373, 1531–1540.
Gulati, O.P., Ottaway, P.B.J.T., 2006. Legislation relating to nutraceuticals in the European Union with a particular focus on botanical-sourced products. 221, 75–87.
Hathcock, J., 2001. Dietary supplements: how they are used and regulated. J. Nutr. 131, 1114S–1117S.
HC, 2009. Compendium of monographs. 2019 Canada.
HC, 2016a. About natural health product regulation in Canada. 2019.
HC, 2016b. About Natural Health Products. 2019.
HC, 2016c. Category specific guidance for Temporary marketing authorization: supplemented food. 2019.
HC, 2018. Guidance Document: classification of products at the food-natural health product interface: products in food formats. 2019.
HC, 2019a. Forward Regulatory Plan 2019-2021: Modernize food regulations to enable innovative and safe foods for Canadians. 2019.
Healy, M.J., et al., 2016. Regulatory bioinformatics for food and drug safety 80, 342–347.
Hosomi, A., et al., 1997. Affinity for α-tocopherol transfer protein as a determinant of the biological activities of vitamin E analogs. 409, 105–108.
Jiang, W.-Y., 2005. Therapeutic wisdom in traditional Chinese medicine: a perspective from modern science. Trends Pharmacol. Sci. 26, 558–563.
Kayne, S.B., 2010. Traditional Medicine: a Global Perspective. Pharmaceutical Press, London.
Klein, R., et al., 2013. Approval of Fulyzaq (Crofelemer) to Relieve Symptoms of Diarrhea in HIV/AIDS Patients Taking Antiretroviral Therapy.
Low, T.Y., et al., 2017. The regulatory framework across international jurisdictions for risks associated with consumption of botanical food supplements. 16, 821–834.
Mahady, G.B., 2001. Global harmonization of herbal health claims. J. Nutr. 131, 1120S–1123S.
Martirosyan, D.M., et al., 2015. A new definition of functional food by FFC: what makes a new definition unique? 5, 209–223.
Mazzanti, G., et al., 2009. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. 65, 331–341.
Medsafe, 2019. Regulation of dietary supplements. 2019.
Molinari, M., et al., 2006. Acute liver failure induced by green tea extracts: case report and review of the literature. 12, 1892–1895.
Moreira, D.d.L., et al., 2014. Traditional use and safety of herbal medicines. 24, 248–257.
Newmaster, S.G., et al., 2013. DNA barcoding detects contamination and substitution in North American herbal products. 11, 222.
NewZealandParliament, 2019. Background on the Natural Health Products Bill 2011.
New Zealand Parliament, 2011. http://www.legislation.govt.nz/bill/government/2011/0324/latest/DLM3984610.html.
Normile, D.J.S., 2003. The new face of traditional Chinese medicine. 299, 188–190.
Nukala, U., et al., 2018. Antioxidant tocols as radiation countermeasures (Challenges to be addressed to use tocols as radiation countermeasures in humans). 7, 33.
NZFS, 2016. Supplemented food. New Zealand food supplemented food standard 2016. https://www.mpi.govt.nz/dmsdocument/11365-new-zealand-food-supplemented-food-standard-2016, Accessed date: 16 April 2020.
Ohama, H., et al., 2008. Health Foods and Foods with Health Claims in Japan. Nutraceutical and Functional Food Regulations in the United States and Around the World. Elsevier, pp. 249–280.
Pettitt, D., et al., 2016. Regulatory barriers to the advancement of precision medicine. 1, 319–329.
Robinson, N., 2006. Integrated traditional Chinese medicine. Compl. Ther. Clin. Pract. 12, 132–140.
Rocha, T., et al., 2016. Adulteration of dietary supplements by the illegal addition of synthetic drugs: a review. 15, 43–62.
Ross, S., 2000. Functional foods: the food and drug Administration perspective. Am. J. Clin. Nutr. 71, 1735S–1738S.
Sahoo, N., et al., 2010. Herbal drugs: standards and regulation. 81, 462–471.
Saito, H.J.P.R., 2000. Regulation of herbal medicines in Japan. 41, 515–519.
Sarma, D.N., et al., 2008. Safety of green tea extracts. 31, 469–484.
Shimizu, T.J. N.r. r., 2003. Health claims on functional foods: the Japanese regulations and an international comparison. 16, 241–252.
Silano, V., et al., 2011. Regulations applicable to plant food supplements and related products in the European Union. 2, 710–719.
Slikker, William, et al., 2018. Emerging technologies for food and drug safety. Regulatory Toxicology and Pharmacology 98, 115–128.
Stickel, F., et al., 2005. Herbal hepatotoxicity 43, 901.
Swann, J.P., 2016. The history of efforts to regulate dietary supplements in the USA. 8, 271–282.
Tanaka, H., et al., 2004. Current system for regulation of health foods in Japan. 47, 436–440.
Terasawa, K.J.E.-B.C., Medicine, A., 2004. Evidence-based reconstruction of Kampo medicine: part I—is. Kampo CAM? 1, 11–16.
TGA, 2011. Australian guidelines for complementary medicines (ARGCM): Part II: listed complementary medicines. 2019.
TGA, 2013. Registered complementary medicines. 2019.
TGA, 2018a. Listed complementary medicines. 2019.
TGA, 2013. An overview of the regulation of complementary medicines in Australia. 2019.
Tong, W., et al., 2015. Genomics in the land of regulatory science 72, 102–106.
Traber, M.G., et al., 2007. Vitamin E, antioxidant and nothing more 43, 4–15.
Vanherweghem, L.J., 1998. Misuse of herbal remedies: the case of an outbreak of terminal renal failure in Belgium (Chinese herbs nephropathy). J Altern Complement Med 4, 9–13.
WHO, 1999. WHO Monographs on Selected Medicinal Plants. World Health Organization.
WHO, 2003. WHO Guidelines on Good Agricultural and Collection Practices [GACP] for Medicinal Plants. World Health Organization.
WHO, 2010. WHO Monographs on Medicinal Plants Commonly Used in the Newly Independent States (NIS). Libros Digitales-World Health Organization (WHO).
Xu, J., Yang, Y.J. H.p., 2009. Traditional Chinese medicine in the Chinese health care system. 90, 133–139.
Yu, F., et al., 2006. Traditional Chinese medicine and Kampo: a review from the distant past for the future. 34, 231–239.
Zhang, Z., et al., 2013. Information and enlightenment on the first oral botanical drug Fulyzaq approved by FDA. 28, 421–423.
Zhu, J., et al., 2019. The landscape of hepatobiliary adverse reactions across 53 herbal and dietary supplements reveals immune-mediated injury as a common cause of hepatitis. Arch. Toxicol. 1–21.