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Safety considerations for dietary supplement manufacturers in the United States

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ABSTRACT

Due to significant dietary supplement use in the US, product manufacturers must understand the importance of implementing a robust approach to establishing safety for all ingredients, including dietary ingredients, components, and finished dietary supplement products. Different regulatory pathways exist by which the safety of dietary ingredients can be established, and thus allowed to be marketed in a dietary supplement. For individual dietary ingredients, safety information may come from a variety of sources including history of safe use, presence of the ingredient in foods, and/or non-clinical and clinical data. On occasion safety data gaps are identified for a specific ingredient, particularly those of botanical origin. Modern toxicological methods and models can prove helpful in satisfying data gaps and are presented in this review. For finished dietary supplement products, issues potentially impacting safety to consider include claims, product labeling, overages, contaminants, residual solvents, heavy metals, packaging, and product stability. In addition, a safety assessment does not end once a product is marketed. It is important that manufacturers actively monitor and record the occurrence of adverse events reported in association with the use of their products, in accordance with the law. Herein, we provide a comprehensive overview of considerations for assessing dietary supplement safety.

1. Introduction

Across geographies, there is no consensus in the terminology used to describe products recognized in the United States (US) as dietary supplements. As such, natural health products, complementary or herbal medicines, and food supplements are terms used to describe products and ingredients that may be similar to those marketed in the US as dietary supplements, but which are regulated differently depending on the country of marketing. Health practices adopted more commonly outside of the US (e.g., Traditional Chinese Medicine, Ayurvedic medicine) may utilize similar ingredients to those classified as dietary ingredients in the US; however, these topics are outside of the scope of this review. For simplification in this review, we use the term 'dietary supplements' to refer to all of these types of products and focus on the safety principles derived from the US regulatory paradigm. However, the reader should note that the objective safety principles discussed in this manuscript may also apply globally (Dwyer et al., 2018).

Dietary supplement manufacturers are responsible for setting quality specifications for dietary ingredients, other components, and finished dietary supplements (e.g., in US refer to 21 Code of Federal Regulations (CFR) 111.70)). Each specification must ensure the quality of the material by addressing its identity, purity, strength, composition, and lack of potential contaminants. Per the regulations, personnel involved in the

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Abbreviations:

DSHEA – Dietary Supplement Health and Education Act
GMP – Good Manufacturing Practices
NDI – New Dietary Ingredient
NDIN – New Dietary Ingredient Notification
SIDI – Standardized Information on Dietary Ingredients
USP – United States Pharmacopeia
NAM – New Approach Methodologies
GRAS – Generally Recognized As Safe
ODI – Old Dietary Ingredient
FEMA – Flavor and Extract Manufacturers Association
IOM – Institute of Medicine
EFSA – European Food Safety Authority
OEHHA – Office of Environmental Health Hazard Assessment
US – United States
NIH – National Institutes of Health
RDA – Recommended Dietary Allowance
ADI – Acceptable Daily Intake
UL – Upper Intake Level
NOAEL – No Observed Adverse Effect Level
NOEL – No Observed Effect Level
MoE – Margin of Exposure
FDA – Food and Drug Administration
CFR – Code of Federal Regulations
GL – Guidance Level
SUL – Safe Upper Limit
EVM – Expert Group on Vitamins and Minerals
SHU – Safe History of Use
ISAPP – International Scientific Association for Probiotics and Prebiotics
FAO – Food and Agriculture Organization
WHO – World Health Organization
FTC – Federal Trade Commission
CRC – Child Resistant Closure
CFSAN – Center for Food Safety and Applied Nutrition
CAERS – CFSAN Adverse Event Reporting System
QPS – Qualified Presumption of Safety
DRI – Dietary Reference Intakes
JECFA – Joint FAO/WHO Expert Committee on Food Additives

setting of specifications must have the appropriate education, training or experience for this. Responsible dietary supplement manufacturers are committed to marketing quality products produced in accordance with Good Manufacturing Practices (GMP; in the US, 21 CFR 111) and understand that product safety is an integral part of GMPs. Safety also spans the entire product lifecycle, including assessment of dietary and other ingredients and the finished products (LeDoux et al., 2015).

The safety of every product must be considered on an individual basis, and any given safety assessment technique is not necessarily suitable for all dietary ingredients and supplements or even all such products in a particular category. Dietary supplement manufacturers must utilize sound scientific principles to arrive at appropriate methodologies for evaluating the safety of their marketed products. Given the rapid increase in the size of the supplement industry (Smith et al., 2022) and reports of the unscrupulous addition of illegal and/or undeclared ingredients to dietary supplements (Pawar and Grundel 2017), it is important that consumers, raw material suppliers, healthcare providers and manufacturers understand the robust safety assessments needed for responsible marketing of a finished dietary supplement product. Herein, we provide a general overview of safety assessment principles to be considered when supporting the safety of dietary ingredients and dietary supplements.

In the US the term “dietary ingredient” includes vitamins and minerals, herbs and other botanicals, amino acids, “dietary substances” that are part of the food supply, such as enzymes and live microbials (commonly referred to as “probiotics”), and concentrates, metabolites, constituents, extracts, or combinations of any dietary ingredient from the preceding categories (Dietary Supplement Health and Education Act of 1994 – DSHEA). We briefly review a number of ingredient safety principles that impact the overall evaluation of dietary supplement safety, including safety evaluation of additional components (e.g., other ingredients, excipients, binders, flavors, colors) used in the manufacture of dietary supplements; assessment of a number of finished product parameters (health and structure function claims, product labeling, overages, contaminants, residual solvents, packaging, stability, known interactions with other substances) and the evaluation of post-marketing adverse events. In addition, we introduce the reader to select modern, 21st century toxicological *in silico* and *in vitro* tools used to assess chemical safety and suggest these might also be relevant for assessing natural ingredients. The intent of this work is not to cover each of the noted topics in detail, merely to review critical topics impacting on the determination and monitoring of the safety of dietary ingredients and dietary supplements and provide citations where additional information can be obtained.

2. Premarket considerations

The Food and Drug Administration (FDA) requirements for demonstrating the safety of a dietary supplement containing a New Dietary Ingredient (NDI) are distinct from those required for drugs. As per DSHEA, dietary ingredients marketed in the US in, or as, a dietary supplement prior to October 15, 1994 (aka, “old dietary ingredients” or “grandfathered” ingredients), are not subject to a safety review by the FDA prior to going to market. Instead, pursuant to the statute, they are presumed to be safe based on historical use and evidence of marketing. However, as there is no FDA authorized list of old dietary ingredients (ODI) to satisfy this requirement, companies are responsible for having evidence of marketing prior to October 15, 1994 for all dietary ingredients, old and new, used in a given dietary supplement thereby establishing the safety of their product. Companies also need to consider differences in manufacturing (e.g., extraction and condensation processes) used to manufacture dietary ingredients. If the new process for manufacturing a dietary ingredient is different from that used previously (i.e., for the ingredient marketed prior to October 15, 1994) or results in chemical alteration, additional steps may need to be taken to demonstrate safety.

Prior to marketing a new dietary ingredient in a dietary supplement, companies must perform a premarket safety assessment. Under DSHEA, a history of safe use is one condition used to establish that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe when used as directed. This is a critical aspect that needs to be covered as FDA has previously cited many instances where manufacturers have failed to provide adequate information on a history of use within a New Dietary Ingredient Notification (NDIN; Emmel et al., 2020). FDA has issued a Guidance detailing helpful information to know when submitting an NDIN (FDA 2016). Supplier qualification is required for manufacturers choosing to rely on the supplier’s Certificate of Analysis for all specifications except identity. Members of industry collaborated to publish a series of Guidelines (Standardized Information on Dietary Ingredients (SIDI)) aimed at assisting a manufacturer in their supplier qualification efforts (SIDI 2021). Each of the Guidelines focuses on different aspects of supplier qualification including streamlining communication, providing recommendations for standardizing the content, format of Certificates of Analysis and development of risk-based

supplier qualification.

When assessing suppliers of dietary ingredients or finished products, several areas could be addressed, including, but not necessarily limited to, the following:

- Preclinical data
- Product specifications
- Regulatory status (e.g., Approved food additive, GRAS, NDIN, ODI, FEMA GRAS, or prior approval as a drug substance)
- Allergens
- Presence of colors/additives
- Nutritional information
- Heavy metal impurities
- Residual solvents
- Organic/non-organic botanical specifications
- Pesticide residues for organic and non-organic botanicals
- Bioengineered ingredients status
- Proposition 65 compliance
- GMP compliance
- Aflatoxins (Pallares et al., 2022) and pyrrolizidine alkaloids (Oketch-Rabah et al., 2020)

Manufacturers are responsible for assessing the available information and deciding whether to utilize a particular supplier. Under GMP regulations for dietary supplements (21 CFR 111.75, 111.95, 111.105), manufacturers must conduct their own analysis and examination of the ingredients or components and qualify the supplier(s) of their dietary ingredients and identity testing is required on all incoming batches of raw materials (21 CFR 111.75). In compliance with GMPs and any applicable quality certification programs, companies should conduct further testing (e.g., to determine compliance with Proposition 65; Akabas et al., 2016). This often includes an assessment of any significant human use of the ingredient from any dietary (food) sources, an evaluation of how the ingredient has been commonly used, including any information on intake amounts, method of administration, frequency, and duration of use. The safety profile of the ingredient in different demographic groups (e.g., children, elderly, pregnancy/lactation), or any known contraindications for use are also important aspects of assessing safety (Dwyer et al., 2013; Gahche et al., 2017; Dietz et al., 2016; Oketch-Rabah et al., 2019). Key endpoints that should be considered include, but may not be limited to oral, systemic, or developmental/reproductive toxicity, allergenicity, genotoxicity, and absorption/distribution/metabolism/excretion. Available adverse event information and the potential interaction profile of the ingredient (e.g., with prescription or OTC medications, dietary supplements, or foods) are also critical for the understanding of the overall safety of an ingredient (Asher et al., 2017).

For botanical ingredients specifically, it is important to note the part of the plant that has historically been used. The type of manufacturing process (i.e., method of extraction) used and the composition of the extract, including the presence of any contaminants (elemental impurities, pesticide residues, solvent residues, microbial contaminants), are also important aspects which must be considered (Mudge et al., 2016; Oketch-Rabah et al., 2020). As botanicals may contain complex mixtures and exhibit variability based on geographical and environmental factors, it is critical to confirm the identity, purity and composition and understand the variability associated with harvesting and preparation of a trusted source material (Mudge et al., 2016; Baker and Regg, 2018; Shipkowski et al., 2018; Upton et al., 2020).

For manufacturers seeking information on botanical ingredients, there are a number of sources which contain information on ingredient names, properties, history and traditional use, known constituents, preclinical and clinical studies, natural ingredient-drug interactions, adverse reactions and general safety information (see Appendix 1). Comprehensive reviews of pharmacopeial standards for botanical, non-botanical, and probiotic ingredients (Sarma et al., 2021) and the safety and regulation of natural products used as food ingredients (Abdel-Rahman et al., 2011) are also available.

It is critical to ensure that all available evidence from both preclinical and clinical studies (including case studies) is evaluated to ensure study robustness and appropriateness. In some cases, this information may be available from an ingredient supplier. Additional data may be available from Health Authority monographs (e.g., Health Canada, European Medicines Agency), the National Institutes of Health (NIH) clinical trial website (ClinicalTrials.gov), published scientific literature (NIH National Library of Medicine PubMed Database; SCOPUS Database), global pharmacopeia (e.g., United States Pharmacopeia, USP), or internal company studies.

When appropriate, standard values should be identified, including the following:

- Recommended Dietary Allowance (RDA)
- Acceptable Daily Intake (ADI)
- Upper Level (UL)
- No Observed Adverse Effects Level/No Observed Effect Level (NOAEL/NOEL) or Benchmark Dose levels established from robust animal studies
- Other limits established by authoritative bodies (e.g., Institute of Medicine (IOM), European Food Safety Authority (EFSA), Office of Environmental Health Hazard Assessment (OEHHA))

Safety data obtained following oral exposure (as compared to parenteral, inhalation, or dermal exposures) is of pivotal importance for the evaluation of potential ingredients to be consumed in dietary supplements. Helpful evaluations of safe levels have also been reviewed and presented by an industry trade association (see Council for Responsible Nutrition Vitamin and Mineral Safety handbook, 2014).. Margins of Exposure (MoE) (the ratio between the NOAEL and the maximum anticipated daily intakes; Roe et al., 2018) from the use of one's product relative to estimated intake levels can be calculated, with application of relevant uncertainty or safety factors to account for inter- and intra-species differences, variation in sensitivity within the human population, and duration of the study relative to the intended duration of use for the dietary supplement (Johanson et al., 2023). While a MoE of 100 is generally considered to be sufficiently protective, higher values may be needed in certain situations depending on the strength of the underlying data.

To ensure the recommended conditions for the supplement result in safe levels of intake, the safety assessment should also take into account total exposure to the ingredient (including dietary intake), the usage pattern of the product (e.g., intermittent, chronic), and the population taking the product including potential sensitive sub-populations (e.g., children; VanderMolen et al., 2020; McClain and Bausch, 2003; Kroes and Walker, 2004). Based on the level of the ingredient in the product, MoEs for potential toxic effects in sensitive subpopulations (e.g., allergic reactions) and intentional or accidental misuse (accidental ingestion by children) can be determined, and child resistant packaging or label declarations may be considered.

Where a history of safe use for a particular ingredient does not exist, one needs to take a systematic approach to evaluating safety. Alternative information can be used to help substantiate a safe intake level based on a 'weight-of-evidence' approach (Weed 2005). Alternative information sources used to substantiate safety may include results from non-clinical and clinical studies conducted to evaluate dietary and nutritional effects, or regulatory or nutritional guidelines.

3. US regulatory pathways for marketing a new dietary ingredient

In the US, a premarket safety notification for a new dietary ingredient might be required. If a proposed ingredient has not been present in the food supply as an article used for food in the same chemical form or

the ingredient has no documented use in a dietary supplement sold in the US prior to October 1994, it would be considered an NDI. Companies intending to market an NDI must submit an NDIN to FDA at least 75 days before introducing the product into interstate commerce (21 CFR 190.6). In a 2016 Draft Guidance, FDA proposed that each manufacturer of a dietary supplement containing an NDI submit an NDI notification to FDA, even if other manufacturers have also submitted a NDIN for the same dietary supplement (FDA 2016).

The NDIN must include a "history of safe use or other evidence of safety that the dietary ingredient, when used under the conditions of use suggested or recommended in the labeling of the dietary supplement will reasonably be expected to be safe." Key aspects required in an NDIN include establishment of the identity of the NDI, availability of clinical or toxicology studies establishing safety, or in some cases documentation of a history of safe use of the ingredient in a food. More recently, to obtain additional safety information on ingredients and products deemed to be marketed without a required NDIN, FDA issued a Draft Guidance informing manufacturers (and other stakeholders) that they intend to exercise enforcement discretion for a limited time and under limited circumstances (FDA 2022).

An NDIN would not be required for a dietary ingredient that is otherwise an NDI but has been used in conventional human food in a non-chemically altered form and is either 1) established as Generally Recognized As Safe (GRAS) for direct addition to food, or 2) approved as a direct food additive in the US (21 CFR) at similar or higher levels of intake. The process of determining GRAS for a particular substance can be based on an existing GRAS regulation or an independent conclusion of GRAS (sometimes called "self-GRAS"). In either case, a GRAS assessment involves a rigorous assessment of safety. The amount and types of data required for either an independent conclusion of GRAS or a GRAS notification submitted to FDA are required to be the same and in each case safety studies are required to be publicly available, and typically published in a peer reviewed journal, thus providing transparency of key safety data. FDA has been clear that as a general matter unpublished data may be supportive of a GRAS determination but is not sufficient to demonstrate that an ingredient is GRAS. In addition, FDA also released a guidance document outlining best practices for convening a GRAS panel (FDA 2022a).

The FDA GRAS Notice inventory (FDA 2023) includes information about GRAS notices filed since 1998. FDA is separately informed of independent conclusions of GRAS affirmations by The Flavor and Extract Manufacturers Association (FEMA). The most recent update by FEMA was published in *Food Technology* in April 2022 (Cohen et al., 2022). The FDA incorporates the information on GRAS substances provided by FEMA into the agency's toxicological database, as well as into the Substances Added to Food inventory (FDA, 2018). A public, voluntary, and non-comprehensive database of substances known to have been evaluated through the independent conclusion of GRAS pathway is maintained by an independent company (AIBMR). Appendix 2 provides a comparison chart of the requirements for NDI and GRAS Notifications and the independent conclusion of GRAS process.

4. Special safety considerations for dietary ingredient categories

In order to qualify as a dietary ingredient in the US, a substance must be ingested and fall under one of the following categories: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, a concentrate, metabolite, constituent, extract, or combination of any ingredient described in these previous categories (section 201(ff) (1) of the Food, Drug & Cosmetic Act (21 U.S.C. 321 (ff) (1)). Often, substances in these various categories require unique consideration, as discussed below.

4.1. Vitamins/minerals

Vitamins and minerals, nutrients required by the body for normal growth and maintenance, are found naturally in the diet. While consumers should strive to meet their nutrient needs through healthy eating practices, supplemental intake of many nutrients can provide clearly established benefits, especially for those in specific age and gender groups, e.g., children and pregnant women. Vitamins may be either water soluble (B vitamins and vitamin C) or fat soluble (vitamins A, D, E, and K). Fat-soluble vitamins are not cleared as readily from the body, which provides a source of resiliency but could also excessively accumulate and present a safety risk when consumed in excess of tolerable upper intake levels over extended periods. Minerals classified as essential include calcium, chloride, cobalt, copper, fluoride, iodine, iron, magnesium, manganese, phosphorus, potassium, selenium, sodium, sulfur, and zinc.

The acceptable upper intake level (UL) is not a regulatory or legal limit for incorporation of vitamins and minerals in products. In some circumstances, intakes above the UL may be warranted. Ideally, essential vitamin and mineral intake should not exceed the UL without adequate scientific rationale. By definition, a UL is the highest level of daily nutrient intake from combined food, water, dietary supplement, and other sources (e.g., International Alliance of Dietary/Food Supplement Associations, 2014; EFSA 2018, 2022; IOM, 2011; 2019) that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As such, UL's provide conservative guidance for the safe use of vitamin and mineral supplements and protection of the general population. However, in practice, since ULs established by various sources can vary significantly dependent on the data and assumptions around dietary intake used in setting the published UL's (see Table 1), this can be a difficult approach to use in the absence of a broader consideration of safe market history for target populations and the available scientific evidence for the specific vitamin and mineral. In addition, key considerations unique to individual ingredients should also be considered, including the potential for zinc to deplete copper (Maret and Sandstead 2006), as well as any hazards associated with intake above defined upper levels (e.g., bioavailable iron).

Strict adherence to UL's should ordinarily not replace the use of a safe market history and a broader scientific evidence and safety risk assessment in determining the safe usage levels of essential vitamin and mineral supplements. A number of authoritative bodies have developed recommendations for safe UL values for vitamins and minerals, with reported adult ULs summarized in Table 1. However, as mentioned previously, these can vary based on the timeliness of the exercise and the approach used by the authoritative body responsible for establishing the UL. As stated in Section 6.3 (Overages), when a nutrient amount above the UL is considered, or where a UL has not been established, an exposure assessment may be conducted and compared to the relevant NOEL's available in the literature and other relevant safety information.

4.2. Botanicals

Fruits and vegetables are essential components of a well-balanced diet and many of these common food ingredients may be included in a dietary supplement formulation. For the safe addition of a botanical raw material to a dietary supplement, the hallmark evidence for a safe history of use (SHU) should include documented human use, in a diverse population of sufficient size, and for a sufficient duration of use (EFSA Scientific Committee, 2014). In dietary supplements where natural extracts may concentrate botanical constituents, this presumption of safety must be further qualified to incorporate a maximum dose that is comparable to historical dietary levels. When considering the adequacy of the evidence for diversity in the healthy population, considerations should include age, gender, race and ethnicity, all of which are important to account for sensitive subpopulations, genetic/metabolic susceptibilities and common cultural co-use scenarios.

Table 1
Safe upper level nutrient intakes for adults.

Nutrient	Institute of Medicine UL[a]	EFSA UL[b]	UK EVM[c] SUL[d] or GL[e]
Vitamin A	3000 μg	3000 μg	1500 μg total (GL)
Vitamin C	2000 mg	ND	1000 mg supplement (GL)
Vitamin D	100 μg	100 μg	25 μg supplement (GL)
Vitamin E	1000 mg	300 mg	540 mg supplement (SUL)
Vitamin K	ND	ND	1 mg supplement (GL)
Vitamin B1	ND	ND	100 mg supplement (GL)
Vitamin B2	ND	ND	40 mg supplement; 43 mg total (GL)
Vitamin B6	100 mg	12.5 mg	10 mg supplement (SUL)
Folate	1000 μg	1000 μg	1000 μg supplement (GL)
Vitamin B12	ND	ND	2000 μg supplement (GL)
Biotin	ND	ND	900 μg supplement (GL)
Calcium	2500 mg (19–50 yrs)	2500 mg	1500 mg supplement (GL)
Magnesium	350 mg (from nonfood sources)	250 mg (from nonfood sources)	400 mg supplement (GL)
Potassium	ND	ND	3700 mg supplement (GL)
Copper	10 mg	5 mg	10 mg total (SUL)
Iodine	1100 μg	600 μg	500 μg supplement; 930 μg total (GL)
Iron	45 mg	ND	17 mg supplement (GL)
Selenium	400 μg	255 μg	350 μg supplement; 450 μg total (SUL)
Zinc	40 mg	25 mg	25 mg supplement; 43 mg total (SUL)

[a] Dietary Reference Intakes for Calcium and Vitamin D. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, 2011. Tolerable Upper Intake Level (applies to total intake unless specified otherwise).

[b] European Food Safety Authority (EFSA), Tolerable Upper Intake Levels for Vitamins and Minerals, Scientific Committee on Food; Scientific Panel on Dietetic Products, Nutrition and Allergies, February 2006 (note that EFSA is currently (as of January 2024 (see https://www.efsa.europa.eu/en/topics/topic/dietary-reference-values) updating the Tolerable Upper Intake Levels for several vitamins and minerals (see Lecarre et al., 2022). Tolerable Upper Intake Level (applies to total intake unless specified otherwise).

[c] Expert Group on Vitamins and Minerals (United Kingdom), Safe Upper Levels for Vitamins and Minerals, May 2003.

[d] SUL = Safe Upper Limit (may apply to either total or supplemental intake).

[e] GL = Guidance Level (may apply to either total or supplemental intake).

The referenced duration of use should be adequate to address chronic risk factors and multigenerational concerns (e.g., carcinogenicity and reproductive/developmental toxicities). Harvesting time, raw material preparation, and extraction methodologies are just some of the critical details that can help establish a botanical SHU (Roe et al., 2018). Finally, adequate analytical characterization of the botanical material intended for formulation is essential to confirm the identity, purity and composition and understand the ordinary variability associated with harvesting and preparation of a trusted source material (Mudge et al., 2016; Baker and Regg, 2018; Upton et al., 2020).

For some botanical preparations, the legacy of safe dietary use is less certain and may require additional consideration. For example, potential differences of closely related species or traditional use of certain plant parts (e.g., roots, stems, leaves, fruits, seeds) should be considered. Broadly, botanical food ingredients may include materials classically understood to be fungal in origin (both mycelium and/or fruiting body components, e.g., culinary mushrooms). A similar SHU can be established for mushrooms but must be qualified for manufacturing using similar criteria as for an herbal ingredient.

Botanical ingredients that are not commonly consumed as food, and/or for which safety data gaps have been identified, are unlikely to meet the broad presumption of safety criteria used for establishing a SHU of a dietary ingredient. For these botanical ingredients, additional safety evidence is necessary before consideration as a dietary supplement ingredient for everyday use. The toxicity evaluation for botanical materials is a rapidly evolving field (Patel et al., 2023) and many *in silico* and *in vitro* New Approach Methodologies (NAM) approaches have been proposed (Little et al., 2017; Liu 2018; Galli et al., 2019; VanderMolen et al., 2020; Mahony et al., 2020). The standard animal-based toxicity testing traditionally used for evaluating single chemical entities often has clear limitations for the evaluation of complex mixtures like a botanical preparation which may have hundreds of nutrients and bioactive constituents. Most recently, the US FDA/NIH-led Botanical Safety Consortium, an international public/private cooperative of scientists from government, industry and academia has recently been established to evaluate various NAM in botanical safety evaluations (Mitchell et al., 2022). Manufacturers of botanical-based supplements should watch this space closely as NAM are rapidly evolving.

4.3. Biotics

Similar to botanicals and vitamin and mineral supplements, the consumer demand for 'biotic'-based products "continues" to increase (O'Connor et al., 2021). The two most popular biotics, prebiotics and probiotics, have a considerable history of safe use in foods and supplement products. However, there are a number of next generation probiotics, derived from species with no history of consumption in the food chain, and probiotic derivatives that also lack substantiation of consumption in food and/or have a definition which may be less clear to both scientists and consumers. Some of these emerging pre, pro, and postbiotics must first be recognized as dietary ingredients (e.g., through the GRAS pathway) before being introduced into dietary supplements (e.g., live microbials not normally part of the diet). Development of consensus definitions of various biotics has been led by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in conjunction with global experts. A description of current biotics and consensus definitions are provided in Table 2 and at the ISAPP website (https://isappscience.org). With increased interest in the use of biotics in dietary supplements, it is important to establish a pragmatic approach for ensuring the safety of these ingredients.

4.3.1. Prebiotics

From a dietary supplement standpoint, prebiotics are primarily, but

Table 2
Consensus definitions for primary biotics as established by ISAPP.

Biotic	Consensus Definition	Examples
Prebiotic	A substrate that is selectively utilized by host microorganisms conferring a health benefit on the host (Gibson et al., 2017)	Inulin, psyllium, galactooligosaccharides
Probiotic	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Hill et al., 2014)	Lactic acid bacteria and bacillus strains
Synbiotic	A mixture comprising live microorganisms and substrate (s) selectively utilized by host microorganisms that confers a health benefit on the host (Swanson et al., 2020)	Inulin + *Bifidobacterium lactics* strains
Postbiotic	Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host (Salminen et al., 2021)	Yeast fermentates used in animal feeds, heat-treated *Bifidobacterium animalis* ssp. *Lactis* strains

not limited to, various sources of dietary fiber. In 2018, FDA expanded their proposed list of non-digestible fibers (FDA, 2018b), Table 3).

In general, the key parameters of a prebiotic safety assessment are similar to those for any other raw material ingredient and should include characterization and quality of the raw material, intended use and exposure, history of use and exposure, toxicological data, and risk characterization. Safety assessments should include specification of the product, details of the source, previous human exposure (e.g., food), extent of use and estimated intake levels.

4.3.2. Probiotics

Probiotics are live microorganisms which, when consumed in adequate amounts, confer a health benefit on the host. For the purpose of this review, the focus is on orally administered probiotics (i.e., in dietary supplements); however, it should be noted that probiotic products are available for other application routes (e.g., dermal). Like other natural ingredients used in dietary supplements, some probiotic strains are presumed to be safe based upon a history of safe use in the food supply (Adams and Marteau, 1995). Nevertheless, it is incumbent on the probiotic suppliers to conduct a thorough safety assessment of their probiotic strains in accordance with the local regulatory requirements before any probiotic strains are used in supplements (Pariza et al., 2015; Sanders et al., 2016; Roe et al., 2022). Probiotic manufacturers seeking to use new strains, species, or even novel probiotics (human commensals not currently found in the food supply), should conduct a robust evaluation of their new species or new genus and species to establish the safety of each new probiotic for its intended use in a dietary supplement. For example, in the US this may require a determination of safety via a GRAS pathway (independent conclusion of GRAS or FDA-notified GRAS submission) or submission of an NDIN.

Although there are no globally harmonized safety requirements for probiotics, a number of regulatory authorities have offered some guidance and considerations over time (Food and Agriculture Organization (FAO)/World Health Organization (WHO), 2001; EFSA 2005; EFSA 2007; Agencia Nacional de Vigilancia Sanitaria ANVISA, 2018) and other regulatory authorities around the world are currently establishing guidelines for probiotic safety (e.g., Therapeutic Goods Administration, Australia). Safety considerations when evaluating a probiotic include strain identity (by 16S rRNA sequence analysis together with whole genome sequencing and alignment with well-characterized genus species Type strains), gene transfer ability, absence of virulence factors and antibiotic resistance genes, antimicrobial susceptibility, and lack of toxigenic activity (e.g., histamine). Another critical aspect of probiotic safety is that the strains must meet quality standards for identity, potency, and purity, and that the manufacturing plant must meet the applicable quality requirements for dietary supplements. These criteria are unique from chemicals which drives the need for different approaches. In some cases, a standard animal toxicity testing paradigm may have limited value for assessing the safety of probiotics due to physiologic differences such as a greater mucus growth rate in the human colon versus the rodent colon and differences in diet (Sanders et al., 2010; Pradhan et al., 2020; Roe et al., 2022).

Recently, scientific experts convened under the auspices of the USP Probiotics Expert Panel to review current approaches to assessing the safety of probiotics used in foods and dietary supplements, including the importance of comprehensive genomic and phenotypic characterization (Roe et al., 2022). The Expert Panel's work culminated in a publication reviewing the requirements from several regulatory authorities across the globe and outlining key parameters to consider when assessing the safety of a probiotic.

4.3.3. Synbiotics and postbiotics

The gut microbiome produces a wide range of compounds that are used by both the host and by other microorganisms within the host's gut. This is referred to as the host-microbe or microbial community interactions. Biotic products (including those already discussed) provide strategies that can drive the gut microbiota towards a healthier status. Synbiotics, a mixture of prebiotics and probiotics, and postbiotics (preparations of inanimate microorganisms and/or their components that confer a health benefit on the host; ISAPP, 2021) are ingredients experiencing increased interest in the marketplace. A safety assessment for synbiotics would logically include aspects previously discussed for prebiotics and probiotics. Similar to synbiotics, a safety assessment strategy for postbiotics may require a hybrid strategy between the approaches for pre- and probiotics.

4.4. Synthetics

Synthetic dietary ingredients are compounds produced artificially through a chemical synthesis. Some examples of common synthetic ingredients include vitamins, minerals, certain flavorings, and/or other food additives (FDA, 2022b). FDA's interpretation of whether synthetically produced substances qualify as a dietary ingredient can be found in a 2016 Draft Guidance (FDA 2016). For example, FDA recognizes synthetic vitamins, minerals and amino acids as legitimate dietary ingredients as these substances are defined by their nutritional function. FDA has expressed the view that synthetic botanicals may fall outside the definition of a dietary ingredient in the US as these substances were never part of an herb or other botanical (e.g., see FDA 2016a). In the US, companies can first introduce a synthetic substance into the food supply through the independent conclusion or notified GRAS processes. Once in the food supply, the synthetic substance would then be considered a "dietary substance for use by man to supplement the diet by increasing the total dietary intake" and thus a dietary ingredient.

4.5. Other ingredients

Substantiation of the safe intake of other types of ingredients not included in the previously mentioned categories (e.g., amino acids, proteins, fish oil) involves a case-by-case basis evaluation of the available data.

Evidence may consist of a history of safe use of the ingredient, pre-1994 use of the ingredient in a dietary supplement, presence of the ingredient in foods, and/or non-clinical and clinical data. Such information may be available from a number of sources including medical literature and authoritative regulatory body evaluations (e.g., see EFSA, 2005; McNeal et al., 2016; Roberts, 2016; Turck et al., 2019). As with all ingredients being evaluated for use in dietary supplements, sufficient evidence should be available to assure the safety of the ingredient when consumed at the recommended level. Consideration should also be given to the context of use, as the mere presence of an ingredient in food at a low level does not suggest that the ingredient may be safe when consumed in larger amounts as a dietary ingredient.

Table 3
The list of non-digestible carbohydrates that meet the dietary fiber definition according to the FDA (FDA 2021).

Initial list	Additions
• Beta-glucan soluble fiber • Psyllium husk • Cellulose • Guar gum • Pectin • Locust bean gum • Hydroxypropylmethylcellulose	• Mixed plant cell wall fibers (e.g., sugar cane fiber, apple fiber) • Arabinoxylan • Alginate • Inulin and inulin-type fructans • High amylose starch • Galactooligosaccharide • Polydextrose • Resistant maltodextrin/dextrin • Cross linked phosphorylated RS4 • Glucomannan • Acacia (gum arabic)

5. Dietary supplement components

A 'component' is any substance intended for use in the manufacture of a dietary supplement (including those that may not appear in the finished batch of the dietary supplement. This definition includes dietary ingredients. The term 'ingredient' refers to any substance used in the manufacture of a dietary supplement that is intended to be present in the finished batch of the dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient. Below we briefly review select examples of components used in the manufacture of dietary supplements.

5.1. Excipients ("Other" ingredients)

"Other" ingredients (excipients) are considered inert substances added to dietary supplements to help form and/or enhance the consistency of formulations – for example, to add color or bulk, to improve resistance to moisture, or to increase shelf life. These can include coatings, coloring agents, binders, fillers, thickeners, emulsifiers, flavors, flow agents, preservatives, and humectants.

All other ingredients contained in dietary supplements are regulated as food additives and must either be an approved food additive (including color additives) or generally recognized as safe (GRAS) for their intended use through inclusion on the FDA GRAS list, recognition through the independent conclusion of GRAS pathway, or as an FDA-notified GRAS substance. All of these ingredients should be evaluated to ensure compliance with state (e.g., Proposition 65) and federal (e.g., food allergen and bioengineered materials) regulations. When assessing the overall safety of inactive ingredients, it is important to consider the target population and duration of use (typical daily exposures) and the safety profile in different demographic groups and the exposure should be below the safety values set by Health Agencies or adequate margin of exposure as compared to a nonclinical NOAEL/NOEL. Companies manufacturing dietary supplements often set internal quality and safety standards to ensure that all inactive ingredients are safe at the levels added to the final dietary supplement product. Although developed in part as an aid to help industry in developing drug products, the FDA's Inactive Ingredient Database may be a useful resource for common excipients that are also used in dietary supplement products (FDA Inactive Ingredients Database). Likewise, the Handbook of Pharmaceutical Excipients (9th edition) is a resource that includes summary information on commonly used excipients including non-clinical safety data.

5.2. Flavors

Flavors used in dietary supplements must be FDA approved or FEMA/GRAS listed. All non-GRAS ingredients must be safe and meet all regulatory requirements for use in ingestible products, manufactured to be food grade and comply with Proposition 65 regulations. Additionally, flavors should also be evaluated for the presence of food allergen and genetically modified organism materials. Synthetic flavoring substances either banned by FDA (pulegone, myrcene, benzophenone, methyl eugenol, ethyl acrylate, and pyridine) or no longer used (styrene) must also not be present (FDA, 2018a).

5.3. Colors/Dyes

Any substance specifically added to impart color to a food is a color additive. Color additives must be approved by FDA prior to use in foods (including dietary supplements) and include both synthetic (also referred to as artificial) as well as natural colors (Perez-Ibarbia et al., 2016). Certain colors are subject to certification to ensure compliance with regulations (i.e., certified color additives as defined in 21 CFR part 74). Other colors derived from naturally occurring sources are exempt from batch certification and are defined in 21 CFR part 73. FDA has established Acceptable Daily Intake (ADI) values for certain colors reflecting the amount of substance (expressed on a body weight basis) that can be consumed per day over a lifetime without appreciable risks to human health.

6. Finished product assessment

Dietary supplements, which by definition must be ingested, are marketed in a number of forms such as tablets, capsules, powders, liquids, gel caps, soft gels, and powders. A comprehensive evaluation of a finished dietary supplement product typically encompasses properties inherent to the form (e.g., size and shape of a tablet), individual components used in the manufacture of a dietary supplement including dietary ingredients (e.g., amounts and presence of additional dietary ingredients and unintentional impurities) and bioavailability. While there is no established standard or guidance for dietary supplement products, the size and shape of the product should be evaluated for choking concerns. An FDA Guidance for generic tablets/capsules can be consulted for reference (FDA, 2022c).

6.1. Safety-related claims

Although not commonly included on the labeling of dietary supplement products, express or implied claims related to the safety of the product must be substantiated by competent and reliable scientific evidence. The Federal Trade Commission (FTC) released a Health Products Compliance Guidance in 2022 (FTC 2022) which provides a number of points to consider when making a safety related claim for a dietary supplement.

6.2. Labeling

Dietary supplement labeling may contain ingredient specific safety-related information to ensure that any allergens are highlighted, and that specific warning statements and on product directions for use are included. For example, dietary supplement products containing iron require a label warning (21 CFR 101.17). Other examples of safety-related label statements could caution use during pregnancy and breastfeeding, concomitant use with medications or in the event of certain disease states (e.g., immunocompromised individuals). Manufacturers of products containing powdered decaffeinated green tea extract that claim compliance with USP standards must include a warning regarding potential hepatotoxic effects (Oketch-Rabah et al., 2020). Labeling requirements should be reviewed on a case-by-case basis.

When necessary, safety considerations should be incorporated into labeling directions to ensure the safe use of dietary supplements. Taking certain supplements with food may reduce potential side effects (e.g., magnesium to reduce the occurrence of diarrhea; and vitamin C, iron, or S-Adenosyl-L-methionine to reduce the chance of stomach upset).

6.3. Overages

For some dietary ingredients included in dietary supplements, FDA regulations permit manufacturers to include additional amounts (i.e., overages) above those expressed on the label to compensate for losses during processing and shelf life (Andrews et al., 2018). While the additional amount included in the product will vary according to the stability of the ingredient and other potential factors that may contribute to loss, including product form (e.g., tablet versus gummy), processing methods, shipping, and storage conditions, the total amount included in the final product must be within known safety levels. This process is consistent with GMPs which recognize the use of overages to ensure that there will be at least 100% of the amount claimed on the label at the end of the shelf life of the product. If the overage amount is above the UL or in cases where a UL has not been established, manufacturers may need to take additional steps to confirm that the final

product is within known safety levels. FDA has denied a Citizen Petition requesting an amendment to 21 CFR 101.36(f) (1) to allow dietary supplement products to be compliant with the regulation if they meet 90% of the claimed amount declared on the label (FDA 1999). In so doing, FDA acknowledged that overages are recognized in the dietary supplement industry.

6.4. Packaging

Several GMP requirements address dietary supplement packaging requirements (see 21 CFR 111). Examples include the need to establish specifications for packaging that may come into contact with dietary supplements and the need to address potential issues such as preventing microbial contamination. Special packaging, also referred to as child-resistant closure (CRC) packaging, is required for dietary supplements containing 250 mg or more of elemental iron in a single package in concentrations of 0.025 percent or more on a weight-to-volume basis for liquids and 0.05 percent or more on a weight-to-weight basis for non-liquids (16 CFR 1700.14). CRC packaging on dietary supplement products that may be mistaken as confectionary by younger children (e.g., chewables and gummies) must be considered.

There are also instances where dietary ingredients can interact with packaging materials, or chemicals present in the packaging materials may leach into the supplement. As such, adequate characterization and safety assessment of extractable and leachable compounds may be necessary (e.g., for a new packaging material used in a dietary supplement product). USP General Chapters (USP 2015, 2018) and FDA Guidance (FDA 1999a) may be consulted for reference. Vendors should always use packaging that is approved through appropriate US food contact regulations.

6.5. Stability

Factors that can potentially impact the stability of a finished dietary supplement product include environmental factors such as temperature, ultraviolet light, and moisture (LeDoux et al., 2015). As these issues can impact product safety, it is important that any deviations are assessed. Most dietary supplement products include an expiration date and/or best by date. If a dietary supplement manufacturer includes an expiration or best by date, they are required to have data demonstrating that this information is not false or misleading. To ensure the highest level of quality, the expiration and best by dates used by supplement manufacturers are conservative, reflecting the date through which the product retains full potency.

6.6. Heavy metals, residual solvents, adulterants, contaminants

The levels of heavy metals and residual solvents, as well as ingredient-specific contaminants (e.g., pyrrolizidine alkaloids, aflatoxins) should be controlled in both raw materials and finished products. They should also be evaluated for safety in the target consumer population of that dietary supplement. Acceptable amounts of residual solvents in dietary supplement products are defined in USP <467> (USP 2020). Manufacturers should seek to reduce levels of contaminants to levels as low as reasonably achievable and ensure exposures are below appropriate health-based guideline values and regulatory requirements (e.g., California Proposition 65).

7. Postmarket surveillance

Post-market surveillance is a critical component of the overall safety assurance program for all products including dietary supplements because it further supports and strengthens the pre-market safety evaluation program. The key objectives of post-market surveillance include but are not limited to:

- Further confirm or enhance pre-market product safety assessment under normal use and any potential misuse conditions
- Identify whether there are any unique population(s) or consumer habits and practices that have not been previously considered and that should be considered in product safety assurance
- Confirm appropriateness of label use instructions and safety related information
- Identify any potential unforeseen intended and unintended effects due to the product

Various regulatory agencies have specific mandates for post-market compliance which must be followed. In the US, the FDA has the authority to enforce mandatory Serious Adverse Event reporting requirements for the "responsible person" (i.e., manufacturers, packers, or distributors of dietary supplements; Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 (Pub. L. 109–462)). Requirements under this law include the collection of all adverse event reports by manufacturers, distributors, and retailers of dietary supplements; reporting of serious adverse event reports to the FDA; firms must maintain records of reports of all adverse events and FDA must be allowed to inspect those records; and dietary supplement labels must bear information to facilitate the reporting of serious adverse events associated with the use of dietary supplements by consumers.

As required by section 3(d)(3) of the law, FDA has published a comprehensive guidance document including questions and answers to help industry navigate through the process (FDA 2013).

Every serious adverse event must be submitted to FDA within 15 business days (FDA, 2018d) after the report is received by the responsible person even if there is missing information. The 15-day submission deadline is set to ensure prompt review and follow up by the FDA to determine whether there could be a potential risk to the public. Case reports or reported consumer complaints may indicate that there can be adverse effects associated with a dietary supplement. Single reports may be helpful but do not necessarily indicate a causal effect. Typically, an accumulation of cases over time would warrant an investigation into a potential causal relationship between an adverse event and intake of a dietary supplement (Ronis et al., 2018).

The Center for Food Safety and Applied Nutrition (CFSAN) maintains an adverse event database system that includes all adverse event and product complaint reports to the FDA for dietary supplements since 2004 (CFSAN Adverse Event Reporting System, CAERS). This information can be accessed by the public via CAERS Data Files, openFDA (FDA, 2022d), or a Freedom of Information Act request to FDA. The FDA clinical reviewers examine the data and will evaluate further if they identify a potential concern. If necessary, regulatory actions are undertaken and may include a warning letter or informing the public of a safety concern. The mere presence of an adverse event in the database does not necessarily mean that FDA has concluded that the product caused the adverse event. CAERS only captures the adverse events as reported by manufacturers, consumers and healthcare professionals, and regulatory agencies. The quality, accuracy and reliability of the adverse event reports may vary depending on who submitted the report and the level of detail included in the report.

To properly manage post-market surveillance, companies must have a comprehensive and robust post-market AE reporting and evaluation process. All product complaints must be handled in accordance with 21 CFR Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements, specifically parts 111.553 111.560 and 111.570. The appropriate point of contact may decide to have an internal system and department to manage post-market surveillance and AE reporting or contract the entire or parts of it to a private company.

A recent review (Kingston et al., 2021) provides an overview of three key steps involved in post-market surveillance: adverse event receipt and documentation; comprehensive review and follow up with the consumer (and health care professional if involved); and product

association and risk assessment. At minimum, the product package should have a mailing address and/or phone number for consumers to be able to contact the appropriate point of contact. Other important sources for monitoring consumer complaints include the company's social media and new digital channels. Additionally, the American Association of Poison Control Centers represents publicly funded national poison control centers and publishes an annual report of adverse events reported in association with exposure to a number of substances including dietary supplements (Gummin et al., 2022).

There are different ways to assess a possible association between intake of a dietary supplement and an adverse event, as well as any resultant risk to the public, an example of which is a scoring scale presented by Kingston et al. The key principle is to have trained personnel – generally with expertise in quality, toxicology/product safety, healthcare/medical and/or regulatory affairs – carefully review each adverse event report in order to make an appropriate decision regarding risk assessment and reportability to the FDA.

In summary, each "responsible person" should have appropriate standard operating procedures in place to clearly define the entire postmarket surveillance process applicable to their products and actively monitor, record, follow up, assess the risk and when applicable report adverse events from a myriad of different sources.

8. Conclusion

The use of dietary supplements in consumer self-care routines continues to increase each year (Mishra et al., 2021; Smith et al., 2022). Current US FDA regulations define procedures intended to ensure that companies marketing dietary supplements produce safe, high-quality products that are accurately labeled. Responsible companies ensure that safety data supports all components used to manufacture a dietary supplement including all dietary ingredients. Further, companies ensure that all steps in the manufacturing, packaging, labeling, and holding of a dietary supplement are followed according to regulatory requirements and ensure the safety of the product.

We have reviewed a number of topics in this paper which are important to consider when assessing the safety of a dietary ingredient or dietary supplement. This includes assessing the safety of all dietary supplement components, including dietary ingredients and other ingredients, as well as regular monitoring of the adverse event profile for the marketed product. By doing so, companies can ensure that safe products, backed by responsible science, are provided to consumers. While our review did not include comprehensive discussion of each specific topic, we have provided numerous references to consult for additional information.

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Jay Sirois: Conceptualization, Writing – original draft, Writing – review & editing. **Sudheer Reddy:** Conceptualization, Writing – review & editing. **Tony Nguyen:** Conceptualization, Writing – review & editing. **Heather Walker:** Conceptualization, Writing – review & editing. **Jessica Rendall:** Writing – review & editing. **Georges Bergen:** Conceptualization, Writing – review & editing. **Mark Reimers:** Writing – review & editing. **Erica Cermak:** Writing – review & editing. **Asheesh Tiwary:** Writing – review & editing. **Emily Helmes:** Writing – review & editing. **Jennifer Palmer:** Writing – review & editing. **Steve Teo:** Writing – review & editing. **Tami Mackle:** Writing – review & editing. **Mimi Park:** Writing – review & editing. **Charlene Wang:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jay E Sirois reports a relationship with Consumer Healthcare Products Association that includes: employment. Corresponding author is employed by a trade association (Consumer Healthcare Products Association) that represents manufacturers and marketers of dietary supplement products. Other co-authors are employed by companies that manufacture and or market dietary supplements.

Data availability

No data was used for the research described in the article.

Appendix 1. Information on botanical ingredients

Information	Database and Website Resources
Ingredient Names	NIH National Library of Medicine Taxonomy Database
	USDA, US National Plant Germplasm System
	USDA PLANTS Database
	International Plant Names Index (IPNI)
Properties	USDA, US National Plant Germplasm System
	WHO Monographs
	The Identification of Medicinal Plants: A Handbook of the Morphology of Botanicals in Commerce
History and Traditional Use	European Medicines Agency
	Health Canada
	United States Pharmacopeia-National Formulary
	United States Pharmacopeia Herbal Medicines Compendium
	European Pharmacopeia
	Japanese Pharmacopeia
	WHO Monographs
	European Scientific Cooperative on Phytotherapy

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Information	Database and Website Resources
	British Herbal Medicine Association
	GlobinMed Medicinal Herbs & Plants Monograph
Known Constituents	United States Pharmacopeia-National Formulary
Chemical Structure	NIH National Library of Medicine PubChem Database
	ChemSpider
Preclinical Studies	AHPA Botanical Safety Handbook
	ABC HerbMedPro Database
	NIH PubMed Database
	European Scientific Cooperative on Phytotherapy
	British Herbal Medicine Association
	GlobinMed Medicinal Herbs & Plants Monograph
Clinical Studies	ClinicalTrials.gov
	AHPA Botanical Safety Handbook
	ABC Herbal Medicine: Expanded Commission E Monographs
	Therapeutic Research Center Natural Medicines Database
	NIH PubMed Database
	Reprotox
	British Herbal Medicine Association
	GlobinMed Medicinal Herbs & Plants Monograph
Herb-Drug Interactions	European Scientific Cooperative on Phytotherapy
	British Herbal Medicine Association
	ABC Herbal Medicine: Expanded Commission E Monographs
	Therapeutic Research Center Natural Medicines Database
	ABC HerbMedPro Database
	AHPA Botanical Safety Handbook
Adverse Reactions	LiverTox
	Therapeutic Research Center Natural Medicines Database
	European Scientific Cooperative on Phytotherapy
	British Herbal Medicine Association
	ABC Herbal Medicine: Expanded Commission E Monographs
	GlobinMed Medicinal Herbs & Plants Monograph
Other Sources for Safety Information	SCOPUS
	National Toxicology Program
	FDA GRAS Notices
	FDA Select Committee on GRAS Substances
	Therapeutic Goods Administration (Australia)
	Medicines Complete (Royal Pharmaceutical Society)
	FEMA Flavor Ingredient Library
	Cosmetic Ingredient Review
	European Food Safety Authority
	Joint FAO/WHO Expert Committee on Food Additives

Appendix 2. Elements of New Dietary Ingredient Notifications, Independent GRAS Conclusions and GRAS Notifications

Parameter	GRAS Notification[1]	Independent GRAS conclusion	NDI Notification
Product category	Food and food ingredients Dietary Supplements		Dietary Supplements
Defined Requirements	21 C.F.R. § 170.30 Eligibility for classification as generally recognized as safe (GRAS)		21 C.F.R. § 190 Subpart B New Dietary Ingredient Notification FDA Draft Guidance: New Dietary Ingredient Notifications and Related Issues (August 2016) NDI Notification Exemptions: (1) NDIs "present in the food supply as an article used for food in a form in which the food has not been chemically altered." 21 U.S.C. § 350b(a) (1) (2) NDIs (a) listed or affirmed by FDA as GRAS for direct addition to food or (b) approved as a direct food additive in the US if the direct food additive or GRAS substance (a) has been used in the food supply (i.e., in conventional foods) and (b) is to be used as a dietary ingredient without chemical alteration. Draft Guidance at p. 23–24. A dietary ingredient is not an NDI if It was marketed in the US before October 15, 1994.
	Finished products in all categories subject to general adulteration provisions		
FDA Submission Required?	No (voluntary)	No	Yes – at least 75 days before introducing product into interstate commerce.

Parameter	GRAS Notification[1]	Independent GRAS conclusion	NDI Notification
Scope of requirements: studies, scientific literature, and/or expert review	21 C.F.R. § 170.30: • recognition may be based on view of experts through either: (1) scientific procedures or (2) through experience based on common use in food (for a substance used in food prior to January 1, 1958)		NDIs are deemed to be adulterated unless an NDI Notification shows "a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will **reasonably be expected to be safe**." (21 U.S.C. § 350b)) Notification is to contain: • Name/address of the manufacture/distributor of the dietary supplement that contains the NDI;

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Parameter	GRAS Notification[1]	Independent GRAS conclusion	NDI Notification
	• requires common knowledge throughout the scientific community • **reasonable certainty that the substance is not harmful** under conditions of its intended use GRAS based upon scientific procedures **shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive.** General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published		• name of the NDI, including the Latin binomial name (including the author) of any herb or other botanical; • description of the dietary supplement(s) that contain the NDI including the: o NDI level in the dietary supplement; and o conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, the ordinary conditions of use of the supplement; • **history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe,** including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer of the dietary supplement that contains the NDI has concluded that the new dietary supplement will reasonably be expected to be safe. (21 C.F.R. § 190.6(b))

Parameter	**GRAS Notification**	**Independent GRAS conclusion**	**NDI Notification**
Key Requirements	7 required elements: • Signed statements and certification. • Identity, method of manufacture, specifications, and physical or technical effect. • Data and information about Dietary exposure. • Description of any self-limiting levels of use. • Experience based on common use in food before 1958 (if relevant). • A narrative that provides the basis for the conclusion of GRAS status, explaining why the data and information in your notice provide a basis for the view that the substance is safe under the conditions of its intended use. • A list of supporting data and information discussed in the GRAS notice.	Suggest following the 7 elements in the GRAS Notification as FDA has stated that same considerations should apply for independent GRAS conclusion even if there is no filing.	Notification should include a safety narrative containing objective evaluation of the history of use or other evidence of safety cited in the notification, along with an explanation of how the evidence of safety provides a basis to conclude that the dietary supplement containing the NDI when used under the conditions described in the notification, will reasonably be expected to be safe. Safety and Toxicology information should include • Comprehensive safety profile for the NDI • In vitro and in vivo toxicology studies • Human studies • Other studies • History of use • Other evidence of safety • Other safety and toxicology references (Draft Guidance at pp. 47–49)

Parameter	**GRAS Notification**	**Independent GRAS conclusion**	**NDI Notification**
FDA Review Period	Within 180 days of filing, FDA will send a letter with an evaluation of the Notice. FDA reserves the right to extend the 180-day timeframe by 90 days. (21 C.F.R. § 170.265)	N/A	75 Days. If the manufacturer or distributor submits additional substantive information in support of the original NDI notification, § 190.6(d) provides that the date of this supplemental submission to FDA becomes the new notification filing date, and the 75-day period restarts.
Potential Scope of Clearance	Limited to the substance, at the level and intended use/s in the GRAS Notice	N/A Arguably also limited to the substance, at the level and intended use in the GRAS notice.	FDA has limited to the specific manufacturer or distributor submitting the NDI at the level of the dietary ingredient and product(s) specified in the Notification.
	Subpopulations cannot be excluded GRAS assumes lifetime exposure		Can target and exclude sub-populations on product labeling Duration and frequency of exposure dictated on product labeling

Parameter	GRAS Notification	Independent GRAS Conclusion	NDI Notification
Is information available for others to rely on?	In 1997, FDA published a proposed rule regarding "Substances Generally Recognized As Safe," 62 Fed. Reg. 18938 (April 17, 1997). In this proposal, FDA allowed for an abbreviated GRAS affirmation notification if a compound could be shown to be "substantially equivalent" to an existing GRAS compound. In the Final Rule, FDA declined to adopt this concept of "substantial equivalence", but in practice uses an approach wherein a GRAS Notification can, to the degree appropriate, use a comparative analysis to a known GRAS substance to establish GRAS status (81 Fed. Reg. 54960, 54977 (August 17, 2016)) Companies do rely on other's filings for their own products GRAS status, if the products and uses match.	Some	Each manufacturer/distributor must file an NDI Notification. "A dietary supplement that contains an NDI is deemed adulterated unless, among other things, **the manufacturer or distributor of the dietary ingredient or the dietary supplement submits an NDI notification at least 75 days before introducing it into interstate commerce**." (21 U.S.C. 350b(a) (2)) FDA 2016 Draft Guidance: sets out certain circumstances under which another manufacturer or distributor **may be able to rely upon the data from another NDI notification or master file**..

Parameter	GRAS Notification	Independent GRAS Conclusion	NDI Notification
Public Disclosure -information made public by FDA? -How much information does FDA publicly disclose?	The data and information in a GRAS Notice are considered a mandatory submission (FOIA and 21 C.F.R. Part 20) and are available for public disclosure as of the date FDA receives the GRAS Notice. Information exempt from public disclosure per FOIA and Part 20 will not be disclosed. (21 C.F.R. § 170.275) FDA website maintains an inventory of GRAS notices which includes copies of letters sent to the notifiers and information on ingredient and its proposed use(s).	N/A	FDA will not disclose the existence of, or the information contained in, an NDI notification for 90 days after the filing date of the notification. After the 90th day, the entire notification, except trade secrets and confidential commercial information, will be placed on public display. 21 C.F.R. § 190.6(e)

[1] This does not address food additive or GRAS petitions that have been incorporated into regulations. See 21 CFR Parts 172–178, 182–186.

Definitions.

Term	Definition	Notes
adverse event	An adverse event is any health-related event associated with the use of a dietary supplement that is adverse.	FDCA Section 761(a)(1) (21 U.S.C. 379aa-1(a) (1))
component	Component means any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as described in section 201(ff) of the act) and other ingredients.	21 CFR 111
contact surface	Contact surface means any surface that contacts a component or dietary supplement, and those surfaces from which drainage onto the component or dietary supplement, or onto surfaces that contact the component or dietary supplement, occurs during the normal course of operations. Examples of contact surfaces include containers, utensils, tables, contact surfaces of equipment, and packaging.	21 CFR 111
dietary ingredient	Dietary ingredient means a vitamin; a mineral; an 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 ingredient described above.	FDCA Section 201 (21 U.S.C. 321)
dietary supplement	(ff) The term "dietary supplement"— (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E); (2) means a product that—. (A) (i) is intended for ingestion in a form described in section 350(c)(1) (B) (i) of this title; or (ii) complies with section 350(c)(1) (B) (ii) of this title; (B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and (C) is labeled as a dietary supplement; and (3) does—. (A) include an article that is approved as a new drug under section 355 of this title or licensed as a biologic under section 262 of title 42 and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 342(f) of this title; and. (B) not include— (i) an article that is approved as a new drug under section 355 of this title, certified as an antibiotic under, or licensed as a biologic under section 262 of title 42, or (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.[3] Except for purposes of paragraph (g) and section 350f of this title, a dietary supplement shall be deemed to be a food within the meaning of this chapter.	FDCA Section 201 (21 U.S.C. 321)
food additives	Food additives includes all substances not exempted by section 201(s) of the act, the intended use of which results or may reasonably be expected to result, directly or indirectly, either in their becoming a component of food or otherwise affecting the characteristics of food. A material used in the production of containers and packages is subject to the definition if it may reasonably be expected to become a component, or to affect the characteristics, directly or indirectly, of food packed in the container. "Affecting the characteristics of food" does not include such physical effects, as protecting contents of packages, preserving shape, and preventing moisture loss. If there is no migration of a packaging component from the package to the food, it does not become a component of the food and thus is not a food additive. A substance that does not become a component of food, but that is used, for example, in preparing an ingredient of the food to give a different flavor, texture, or other characteristic in the food, may be a food additive.	21 CFR 170
ingredient	Ingredient means any substance that is used in the manufacture of a dietary supplement and that is intended to be present in the finished batch of the dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as defined in section 201(ff) of the act.	21 CFR 111
in-process material	In-process material means any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary supplement.	21 CFR 111
serious adverse event	A serious adverse event is an adverse event that: • Results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or • Requires, based on a reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above.	FFDCA Section 761(a)(2) (21 U.S.C. 379aa-1(a) (2)).

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Further reading

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