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25 years of DSHEA: Impact on Supply, Conservation and Sustainability, GACPs and Regulatory Compliance of Botanical Ingredients

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ABSTRACT

Prior to October 1994 in the United States, botanical substances were regulated as ingredients of drug products, both over-the-counter (OTC) and prescription (Rx), or as components of food products. Most of the thousands of medicinal plant species in global commerce were not expressly permitted for use in food products. This fact, coupled with the reality that the U.S. Food and Drug Administration (FDA) had established panels to review all old drugs and establish new monographs, led to the eventual re-classification of most botanicals as non-monograph. Thus, by the early 1990's many botanicals had no safe harbor, as they were determined to be unlawful for use as components of both foods and drugs.

The tension caused by these facts is a backdrop, that leads to the U.S. Congress establishing a new regulatory framework, between food and drug, the Dietary Supplement Health and Education Act of 1994 (DSHEA). With the passage of DSHEA, most herbs of commerce, if intended for oral ingestion, became "old dietary ingredients" and could now be marketed with "nutrient content" or "structure function" claim statements. Botanicals intended for topical application were not protected by DSHEA however, and, for the most part, transitioned to use in non-drug cosmetic products, with the exception of a few that remained in the FDA monographs.

Post-DSHEA, the U.S. market for herbal supplements boomed and continues to grow. This paper examines the impacts of DSHEA, 25-years on, on the ever-increasing market demand for botanical ingredients, including legal and regulatory issues (state, federal, and international) affecting production, import, trade and use of botanical supplement ingredients, and the necessary developments of (a) quality management systems such as good agricultural and collection practices (GACPs) linked to good manufacturing practices (GMPs); (b) ingredient quality standards such as pharmacopoeial monographs that can serve as the basis of

specifications for testing composition, identity, purity, and strength; (c) conservation status assessments of popular species, as many are obtained through wild-collection; and (d) standards (national and voluntary) for sustainable agriculture and wild collection practices in order to meet increasing market demand without detriment to biodiversity.

Key words: Biodiversity; Botanical supplements; Conservation; Quality management, Sustainable production.

Abbreviations: ABC, American Botanical Council; AHP, American Herbal Pharmacopoeia; AHPA, American Herbal Products Association; CBD, Convention on Biological Diversity; CFR, Code of Federal Regulations; CITES, Convention on International Trade in Endangered Species; CR, Critically Endangered; DSHEA, Dietary Supplement Health and Education Act of 1994; E, Endangered; EPA, U.S. Environmental Protection Agency; FCC, Food Chemicals Codex; FDA, U.S. Food and Drug Administration; FD&C Act, Federal Food, Drug, and Cosmetic Act; FEMA, Flavor and Extract Manufacturers Association; FLO, Fair Trade International; FR, Federal Register; FSMA, Food Safety Modernization Act; FWF, FairWild Foundation; JECFA, The Joint Expert Committee on Food Additives; GACP, Good Agricultural and Collection Practices; GMP, Good Manufacturing Practices; GRAS, Generally Recognized as Safe; GRASE, Generally Recognized as Safe & Effective; HARPC, Hazard Analysis and Risk-Based Preventive Controls; IUCN, International Union for Conservation of Nature; LC, Least Concern, MAP, Medicinal and Aromatic Plants; MPWG, Medicinal Plant Working Group (of USFWS); MPSG, Medicinal Plant Specialist Group (of IUCN); NOP, National Organic Program; NT, Near Threatened; OTC, Over-the-counter drug product; R, Rare; UEBT, Union for Ethical BioTrade; UpS, United Plant Savers; USC, U.S. Congress; USDA, U.S. Department of Agriculture; USFWS, U.S. Fish and

Wildlife Service; USP-NF, U.S. Pharmacopeia and National Formulary; VSS, Voluntary Sustainability Standards; VU, Vulnerable; WHO, World Health Organization.

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I. INTRODUCTION

A. Pre-DSHEA Regulatory Landscape

In the United States (U.S.), prior to the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA) (USC 1994), botanicals were regulated as either botanical drug ingredients (over-the-counter (OTC) or prescription (Rx)), as non-drug cosmetic ingredients, or as conventional food ingredients. There was no middle ground between drug and food.

A famous case that begged for a middle ground began in 1988, when a shipment of black currant (*Ribes nigrum* L.) seed oil from England was seized by U.S. Marshals. The U.S. Food and Drug Administration (FDA) argued that by merely filling the seed oil into gelatin capsules, the botanical substance would become an unsafe food additive and therefore an adulterated food, i.e. the gelatin capsule being the food. In 1991, the U.S. District Court for the Central District of Illinois ruled in favor the importing company and dismissed the case. In 1992, the FDA appealed the decision to the United States Court of Appeals for the Seventh Circuit. In January 1993, the appeals court affirmed the lower court decision, again, in favor of the importing company (Blumenthal 1994a).

For a botanical to have been permitted for use as a food ingredient, it required FDA classification as either a (1) Generally Recognized as Safe (GRAS) substance (listed in FDA regulations, Title 21 Code of Federal Regulations [21 CFR], Parts 182 and 184); or, as a (2) food additive or color additive (listed in 21 CFR Parts 172, 173 and Parts 73, 74, respectively), and/or flavoring substance evaluated by the Flavor and Extract Manufacturers Association (FEMA) and the Joint Expert Committee on Food Additives (JECFA); or, as a (3) prior-sanctioned substance, approved for specific uses in foods prior to September 6, 1958 (listed in 21 CFR Part 181) (FDA 2018a).

While many botanical substances had been classified as old drugs, i.e. as active ingredients of medicinal products sold from the early 19th century through the late 20th century, in the mid-1970's, the FDA established expert review panels for the purposes of assessing the available evidence of safety and efficacy for all existing OTC drug active ingredients and establishing new labeling standards monographs. This process included the review of hundreds of "old" botanical drugs that were still on the pharmacy shelves in the 1970's. This is an important fact to consider in the historical context that led to the creation of DSHEA in the 1990's. From the mid-1970's through the mid-1990's, most botanical substances listed in FDA's proposed and tentative final monographs were removed, due to the agency's inability (at that time) to determine sufficient levels of evidence to support the claimed therapeutic uses. It is worth noting, however, that during the same time frame, other national health authorities (notably the German Federal Health Office (BGA)), were publishing positive therapeutic monographs for many of the same botanical drugs. Levels of evidence were defined differently in different countries. FDA's reclassification of many important botanicals as "non-monograph" created a tension between industry and government. Suddenly non-monograph botanicals had no safe-harbor for market access, as they were determined to be unlawful for use as components of both foods and drugs.

In 1992, as a strategy to address the issue, the European-American Phytomedicines Coalition (EAPC), a group of European and American phytomedicine manufacturers petitioned the FDA to expand its review of OTC drugs "to include products that have a long and safe history of use as nonprescription drugs in Western Europe." To no avail, the EAPC subsequently filed two citizens' petitions with the FDA, to allow the sale of (1) valerian as an OTC nighttime sleep aid; and (2) ginger as an OTC antiemetic drug product (Blumenthal 1994, 1995).

Also in 1992, the American Herbal Products Association (AHPA) listed about 550 botanical species in their *Herbs of Commerce*, the majority of which had evidence of acceptable uses in food products (e.g. species listed in 21CFR, Parts172.5100,182.10 and 182.20), although the AHPA list also included species that were used only as botanical drugs (Foster 1992). In 1997, the FDA incorporated the AHPA list into regulation (21 CFR §101.4), requiring that the common or usual name of ingredients of dietary supplements (algal, botanical, and fungal) shall be consistent with the names standardized in the 1992 version of *Herbs of Commerce* (FDA 1997). The second edition of AHPA's *Herbs of Commerce* increased the estimated number of species in U.S. commerce to 2,048 (AHPA 2000), and, in 2007, the International Union for Conservation of Nature (IUCN) estimated that about 3,000 medicinal and aromatic plant (MAP) species were in import-export trade (IUCN 2007). The point being that, of the thousands of herbs of commerce, most were not expressly listed as permitted for use in conventional food products. And, given the fact that only 2 new botanical drugs (out of over 600 applications) have been approved by the FDA in the 25 years since DSHEA, most botanicals must continue to navigate the middle ground between drug and food, as botanical dietary supplements. Both of the recently approved botanical drugs are prescription-only medicines with narrow indications for use, (1) an ointment containing a partially purified extract of green tea (*Camellia sinensis* (L.) Kuntze) leaf for treating genital/perianal warts, approved in 2006, and (2) a preparation of dragon's blood (*Croton lechleri* Müll.Arg.) latex for treating HIV-related diarrhea, approved in 2012 (Wu 2017).

After the passage of DSHEA, most oral ingestion herbal medicinal products transitioned to labeling as per the newly established dietary supplement subset of food regulations. However, the new regulatory framework provided no safe harbor for topical application botanical substances. While several of these did remain as Generally Recognized as Safe and Effective

(GRASE) active ingredients in FDA tentative-final monographs in the *Federal Register* (FR) or final monographs in the *Code of Federal Regulations* (CFR), e.g. Capsicum Oleoresin USP, Cocoa Butter NF, Colloidal Oatmeal USP, Topical Starch USP, and Witch Hazel USP, most external application botanical products in the market transitioned to non-drug cosmetic labeling.

B. Post-DSHEA Market Boom

The botanical ingredient sector experienced an initial market boom due to the fact that DSHEA removed considerable market access barriers and afforded the opportunity to make claim statements on labeling, including many formerly OTC drug monograph structure function claim statements. At first, the boom benefited a range of clinically-tested herbal extract products that already had marketing authorizations as OTC medicines in European countries and in neighboring Canada. These same herbal medicinal products quickly poured into the U.S. market, although labeled as dietary supplement products rather than as medicines. At the same time, scores of lower-cost look-alike products entered the market making it difficult for consumers to differentiate the good from the bad. It wasn't unusual in the 1990's to read market reports of ginseng (*Panax* spp.) product retail sales increasing by nearly 250% over previous year (Anon 1994) or St. John's wort (*Hypericum perforatum* L.) product sales increasing by over 2,800% from 1997 to 1998 (Brevoort 1998).

Although the top botanical products of the 1990's had relatively stable markets established in Europe, the new rapidly increasing market demand in the U.S. stimulated by the passage of DSHEA triggered considerable supply chain challenges, in terms of both quality and quantity. Suppliers of botanical raw materials spent the 1990's scaling up production to keep up with spikes in demand, significantly increasing farm acreage and wild collection areas. But, then, booms do lead to busts, which hit the sector hard by the end of the decade. While the top-selling

botanical supplements of the 1990's are still important today, their rankings have dropped and stabilized as new entries have displaced them. For example, turmeric (*Curcuma longa* L.) rhizome supplements are top-sellers today but were unheard of in the 1990's. Table 1 shows the top-selling botanical supplement products in the U.S. mass market in 1998 compared with their rankings in 2017.

Table 1: Top-selling botanical supplements – U.S. Mass Market – 1998 vs. 2017 ranking

Primary ingredient(s) of supplement	**1998 ranking**	**2017 ranking**
Ginkgo (*Ginkgo biloba* L.)	1	21
St. John's wort (*Hypericum perforatum* L.)	2	37
Ginseng (*Panax ginseng* C.A.Mey. or *P. quinquefolius* L.)	3	25
Garlic (*Allium sativum* L.)	4	18
Echinacea (*Echinacea angustifolia* DC., *E. pallida* (Nutt.) Nutt., or *E. purpurea* (L.) Moench)	5	2
Saw palmetto (*Serenoa repens* (W.Bartram) Small)	6	14
Grape seed (*Vitis vinifera* L.)	7	Not in top-40
Kava-kava (*Piper methysticum* G.Forst.)	8	Not in top-40
Evening primrose (*Oenothera biennis* L., *O. lamarckiana* Ser.)	9	40
Echinacea/Goldenseal (*Echinacea* spp. and *Hydrastis canadensis* L.)	10	Not in top-40
Cranberry (*Vaccinium macrocarpon* Aiton)	11	3
Valerian (*Valeriana officinalis* L.)	12	16

Source: Data extrapolated from Brevoort (1998) and Smith et al. (2018).

C. Botanical Supply Chain Challenges

While the botanical ingredients market was booming, feeding the new dietary supplement finished product sector, the fundamentals to support it were lacking and yet to be developed. At that time, quality assurance and management systems such as good agricultural and collection practice (GACP) guidelines and implementable standards for sustainable production, suitable for cultivated and/or wild-collected botanical crops, were non-existent.

The U.S. Department of Agriculture (USDA) organic regulations, inclusive of a wild-crop harvesting practice standard, of particular relevance to botanicals, came into force in 2001 (USDA 2000). Guidance on how to comply with the new wild-crop standard, however, was not published for another decade, in July of 2011 (USDA 2011). In the meantime, in 2006, a nonprofit organization, the American Herbal Products Association (AHPA) published GACPs

for herbal raw materials (relevant to both farmed and wild-collected botanicals), in collaboration with another nonprofit, the American Herbal Pharmacopoeia (AHP). As members of the AHPA Botanical Raw Materials Committee, authors of this paper were deeply involved with the development of the GACP document (AHPA 2006).

Authoritative or official quality standards from which to establish ingredient specifications for testing and verifying botanical identity, composition, strength and purity, were also lacking. From the first publication of the *Pharmacopoeia of the United States of America* in 1820 (USPC 1820) until 1920, around 875 botanical monographs were published in the USP (USPC 2016). including botanical drug substances and botanical preparations. However, with late nineteenth century advances in chemistry, the USP began to withdraw many botanical drug monographs. In the early twentieth century, only 170 botanical monographs remained, and by 1995, there were fewer than 40 USP monographs for botanicals and their preparations (Schiff et al 2006). In 1995, two important initiatives commenced, (1) the United States Pharmacopeial Convention (USPC) adopted a resolution that led to the election of a 5-year term (1995-2000) subcommittee to explore candidate botanicals for dietary supplement monograph development work; and (2) the nonprofit organization AHP was established for the express purpose of developing comprehensive monographs for quality control testing of botanical raw materials and extracts used in dietary supplement products.

Another considerable challenge for the rapidly growing botanical supplement sector was the fact that many of the most popular botanical ingredients were procured, for the most part, from wild harvesting networks in rural and remote areas often through informal, non-documented cash trade lacking transparency and traceability. It wasn't until the early 2000's that the new USDA organic regulations enabled chain-of-custody and traceability of wild crops, due to the

documentation and mapping requirements for inspection and certification. Popular high-demand wild harvested botanicals at that time included (European) bilberry (*Vaccinium myrtillus* L.) fruit and leaf, black cohosh (*Actaea racemosa* L.) rhizome, cascara sagrada (*Frangula purshiana* Cooper) bark, (Peruvian) cat's claw (*Uncaria tomentosa* (Willd. ex Schult.) DC.) bark, (European) dog rose (*Rosa canina* L.) hip, echinacea (*Echinacea angustifolia* DC.) root, (Siberian) eleuthero (*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.) root, goldenseal (*Hydrastis canadensis* L.) rhizome, licorice (*Glycyrrhiza glabra* L., *G. uralensis* Fisch.) root, saw palmetto (*Serenoa repens* (W.Bartram) Small) berry, slippery elm (*Ulmus rubra* Muhl.) bark, St. John's wort (*Hypericum perforatum* L.) flowering tops, and wild yam (*Dioscorea villosa* L.) rhizome, among many others.

The conservation status of most medicinal plants had yet to be assessed, and the development of international standards for sustainable wild collection and ecosystem management were still a decade away. While the World Health Organization (WHO) 1993 "*Guidelines on the Conservation of Medicinal Plants*" existed (WHO, IUCN & WWF 1993), which provided a framework with recommended actions, they had little impact on industry. It was probably not until 1996 that the industry really sat up and took notice, when the World Wildlife Fund-US (WWF) suggested that the U.S. Fish & Wildlife Service (USFWS) propose listing the popular botanical goldenseal onto Appendix II of the Convention on International Trade in Endangered Species (CITES) (USFWS 1996).

And, it wasn't until the early 2000's, that rigorous international standards and corresponding guidance documents for sustainable wild collection of botanicals were being developed and test-implemented globally for feasibility, in collaboration with herbal companies (some American) and nature conservation organizations (e.g. WWF), with the financial and

technical support of European governmental agencies. This included the (1) German-government supported "*International Standard for the Sustainable Wild-Collection of Medicinal and Aromatic Plants*" (ISSC-MAP) Draft 1 (Leaman 2004), Draft 2 (Leaman & Salvador 2005), Working Draft (MPSG 2006), and Version 1.0 (2007) (MPSG 2007); and (2) the Swiss-government supported "*FairWild Standard*," Version 1.0 (Meinshausen et al. 2006) and Version 2.0 (FWF 2010), the latter which incorporated the ISSC-MAP as the result of the two initiatives merging in October 2008 (Brinckmann 2009).

II. Managing quality and sustainability

When DSHEA came into being, the U.S. botanical ingredients and products sectors, for the most part, did not yet have the requisite standards and tools developed to cope with, not only exponential market growth and strains on capacity, but also a series of regulations that would require development and implementation of standards for quality management and sustainability of botanical ingredients from the field to post-harvest processing, and on to finished product manufacturing. This chapter will tie the thread of quality management from implementation GACPs and sustainable production standards in the field to GMPs in the processing facilities with application of pharmacopoeial quality standards in the testing laboratories as the basis of specifications for ensuring the proper composition, identity, purity, and strength of the botanical ingredient. Table 2 provides a chronology of significant post-DSHEA developments related to managing the quality and sustainability of botanical supplement ingredients in the U.S.

Table 2: Historical timeline of significant post-DSHEA events impacting quality and sustainability of botanical supply

Date	Event
1994, Oct. 25	U.S. Congress "Dietary Supplement Health and Education Act of 1994" (DSHEA) becomes law. The Act afforded legal recognition to USP-NF standards for dietary supplement quality.
1995, Mar. 9-12	U.S. Pharmacopeial Convention (USPC) adopted Resolution No. 12, a resolution that "encouraged the USP to explore the feasibility and advisability of establishing standards and developing information concerning dietary supplements."

Date	Event
1995	Nonprofit organization, the American Herbal Pharmacopoeia (AHP) is established with a purpose to produce comprehensive monographs that outline the quality control criteria needed for ensuring the identity, purity, and quality of botanical raw materials.
1995	Nonprofit organization, the United Plant Savers (UpS) is founded with a mission "to protect native medicinal plants of the United States and Canada and their native habitat while ensuring an abundant renewable supply of medicinal plants for generations to come."
1997, Sept. 18	Goldenseal (*Hydrastis canadensis*) enters Appendix II of the Convention on International Trade in Endangered Species (CITES) as proposed by the U.S. Fish and Wildlife Service (USFWS).
1997, Dec. 16	USDA proposes establishment of a national organic program to include wild-crop harvesting.
1999	The Medicinal Plant Working Group (MPWG) was established under the umbrella of the Plant Conservation Alliance (PCA), facilitated by the USFWS.
2000	Nonprofit UpS publishes At-Risk and To-Watch list of native American botanicals.
2000, Dec. 21	USDA National Organic Program (NOP) final rule, which, of particular relevance to sustainable botanical supply, includes a "Wild-crop Harvesting Practice Standard" (7 CFR § 205.207).
2004, Nov.	Nonprofit organization, the American Herbal Products Association (AHPA) publishes "Background on California Proposition 65: Issues related to heavy metals and herbal products."
2006, Dec.	AHPA publishes "AHPA-AHP Good Agricultural and Collection Practice for Herbal Raw Materials," prepared by members of the AHPA Botanical Raw Materials Committee.
2007, Jun. 25	U.S. FDA final rule "Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements (21 CFR Part 111).
2008, Dec. 29	USDA Forest Service final rule on "Special Forest Products and Forest Botanical Products."
2010, Oct. 29	United Nations treaty affecting access & trade of medicinal plants adopted: "Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity," and came into force Oct. 12, 2014.
2011, Jan. 4	U.S. Congress "FDA Food Safety Modernization Act" becomes law.
2011, Jul. 22	USDA NOP issues guidance on organic "Wild Crop Harvesting."
2011, Nov. 2	Three nonprofit organizations, the American Botanical Council (ABC), the AHP, and the University of Mississippi's National Center for Natural Products Research (NCNPR) initiated the "ABC-AHP-NCNPR Botanical Adulterants Program" to educate members of the herbal and dietary supplement industry about ingredient and product adulteration.
2012	USPC published first edition of the Dietary Supplements Compendium (DSC), which brought together monographs and general chapters of FCC, NF and USP.
2015, Sept. 17	U.S. FDA final rule "Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food" (21CFR Part 117).
2016, Jan. 15	USDA NOP issues guidance on "Natural Resources and Biodiversity Conservation" for organic operations (farms and wild-collection operations).
2017, March	AHPA publishes updated "*Good Agricultural and Collection Practices and Good Manufacturing Practices for Botanical Materials*."

A. 1995-2000: AHP and USP begin to develop botanical monographs

Due to the passage of DSHEA, the advisability of developing botanical supplement monographs was deliberated at the 1995 Quinquennial Meeting of the United States Pharmacopeial Convention (USPC). The Convention adopted a resolution to encourage USP to explore the feasibility and advisability of establishing standards and developing information concerning dietary supplements. A subcommittee on natural products was elected for a five-year

term (1995-2000). The subcommittee, with the assistance of an appointed advisory panel, began the work to select candidate botanicals for monograph and methods development (Schiff et al 2006). Also in 1995, the nonprofit AHP was founded, and, in the meantime, has developed and published nearly 40 botanical monographs, possibly the most comprehensive compendium available providing standards for identity, analysis, and quality control.

While the use of official pharmacopoeial standards is mandatory for quality specifications of botanical drugs, their use is voluntary for botanical dietary supplements in the U.S.

> "The Dietary Supplement Health and Education Act of 1994 (DSHEA) amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act) named the United States Pharmacopeia and National Formulary (USP-NF) as official compendia for dietary supplement ingredient quality standards. At the same time, industry compliance with USP-NF standards was made voluntary. Nonetheless, the amendments stipulate that if an herbal dietary supplement that is covered by the specifications of an official compendium is represented as conforming to the specifications of an official compendium, and fails to conform to such specifications, it shall be deemed misbranded. Thus, compliance with a USP monograph becomes mandatory only in cases where the product label specifies that it contains components with a USP quality designation" (Brinckmann 2011).

One of the co-authors of this paper (JAB) submitted comments on FDA's draft cGMPs suggesting that use of authoritative quality standards, such as those published in pharmacopoeial monographs, should be a required minimum basis for the establishment of botanical supplement ingredient specifications, in that it could be disingenuous or fraudulent for companies to market products with claim statements, where the evidence to support the claim is based on the use of a specified pharmacopoeial quality, if, in fact, the company was using inferior quality grades of

botanical raw materials. In the preamble of the final rule, while FDA stated that companies may use validated methods that can be found in official references, such as AOAC International, USP, and others, the agency rejected the argument that pharmacopoeial quality should be a minimum requirement for ingredients that are the subject of structure function claim statements (FDA 2007).

In a critique of the FDA cGMPs, published in *Food and Drug Law Journal*, representatives of the USPC stated:

> "Unfortunately, these cGMPs establish no minimum requirement for quality. The manufacturer is entitled to use its best judgment in establishing a standard. Moreover, although the cGMPs will help ensure that one manufacturer's product is similar from batch to batch, the specifications for similar articles can vary widely from manufacturer to manufacturer. Effectively, the cGMPs call for standards without standardization. A manufacturer may create essentially private standards for a particular dietary ingredient or dietary supplement, but the manufacturer need not make these standards public. One manufacturer's standards may bear little or no resemblance to the standards created by other manufacturers for the same ingredient or product. Thus multiple manufacturers may establish different standards of identity, strength, quality, and purity for articles that are introduced into commerce under the same name" (Miller et al 2008).

Regardless of the fact that it was not mandatory for manufacturers of supplement products to base their ingredient quality specifications on pharmacopoeial standards, considerable progress has been made over the past 25 years. Monographs relevant to specifying the quality of botanical supplement ingredients have been made available through the American Herbal Pharmacopoeia (AHP), Food Chemicals Codex (FCC), National Formulary (NF) and United States

Pharmacopeia (USP). Furthermore, the USPC, since 2012, publishes a separate Dietary Supplements Compendium (DSC), which provides monographs and general chapters of FCC, NF and USP along with supplemental information such as color plates and illustrations (USPC 2019). Table 3[1] provides a list of monographs available for botanical raw materials and extracts and oils obtained from them.

B. 2000: USDA final rule for NOP (7 CFR Part 205)

In 2000, the USDA NOP final rule was published, which, of particular relevance to sustainable botanical supply, included the "Wild-crop Harvesting Practice Standard" (7 CFR § 205.207).

Experience has shown that the implementation of sustainability standards may also contribute to compliance with certain aspects of FDA's cGMPs, especially where they pertain to management and control of contamination. For example, the USDA NOP soil fertility and crop nutrient management practice standard (7 CFR §205.203) requires producers to manage plant and animal materials to maintain or improve soil organic matter content in a manner that does not contribute to contamination of crops, soil, or water by plant nutrients, pathogenic organisms, heavy metals, or residues of prohibited substances. Furthermore, if a botanical supplement component is certified organic, 7 CFR §205.670(c) requires pre-harvest or post-harvest tissue test sample collection to be performed by an inspector or certifying agent.

> "Sample integrity must be maintained throughout the chain of custody, and residue testing must be performed in an accredited laboratory. Chemical analysis must be made in accordance with AOAC methods or other current applicable validated methodology determining the presence of contaminants in agricultural products" (USDA 2000).

[1] Due to its large size, Table 3 is presented under ANNEX I

C. 2006: AHPA-AHP GACPs

The genesis of the development of GACPs, specifically designed for MAP crops (farmed and wild), can be traced to an initial 1983 round-table discussion at the 4th International Society for Horticultural Science (ISHS) Symposium in Angers, France (Máthé & Franz 1996). It would however be another 20 years before an elaboration of general international GACP guidelines for medicinal plants would be published by the World Health Organization (WHO 2003a). The "*WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants*" were developed in response to Resolution WHA56.31 from the Fifty-sixth World Health Assembly on Traditional Medicine which requested the Director-General to provide technical support for development of methodology to monitor or ensure product quality, efficacy and safety, preparation of guidelines, and promotion of exchange of information (WHO 2003b). The WHO GACP guidelines were primarily intended to provide "general" yet globally applicable technical guidance with the awareness that the GACPs would need to be adjusted according to each country's actual situation. One of the main objectives of these general guidelines was to provide the basis for the formulation of national and/or regional GACP guidelines, species-specific GACP monographs, and related standard operating procedures (SOPs).

While many national and international governmental organizations have developed and implemented national GACPs for MAPs, for example, the China Food and Drug Administration (CFDA 2002), Japanese Ministry of Health, Labour and Welfare (WHO 2003a), European Medicines Agency (EMA) (HMPC 2006), and India's National Medicinal Plants Board (NMPB 2009a, 2009b), the U.S. has not yet. While GACP compliance is mandatory for botanical drugs it is voluntary for botanical supplements. In their 2004 guidance for industry on botanical drug products (FDA 2004), the FDA deferred to the EMA GACPs:

> "Starting materials of botanical origin that are used to produce a botanical drug substance should be evaluated for quality. The use of appropriate starting materials and the drug substance manufacturer's ability to control the source depend on appropriate specifications (tests, analytical procedures, and acceptance criteria). In addition to establishing specifications, manufacturers can achieve adequate quality control of starting materials by applying the principles outlined in FDA's botanical guidance and by following good agricultural and good collection practice for starting materials of herbal origin (e.g., European Medicines Evaluation Agency HMPWP/31/99)" (FDA 2004).

However, in the FDA's revised botanical drug guidance (FDA 2016), the agency deferred to both the EMA and WHO GACPs:

> "To assess quality and therapeutic consistency, it is important to select representative raw material batches (i.e., raw material from three or more representative cultivation sites or farms) for the manufacturing of the clinical drug substance for multiple batch Phase 3 studies. The sponsor should establish large growing regions with three or more cultivation sites or farms whose locations are purposefully selected to be representative of the regions for each of the botanical raw materials following the principles of Good Agricultural and Collection Practices (GACP)." [Note: FDA footnotes this statement with "See the World Health Organization's "*WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants*" and the European Medicines Agency's "*Guideline on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin*"]" (FDA 2016).

And, while the USPC has, in the past, proposed to develop a new General Chapter section on GACPs, USP General Chapter <2030> "*Supplemental Information for Articles of Botanical Origin*" provides general guidance deferring to the WHO GACP:

> "It is recommended that, at a minimum, growers and others involved in the handling and distribution of botanical products should become familiar with and follow the *WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants*" (USPC 2018a).

Thus, for the U.S. context of quality management of botanical crops, in lieu of official GACPs from either the FDA or USP, two nonprofit organizations, AHPA and AHP collaborated in the production of the "*AHPA-AHP Good Agricultural and Collection Practice for Herbal Raw Materials*," initiated under the auspices of the AHPA Botanical Raw Materials Committee (AHPA 2006). While it has no legal standing in the U.S., AHPA states that its GACP has relevance to herbal raw materials used in all herbal products, including cosmetics, dietary supplements, drugs, and foods. However, it should also be noted that the Canadian government officially recognized the AHPA-AHP GACP in their "*Quality of Natural Health Products Guide*" as acceptable for botanical medicinal ingredients of licensed natural health products in Canada (NNHPD 2015).

D. 2007: U.S. FDA final rule cGMPs (21 CFR Part 111)

FDA's 2007 final rule on cGMP in manufacturing, packaging, labeling, or holding operations for dietary supplements (21 CFR Part 111) required the establishment of quality specifications with scientifically valid methods for ensuring the composition, identity, purity and strength of dietary supplement components, as well as the establishment of limits on types of contamination that may adulterate or may lead to adulteration (FDA 2007). Experience of some companies has

shown that compliance with the cGMP can be accomplished by implementing other standards earlier in the botanical supply chain. For example, GACP compliance generally requires written agreements between producers and buyers of botanicals with regard to quality such as content of active principle, macroscopical and olfactory properties, limit values for microbial contamination, chemical residues and heavy metals, and that specifications should be based on recognized national pharmacopoeial monographs (HMPC 2006). And, basing one's quality specification on quality standards monographs such as those of the USP ensure that scientifically valid methods and limits will be established for determining composition, identity, purity, and strength.

Subsequently, in 2011, also impacting the production and trade of botanical dietary supplement ingredients, Congress enacted the Food Safety Modernization Act (FSMA)

> "in response to dramatic changes in the global food system and in our understanding of foodborne illness and its consequences, including the realization that preventable foodborne illness is both a significant public health problem and a threat to the economic well-being of the food system. FSMA is transforming the nation's food safety system by shifting the focus from responding to foodborne illness to preventing it" (FDA 2018b).

As part of the FSMA, Congress has enacted several rules:

- Preventive Controls for Human Food
- Foreign Supplier Verification Program for Importers of Food for Human and Animals
- Sanitary Transportation of Human and Animal Food
- Mitigation Strategies to Protect Food against Intentional Adulteration
- Accredited Third Party Certification
- Preventive Controls for Food for Animals

- Standards for Produce Safety

While these rules are now final, all corresponding guidance documents are not yet finalized.

III. Control of adulterants and contaminants

This section discusses the problems and solutions concerning adulteration of botanical ingredients, whether intentional (economic) or unintentional (look-alike species growing in proximity to target species). Additionally unavoidable contamination of botanical ingredients has become one of the most disruptive quality problems negatively impacting trade and quality of products. Our planet is not getting cleaner. Anthropogenic pollution and related contamination to the natural environment is now global and pervasive. Types of pollution affecting botanical crops, whether farmed or wild-collected, include heavy metals contamination from industrial pollution, nonpoint source pesticide pollution from conventional agriculture operations negatively impacting certified organic crops and wild crops, pharmaceutical drugs in irrigation water, plastic pollution, polycyclic aromatic hydrocarbons (PAHs), and radioactive residues.

i. Economic adulteration

In 2011, three nonprofit organizations, the ABC, the AHP, and the University of Mississippi's National Center for Natural Products Research (NCNPR) initiated the "*ABC-AHP-NCNPR Botanical Adulterants Program*" to educate members of the herbal and dietary supplement industry about ingredient and product adulteration. To date, seventeen comprehensive Botanical Adulterant Bulletins have been published and seven laboratory guidance documents (Table 4), among other materials useful for the industry

Table 4: Botanical Adulterants Program bulletins and laboratory guidance documents list

Date	Title
2015, January	Skullcap Adulteration Laboratory Guidance Document
2015, August	Bilberry Fruit Extract Laboratory Guidance Document
2015, November	Black Cohosh Adulteration Laboratory Guidance Document
2016, April	Adulteration of Bilberry (*Vaccinium myrtillus*) Extracts
2016, April	Adulteration of Grape Seed Extract (*Vitis vinifera*)

Date	Title
2016, April	Adulteration of Skullcap (*Scutellaria lateriflora*)
2016, June	Adulteration of Black Cohosh (*Actaea racemosa*)
2016, June	Adulteration of *Hydrastis canadensis* root and rhizome
2016, August	Adulteration of Arnica (*Arnica montana*)
2017, January	St. John's Wort (*Hypericum perforatum*) Adulteration
2017. March	Adulteration of Grapefruit Seed Extract (*Citrus paradisi*)
2017, May	Grapefruit Seed Extract Laboratory Guidance Document
2017. August	Tea Tree (*Melaleuca alternifolia* and *M. linariifolia*) Oil
2017, October	Adulteration of Rhodiola (*Rhodiola rosea*) Rhizome, Root, and Extracts
2017, December	Adulteration of Cranberry (*Vaccinium macrocarpon*)
2018, January	Adulteration of *Ginkgo biloba* Leaf Extract
2018, April	Pomegranate Products Laboratory Guidance Document
2018, May	Turmeric (*Curcuma longa*) Root and Rhizome, and Root and Rhizome Extracts
2018, June	*Boswellia serrata* Adulteration
2018, September	Adulteration of Maca (*Lepidium meyenii*)
2018, September	Tea Tree Oil Laboratory Guidance Document
2018, October	Adulteration of Saw Palmetto (*Serenoa repens*)
2018, November	Cranberry Products Laboratory Guidance Document
2019, January	Adulteration of Ashwagandha (*Withania somnifera*) Roots, and Extracts
2019, February	Grape Seed Extract Laboratory Guidance Document

SOURCE: American Botanical Council: http://cms.herbalgram.org/BAP/

ii. Heavy metal pollutants in the environment

Medicinal plant crops can be contaminated by absorbing heavy metals from soil, water and air, i.e. from industrial emissions, mining, smelting, landfills, conventional agriculture (fertilizers and pesticides; polluted water used for irrigation, sewage sludge), transportation (traffic-induced contaminated atmosphere), rainfall, and atmospheric dust:

- Air: Aerial plant parts accumulate heavy metals by uptake of airborne pollution relative to proximity to industrial zones and traffic (Serbula et al. 2013).
- Soil: "Absorption of heavy metal in medicinal plants is governed by soil characteristics such as pH, salinity, conductivity and organic matter content" (Rădulescu et al. 2013).
- Water: "Toxic elements from wastewater may contaminate agricultural soils, water supplies and environment… Elevated levels of heavy metals in plants are reported from the areas having long-term uses of treated or untreated wastewater" (Shaban et al. 2016).

While the United States Pharmacopoeia (USP) prescribes general limits for elemental impurities in general chapter ⟨561⟩ ARTICLES OF BOTANICAL ORIGIN (USPC 2018b) [see Table 5], the State of California enacted its own limits through implementation of the Safe Drinking Water and Toxic Enforcement Act of 1986, more commonly known as California Proposition 65.

Table 5: USP General Chapter ⟨561⟩ Articles of Botanical Origin - Limits of Elemental Impurities

Element	Limit (µg/g)
Arsenic (inorganic)	2
Cadmium	0.5
Lead	5
Mercury (total)	1
Methylmercury (as Hg)	0.2

The California Proposition 65 limits for heavy metals continue to impact the botanical dietary supplement trade, from increased testing for selection of California-compliant lots, to product brands lowering their daily serving size instructions on labeling in order to comply. That is, because the limits are not based on content but on daily ingestion levels. For example, the California maximum allowable daily level (MADL) for lead content in an herbal dietary supplement product is not-more-than 0.5 µg per day. Depending on the recommended daily serving size for a product, the USP limit of 5 µg per gram (in botanical material) may, or may not, prove to be compliant in California. In 2004, the American Herbal Products Association (AHPA) published its "*Background on California Proposition 65: Issues related to heavy metals and herbal products*," (McGuffin & Norris 2004), which was revised in 2008, and in 2010, and again in 2017, retitled as "*Guidance on California Proposition 65 and Herbal Products*" (AHPA 2017). AHPA's document provides guidance for industry on regulatory and liability implications of Proposition 65 for constituents that may be present in herbal products sold in California.

iii. Nonpoint source pesticide contamination

In the decades since the passage of DSHEA, pesticide drift from conventional agriculture sites has become ubiquitous in the natural world. Residues can now be detected the world over, in the air, ice, snow, soil and water, and on crops grown without the intentional use of pesticides.

- Residues of "legacy" (e.g. DDT) and "current use pesticides" (CUPs) are now detected in Arctic ice caps (evidence of long range atmospheric transport).
- In rural and remote areas, there is widespread contamination of wildflowers and bee-collected pollen with agricultural pesticides.
- Nonpoint source pesticide detection is an increasing problem even with certified organically grown and/or wild-collected botanicals, where pesticides have not been applied.

As per FDA's 21 CFR Part 111 cGMPs for dietary supplements, specifications are required to ensure that a dietary supplement derived from a botanical source does not contain contaminants such as an unlawful pesticide. Pesticide tolerances, however, are established by the Environmental Protection Agency (EPA) on a crop-specific and/or crop-group basis. While FDA enforces the EPA limits that were established mainly for food crops, tolerances have been established for only a relatively small number of botanical crops such as certain aromatic or culinary herbs that are grown in the U.S. on a large scale, e.g., spearmint (*Mentha spicata*) and hops (*Humulus lupulus*). EPA tolerances have not been established for thousands of other botanicals in commerce. Thus, when *de minimis* levels of pesticide residues are found at above the limit of quantitation (LoQ), even on wild-collected botanicals or on certified organically grown botanicals, where no pesticides were intentionally applied, there is a risk of FDA detention or import refusal at the port of entry.

Although USP General Chapter ⟨561⟩ Articles of Botanical Origin provides reasonable limits for pesticide residues, in the U.S. the USP limits are applicable only to botanical drugs and not to botanical dietary supplements. That is because dietary supplements are regulated as a subset of foods. EPA establishes limits for food crops while USP has the authority to establish limits for botanical drug crops.

In 2016, a stimuli article titled "*Need for Clear Regulation of Pesticide Residue Limits for Articles of Botanical Origin*," was published in the *Pharmacopeial Forum* for public comment (USP Botanical Dietary Supplements and Herbal Medicines Expert Committee 2016). This was followed-up with a USP roundtable on pesticide residues in botanical dietary supplements with participants from governmental agencies, trade associations, and industry.

IV. Conservation and Sustainability

This chapter looks at impacts of international conventions such as the Convention on Biological Diversity (CBD) and the Convention on International Trade in Endangered Species (CITES) on botanical ingredient production and import trade, as well as conservation status assessments of botanical species carried out by non-governmental organizations such as IUCN Red List assessments, and the emergence of voluntary standards for demonstrating economic, environmental and social sustainability in the botanical supply chain.

By the start of the 21st century, awareness grew in the global botanical trade that conserving biodiversity and improving rural economies appeared to be linked to access to traditional harvesting areas, sustainable production, trade and use of ever-increasing quantities of botanicals needed for the natural cosmetic, dietary supplement, botanical drug, and functional food sectors. This was evidenced by the fact that numerous sustainability standards (both national and private voluntary) as well as GACP standards designed for MAP crop production were being developed

through multi-stakeholder processes and implemented with funding support from governmental agencies (e.g. German Federal Agency for Nature Conservation (BfN)), intergovernmental organizations (e.g. agencies of the United Nations), and non-governmental organizations (e.g. WWF).

> "Implementation of voluntary sustainability standards (VSS) that include economic, environmental and social criteria and indicators is an emerging market-based approach to biodiversity conservation, sustainable harvesting and commercial use of MAPs, and to demonstrate compliance with international agreements. While such standards are voluntary, in that compliance is not required by governmental regulations, independent third-party inspection and certification organisations determine if companies are operating in compliance with the standard" (Brinckmann 2017; Komives & Jackson 2014).

From 2010 to 2014, international botanical ingredient and finished product companies also needed to learn the (new) ropes for compliance with a United Nations multilateral treaty, adopted in 2010 for enforcement by 2014, the "*Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity*" (Secretariat of the Convention on Biological Diversity 2011). Some of the aforementioned voluntary sustainability standards provide ways for companies to demonstrate compliance with the access and benefit sharing (ABS) requirements of the protocol, for example, the Ethical BioTrade Standard, developed by the Union for Ethical BioTrade (UEBT), and the FairWild Standard (FWS), developed by the FairWild Foundation. Criterion 4.2 of the FWS requires that agreements made with local communities and/or indigenous peoples are executed in compliance with relevant international and national laws and ABS regulations including

protection of traditional knowledge (FWF 2010). Written and mutually accepted fair and equitable agreements on use of medicinal plants and associated traditional knowledge must be in place to maintain FairWild certification (FWF 2013). Section 3 of the Ethical BioTrade Standard "*Fair and Equitable Sharing of Benefits derived from the Use of Biodiversity*" includes comparable requirements (UEBT 2012).

Table 6 provides a listing of selected botanicals with information on their conservation status, for example if the species is listed in the CITES appendixes, or has been assessed according to the IUCN Red List criteria or the UpS ranking tool. Species prioritized in the AHPA tonnage survey are also included in the table if the species has been assessed according to UpS, IUCN or CITES.

Table 6: Conservation status of selected botanicals used in botanical supplement products

Botanical name	CITES	IUCN Red List	UpS
Agarwood (*Aquilaria* spp.)	II	CR, *Aquilaria crassna*; CR, *A. malaccensis*; VU, *A. sinensis*	
American ginseng (*Panax quinquefolius* L.)	II	Not assessed	ATR
Asian ginseng (*Panax ginseng* C.A.Mey.) from Russia	II	Not assessed	
Arnica (*Arnica* spp.)		LC, *Arnica montana*	TW
Bethroot (*Trillium erectum* L.)		Not assessed	ATR
Bletilla (*Bletilla striata* (Thunb.) Rchb.f.)	II	Not assessed	
Bloodroot (*Sanguinaria canadensis* L.)		Not assessed	ATR
Black cohosh (*Actaea racemosa* L.)		Not assessed	ATR
Blue cohosh (*Caulophyllum thalictroides* (L.) Michx.)		Not assessed	ATR
Brazilian rosewood (*Aniba rosaeodora* Ducke)	II	EN	
Candelilla (*Euphorbia antisyphilitica* Zucc.)	II	No assessed	
Cape aloe (*Aloe ferox* Mill.)	II	Not assessed	
Cascara sagrada (*Frangula purshiana* Cooper)		LC	TW
Chun lan (*Cymbidium goeringii* (Rchb.f.) Rchb.f.)	II	Not assessed	
Common pleione (*Pleione yunnanensis* (Rolfe) Rolfe)	II	Not assessed	
Costus (*Saussurea costus* (Falc.) Lipsch.)	I	CR	
Dendrobium (*Dendrobium* spp.)	II	CR, *D. huoshanense*; CR, *D. officinale*;	
Desert broomrape (*Cistanche deserticola* Y.C.Ma)	II	Not assessed	
Echinacea (*Echinacea* spp.)		Not assessed	ATR
Elephant tree (*Bursera microphylla* A.Gray)		Not assessed	TW
Eyebright (*Euphrasia* spp.)		Not assessed	ATR
Fragrant rosewood (*Dalbergia odorifera* T.C.Chen)	II	VU	
False unicorn (*Chamaelirium luteum* (L.) A.Gray)		Not assessed	ATR
Gastrodia (*Gastrodia elata* Blume)	II	VU	
Gentian (*Gentiana* spp.)		CR, *G. kurroo*	TW
Goldenseal (*Hydrastis canadensis* L.)	II	VU	ATR
Goldthread (*Coptis* spp.)		EN, *C. teeta*	TW

Botanical name	CITES	IUCN Red List	UpS
Guaiacum (*Guaiacum* spp.)	II	EN, *G. officinale*; NT, *G. sanctum*	
Hoodia (*Hoodia gordonii* (Masson) Sweet ex Decne.)	II	Not assessed	
Indian rosewood (*Dalbergia sissoo* DC.)	II	Not assessed	
Jatamansi (*Nardostachys grandiflora* DC.)	II	CR	
Jivakah (*Malaxis acuminata* D.Don)	II	Not assessed	
Lady's slipper orchid (*Cypripedium* spp.)	II	LC, *C. acaule*; LC, *C. parviflorum*	ATR
Lobelia (*Lobelia* spp.)		LC, *L. cardinalis*; LC, *L. siphilitica*	TW
Lomatium (*Lomatium dissectum* (Nutt.) Mathias & Constance)		Not assessed	ATR
Oregon grape (*Mahonia aquifolium* (Pursh) Nutt., *M. nervosa* (Pursh) Nutt., *M. repens* (Lindl.) G. Don))		Not assessed	TW
Osha (*Ligusticum porteri* J.M.Coult. & Rose, L. spp.)		Not assessed	ATR
Partridge berry (*Mitchella repens* L.)		Not assessed	TW
Perry's aloe (*Aloe perryi* Baker)	II	NT	
Picrorhiza (*Picrorhiza kurrooa* Royle)	II	Not assessed	
Pleurisy (*Asclepias tuberosa* L.)		Not assessed	TW
Pygeum (*Prunus africana* (Hook.f.) Kalkman)	II	VU	
Red saunders (*Pterocarpus santalinus* L.f.)	II	NT	
Riddhi (*Habenaria intermedia* D.Don)	II	Not assessed	
Sandalwood (*Santalum* spp.)		VU, *S. album*	ATR
Scythian lamb (*Cibotium barometz* (L.) J.Sm.)	II	Not assessed	
Skullcap (*Scutellaria lateriflora* L.)		LC	
Slippery elm (*Ulmus rubra* Muhl.)		LC	ATR
Sundew (*Drosera* spp.)		Not assessed	ATR
True unicorn (*Aletris farinosa* L.)		Not assessed	ATR
Venus' fly trap (*Dionaea muscipula* J.Ellis)		VU	ATR
Wild cherry (*Prunus serotine* Ehrh.)		LC	
Wild indigo (*Baptisia tinctoria* (L.) Vent.)		Not assessed	TW
Wild yam (*Dioscorea villosa* L., D. spp.)		Not assessed	ATR
Witch hazel (*Hamamelis virginiana* L.)		LC	
Yerba mansa (*Anemopsis californica* (Nutt.) Hook. & Arn.)		Not assessed	TW

Legend:
CITES Appendices: **Appendix I**: lists species that are the most endangered; threatened with extinction. CITES prohibits international trade in specimens of these species except when the purpose of the import is not commercial, for instance for scientific research. **Appendix II:** lists species that are not necessarily now threatened with extinction but that may become so unless trade is closely controlled. It also includes so-called "look-alike species", i.e. species whose specimens in trade look like those of species listed for conservation reasons. **Appendix III:** is a list of species included at the request of a Party that already regulates trade in the species and that needs the cooperation of other countries to prevent unsustainable or illegal exploitation.
IUCN Categories: CR, critically endangered; DD, data deficient; EN, endangered; LC, least concern; NT, near threatened; VU, vulnerable.
UpS Ranking: ATR, at-risk; TW, to watch.

A. AHPA tonnage survey

The American Herbal Products Association (AHPA) initiated and has conducted "Tonnage Surveys" since 1999 for the purpose of quantifying the annual harvests of specific North American botanicals in commerce. AHPA's Tonnage Survey is considered "a vital index of

native U.S. botanical consumption," according to the Fish and Wildlife Service of the U.S. Department of the Interior. According to AHPA:

> "Harvest information is a more powerful tool when harvest amounts are tabulated to include combined total usage. By working together, AHPA and the herbal products industry generate valuable information that helps ensure sustainable growth and stability. Participation in this survey also demonstrates the industry's commitment to sustainable harvests" (AHPA 2019).

The first of these surveys addressed only the plant goldenseal (*Hydrastis canadensis*) and solicited information about both wild and cultivated harvests for 1998, as well as certain harvest and cultivation practices. The second survey extended this attention on goldenseal for the 1999 harvest year and also compiled information for the years 1997–1999 for a number of other plants. The 2000–2001 survey identified all of the plants from these earlier efforts and a number of additional species. These surveys have continued to evolve by adding new species, more cultivation oriented, fresh and dried material numbers and other information based on the need of new data for today's market. Figure 1 provides a chart illustrating the annual harvested quantities of four high-volume American botanicals from 1999 through 2010.

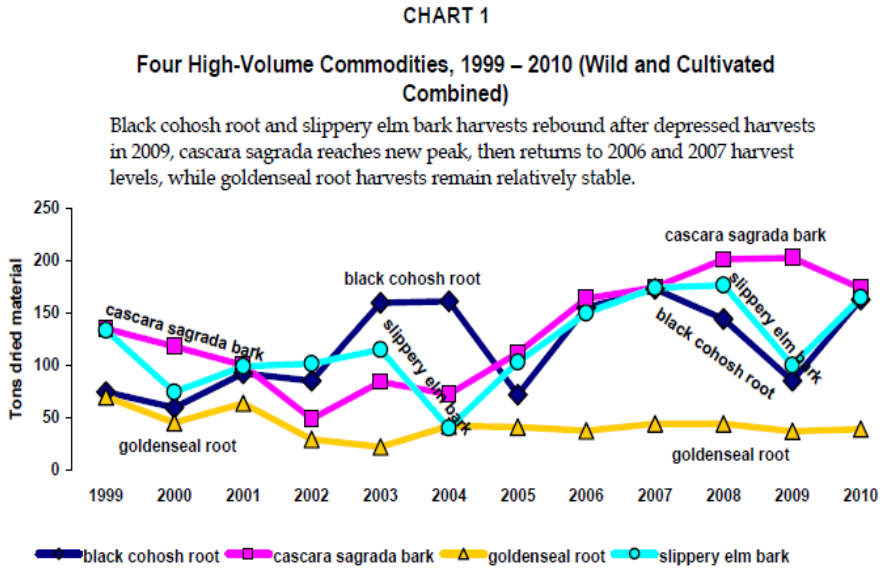

Fig. 1 Annual harvested quantities (dry weight basis) of four high-volume botanicals, 1999-2010, excerpted with permission from the "*Tonnage Surveys of Select North American Wild-Harvested Plants, 2006–2010*" (AHPA 2012).

According to AHPA, with regard to its 14 years of harvest data for goldenseal:

> "Annual variations in harvest quantities for certain of these commodities are consistent with market factors over the past several years. This review of data over the fourteen-year period reveals that patterns in market demand are reflected in annual variations of harvests of both wild and cultivated sources of these botanical commodities. Several species for which there are large market demands are cultivated to a sufficient degree so that some meaningful portion of the total usage is provided by farmers rather than by harvesters of wild plants. The most recent surveys affirm that this continues to be the case for the goldenseal market… "However, market demand, not plant availability, seems to be the primary driver of total harvest quantities. As has been noted in other publications, information about the population dynamics of many of these species in their native habitats is not well understood" (AHPA 2012).

The latest survey (with submission deadline of 26 April 2019), continues to focus on selected North American botanicals that are produced in part from wild-harvested populations, but has been expanded to track 51 herbal commodities representing 44 species, including American

ginseng, black cohosh, cascara sagrada, *Echinacea* spp., saw palmetto, slippery elm, and witch hazel (AHPA 2019).

Data from the AHPA tonnage surveys are the foundational information needed to both track and assess the sustainability of harvests of North American species in trade within the herbal dietary supplement and herbal medicine industries. It may still require a collaborative effort between industry, regulatory and nature conservation organizations to objectively and impartially study the data thoroughly enough to better understand the impact on native species relative to each species' life cycle, while considering other impacts such as human expansion and habitat depletion.

B. Medicinal Plant Working Group

Facilitated by the USFWS, the Medicinal Plant Working Group (MPWG) formed in 1999: "Recognizing that commercial demands may pose threats to native plants in the United States, representatives from industry, government, academia, tribes, and environmental organizations joined together to form the Medicinal Plant Working Group (PCA-MPWG) under the umbrella of the Plant Conservation Alliance (PCA)" (Lyke 2000). The primary focus of the MPWG has been to facilitate action in cases where the conservation status of a native medicinal plant is of concern.

C. UpS ranking tool

While UpS launched their medicinal plant species "At Risk" and "To Watch" lists in 2000, it was initially informed by input from UpS-member herbalists, ecologists, growers, and buyers. As the botanical industry continued to grow rapidly, UpS realized that a more transparent methodology was needed. As the result of a multi-year, multi-stakeholder process, in 2014, UpS launched what it called a "*Ranking Tool Created for Medicinal Plants*." The tool can be used to quantify and compare vulnerability to overharvest for wild collected medicinal plants, scoring

species "according to their life history, the effects of harvest, their abundance and range, habitat, and demand" (Castle et al. 2014).

D. USDA NOP biodiversity conservation guidance

The general natural resources and biodiversity conservation requirement of the USDA organic regulations (7 CFR §205.200) requires producers (both farms and wild collection operations) to "maintain or improve the natural resources of the operation, including soil and water quality." And the wild-crop harvesting practice standard (7 CFR §205.207) states that a "wild crop must be harvested in a manner that ensures that such harvesting or gathering will not be destructive to the environment and will sustain the growth and production of the wild crop" (USDA 2000). In 2011, USDA published guidance aiming to clarify the ways in which certified operations could demonstrate compliance with the standard (USDA 2011). Then, 16 years after the organic regulations came into force, guidance was finally published on the biodiversity conservation requirements of organic operations (USDA 2016a). In response to public comments, USDA stated:

> "There are many ways for operations to meet the requirements of § 205.200… Wild harvest operations may voluntarily elect to follow the FairWild Foundation (FWF) standards in order to meet the NOP requirements for biodiversity conservation; however the change was not made to the final guidance" (USDA 2016b).

E. Emergence of voluntary sustainability standards

The end of the 20th century saw the emergence of voluntary sustainability standards (VSS) relevant to the production and trade of medicinal and aromatic plants according to principles of economic, environmental, and social sustainability. For example, Fair Trade International (FLO) was founded in 1997 in Bonn, Germany, and soon afterwards developed fair trade standards for

herbs, herbal teas, and spices. In 2000, the USDA National Organic Program (NOP) standards were published. In the first two decades of the 21st century, there has been a proliferation of VSS, with several hundreds of botanical species being traded globally with one or more certifications. Table 7 provides a list of selected VSS that are being applied to botanical crops. Implementation of VSS by botanical producers can, not only fill in some of the gaps in GACP guidelines and organic agriculture regulations, respectively, but also provide producers with the value-addition of certifications that demonstrate compliance with credible sustainability standards, that can strengthen their economic viability and market position (Brinckmann 2016).

Table 7: Selected voluntary sustainability standards applicable to botanical crops

Name of standard	Owner of the standard	Economic sustainability	Environmental sustainability	Social sustainability
Agricultural Production Standard	Fair Trade USA (FTUSA)	✔	✔	✔
Biodynamic® Farm Standard	DEMETER Association Inc.		✔	
EcoSocial Fair	Instituto Biodinâmico de Desenvolvimento Rural (IBD)	✔	✔	✔
Ethical BioTrade Standard	Union for Ethical BioTrade (UEBT)	✔	✔	✔
Fair Choice Social and Fair Trade Standard	CONTROL UNION (CU)	✔	✔	✔
Fair For Life Standard	ECOCERT SA	✔	✔	✔
Fairtrade Standard for Herbs, Herbal Teas & Spices for Small Producer Organizations and traders	Fairtrade Labelling Organizations International, e.V. (FLO)	✔		✔
Fairtrade Standard for Herbs and Herbal Teas for Hired Labour and Traders	Fairtrade Labelling Organizations International, e.V. (FLO)	✔		✔
FairTSA Consolidated standards for the production of agricultural products, processed foods, wild collected plants, handicrafts and personal-care products	Fair Trade Sustainability Alliance (FairTSA)	✔	✔	✔
FairWild Standard	FairWild Foundation (FWF)	✔	✔	✔
National Standard for Organic Production	United States Department of Agriculture (USDA)		✔	
Non-GMO Project Standard	Non-GMO Project		✔	
Regenerative Organic Certification Standard	Regenerative Organic Alliance	✔	✔	✔
Sustainable Agriculture Standard	Rainforest Alliance and UTZ		✔	
UEBT-UTZ Sustainable Herbal Tea Standards	UEBT and UTZ	✔	✔	✔

SOURCE: Table created by J.A. Brinckmann for the AHPA Sustainability Sub-committee.

V. Conclusion and Recommendations for the future

This paper shows that, twenty-five years since DSHEA, in response to strains caused by a continually growing market demand for botanical ingredients and products in the United States, a considerable range of useful standards, guidance manuals, and tools have been developed by educational organizations (e.g. ABC-AHP-NCNPR), governmental organizations (e.g. FDA, USDA-NOP), medicinal plant conservation organizations (e.g. IUCN-MPSG, PCA-MPWG, UpS), quality standards setting organizations (e.g. AHP, USP), sustainability standards setting organizations (e.g. FLO, FWF, UEBT), and trade associations (e.g. AHPA). ***While compliance with FDA regulations governing the manufacture and marketing of herbal dietary supplement products is mandatory, the use of pharmacopoeial quality standards, GACP standards, and sustainability standards (all of which support regulatory compliance), is voluntary.***

The way that botanical ingredients and products are regulated and marketed in the United States, for the most part, remains unique and possibly an anomaly in the world, certainly by comparison to the frameworks of our neighbors and trading partners, such as Canada, Mexico, the European Union, Australia, Japan, and China. In the aforementioned countries, the same types of ingredients are generally viewed today as active ingredients for use in licensed, listed, or registered medicinal products that require pre-marketing authorization. This means that implementation of suitable GACPs is expected for quality assurance of active ingredients and use of pharmacopoeial monographs, to serve as the basis for quality specifications, is mandated. In the United States, GACP implementation and compliance with pharmacopoeial quality standards is mandatory only for botanical drugs but voluntary for botanical dietary supplements. This difference leaves it up to the individual company whether, or not, they will make such commitments to quality that will increase the price of their finished products. It is difficult for

the consumer in the United States to understand and sort out quality differences between similarly packaged dietary supplement products (and just about every company claims that they have the highest quality!).

Commitments to nature conservation, sustainable production and trade is a different matter and perhaps easier for American companies to communicate. For example, in the European Union, registered herbal medicinal products are not permitted to carry any certification logos on the retail packages. That is because of EU medicines policy stating that the conservation and sustainability status of medicinal ingredients and products have nothing to do with pharmaceutical quality or safety and efficacy of the medicine. That is an unfortunate policy (for European consumers concerned with ethical trade and sustainability). However, in the United States, it is not unusual to find herbal dietary supplement products with multiple credible certification marks on the labeling, demonstrating to the consumer that the product and its ingredients conform to a range of environmental, economic, and social sustainability standards.

Regardless of market trends and consumer preferences, companies intrinsically concerned with reproducible quality, safety and efficacy of their botanical products may need to engage more deeply in the ecological-economic viability of the rural and remote communities where so many medicinal plants are produced. With mass migration of youth to urban areas, happening at a scale never before seen in the world, labor is rapidly disappearing in rural farming and wild-collection regions. Non-sustainable rural livelihoods can lead to land-use changes, loss of ecosystem stewardship and biodiversity. The rapid loss of biodiversity in recent decades, not only impacts access to and quality of wild botanicals, but is reportedly an existential threat (IPBES 2019). There may be a correlation between sustainable resource management and

equitable trade, with a companies' ability to procure increasing quantities of botanicals of a specified and consistent quality.

VI. References

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ANNEX I: Table 3: Botanical, algal, fungal quality standards monographs available from AHP, FCC, NF, USP

Table 3: Botanical, algal, fungal quality standards monographs available from AHP, FCC, NF, and USP

Monograph	AHP	FCC	NF	USP
Acacia (Gum Arabic)		X	X	
Acacia Syrup			X	
Agar		X	X	
Aloe (Dried Latex)				X
Aloe Vera Leaf, Leaf Juice & Inner Leaf Juice	X			
Ambrette Seed Oil		X		
American Ginseng Root	X			X
American Ginseng Root Dry Extract				X
Amla Fruit	X			
Amyris Oil, West Indian Type		X		
Andrographis (Leaf and Stem)				X
Andrographis Dry Extract				X
Angelica Root Oil		X		
Angelica Seed Oil		X		
Anise Oil		X	X	
Annatto Extracts		X		
ARA from Fungal (*Mortierella alpina*) Oil		X		
Arabinogalactan		X		
Astaxanthin Esters (from *Haematococcus pluvialis*)		X		X
Ashwagandha Root	X			X
Ashwagandha Root Dry Extract				X
Asian Ginseng Root				X
Asian Ginseng Root Dry Extract				X
Astragalus Root	X			X
Astragalus Root Dry Extract				X
Aztec Marigold Zeaxanthin Extract				X
Bacopa (Leaf and Stem)				X
Bacopa Dry Extract				X
Balsam Peru Oil, Cold-pressed		X		
Banaba Leaf				X
Banaba Leaf Dry Extract				X
Basil Oil, Comoros Type		X		
Basil Oil, European Type		X		
Bay Oil		X		
Belleric Myrobalan Fruit	X			
Bergamot Oil, Cold-pressed		X		
Bilberry Fruit	X			
Bilberry Fruit Dry Extract				X
Birch Tar Oil, Rectified		X		
Black Cohosh (Rhizome)	X			X
Black Cohosh Dry Extract				X
Black Cohosh Fluidextract				X
Black Haw Bark	X			
Black Pepper (Fruit)				X
Black Pepper Dry Extract				X
Black Pepper Oil		X		
Blue Cohosh Root / Rhizome	X			
Bois de Rose Oil		X		
Borage Seed Oil				X
Boswellia serrata (Oleogum Resin)				X

Monograph	AHP	FCC	NF	USP
Boswellia serrata Extract				
Cananga Oil		X		
Candelilla Wax		X	X	
Cannabis Inflorescence	X			
Capsicum (Ripe Fruit)				X
Capsicum Oleoresin				X
Capsicum Tincture				X
Caraway Fruit			X	
Caraway Oil		X	X	
Cardamom Seed			X	
Cardamom Oil		X	X	
Cardamom Tincture, Compound			X	
Carnauba Wax		X	X	
Carrageenan		X	X	
Carrot Seed Oil		X		
Casanthranol				X
Cascara Fluidextract, Aromatic				X
Cascara Sagrada (Aged Bark)				X
Cascara Sagrada Dry Extract				X
Cascara Sagrada Fluidextract				X
Cascarilla Oil		X		
Cassia Oil		X		
Castor Oil		X		X
Castor Oil, Aromatic				X
Castor Oil Emulsion				X
Cat's Claw (Stem Inner Bark)				X
Cat's Claw Dry Extract				X
Cedar Leaf Oil		X		
Celery Seed Oil		X		
Centella asiatica (Aerial Parts)				X
Centella asiatica Dry Extract				X
Centella asiatica Triterpenes				X
Chamomile (Flower Heads)				X
Chamomile Oil, English Type		X		
Chamomile Oil, German Type		X		
Chaste Tree Fruit	X			X
Chaste Tree Fruit Dry Extract				X
Chebulic Myrobalan Fruit	X			
Cherry Juice			X	
Cherry Syrup			X	
Chia Seed Oil				X
Chinese Salvia (Root and Rhizome)				X
Chocolate			X	
Chocolate Syrup			X	
Cinnamomum cassia Twig				X
Cinnamon Bark Oil, Ceylon Type		X		
Cinnamon Leaf Oil		X		
Clary Oil		X		
Clove Flower Bud Oil		X	X	
Clove Leaf Oil		X		
Clove Stem Oil		X		
Cocoa Butter			X	
Coconut Oil (Refined)			X	
Coconut Oil (Unhydrogenated)		X		

Monograph	AHP	FCC	NF	USP
Coffee Fruit Dry Extract				X
Cognac Oil, Green		X		
Coix Seed				X
Copaiba Oil		X		
Coriander Oil		X	X	
Costus Root Oil		X		
Cramp Bark	X			
Cranberry Fruit	X			
Cranberry Liquid Preparation				X
Crypthecodinium cohnii Oil				X
Cubeb Oil		X		
Cumin Oil		X		
Curcuminoids				X
Dammar Gum		X		
Dang Gui Root	X			
Dill Seed Oil, European Type		X		
Dill Seed Oil, Indian Type		X		
Dillweed Oil, American Type		X		
Echinacea angustifolia Root	X			X
Echinacea angustifolia Dry Extract				X
Echinacea pallida Root	X			X
Echinacea pallida Dry Extract				X
Echinacea purpurea Aerial Parts	X			X
Echinacea purpurea Dry Extract				X
Echinacea purpurea Root	X			X
Eleuthero Root and Rhizome				X
Eleuthero Root and Rhizome Dry Extract				X
Eucalyptus Oil		X	X	
European Elder Berry Dry Extract				X
Evening Primrose Oil				X
Fennel Oil		X	X	
Fenugreek Seed				X
Fenugreek Seed Dry Extract				X
Feverfew Aerial Parts	X			
Feverfew Leaf				X
Fir Needle Oil, Canadian Type		X		
Fir Needle Oil, Siberian Type		X		
Flax Seed Oil				X
Forskohlii (Root)				X
Forskohlii Dry Extract				X
Galageenan			X	
Ganoderma lucidum Fruiting Body				X
Garcinia cambogia (Pericarp)				X
Garcinia Hydroxycitrate Dry Extract				X
Garlic (Bulb)				X
Garlic Dry Extract				X
Garlic Fluidextract				X
Garlic Oil		X		
Gellan Gum		X	X	
Geranium Oil, Algerian Type		X		
Ginger (Rhizome)				X
Ginger Oil		X		
Ginger Tincture				X
Ginkgo Leaf	X			X

Monograph	AHP	FCC	NF	USP
Ginkgo Leaf Dry Extract	X			X
Goldenseal (Root and Rhizome)	X			X
Goldenseal Dry Extract				X
Grape Seeds Oligomeric Proanthocyanidins				X
Grape Skin Extract		X		
Grapefruit Oil, Cold-pressed		X		
Green Tea Dry Extract, Decaffeinated				X
Guar Gum		X	X	
Guggul (Oleo-gum-resin)				X
Guggul Native Extract				X
Guggul Purified Extract				X
Gum Ghatti		X		
Gum Guaiac		X		
Gymnema (Leaf)				X
Gymnema Native Extract				X
Gymnema Purified Extract				X
Hawthorn Berry	X			
Hawthorn Leaf with Flower	X			X
Holy Basil Leaf				X
Holy Basil Leaf Dry Extract				X
Hops Oil		X		
Horse Chestnut Seed				X
Horse Chestnut Seed Dry Extract				X
Japanese Honeysuckle Flower				X
Japanese Honeysuckle Flower Dry Extract				X
Juniper Berries Oil		X		
Karaya Gum		X		
Kelp		X		
Konjac Flour		X		
Labdanum Oil		X		
Laurel Leaf Oil		X		
Lavandin Oil, Abrial Type		X		
Lavender Oil		X		
Lemon Oil			X	
Lemon Oil, Cold-pressed		X		
Lemon Oil, Desert Type, Cold-pressed		X		
Lemon Oil, Distilled		X		
Lemon Tincture			X	
Lemongrass Oil		X		
Licorice (Root, Rhizome, Stolon)				X
Licorice Dry Extract				X
Licorice Fluidextract			X	
Lime Oil, Cold-pressed		X		
Lime Oil, Distilled		X		
Linaloe Wood Oil		X		
Locust (Carob) Bean Gum		X		
Lovage Root Oil		X		
Lutein				X
Lycium (goji) Berry	X			
Lycopene				X
Lycopene Extract from Tomato		X		
Lycopene from *Blakeslea trispora*		X		
Lycopene Preparation				X
Mace Oil		X		

Monograph	AHP	FCC	NF	USP
Malabar-Nut-Tree Leaf				X
Malabar-Nut-Tree Leaf Dry Extract				X
Mandarin Oil, Cold-pressed		X		
Maritime Pine (Stem Bark)				X
Maritime Pine Extract		X		X
Marjoram Oil, Spanish Type		X		
Marjoram Oil, Sweet		X		
Masticatory Substances, Natural		X		
Mentha arvensis Oil, Partially Dementholized		X		
meso-Zeaxanthin		X		X
meso-Zeaxanthin Preparation				X
Milk Thistle (Ripe Fruit)				X
Milk Thistle Dry Extract				X
Monk Fruit Extract		X		
Motherwort Aerial Parts	X			
Mustard Oil		X		
Myrrh (Oleo-Gum-Resin)				X
Myrrh Oil		X		
Nutmeg Oil		X		
Olibanum Oil		X		
Olive Leaf				X
Olive Leaf Dry Extract				X
Onion Oil		X		
Orange Oil			X	
Orange Oil, Bitter, Cold-pressed		X		
Orange Oil, Cold-pressed		X		
Orange Oil, Distilled		X		
Orange Peel Tincture, Sweet			X	
Orange Spirit, Compound			X	
Orange Syrup			X	
Origanum Oil, Spanish Type		X		
Orris Root Oil		X		
Osha Root	X			
Palm Kernel Oil			X	
Palm Kernel Oil (Unhydrogenated)		X		
Palm Oil, Hydrogenated			X	
Palm Oil, Refined			X	
Palm Oil (Unhydrogenated)		X		
Palmarosa Oil		X		
Papain				X
Parsley Herb Oil		X		
Parsley Seed Oil		X		
Pea Starch		X	X	
Pectin				X
Pennyroyal Oil		X		
Peppermint			X	
Peppermint Oil		X	X	
Peppermint Spirit				X
Peppermint Water			X	
Petitgrain Oil, Paraguay Type		X		
Phyllanthus amarus (Aerial Parts)				X
Pimenta Fruit Oil		X		
Pimenta Leaf Oil		X		
Pine Needle Oil, Dwarf		X		

Monograph	AHP	FCC	NF	USP
Pine Needle Oil, Scotch Type		X		
Plant Stanol Esters		X		X
Plantago Seed				X
Psyllium Husk				X
Pygeum Bark				X
Pygeum Bark Extract				X
Rebaudioside A		X		
Red Clover Aerial Parts				X
Red Clover Aerial Parts Isoflavone Aglycones Dry Extract				X
Red Clover Aerial Parts Dry Extract				X
Red Clover Flowering Tops, Aerial Parts, and Dry Extracts	X			
Reishi Mushroom	X			
Rhodiola crenulata Root and Rhizome				X
Rhodiola crenulata Root and Rhizome Dry Extract				X
Rhodiola rosea Root and Rhizome				X
Rhodiola rosea Root and Rhizome Dry Extract				X
Rhodiola rosea Root and Rhizome Tincture				X
Rose Oil		X	X	
Rosemary Extract		X		
Rosemary Leaf				X
Rosemary Leaf Dry Aqueous Extract				X
Rosemary Oil		X		
Rose Water, Stronger			X	
Rue Oil		X		
Sage Oil, Dalmatian Type		X		
Sage Oil, Spanish Type		X		
Sandalwood Oil, East Indian Type		X		
Salix Species Bark				X
Salix Species Bark Dry Extract				X
Savory Oil (Summer Type)		X		
Saw Palmetto (Ripe Fruit)				X
Saw Palmetto Extract				X
Schisandra Berry	X			
Schisandra Fruit, Northern				X
Schisandra Fruit, Northern, Dry Extract				X
Schizochytrium Oil				X
Senna Fluidextract				X
Senna Leaf				X
Senna Oral Solution				X
Senna Pods				X
Sennosides				X
Sheanut Oil, Refined		X		
Skullcap Aerial Parts	X			
Slippery Elm Inner Bark	X			X
Solin Oil		X		
Soy Isoflavones Dry Extract				X
Spearmint Oil		X		
Spice Oleoresins		X		
Spike Lavender Oil		X		
Spirulina		X		X
Star Anise Fruit	X			
Steviol Glycosides		X		
Stinging Nettle Herb	X			
Stinging Nettle Root	X			X

Monograph	AHP	FCC	NF	USP
Stinging Nettle Root Dry Extract				X
St. John’s Wort Flowering Top	X			X
St. John's Wort Flowering Top Dry Extract				X
Storax (Balsam)				X
Tagetes Extract		X		
Tangerine Oil, Cold-pressed		X		
Tangerine Peel				X
Tangerine Peel Dry Extract				X
Tannic Acid (from nutgalls on *Quercus* tree twigs)		X		X
Tara Gum		X		
Tarragon Oil		X		
Tea Polyphenols from Green Tea, Decaffeinated		X		
Thyme Oil		X		
Tolu Balsam				X
Tolu Balsam Syrup			X	
Tolu Balsam Tincture			X	
Tapioca Starch			X	
Tienchi Ginseng Root and Rhizome				X
Tienchi Ginseng Root and Rhizome Dry Extract				X
Tomato Extract Containing Lycopene				X
Tragacanth		X	X	
Turmeric (Rhizome)				X
Turmeric Dry Extract				X
Turmeric Oleoresin		X		
Uva Ursi Leaf	X			
Valerian Root	X			X
Valerian Root Dry Extract				X
Valerian Root Tincture				X
Vanilla (Unripe Fruit)			X	
Vanilla Tincture			X	
Vegetable Oil Phytosterol Esters		X		
Wheat Bran				X
Willow Bark	X			
Wintergreen Oil		X		