Chapter 1

Botanical Quality Initiatives at the Office of Dietary Supplements, National Institutes of Health

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Quality of botanical products is one of the biggest uncertainties that consumers, clinicians, regulators, and researchers face. Definitions of quality abound, and include specifications for sanitation, adventitious agents (pesticides, metals, weeds), and content of natural chemicals. Because dietary supplements (DS) are often complex mixtures, they pose analytical challenges and methods validation may be difficult. In response to product quality concerns and the need for validated and publicly available methods for DS analysis, the U.S. Congress directed the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) to accelerate an ongoing methods validation process. The Dietary Supplements Methods and Reference Materials Program was created. The program was constructed from stakeholder input and incorporates several federal procurement and granting mechanisms in a coordinated and interlocking framework. The framework facilitates validation of analytical methods, analytical standards, and reference materials.

Wang et al.; Herbs: Challenges in Chemistry and Biology
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The Dietary Supplement Health and Education Act (DSHEA) of 1994 (United States Public Law 103-417) amended the Federal Food, Drug and Cosmetic Act by defining as a dietary supplement any product (other than tobacco) that contains a vitamin, mineral, herb or other botanical, or amino acid and is intended as a supplement to the diet (*1*). The new law also established the Office of Dietary Supplements (ODS) within the Office of the Director at the U.S. National Institutes of Health (NIH). The mission of the ODS is to "strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population."

The regulatory category into which a product falls is determined in the U.S. by the intended use of the product. The Act was significant because it established dietary supplements as a separate legal category and defined a framework for Food and Drug Administration (FDA) regulation of this category (*2*). It also established the regulatory framework for supplements as foods, not drugs, set rules for what information labels must contain, and gave FDA the authority to write supplement specific Good Manufacturing Practices based on a food model.

Briefly, companies that sell products intended for use as dietary supplements are prohibited from selling a product that is toxic or unsanitary, makes false or unsubstantiated claims, or claims to cure, treat, mitigate, or prevent a disease. Companies are also not permitted to introduce a new dietary ingredient into the marketplace without notifying FDA in advance, and are prohibited from selling a product that has not been produced according to current good manufacturing practices. Finally, companies must make sure that products are labeled properly (*3*).

When the DSHEA became law in 1994, there were an estimated 600 U.S. dietary supplement manufacturers producing about 4,000 products (*4*). According to Food and Drug Administration estimates, there were more than 29,000 different dietary supplement products on the market by the year 2000 with an average of 1,000 new products being added annually (*5*). A full overview of the regulatory history of botanical and other products is beyond the scope of this chapter. Readers interested in a brief but thorough overview of the subject should consult Israelsen and Barrett (*6*). Growth of the marketplace was fueled by increased consumer demand, often following publicity about the utility and efficacy of a particular herb. For example, in 1996 Linde *et al.* (*7*) published a meta-analysis of randomized clinical trials of the herb St. John's wort (*Hypericum perforatum* L.) in the prestigious *British Medical Journal* (BMJ) that concluded that the herb was more effective than placebo in treating certain types of mild to moderate depression. A June 27, 1997 broadcast of the popular television news magazine *20/20* (**Using Herb St. John's Wort To Treat Depression**) highlighted the BMJ article, and sales of the herb boomed. Other

mainstream media outlets quickly followed with articles on herbal medicine (*8,9*) and the industry went through several years of rapid growth (*10*).

Only a short time later, the mainstream media began to take a closer look at the subject of herbs. In 1998, the Los Angeles Times commissioned a survey of St. John's wort products purchased from retail stores. The contract laboratory that did the work was asked to measure the amount of the phytochemical marker compound hypericin. The newspaper reported that 3 of 10 tested products contained no more than 50% of the hypericin content declared on the label and that another 4 of 10 contained less than 90% of claim (*11*). A later survey conducted by the Boston Globe in 2000 reported similar results (*12*). Publications in the peer-reviewed scientific literature have reported complementary findings. Draves and Walker observed that only two products (of 54) had a total naphthodianthrone concentration within 10% of label claim (*13*). Edwards and Draper examined levels of berberine and hydrastine in 20 goldenseal *Hydrastis canadensis*) products and found that only 10 of 17 root products met alkaloid content standards proposed by the United States Pharmacopeia (USP) and that 5 products contained little or no hydrastine, unusual berberine:hydrastine ratios, and additional peaks not observed with other products (*14*). Harkey *et al.* tested ginsenoside content of 24 commercial ginseng products and found that concentrations of marker compounds differed significantly from the amounts listed on the labels (*15*).

Unexpectedly, and in contrast to the picture for pharmaceutical products, there are frequently several analytical methods available for determination of phytochemicals in botanical products. An unpublished 2002 literature search performed for an AOAC International review panel found twenty-two different methods for constituents of St, John's wort. Many of these methods are based on different physical principles that would be expected to lead to different numerical results. Internal validation of methods is often lacking, as is cross-validation between methods. Lack of standard methods also leads individual investigators new to the field to invent a method when they become interested in a particular plant. This has led to the the publication in peer reviewed journals of results that can only be described as improbable. The report of the presence of colchicine in ginkgo and Echinacea products following discovery of this compound in the placental blood of women who were consuming dietary supplements is an example of this phenomenon (*16*), and repeated attempts to reproduce the results have failed (*17,18*).

Product Quality

Product quality is one of the biggest question marks facing consumers, clinicians, regulators, and researchers (*19*). As expected, there are some

differences between definitions of quality for herbal preparations and for chemically synthesized products. Despite this, fundamental quality parameters are the same for both: identity, purity, content determination (i.e. strength) (*20*).

The DSHEA does not set a detailed framework for quality except to state that manufacturers are prohibited from introducing products posing "significant or unreasonable risk" into interstate commerce; must follow labeling regulations (accuracy, disclaimers, notification of claims); and must have substantiation that claims are truthful and not misleading (*1*). Compliance with quality standards set out in official compendia is voluntary. Working definitions of quality within the supplement industry vary. Quality parameters used by individual companies in the U.S. range from the simple to the complex. For example, for some companies, quality is ascertained from determination that the material was grown or wildcrafted organically, that the correct plant species and plant part (or extracts thereof) are in fact present in the product and that the product has been manufactured in a sanitary fashion. Other companies may set (or follow) explicit specifications for microbial load, adventitious agents (poisonous and otherwise), and content of desirable and undesirable natural chemicals (see the United States Pharmacopeia, American Herbal Pharmacopoeia (AHP), or European Pharmacopoeia (EP)). Swanson (*21*) provided a useful overview of the sorts of parameters that researchers and others should keep in mind when performing research or establishing quality assurance procedures for botanicals.

Analytical Challenges

Analytical challenges in quality assurance range from establishing the identity of the botanical source from which an extract was derived to measuring the amount of one or more desirable or undesirable natural constituents, such as pesticides, toxic elements, natural toxins, or marker compounds. Analytical methods are intended to generate reliable, accurate data for use by manufacturers or regulators for quality control or enforcement actions, respectively. Reliability, accuracy, precision and specificity are the keys to the utility of a method, but analysts must take steps to prove that any method they use has these features, especially if the method is to be used in a critical setting such as a quality control lab, a regulatory enforcement action, or a clinical laboratory. Fortunately, there are systematic approaches to validating that a particular method yields accurate and precise data. Manufacturers generally need methods applicable throughout the manufacturing process, while regulators require versatile methods that can be used for the same analyte(s) in a number of dissimilar finished products. The ability of a particular method to fit the specified purpose is one element of validation that is important but often overlooked.

In addition to the difficulties noted above, botanicals are complex mixtures that originate from biological sources. Such products and their ingredients pose particular analytical challenges for a number of reasons, and methods validation has proven particularly difficult. Raw materials are invariably "irregular" because their chemical composition depends on factors such as geographical origin, weather, harvesting practices, etc., while finished products frequently contain multiple botanical ingredients (*20*).

Role of the Office of Dietary Supplements

As noted above, the DSHEA empowered the FDA to establish current good manufacturing practices (CGMPs) for dietary supplements, and a proposed rule has been published (*22*). The law requires that any enforcement action taken against dietary supplement products use "publicly available" methods. In response to general concerns about the lack of properly validated publicly available methods, and general concerns about product quality, the U.S. Congress directed the Office of Dietary Supplements (ODS) at NIH to accelerate an ongoing methods validation process (*23*).

The ongoing process was a collaboration between AOAC International (the Scientific Society devoted to quality analytical measurements) and various representatives of the dietary supplements industry, regulatory and other governmental bodies, consumer groups, non-governmental organizations, and research scientists. The effort was embodied in a Dietary Supplements Task Group (DSTG) established by AOAC International. The group was originally proposed by several dietary supplement trade associations and was in existence before the congressional language. The DSTG met to select analytes and ingredients for study and to facilitate selection, solicitation, and validation of methods by AOAC International.

Parallel to the development of the DSTG by AOAC International, the ODS and FDA's Center for Food Safety and Applied Nutrition (CFSAN) had entered into an Interagency Agreement (IAG) for the purpose of funding validation of analytical methods for Ephedrine-type alkaloids and an FDA method for aristolochic acids in dietary supplements through the AOAC *Official Methods*^{SM} program. The task group was asked to decide which of several available ephedra methods were to be validated. Eventually, the group selected a LC/MS/MS method and a LC-UV method to be validated for botanical raw material, a commercial raw material extract, a finished ephedra product, a complex mixture of multiple supplement products, and an ephedra containing high protein drink. The methods were also to be validated on human specimens (serum and urine). Collaborative studies have been completed and study reports published (*24*,*25*,*26*). The LC/MS/MS method for six ephedrine alkaloids in

biological fluids and the LC/UV method for ephedrine and pseudoephedrine were approved as "First Action" methods by AOAC's Official Methods Board.

The aristolochic acid method has not fared as well. The contract with AOAC called for validation of an LC/MS method for determination of aristolochic acids in *Aristolochia* spp. and *Asarum* spp, as well as in *Akebia* spp., *Clematis* spp., and *Stephania* spp. spiked with aristolochic acid. A single laboratory validation study failed, and AOAC is in the process of optimizing the method for another study, and a full collaborative study of the optimized method is scheduled for the Spring of 2005.

Once the Congressional language went into effect and the budget appropriation for ODS was signed, ODS was able to begin the new program. The first activities of the newly formed Dietary Supplement Methods and Reference Materials Program were two public meetings. The meeings were intended to gather stakeholders and get input on establishing goals and a direction for the new program and to solicit advice on mechanisms by which various groups select and validate methods. The meetings also began the process of establishing priorities (botanicals and others) and identifying potential research partners. The purposes of the program are fairly straightforward: to develop, validate, and share analytical methods and reference materials. The first public meeting was a Stakeholders meeting. It was convened in early 2002 at the Natcher Center on the NIH campus. Representatives of the supplements industry (manufacturers, suppliers, trade associations), the analytical laboratories industry, regulatory and other governmental entities, non-governmental organizations, and consumer groups met to identify needs that might be met by the new program. These stakeholders advised ODS that the new program should emphasize basic quality issues such as identity and contamination; accept the role of existing frameworks for methods vaidation (i.e. AOAC International; www.aoac.org); and accept the recommendations of the AOAC DS task group for prioritization of ingredients (*27*).

The second public meeting was an Analytical Methods Workshop held in the Spring of the same year. The workshop was intended to solicit ideas from stakeholder groups on the process that these groups use to select and prioritize methods for for their own uses. The groups were also invited to make formal presentations on the technical evaluation criteria they use for selecting analytical methods. Following these presentations, ODS hosted a series of breakout sessions to discuss needs, approaches, and capabilities. Details of the discussions and recommendations can be found in Saldahna et al. (*27*), but the key points were continuation of the DSTG to set broad priorities, the establishment of a small expert steering group for prioritorization of method selection, focus on qualitative medods for confirming botanical identity as well as quantitative methods for measuring individual constituents, and promoting basic research for identifying compounds of interest.

The operational program four major areas: methods development, methods validation, reference materials, and "other."

The bulk of the methods development work is being done by the Food Composition Laboratory at the United States Department of Agriculture (USDA) through an interagency agreement between the ODS and the National Heart, Lung, and Blood Institute (NHLBI) at NIH. The NHLBI had an existing contract with USDA to develop analytical methods for food constituents, including nutrients. ODS provided supplemental funds to allow USDA to develop validated methods for phenolic glycosides in foods and supplements. In addition, ODS has recently entered into agreements with experts at the FDA's CFSAN to develop or extend validated methods for determination of mycotoxins, pesticides, and toxic elements in Dietary Supplement raw materials and finished products.

The second and largest part of the program is analytical methods validation. As noted above, the problem facing manufacturers, regulators, and researchs for the top selling botanicals was not a lack of methods, but an overabundance of methods. At the start of the the ODS process, a literature review turned up no less than 22 different methods just for the constituents of St. John's wort *(Hypericum perforatum)*. The methods make different analytical assumptions, use different chemical or physical principles, or measue different chemical entities. In addition, methods had not undergone validation to assure accuracy or precision. As a result, no two analyses of the same product could be expected to be in agreement. In order to facilitate availability of valid methods to the user community, ODS expanded the original FDA/AOAC contract mentioned above to support infrastructure development and maintenance at AOAC. The stated deliverable for the contract is 20 AOAC Official Methods of Analysis after 5 years. However, the main purpose of the contract is to allow AOAC International to build its programs so that it has the capacity to process many more than the bare minimum of 20 methods.

Specific areas implemented by the contract include increases in AOAC staff for the purposes of coordinating and planning the DSTG and the the small steering group for methods prioritization recommended by the stakeholders (see above) (the Ingredient Ranking Subcommittee, or IRS), and the establishment and maintenance of a series of ad hoc Expert Review Panels (ERP). The latter is modeled after NIH technical peer review panels and serve to evaluate the technical merits of methods prior to AOAC selection for collaborative study. Ingredients are ranked by the IRS and weighted scores are assigned based on elements such as ingredient market share, safety concerns, positive public health implications of better measurements, and availability of methods that are sufficiently well developed to undergo the collaborative study process. The contract also supports AOAC volunteer committee functions, development and implementation of an AOAC short course on Single Laboratory Validation and

on designing and conducting Collaborative Studies. Development, implementation, and maintenance of an electronic peer-review process for AOAC protocols and completed collaborative studies was also provided in the contract.

At present, AOAC International is in the process of convening Expert Review panels, conducting Single Laboratory Validation studies or collaborative studies for one or more constituents of SAMe, β-carotene, chondroitin sulfate, glucosamine, St. John's wort, ginkgo, and saw palmetto. The Ingredient Ranking Subcommittee has begun to solicit methods for L-carnitine, B vitamins, black cohosh, Ω-3 fatty acids, soy isoflavones, green tea catechins, lutein, turmeric, ginger, milk thistle, African plum, and flax seed. Unprioritized ingredients include hawthorne, biotin, feverfew, and pyrrolizidine alkaloids.

As suggested by its title, the third part of the Dietary Supplements Methods and Reference Materials Program provides for the production of reference materials. The stakeholder's meetings pointed out that there are several different types of reference material. These range from the pure chemical entity (analytical standard) used for determination of chromatographic retention time and quantitative instrument calibration, to matrix materials for evaluating method performance, to reference plant material used for comparison with unknown biomass for the purpose of plant identification.

One of the most important features of any analytical testing protocol is the ability of the analyst to verify whether or not the analytical instrument is operating properly and whether the assay has been performed correctly. One of the most useful ways of making this determination is to perform the method on a material that has had values for the analyte of interest assigned to it through a formal certification process. If the analyst succeeds in reproducing the certified values, then he or she can have confidence that the analysis was properly performed. The ODS has funded a five year Interagency Agreement with the NIST (National Institute of Standards and Technology, U.S. Department of Commerce) for the production of "suites" of Standard Reference Materials (SRM^{TM}). Each suite consists of properly identified dried, powdered botanical raw material, a commercial raw material extract, and one or more representative commercial products. The NIST process involves obtaining authentic botanical raw material, developing and validating analytical methods (if none exist) to determine compounds to be certified, using two or more methods and laboratories to analyze for the compounds of interest, and assigning values to be written into oa certificate of Analysis. Materials are then appropriately packaged and made available for purchase. The original goal was to develop SRM suites for 6-8 botanicals (beginning in 2002), but the program is progressing more rapidly than anticipated. By 2006, suites of ephedra, Saw palmetto, St. John's wort, ginkgo, green tea, β-carotene, tocopherols, bitter orange, and black cohosh should be available. In addition to these materials, NIST is in the process of

certifying Ω-3 fatty acid values in an existing cod liver oil SRM and developing a multivitamin/multimineral SRM.

Other projects within the ODS program include production by the National Research Council (Canada) of Certified Reference Materials for *Panax* spp. (ginseng) and production of pure analytical reference standards. In the past, inhibitions to methods development and validation have been that with some exceptions (caffeine) highly purified plant secondary metabolites are very rare and therefore very expensive. The usual research practice was for the individual investigator to isolate pure compounds from the plant of interest, but this process is time consuming, expensive, and has low yields. In addition, the compounds may also be unstable in pure form. In order to expedite development and validation of methods, ODS has sponsored research into small- to medium-scale isolation methods for production of pure compounds as well as acquisition of these compounds for use in collaborative studies. It has also sponsored research into methods for stabilizing labile compounds. While quantities of the materials produced for collaborative are large by historical standards, they remain quite small. In practice, at the moment most part these compounds are valuable only to analytical chemists, and the marketing incentive for production of kilogram quantities of pure natural products (as for drugs such as paclitaxel) does not exist. ODS has therefore funded production of larger quantities of very high purity standards for national standard setting bodies such as the United States Pharmacopeia.

Additional projects include funding of Single Laboratory Validation studies for ingredients that are deemed important by NIH or FDA but are not highly ranked by the IRS (e.g. constituents of bitter orange, anthocyanins in berries) as well as a study for validation of thin layer chromatographic fingerprinting methods for determining botanical identity. This latter project is in keeping with stakeholder recommendations about pursuing methods for verification of plant identity and is complemented by funding for an electronic herbarium pilot project and for production of a handbook of botanical microscopy to replace the botanical drug microscopy texts of the late 19th and early 20th Century. An additional project related to plant identification is the development of a system for the identification, isolation, and characterization of compounds in plants that may indicate the presence of undesirable plant species (adulterants) in the botanical raw material or finished product. Identification of these "negative marker" compounds by bioassay-directed fractionation will be followed by development and validation of analytical methods for these compounds.

In conclusion, one of the explicit goals in the original and the current ODS strategic plan (*28*) was that the Office would "promote and support the development and improvement of methodologies appropriate to the scientific study of dietary supplement ingredients." In 2002, the stimulus provided by the

language from the Congressional Appropriations Committee (23) as well as an increase in the ODS appropriation permitted a substantial expansion of efforts in this area, and the Dietary Supplements Methods and Reference Materials Program was created.

There remains an enormous challenge in developing, validating, and disseminating methods and reference materials for the projected 40,000 or so supplement products projected to be on the U.S. market by 2010 (*5*). But the goal of the U.S. Congress when it created the ODS was to provide an organization to coordinate and conduct basic and clinical research, develop education and communication programs directed to all segments of the public and private sectors with an interest in dietary supplements, and coordinate federal efforts related to issues associated with dietary supplements. These directions, especially the last, give the ODS a great deal of latitude in leveraging its resources across the NIH and other federal departments (*28*). The Dietary Supplement Methods and Reference Materials program has begun to lay the groundwork for addressing this challenge, but the challenge cannot be met by ODS alone. Congressional appropriations language (*29*) continues to support the program, and the program will grow, but only for as long as stakeholders from government agencies, the dietary supplements industry, and the academic world step forward, embrace the need for rigorous pursuit of excellence in analytical measurements, and actively participate in the process of achieving that excellence.

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