Health Canada Santé Canada

An Exploration of Current Issues in Botanical Quality: A Discussion Paper

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The views expressed in this paper are those of the author and do not necessarily represent those of Health Canada

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Executive Summary

This report was commissioned by the Natural Health Products Directorate (NHPD) at Health Canada to provide background reading for participants invited to a two-day priority setting conference to discuss natural health product (NHP) standards and quality control, and to provide recommendations to the Directorate with respect to future initiatives in this area. The proceedings and recommendations from this conference will be available from the NHPD in the spring of 2002.

Throughout the entire consultation process on NHPs, from the Standing Committee on Health's hearings in 1997-98 to the present time, product quality has been consistently identified as one of the most critical issues. At the Natural Health Products Research Priority-Setting Conference in Halifax in 1999, sponsored by the Office of Natural Health Products (now the Natural Health Product Directorate), product quality was identified as a top priority in NHP research, especially with regards to botanical products. In consultations, stakeholders have urged the NHPD to take a leadership role in setting standards and facilitating research in this field. However, while there appears to be widespread agreement as to the importance of product quality based research and standards, stakeholders' views on the specific research priorities vary substantially.

As a result, the NHPD invited stakeholder participation in the Quality Control and Product Standards Research Priority-Setting Conference in Vancouver, BC on March 8-9, 2002. This background document was written to lay a common groundwork for the conference discussions, by familiarizing participants with the diversity of issues and perspectives on the subject as well as some of the common themes. The contents of this discussion paper are based upon a survey of the literature and pertinent organizations, and the paper focuses on botanical quality as the area of greatest concern.

Since a key determinant of the scope of any discussion on product quality is how one defines the term 'quality,' some of the semantic issues surrounding the use of the word quality and related terms such as standardization are first explored. A brief overview of the criteria and methods that have been used to assess quality over the past 2,000 years provides an historical context for the subsequent discussion of existing and proposed new product quality regulations in Canada and the US.

In the survey of the scientific literature, no information specific to the quality of Canadian NHPs was found. Globally, three main issues were identified. These were the botanical identity of ingredients, product purity and potency. Reliable scientific data on product potency were especially scant. In comparison, a substantial body of evidence on serious safety problems caused by incorrect botanical identifications and product impurities was found. The majority of reported adverse events were caused by the unintended or undeclared inclusion of a toxic plant, not the ingredients listed on the label.

Similarly, numerous examples of risks posed by non-botanical impurities were identified, including microbial contamination, heavy metal contamination and pesticide residues. The presence of heavy metals was the second most common cause of adverse events. Of equal or possibly greater concern was the high level of risk posed by adulteration with pharmaceutical

drugs. A substantial number of both Canadian and foreign cases of herbal products containing pharmaceutical adulterants were found. These cases encompassed a wide range of drugs, including narcotics, stimulants, sedatives, corticosteroids and antibiotics.
Based upon this documentation of product quality deficits, some of the issues and challenges involved in assessing product quality are explored in this paper. For the assessment of product potency, some of the key issues include the selection of markers, validation of analytical methods, analytical competence and reference standards. For the assessment of identity and purity, many of the same key issues are identified, along with the lack of appropriate education and training, and the use of inappropriate technologies.

Throughout these discussions, several common themes clearly emerge, including methods validation, reference materials and quality standards. Although Canada has the technical capacity, no constructive strategies for addressing these issues have been proposed to date. Other points include a lack of infrastructure and capacity needed to address the need for product quality assessment, the need for education and training of researchers, and the need for effective information dissemination and retrieval.

One of the key challenges in bridging these gaps is to obtain consensus on:

- research leaders and leadership roles;
- the appropriate scope of research programs to address these gaps;
- the appropriate balance between scientific rigor and practicality;
- specific botanical priorities within each area; and
- the most effective strategies for facilitating the accomplishment of research goals.

At the present time, research on product quality in Canada appears to be largely uncoordinated, with most projects conducted in isolation and the results often not widely disseminated. Knowledge transfer, especially from academia to industry and government, and information dissemination between industry members is quite limited. Fostering partnership and collaboration between stakeholders, possibly through the development of a cohesive quality research network, could make significant inroads in addressing these problems, and could generally assist in the successful execution of strategies to close quality research gaps.

Botanical Quality, Quality Control and Product Standards

1. Introduction

Throughout the consultative process with very diverse stakeholder groups[1, 2], natural health product (NHP) quality, and herb quality in particular, has stood out as one of the most frequently cited critical issues. There seems to be a fairly strong consensus that the Natural Health Product Directorate (NHPD) should take a leadership role in setting standards and facilitating research in this field. The development of appropriate quality assessment methodologies and quality standards was specifically identified as one of the top research priorities at the Halifax NHP Research-Priority Settings Conference[3].

While there appears to be widespread agreement as to the importance of the subject, the research priorities that have been subsequently identified have varied substantially in their scope – and it is expected that additional items will arise during the Quality Control and Product Standard Research Priority-Setting Conference in Vancouver, BC on March 8-9, 2002. This document does not presume to provide an exhaustive summary of the potential priorities, but rather endeavours to lay a common groundwork for those discussions by familiarizing participants with the diversity of issues and perspectives on the subject, as well as some of the common themes. The discussion in this paper focuses primarily on issues related to botanicals and botanical quality.

The contents of this paper are based upon a survey of the literature and pertinent organizations, to identify and explore the following:

- definitions of quality and related terms (e.g., standardization)
- parameters for assessing quality: past and present
- existing product quality standards
- the nature and extent of the existing data on product quality
- the issues and challenges involved in assessing quality, including the advantages and limitations of current analytical technologies
- research initiatives planned or already underway in Canada and abroad
- gaps in our knowledge and research capacities
- federal and provincial research support and funding resources
- common themes, research challenges and key issues

A key determinant of the breadth and scope of any discussion on product quality is how one defines quality. Hence, a secondary objective is to stimulate thought, participant input and consensus building on the definition of quality and related terms, as the apparent divergence of opinions may in part be due to semantics rather than fundamental differences in ideology.

2. Semantics – defining quality and related terms

a. What is quality and how do we assess or measure it?

Although product quality has been continually identified as a priority during the ongoing stakeholder consultations, a closer examination of the comments reveals that the word quality means very different things for different people. Public commentaries suggest that many people equate product quality with efficacy and/or potency. Others have asserted that while quality certainly may impact upon the potential efficacy of a product, in terms of risks, it is far more important to focus upon the relationship between product quality and safety. These two broad themes, efficacy and safety, are used to frame this exploration of product quality.

Consumer perspective

What exactly constitutes a good quality product from the consumer's perspective? It would seem that many Canadians take for granted that all NHPs on the market are inherently safe – and that they are subjected to the same regulatory scrutiny and safeguards as foods and drugs, which ensure that products are free from harmful contaminants and adulterants. Presumably, consumers who purchase NHPs also believe that they are potentially efficacious.

Over the past decade, manufacturers have increasingly focused on the issue of quality, and standardization in particular, as the key feature differentiating otherwise generic herbal products. Marketing campaigns have emphasized the use of modern scientific techniques to ensure that products contain specified amounts of marker compounds, asserting that this process of standardization guarantees potency. Focusing exclusively on competitive analyses of marker contents as a measure of potency, recent media coverage on NHP product quality has also implied that 'standardized' products are superior to non-standardized products and, more importantly, that product potency is the most critical, or even the sole measure, of product quality.

Consumer testimony before the Standing Committee on Health[4] in 1997-98 and subsequent comments throughout the NHPD consultation process suggest that consumers have largely bought into this definition of NHP quality – that standardization to a specified marker content ensures potency and hence product quality. However, consumers do not have any means of determining whether products in fact meet their label claims. What other features can consumers use to discern product quality? While aesthetic and/or organoleptic characteristics may be used to judge the quality of bulk botanicals and liquid extracts, these criteria cannot be applied to packaged products. For the encapsulated and tabletted products that now dominate the marketplace, the only potential indicator of product quality is the manufacturer's reputation. Although the majority of consumers may equate quality to potency, assessing product quality based upon claimed marker content, some consumers employ a much broader definition of

quality. Many informed consumers are more concerned about issues such as origin, growing and harvesting conditions, organic certification, contaminants and adulterants. Some consumers and practitioners have a much more holistic definition of quality that encompasses a gestalt of characteristics, which in some cases may include energetics and even spiritual or metaphysical attributes. These consumer sub-groups may base their assessments of product quality largely upon the manufacturer's reputation and previous product usage.

Industry perspective

What constitutes a good quality product for industry members? For purchasing decisions, quality control and marketing, marker content certainly may be a key issue. However, marker content is not the only aspect of product quality that industry members must concern themselves with. Marker analyses alone may not be sufficient to ensure the correct botanical identity of raw materials. There are numerous other physical characteristics (such as particle size, moisture content, homogeneity, acidity/alkalinity [pH], polarity, foreign matter, etc.) that may affect the manufacturing process, product stability/shelf-life and/or bioavailability. Appropriate measures must also be taken to ensure regulatory compliance and product safety (correct ingredients and labelling, no contaminants or adulterants). Failures in either of these areas can be potentially fatal to a company's continued existence. Thus, for industry members, product quality extends far beyond questions of marker content: the quality of raw materials, the manufacturing process and the finished products must also meet regulatory requirements and company specifications for identity, physical attributes, purity, labels, packaging, stability and bioavailability.

Government perspective

How is quality defined from the regulatory perspective? Health Canada's mission is to protect and promote the health of Canadians. In terms of protection, this means appropriate measures to ensure that products do not contain any toxic ingredients or undeclared or unintended substances (contaminants or adulterants) that pose unacceptable levels of risk. In terms of health promotion, this may be interpreted to mean appropriate measures to ensure the claimed potency and efficacy. In order to meet their mandate, quality issues that regulators must address include such things as botanical identity, purity, potency, stability and bioavailability.

b. Defining quality

Although the media and marketers have focused attention on the issue of marker content, a closer examination suggests that stakeholder's definitions of quality are not necessarily far apart. While there may be a consensus that marker content plays an important role, many would also agree, that "A fallacy exists in assuming that a particular quantity of a given marker….assures quality."[5]

Defining quality strictly in terms of marker content or even potency is an oversimplification of the numerous factors that have an impact on efficacy. The exclusion of safety issues also seems to make this definition far too narrow from the industry or regulatory perspective. At the other extreme, more holistic definitions of quality are based largely upon a gestalt of features that are difficult to articulate and quantify. An intermediate position may be to define quality as the sum

of the variable characteristics and properties that may significantly impact upon product efficacy and safety. Quality assurance would then be the process by which the manufacturer ensures that potential variations in raw materials, in process and finished products remain within acceptable limits.

In discussing "what is quality?" Micheal McGuffin[6], President of the American Herbal Products Association (AHPA) states that it ultimately comes down to the question of whether the product completely delivered everything the customer expected. Using cooking as an analogy, he asserts that good quality raw materials are an essential foundation for the production of a quality product and that while objective criteria such as quantitative markers may be useful or even necessary in some cases, there is no substitute for subjective experience in evaluating the quality characteristics: "To ignore this experience and expertise is to assume that a gourmet meal may be made with poor ingredients."

McGuffin goes on to note that given good quality raw herbs, to produce a quality finished product the amount and form of each ingredient must be relevant to the intended use of the product. Also, one must have a properly designed and monitored manufacturing process to ensure that the right quantity of each ingredients goes into every batch, that it is well blended and is not deteriorated by processing. He concludes, "any attempt to measure quality is bound to fail if it relies solely on quantitative tools." McGuffin suggests that essential components for the production of quality products include:

- high quality herbs
- knowledgeable and experienced staff
- proper formulation
- excellent manufacturing process
- adequate finished product testing throughout the intended shelf-life

c. Defining efficacy and potency

Much of the public discussion and debate surrounding NHP quality has been polarized around the issues of efficacy and potency. However, as with the term 'quality,' there are diverse viewpoints as to what these terms mean. In common speech, the terms 'efficacy' and 'potency' are frequently used interchangeably. According to the dictionary[7, 8, 9] definitions, 'efficacy' is essentially a qualitative term, defined as "the power to produce an effect." In contrast, 'potency' is a quantitative term, defined as the "amount of active ingredient or drug required to produce a therapeutic effect." Although potency is often considered to be a quantitative measure of potential efficacy, it is not the only factor that determines efficacy. If chemical assays are used to measure potency, then a product may be extremely potent but fail to be efficacious if:

- a sub-therapeutic dosage or dosage schedule is used

- it is not bioavailable (not absorbed, poorly distributed, or metabolized and/or eliminated too rapidly)

- it is neutralized by other ingredients or other substances in the body

- it is countered or antagonized by other substances (excipients, contaminants, adulterants)

- the patient's constitution significantly differs from that of the average person (genetic, environmental or idiosyncratic factors)

- the product is not used appropriately

In the context of a pharmaceutical drug, there is little debate over the definition of potency, as the terms active ingredient and drug are essentially equivalent. However, in the context of herbal medicines, the semantic differences are absolutely critical. If one adheres to the World Health Organization (WHO)[10] and the European Community (EC)[11] definitions that the entire herb is the "active ingredient," then the potency of an herbal product might be quantified as the amount of herb per dosage unit. Although many complementary and alternative health practitioners embrace this approach, it is a hard sell to marketers and consumers who seem to believe that one can have the best of both worlds: using natural medicines instead of drugs, and using modern scientific techniques to ensure that they contain the proper amount of "active ingredient."

In reality, there are only a few herbs for which there is some consensus as to the identity of the active ingredients [Ephedrine in Ephedra (*Ephedra sinensis*), silymarin in Milk thistle (*Silybum marianum*)]. Even in these cases, there is more than one "active" constituent. For example, Ephedra contains a number of other pharmacologically active alkaloids including pseudoephedrine (a common ingredient in cold medicines) and norpseudoephedrine, and the "silymarin" in Milk thistle is actually a mixture of complex flavanolignans. More importantly, the pharmacological impact of these compounds will vary, depending upon the actual make-up of the plant matrix, the type of excipients and dosage form. "Even when one compound is judged primarily responsible for a particular activity, the combined effect of numerous auxiliary components with less dramatic impact may provide vital influences in the complexity of a living subject."[12] The preceding examples are the exception, for even amongst the top-selling and most well-researched herbs such as Echinacea (*Echinacea* sp.) and St. John's wort (*Hypericum perforatum*), numerous classes of compounds with *in vitro* activity have been identified with no clear or convincing evidence as to which, if any, are the (most) "active" *in vivo*.

For the vast majority of botanicals, it is impossible to determine potency using chemical analytical methods, since the quantity of active principles can neither be conclusively identified nor measured. Even in the few cases where "actives" have been identified, relevant biological activity assays are required to obtain meaningful measurements of potency. This point is reinforced in the American Herbal Products Association (APHA) manufacturing guidance document[13] where it is stated, "the presence of predetermined amount(s) of marker compound(s) does not guarantee the potency of an extract. The term potency…requires a biological

assessment of an extract and cannot be determined solely by marker or active compound measurement."

Given the current state of our knowledge and technology, potency may be a misleading and inappropriate term. It may be more accurate to state that assessing the amount of marker compound provides an indication of the product's strength, rather than its potency.

Markers

"Marker compounds are one or more constituents that occur naturally in the botanical material and that are selected for special attention by a researcher or manufacturer."[14] The amount of marker compounds as well as the marker compound(s) themselves are often chosen arbitrarily. This selection may be based upon a variety of different factors such as:

- stability of the constituent(s)
- technical ease of analysis
- amount of time and cost of analysis
- utility in confirming identification of the botanical
- potential relevance to therapeutic effect(s)
- indicator of product quality or stability
- previous use by other manufacturers or researchers

Markers are not necessarily "active" compounds. The "actives" may be unknown or the active compounds may be highly unstable or extremely difficult/expensive to analyse. Markers may be chosen to help ensure the correct species identity (e.g., echinacoside for *Echinacea angustifolia*) or the correct chemotype (parthenolide for Feverfew, *Tanacetum parthenium*). Ubiquitous plant constituents such as flavonoids or ferulic acid may be used as indicators of product quality during manufacture, or product stability during storage. In some cases, more than one constituent or more than one class of constituents may be used as marker compounds. This may reflect analytical difficulties, the evolution of our scientific knowledge/technical capacity or markers used for different purposes.

In light of the WHO/EC definitions that the "active ingredient" is the whole herb or herbal preparation in its entirety, European experts have adopted a new set of terminology that describes and differentiates the various roles of marker compounds very clearly. These terms are active principle(s), active marker(s), analytical marker(s) and negative marker(s). Busse has defined these terms as follows.[15] Active principles are compounds with known pharmacological activity that are chemically well defined and generally accepted as the major contributors to the therapeutic effect. As discussed in the previous section, only a very few herbs fall into this category where the potency of the product may be assumed to highly correlated with the content

of active principles, thereby justifying adjustments in their content. The herbs for which active markers are known constitute a somewhat larger group. Active markers are pharmacologically relevant, chemically defined constituents that contribute to efficacy, but for which proof that they are alone responsible for clinical efficacy is still lacking. The majority of herbs fall into the third category: herbs for which neither active principles nor active markers are known. In these cases, characteristic compounds or major constituents may be used as analytical markers for which content ranges may be specified. Negative markers are undesirable constituents such as allergens, toxins, or compounds that interfere with bioavailability. Negative markers may be used to screen for the presence of toxic botanicals or undesirable botanical varieties or chemical races, as well as unwanted constituents.

Standardization

In a recent article on standardized extracts,[16] Kerry Bone starts out by emphasizing that the term means different things to different people. Most consumers and even many manufacturers think of standardization as a fairly recent phenomenon, brought about by applying modern "state of the art" scientific methods to the production of herbal products. They would undoubtedly be quite surprised to learn that the call for standardized products has been a rallying cry in the industry for at least three hundred years.[17, 18, 19] Even today, some manufacturers use the term in its historical context to mean an herbal extract produced to a consistent standard such as a specific extraction ratio, master formula or standard operating procedure.

For the most part though, marketers have largely been successful in convincing consumers and the media that standardized means the product contains a specified amount of "active ingredient." "What is increasingly done now is to fixate on one plant component or similar components identifiable by assay and to standardize extracts to their content."[20] Some believe that this quantitative measure will ensure qualitative results (i.e., an efficacious product). Others interpret this in a negative sense to mean that the product is an artificially manipulated extract in which:

- one or more compounds have been isolated and/or concentrated at the expense of all other constituents, or
- the extract is spiked with pure chemicals to achieve the claimed marker content, or
- fractionation and isolation procedures result in a substance that is no longer natural and is better defined as a pharmaceutical drug.

At the heart of the controversy surrounding standardization appears to be a great deal of confusion and misunderstanding as to what the purpose of standardization is and what the process actually involves. By nature, botanicals may be highly variable in their chemical make-up. The variability in the flavour, aroma and physical characteristics of wine and coffee from year to year and region to region provides a good analogy.

There are numerous factors that may affect the ultimate chemical profile of a herb and the content of a specific marker, including intrinsic factors such as genetics and extrinsic factors

such as growing, harvesting, drying and storage conditions. For example, a common garden breeding study[21] of several St. John's wort accessions found that there was significant variation, not only in marker content throughout the growing seasons, but also between the same accessions grown at different sites, as well as between different accessions grown at the same site. This natural variation in the chemical make-up of herbs presents a considerable challenge, especially for researchers who must use products that are consistent in strength in order to obtain reproducible results. With the current technology, it is not possible to quantify the hundreds of chemical constituents present in herbal material in a timely and cost efficient manner. The compromise solution to this dilemma is to select a marker compound(s) and then ensure that every batch of product contains the same amount of that marker compound(s). This approach to ensuring consistency is based upon the assumption that the content of other constituents will vary in proportion to the marker compound; that if each batch contains the same "standardized" amount of marker, the content of other constituents will also be relatively consistent.

How does a manufacturer actually produce these standardized products with the same amount of marker in every batch? Strictly speaking, "standardization" of marker content is achieved by blending different batches.[22] This is the superior method for attaining consistency, according to the American Herbal Products Association (AHPA) guidelines.[23] However, in spite of claims that their products are "standardized", many manufacturers employ *normalization* to produce products with the targeted marker content – adjusting the extraction ratio and/or adding fillers to achieve the targeted marker content. According to the APHA guidelines, this is acceptable only within narrow limits and large adjustments are only appropriate in cases where it has been established that the marker is responsible for the pharmacological activity. It is further specified that the addition of marker compounds to an extract is not an acceptable method for achieving "standardized" marker content, and if such additions are not stated on the label, the resulting product must be considered adulterated.

By itself, "providing a certain quantity of a particular marker, while psychologically reassuring, in many cases does not necessarily guarantee superior quality or better results."[24] Several researchers have reported that even in products that contain the specified amount of marker, the content of other important constituents and/or therapeutic effectiveness can vary substantially.[25, 26, 27, 28] In Germany, where this practice originated, standardization to a specific content of active or analytical marker is only one of several means of maintaining product quality.

In the recent guidance documents published by the APHA,[29] a much broader definition of standardization is delineated: "Standardization refers to the body of information and controls necessary to produce material of reasonable consistency. This is achieved through minimizing the inherent variation of natural product composition through quality assurance practices applied to agricultural and manufacturing processes." Standardization can serve a number of purposes, including:

- batch-to-batch consistency
- confirmation of the correct amount of extract per dosage unit
- positive control to indicate possible loss or degradation during manufacturing

While ensuring consistent marker content is an important aspect of standardization, it does not in itself equate to a standardized product – standardization requires careful control of both raw material quality and manufacturing processes.[30] This definition of standardization is reflective of the European view, although some experts further qualify this definition, asserting that standardization comprises all measures leading to a reproducible product, without the addition of foreign substances (excipients, isolated active principles, etc.).

3. Historical overview of parameters and methods for assessing quality

For as long as humans have been using medicinal plants, undoubtedly they have also been assessing the quality of these medicines. It is probably safe to assume that as soon as people began to trade in herbal medicines, detecting adulterations was an important aspect of these quality evaluations. The works of several of the ancient Greek and Roman scholars discussed not only the therapeutic properties of natural medicines but also various aspects of their quality. Over 2,000 years ago, Theophrastus[31] (circa 370-287 BC) described the factors that could affect herb quality (age of the plant, the method of collection, part of the plant used, geographical origin, preparation method and storage conditions) and the use of organoleptic methods to assess quality. One of the most influential medical texts was *De Materia Medica*[32] by Dioscorides (1st century, circa AD 40-80), a treatise on the preparation, properties and testing of more than1,000 natural medicines. Dioscorides also warned his readers about potential quality issues (such as substitutions; contaminants; adulterants; and deterioration due to age, pests or improper storage) and gave specific tests and instructions for their detection. Although these were predominantly organoleptic, he also described a number of physio-chemical tests such as flame tests and solubility. In the classic, *Natural History,*[33] Pliny the Elder (circa AD 23-79) frequently commented on fraudulent propensities and adulterations, railing against man's avarice and greed. The tests he advocated to detect quality deficits were also primarily organoleptic, although he also described some physio-chemical tests such as acid reactions, viscosity, volatility and density. Galen[34] (circa AD 129-210) also emphasized the importance of learning how to distinguish good quality products based upon organoleptics, pharmacological potency and geographical source.

The works of Dioscorides and Galen in particular remained the ultimate authorities in European medicine for the next 1,800 years. According to Stieb,[35] effective solutions to the problem of variable herb quality did not evolve until the 19th century, even though the same problem with minor variations had been facing man for thousands of years. A number of publications from the late 18th and early 19th centuries reported that the practices of drug falsification and adulteration were rampant during this period. Common practices included specially preparing a substance to conceal its deficits and/or make it appear better than it was, the undisclosed addition of extraneous substances, subtraction of important constituents, and the sale of products that were simply sub-standard in strength or quality.[36, 37, 38]

The introduction of microscopic analysis in the 1850s resulted in the single greatest improvement in botanical quality, although its truly revolutionary impact is hard to comprehend in retrospect. The English physician Arthur Hill Hassle was the first to make a systematic and comprehensive application of microscopy to food and drug quality, opening up a whole new area

of analytical science and providing the first certain means of detecting adulteration.[39] The fraudulent practices that experts had tacitly recognized for hundreds of years were finally visibly revealed under the microscope. Hassle's objective proof of the frequency and extent of adulteration in almost every common drug and food raised such a public furor that the British government was forced to address the problem by enacting the first British Adulteration Act in 1860.

Even after the passing of this law, health professionals in particular continued to stress the need for stricter and more effectively enforced quality standards and more standardized products. Considering that the same sentiments also prevailed in North America, it is even harder to understand why it took almost another 50 years before similar acts were passed in Canada and the United States (US). It is equally puzzling that although microscopy quickly became a cornerstone of the newly emerging science of pharmacognosy, microscopic descriptions did not became standard features in pharmacopoeias until the early 20th century. Throughout the 19th and early 20th centuries, most of the other drug identity and purity assessments employed were simple physical and chemical tests that had very limited utility in assessing in botanicals.

In the US, the enactment of the first Food and Drug Act in 1906 made the US Pharmacopoeia (USP) and the National Formulary (NF) the national standards for drugs.[16] Canada has never had an official national pharmacopoeia or formulary, and the Canadian Food and Drug Act does not cite specific pharmacopoeias or formularies as national standards.

During the early 20th century, the quality parameters and tests for botanicals continued to be based mostly upon macroscopic and microscopic evaluations. For example, the botanical monographs in the 1916 edition of the NF included specifications for the species, part of plant, permissible level of foreign matter, odour, colour and taste, as well as macroscopic and microscopic descriptions.[16] As advances were made in organic chemistry, though, qualitative and then quantitative chemical assays were gradually introduced.

In the 1950s, more complex technologies for determining identity, purity and strength, such as spectrophotometry and chromatography, were developed. During the following decades, the pace of advancement in analytical technology steadily increased, as evidenced by the rapid progression from paper, to column, to high pressure liquid chromatography (HPLC). However, during the same period, the number of herbs used as medicines dwindled just as rapidly. By 1970, only a handful of botanicals remained in common use and there was little motivation to apply the newer, more sophisticated techniques to analyze their quality. In fact, more advanced techniques such as mass spectrophotometry (MS) and nuclear magnetic resonance (NMR) – which are commonly used to analyze pure, isolated drug compounds – have limited applications in the analysis of botanicals.

At the present time, there are no official botanical quality standards or testing methods in Canada. Although research scientists have adapted techniques such as HPLC analysis to the study of natural products, it has only been in the last decade that these methodologies have been widely employed in the North American NHP industry. Similarly in the US, although numerous HPLC methods are used in industry, there are only quality standards for those few botanicals still listed in the USP-NF. In 1996, the USP-NF commenced the development of modern monographs

for botanical dietary supplements with analytical methods for identification and characterization of natural products.[40] To date, they have published monographs on 12 herbs that contain descriptions, specifications and assays for identification and marker content. When the project is competed, each monograph will contain official methods and quality standards for the whole herb, the powdered herb and common preparation forms such as liquid and powdered extracts.[37] However, compliance to these monographs will be voluntary and only legally enforceable in the US if the manufacturer claims to conform to these standards. In comparison, the current edition of the European Pharmacopoeia contains around 130 monographs on the pharmaceutical quality of herbal medicines.[41]

4. Product quality standards – past and present

a. Canadian regulations

Until the new regulatory framework proposed for NHPs – set out in *Canada Gazette Part I,* December 22, 2001 – comes into effect, NHPs are subject to the regulations contained in the Canadian Food and Drug Act and Regulations. Health Canada's Therapeutic Products Directorate (TPD) is responsible for the regulation of NHPs bearing health claims as well as for products containing substances with a demonstrated pharmacological activity. The TPD has systems in place to grant drug approval for some herbal medicines (www.hc-c.gc.ca/hpb-dgps/therapeut/htmleng/guidmain.html#TradHerb). Products that have been granted this pre-marketing approval bear a drug identification number (DIN) on their label.

The assessment of DIN applications is based upon the submitted documentation and the herb's history of safe use. The choice of ingredient(s), dosage, indications and other basic labelling information must be supported by at least two recognized traditional herbal references. One of the frequently cited references is the British Herbal Pharmacopoeia, which does include botanical descriptions and some minimal quality standards. Since the approval process does not include any physical assessments of the actual product, a DIN does not provide any guarantee of product quality. Theoretically, these products are subject to the same regulatory standards as drugs.

The therapeutic claims permitted by the TPD for a traditional herbal medicine DIN are very limited, as they must pertain to self-limiting conditions that are amenable to self-diagnosis and self-medication. As a result, many companies sell botanicals as "food" products with no medicinal claims, which are subject to the food regulatory standards for label compliance and product purity.

Whether NHPs are sold as foods or drugs, these products are not subject to routine regulatory scrutiny of product quality. The regulatory stance is essentially reactive, taking action on product complaints, adverse event reports and information from other jurisdictions. Imported products originating from foreign manufacturers with a history of quality problems (such as the presence of heavy metals and/or undeclared pharmaceutical ingredients) may be subject to more frequent scrutiny at customs.

GMP requirements

In addition to the required documentation, Canadian companies applying for a DIN must be in compliance with the traditional herbal Good Manufacturing Practices (GMP) guidelines (www.hc-sc.gc.ca/hpb/drugs/). The GMP guidelines describe the principles and practices that need to be followed during the manufacturing and distribution of NHPs in Canada. The GMP guidelines set out the standard practices necessary to ensure product quality and to specify the requirements for:

- premises sanitation and pest control programs
- processing equipment design and effectiveness
- quality control testing programs for raw materials, packaging materials and finished products
- product stability testing programs
- the maintenance of adequate processing and distribution documentation

Before DIN approval is granted, a site audit is conducted to assess whether the company's facilities, programs and personnel comply with the herbal GMP guidelines. Following the initial GMP certification, annual inspections are made to ensure continued compliance. For Traditional Herbal Medicines, Division 1A exempts them from Establishment licence. Hence, there is no guarantee of quality even though they have to comply to GMP.

Proposed new NHP regulatory framework

The proposed new regulatory framework[42] does not differ dramatically from the current standards for traditional medicines. The primary control points would be the product license submission and site licenses (requiring NHP GMP certification). As currently conceived, the applicant would be responsible for specifying appropriate methods for ensuring that the product meets its label claim. Once a product license is issued, the main regulatory control would be annual inspections to ensure continued compliance to the GMP guidelines. Again, as presently conceived, these guidelines require that the manufacturer have raw material, packaging and finished product specifications which set out the criteria and testing methods for assessing product quality.

b. American regulations

Prior to 1994, the American Food and Drug Act was similar to Canada's, in that substances sold for human consumption were defined either as a food or a drug. The passage of the Dietary Supplements and Health Education Act (DSHEA) in 1994[43] represented a substantial change in the legal status of dietary supplements. Under DSHEA, dietary supplements were recognized as a distinct category of products that were to be regulated as foods, although some health claims (structure-function claims) were permitted. [44]

Manufacturers are responsible for ensuring that a dietary supplement is safe but they do not need to obtain FDA approval before producing or selling dietary supplements. The FDA has the authority to take action against any unsafe dietary supplement product(s) after they reach the market. DSHEA states that dietary supplements in the US marketplace as of October 15, 1994 may remain on the market and are thus 'grandfathered' as they relate to the expected safety of the article. New dietary supplements are allowed to enter the market based on a notification process in which the FDA has 75 days to review safety substantiation submitted by a manufacturer.

In 1997, the FDA issued proposed regulations on Good Manufacturing Practices (GMPs) for dietary supplements."[45] Manufacturers also have to ensure that their product label information is truthful and not misleading. One of the requirements specified in DSHEA is that each ingredient must be quantified on the label. The FDA has ruled that its definitions for Class I and Class II nutrients will be used for regulatory standards for assessing label conformity. Class I ingredients (added nutrients) must be present at 100 percent of the label claim, while for Class II ingredients (naturally occurring nutrients) at least 80 percent must be present.[46] The tolerances for these standards range from five to 25 percent, based upon the margin of error for the analytical method used. Since markers are not added to the product, it would seem that standardized extracts should be considered as Class II nutrients. However, the FDA has ruled that the Class I definition applies not only when a constituent is added, but also when its level is controlled, adjusted or manipulated.[38] Therefore, standardized products are included in the Class I category. Products adulterated with pharmaceutical drugs are regulated under the Drug Act. For contaminants such as foreign matter, heavy metals, pesticides and microorganisms, the standards for food apply.

In addition, the US Federal Trade Commission (FTC) regulates packaging and labeling of household consumer products under the Fair Packaging and Labeling Act (FPLA).[47] The FPLA, enacted in 1967, prevents unfair or deceptive packaging and labeling of consumer products. The FPLA requires that a label disclose the identity of the commodity; the name and place of business of the manufacturer, packer or distributor; and the net quantity of contents in terms of weight, measure or numerical count.

5. Nature and extent of existing data on efficacy/potency

There is very little accurate information available on the potency of NHPs on the Canadian market. The best quality data comes from the American Botanical Council's (ABC) Ginseng Evaluation Project (GEP).[48] The ABC contracted academic labs specializing in botanical analysis to assess the products using a validated method. They tested single ingredient formulations of the three commercial species (*Panax ginseng*, *P. quinquefolius* and *Eleutherococcus senticosus*) and included some brands available in the Canadian marketplace. Some of the products tested did not meet their label claims regarding the equivalent amount of ginseng they contained and/or claimed marker content.

A recent paper on Ginkgo reported on the terpene lactone content of commercial products from Europe, Asia and the US.[49] With one exception, all of the German and French manufactured products met their label claims, but more than half of the Asian manufactured products did not.

In two samples, no terpenes were detected and two products significantly exceeded the claimed marker content. The finding that the ratios of the various terpenes also varied significantly in the finished products is noteworthy as well. Fifteen products had no detectable amounts of bilobalide, but four of these 15 products still met their label claim for total terpene content. In one product, the disproportionately higher level of bilobalide in relation to the other constituent terpenes was suggestive of possible marker spiking. A double-blind crossover study with 12 healthy volunteers provided evidence of the clinical relevance of variations in marker ratios. In this study, only one of the three purportedly standardized ginkgo products produced significant cognitive activation.[50] In a dose-response randomized clinical trial of two St. John's wort (*Hypericum perforatum*) products that differed in their hyperforin content (0.5 percent and five percent) versus placebo,[51] it was found that only the product with the higher (five percent) hyperforin content produced statistically significant improvements. Both products contained 0.3 percent hypericin. Based on this and other in vitro evidence, it has been proposed that hyperforin, and not hypericin, plays a major role in the antidepressant activity of St. John's wort.[52] In another HPLC study of seven American St. John's wort products purportedly standardized to contain 0.3 percent hypericin, the hyperforin content ranged from zero to 3.26 percent.[53] These studies show that not only can the total marker content vary in "standardized" commercial products, but the content of other pharmacologically important constituents may also vary significantly. These variations may account for the conflicting clinical results that have been reported for herbal preparations such as St. John's wort and Ginkgo. More importantly, these studies provide clear evidence that standardization to a specific marker content does not necessarily guarantee potency or clinical efficacy.

Other factors that impact on efficacy are stability and bioavailability. Very little has been published on the stability of herbal products but the available data suggests that it is an important factor. For example, studies assessing the effects of storage conditions on the alkamide and cichoric acid levels in *Echinacea purpurea* found that in a liquid extract, alkamide levels were not affected, but the cichoric acid levels declined significantly after seven months of storage at room temperature.[54] Conversely, in a powdered extract, there was no significant change in the cichoric acid levels, but the alkamide levels declined significantly.[33] After 16 months storage, alkamide levels had fallen by more than 80 percent in dried root samples.[55]

Bioavailability data is also fairly limited, but, again, the existing information indicates that it may be a critical factor. In the case of Milk thistle, bioavailability varied *more than tenfold* between two different preparation forms (extract and extract conjugated with phosphotidylcholine).[56, 57, 58] It has been reported that only 20 to 50 percent of the unconjugated extract is absorbed.[59]

Over the past five years, CBC's *Marketplace*, WTN's *Shopping Bag*, the *Toronto Star* newspaper and the manufacturer Wampole have conducted competitive analyses of the marker content in some Canadian NHPs. The CBC, the *Toronto Star* and Wampole[60] surveys reported that some products did not meet their label claims for marker content. Similar findings have been reported in American studies conducted by ConsumerLab[61] and various newspapers. However, testing results may vary significantly, depending upon the analytical methods used. In the absence of any data on the lot numbers assayed, or on the sampling procedures and testing

protocols used, these findings cannot be reproduced or rebutted, and therefore have limited scientific credibility.

The issue of variations in analytical results has become a major concern within the industry. When samples from the same batch are submitted to multiple labs, the reported marker content can vary significantly between lab s– in some extreme cases, up to tenfold. Differences in analytical methods may account for some of these differences; however, analytical competence is also a critical factor. For example, a pilot lab validation program[62] found a wide variation in analytical results (~40 percent), even though a validated method was used.

6. Nature and extent of existing data on safety

a. Botanical identity

When adverse event reports (AERs) from herbal products are rigorously investigated, it is invariably found that the AER was not due to the intended herb, but rather due to the presence of an unintended or undeclared substance – most commonly, a toxic botanical.[63] The occurrence of toxic plants may be classified as substitutions, contamination or adulteration.

Substitutions

In some cases, the medicinal species may be substituted by an inferior species to save money. While most often this only causes consumer deception and not danger to the user, some substitutions may have a serious impact on the safety of the product. In the infamous 'hairy baby' case, a Toronto woman gave birth to a baby boy with neonatal androgenization (precocious sexual development and excessive body hair). It was first reported in the *Journal of the American Medical Association* (JAMA) that this condition was due to the so-called Siberian ginseng (*Eleutherococcus senticosus*) that the pregnant mother had been consuming.[64] However, when the identity of the herbal product in question was scientifically assessed, it was found that there was no trace of Siberian ginseng in the suspect product. In fact, it contained the common substitute Chinese silk vine or *Periploca sepium*.[65] Subsequent investigations found that the material in a number of other Siberian ginseng products on the Canadian market (and one "Panax ginseng" product) was also *Periploca sepium*.[66]

Cases of Aristolochia substitution provide even more dramatic evidence of the extremely serious consequences of some substitutions. In the early 1990s, 33 cases of nephropathy in Belgian women taking a weight-loss product were initially reported.[67] In addition to several herbs, including *Stephania tetrandra* and *Magnolia officinalis*, the product contained a number of pharmaceutical drugs. While the pharmaceutical drugs present may have contributed to the nephrotoxicity, concerns were also raised about the herbal ingredients. Careful investigation of the product revealed that *Aristolochia westlandii* (guan fang ji or guan fang chi), which contains a known nephrotoxin aristolochic acid,[68] had been substituted for *S. tetrandra* (han fang ji or han fang chi). Two other cases of terminal kidney failure were reportedly caused by the substitution of another herb containing aristolochic acid, *A . manshuriensis,* for *Clematis armandii*, both sources of the traditional medicine chuan mu tong, according to the Pharmacopoeia of the

People's Republic of China.[69] Numerous cases of nephropathy associated with another member of the genus *Aristolochia, A. fangchi,* have been reported in both Europe and Asia. [70, 71, 72, 73] To date, there are more than 100 documented cases of Aristolochia nephropathy, 30 of which resulted in terminal renal failure necessitating kidney transplants.[74] In 2002, both Health Canada and the FDA put out a new series of advisories cautioning consumers not to use products containing Aristolochia or any of the herbs for which it may be used as a substitute.[75]

In Taiwan alone, there more than 30 reported cases of serious AERs were attributed to the presence of another potentially poisonous herb, Monkshood (*Aconitum* sp.). Other examples of potentially fatal substitutions include the root of *Atropa belladonna* substituted for marshmallow root, *Veratrum album* root substituted for Primula root, and Cola nut (*Cola acuminata*) for Gotu kola (*Centella asiatica*, syn. *Hydrocotyle asiatica*).[76, 77, 78]

Contamination with other botanicals

The term 'contamination' is generally used to describe the accidental inclusion of undeclared substances. There have been numerous cases of contamination with toxic botanicals of which the following are just a few examples:

- *Rauwolfia serpentina* and *Mandrogora officinarium* (toxic alkaloids) in Ginseng[45]
- seeds of Poison hemlock in Anise seed[44]
- Burdock root contaminated with *Atropa belladonna*[79, 80, 81]
- two Canadians poisoned by Comfrey tea contaminated with *Atropa belladonna*[82]
- Belladonna has also been reported as a contaminant of Mallow, Nettles and Mate[83, 84]
- Plantain contaminated with *Digitalis lanata* (Foxglove) – disseminated to more than 150 companies over two years before ADRs prompted a FDA investigation[85]

Some toxic botanical contaminants that are reported to be commonly found[86, 87, 88] in industry include *Atropa belladonna, Conium maculatum, Digitalis lanata, Illicium anisatum* and *Symphytum* x *uplandicum*.

Adulteration with other botanicals

The term 'adulteration' is used to refer to the intentional addition of undeclared substances. Not surprisingly, the most commonly adulterated herbs are those that command the highest market value. In many cases, it is difficult to obtain definitive proof that the inclusion or substitution was intentional. Some substitutions and/or adulterations encountered in the industry (* potentially

toxic or allergenic species)[52] include:

Herb of commerce	Adulterant
Arnica *(Arnica montana)*	*Heterotheca inuloides, Calendula officinale*
Chamomile (*Matricaria recutita*)	*Anthemis cotula*
Dandelion (*Taraxacum officinale*)	*Leonotodon* sp., *Cichorium intybus*
Devil's claw (*Harpagophytum procumbens*)	other bitter species
Gentian sp. (*Gentiana* sp.)	*Podophyllum emodii*
Nettle (*Urtica dioica*)	*Lamium album*
Plantain leaf (*Plantago lanceolata*)	*Digitalis lanata*
Primula root (*Primula* sp.)	*Veratrum album**, *Vincetoxicum hirundinaria, V. officinale**
Skullcap herb (*Scutellaria lateriflora*)	*Teucrium chamaedrys*
Stephania root (*Stephania tetrandra*)	*Aristolochia fangchi*
Siberian ginseng (*Eleutherococcus senticosus*)	*Periploca sepium*
Uva ursi (*Arctostaphylos uva-ursi*)	*Vaccinium* sp.
Valerian (*Valeriana officinalis*)	Apiaceae sp.*

In general, the most common botanical substitutes/contaminants/adulterants encountered are other members of the same genus or closely related genera. The presence of related species occurs quite often in the following medicinal species[52] (* potentially toxic):

Coltsfoot (Petasites sp.)	Raspberry (Rubus sp.)
Comfrey (Symphytum sp.*)	Sage (Salvia sp.)
Echinacea (Echinacea sp.)	Senecio (Senecio sp.*)
Elderberry (Sambucus sp.)	Spearmint (Mentha sp.)
Feverfew (Tanacetum sp.)	St. John's wort (Hypericum sp.)
Hawthorn (Crataegus sp.)	Strawberry (Fragaria sp.)
Horsetail (Equisetum sp.*)	Thyme (Thymus sp.)
Lime tree (Tilia sp.)	Valerian (Valeriana sp.)
Passionflower (Passiflora sp.)	Willow herb (Epilobium sp.)

Herb research and scientific publications

Unfortunately, the scientific literature is also fraught with reports based upon misidentified or unidentified "herbal" products. The most common mistake made by health professionals and scientists new to the field of phytomedicine research is the failure to adequately identify and characterize the herbal material being used. For example, much of the *Echinacea angustifolia* research published prior to 1989 must now be considered suspect for two reasons. Chemotaxonomic research provided irrefutable evidence that at least some of the "angustifolia" material under study must have been a common substitute for Echinacea, *Parthenium integrifolium*.[89] Secondly, taxonomic studies revealed that most of the genuine Echinacea material supplied was, in fact, *E. pallida,* not *E. angustifolia*.[90] In North America, investigations

have revealed there is widespread contamination of commercial *E. angustifolia* crops with non-medicinal species.

Undeserved reputations for toxicity have dogged a number of herbs because the correct identity and plant part were not indicated or properly established in the original report. Unfortunately, authors continue to cite these erroneous reports and so perpetuate the misinformation. Some of these cases are summarized below.[91]

Herbs incorrectly blamed for toxic effects

Burdock	(*Arctium lappa*)
Borage	(*Borago officinalis*)
Chamomile	(*Matricaria recutita*)
Eleuthero	(*Eleutherococcus senticosus*)
Ginseng	(*Panax ginseng*)
Magnolia	(*Magnolia officinalis*)
Mallow	(*Malva sylvestris*)
Mate	(*Ilex paraguariensis*)
Nettle	(*Urtica dioica*)
Stephania	(*Stephania tetrandra*)
Skullcap	(*Scutellaria lateriflora*)
Valerian	(*Valeriana officinalis*)

b. Purity

An important initial point is to distinguish the terms ‘contamination’ and ‘ adulteration.’ The intentional addition of a substance that is not declared on the label is referred to as ‘adulteration.’ Adulterants may be marker compounds, pharmaceutical drugs or other botanicals that are added to increase the perceived potency. Or, they may be inexpensive substances such as starch, brick dust or exhausted (previously extracted) botanicals that are added to increase the weight or to decrease cost.

The unintentional or accidental inclusion of an undeclared substance is referred to as ‘contamination.’ Potential contaminants include microorganisms; heavy metals; pesticide, herbicide or fungicide residues; and radioactivity; in addition to the wrong plant (weed) or wrong plant part.

Contamination

Microbial contamination

Bacterial and fungal contamination of botanicals is a very serious concern, in terms of health risks and financial losses to producers and manufacturers. Unacceptable levels of microbial contamination are most often due to improper drying or storage of the plant material, and typically result in degradation of the plant material. This is an important problem, since even very low-level contamination may result in serious infections. A Swedish study[92] found that

contamination with pathogenic organisms could cause clinical infections, a fact that is of real concern for immunocompromised and immunosuppressed consumers, such as people living with HIV/AIDS, elderly people and infants. (No data on the microbial levels in North American NHPs were found.)

Assessments of the microbial load on European herbal products found that 70 percent had unsatisfactory levels. In most cases, this was due to high plate counts, although in 10 percent of the samples, pathogenic organisms such as *Pseudomonas* sp, and *Klebsiella* sp. were found.[93]

Microbial contamination can also render plant material toxic in some cases, either by transforming the benign chemicals in the plant into harmful substances, or through the microbes' production of toxic compounds. For example, the moulding of sweet clover (*Melilotus officinalis*) causes a chemical transformation of clover's constituents; the resultant compounds can cause hemorrhaging.[94] Although this particular problem is most frequently seen in cattle, a human case has also been reported.[95] The potentially toxic effects of bacterial and fungal endotoxins such as *Escherichia coli* endotoxin and aflatoxin from *Aspergillus* sp. are well known.

Pesticide and herbicide contamination

Contamination with pesticides or herbicides is a frequently cited consumer safety concern. While there is a trend toward organic products, which consumers assume are free from these substances, a survey of product labels suggests that less than 10 percent of the herbal products presently on the market claim to be certified organic. Several European studies have found that a significant percentage of herbal products tested contained pesticide residues greatly exceeding allowable limits for food.[96, 97, 98, 99, 100] In one of these quality surveys,[101] 26 percent of herbal products tested had more than 100 times the allowable pesticide residues. Specific examples amongst these products were:

- 18 percent of 293 chamomile samples
- 29 percent of 130 peppermint samples
- 62 percent of 115 senna samples, and
- 69 percent of 132 pumpkin seed samples

However, two studies found that when these herbs were extracted with hot water or ethanol, only a small proportion (zero to 25 percent) of the pesticide residue was present in the extract.[102, 103]

Heavy metal contamination

Manufacturers of quality products routinely screen for heavy metals, as this type of contamination may cause serious adverse effects. A recent paper presented a compilation of heavy metal testing results from three German manufacturers, representing more than 12,000 samples of 118 medicinal herbs. Their results showed that not only is heavy metal contamination

commonly detected in herbs, but also indicated that some herbs naturally accumulate specific heavy metals.[104] There are a number of reports of heavy metal poisoning in the literature,[105] and some products on the Canadian market have been found to contain heavy metals. European survey studies assessing the heavy metal content of herbs have found levels significantly higher that those allowed for food (see table below).[106, 107, 108]

	Study results	Tolerable level/week
LEAD	42% had > 1.2 mg/kg 22% had > 1.2 mg/kg Nettle sample 6.1 mg/kg	0.05 mg/kg Adults 0.025 mg/kg Child
CADMIUM	58% had > 0.1 mg/kg 40% had > 0.1 mg/kg Hypericum sample 0.85 mg/kg	0.007 mg/kg
MERCURY	14% had > 0.03 mg/kg	0.005 mg/kg

A survey of the current and archived warning posted on Health Canada's website (www.hc-sc.gc.ca) indicates that heavy metal contamination is an ongoing problem. For example, within a six-month period in 1998, warnings were issued for six products found to contain heavy metals.[109] In April 1996, Health Canada sent a letter to trade requesting the removal of 27 products from the market because analyses indicated that they contained toxic heavy metals.

Radioactivity

In Canada, one usually does not think of radioactivity as a potential problem. However, given that much of the commercial supply of European herbs comes from the former Eastern Block countries, it may potentially pose health risks. Since the Chernobyl incident, a number of European studies have found significant contamination; in one extreme case, 61 percent of the herb samples tested had levels exceeding the European limit of 600 Bq/kg.[110, 111, 112, 113, 114, 115, 116] Although practically unknown in North America, testing for radioactivity has been performed by some European manufacturer, and at least one American manufacturer.

Adulteration

Product adulteration may come in many different forms. The most common form is the addition of inexpensive materials (e.g., starch, lead, cheap herbs, etc.) to increase the weight or the sale of exhausted botanicals (herbs are extracted and then the marc or remaining plant material is dried and resold).

A form of adulteration that potentially poses significant health risks is the addition of undeclared pharmaceuticals to herbal products. Based on the evidence in the scientific literature, it appears that this is a common practice in some countries, and includes a wide range of pharmaceuticals such as amphetamines, narcotics, barbiturates, corticosteroids and antibiotics.[41] Pharmaceutical

adulteration rates reported in screening studies of Asian patent herbal medicines range from seven to 23.7 percent of the samples.[117, 118]

The warnings posted on the Health Canada website indicate that the presence of pharmaceutical adulterants poses ongoing problems, only a few of which are cited here. On February 8, 2002, Health Canada put out a warning advising Canadians not to use the products PC-SPES and SPES because they had been found to contain undeclared prescription drugs warfarin and alprazolam.[119] A week later, consumers were advised not to use Hua Fo tablets, which had been found to contain sildenafil (Viagra).[120] Warnings had previously been issued on two other products that were found to contain sildenafil, V-King and V-King Extra.[121] In another case, Canadians were cautioned against the use of a patent product found to contain the compounds strychnine and brucine.[122] At least two West Coast women became addicted to an "herbal" sleeping preparation that was found to contain benzodiazipenes and traces of narcotics. The bottle of the product analysed contained several different colours of capsules, some of which contained only herbs and some of which contained herbs and drugs.[123, 124] In 1996, Health Canada called for the removal of 12 imported products in 1996 due to the presence of undeclared pharmaceuticals.

More recently, there have also been industry reports of herbs being deliberately spiked or fortified with marker compounds so that analysis would indicate an extremely high marker content and therefore be perceived as high potency material. Another new variation is to blend in material from other plant species that also contain the same marker compound.
'Fortifying' refers to the practice of adding undeclared substances that will increase the pharmacological effect of the product, while 'spiking' refers to the practice of adding undeclared chemicals to artificially increase the marker content. In the North American market, particularly products that claim to promote weight-loss, to increase energy, to enhance athletic performance – as well as even reputed aphrodisiac products – may be spiked with stimulants such as caffeine, ephedrine, amphetamines, etc. According to industry members, other herbs that may commonly be spiked or fortified include:

Intended herb	Adulterant
Chamomile	Chamazulene
Echinacea angustifolia	Echinacoside
Echinacea purpurea	Cichoric acid
Ephedra	Ephedrines
Feverfew	Parthenolide
Ginseng	Kola or pure caffeine
Goldenseal	Oregon grape or pure berberine
Guarana	Caffeine
St. John's wort	Hypericin

An example that made international headlines was the positive doping case of a professional cyclist who had taken an herbal supplement purported to contain Ephedra. In this case, the unusual ratio of norpseudoephedrine to ephedrine and other constituents provided clear proof of undeclared fortification and the cyclist's reputation was cleared.[125] Upon closer investigation, it

has been found that many of adverse effects attributed to purportedly natural products containing the herb Ephedra were due to fortification with ephedrine; in some cases, the only "Ephedra" that the products contained was the alkaloid ephedrine.

7. Issues and Challenges in Botanical Quality

a. Potency

Bioassays

Although validated biological assays with a demonstrated high correlation between *in vitro* activity and clinical efficacy would provide the most reliable laboratory measurement of product potency,[126] the development and validation of relevant bioassays pose significant challenges. Given our present technology, it is extremely difficult, if not impossible, to conceive of appropriate bioassays for some applications, such as increased lifespan. On the other hand, there are numerous bioassays in routine use in academic and pharmaceutical labs that could be adapted to botanicals. Some industry members may not be aware that these tools exist or that they may offer a more cost effective approach.

Coordinated research directed towards the development and validation of bioassays has been very limited to date. Two techniques that are already in use in industry, as well as in several academic labs, are antioxidant assays and lipoxygenase assays (used as an indicator of immunostimulant activity). The advent of affordable gene chip technology has opened up a whole new avenue of approach that may eventually provide more clinically relevant measures of potency. Given the market trend towards greater usage of bioassays, strategies for bridging the gap between academics and industry would not only help companies remain competitive, but would also facilitate the adoption of more accurate measures of potency.

For those products that currently defy meaningful analysis using bioassays, the challenge is to ensure that the techniques employed provide the best possible approximation of product strength. In this regard, there is no question that the primary issue is determining what parameter(s) or feature(s) should be used to make the assessment, especially considering that, in most cases, the active ingredients have not been conclusively identified. There is a plethora of concerns that may be raised under this heading, starting with the issue of marker compounds.

Markers

Based upon the current scientific knowledge, compounds with demonstrated *in vitro* activity are usually chosen as markers, although there may be other, unidentified, constituents that play a more important role in determining potency. In most cases, the targeted amount of marker compound is arbitrarily chosen, often based upon the average content of that marker in the raw material or semi-purified extract. As our knowledge base expands, additional or new markers may be targeted.

Although the selection and use of markers have unregulated and somewhat haphazard in North America to date, they have been driven primarily by scientific advancements and market forces. While this laissez-faire system has worked to a certain degree, there are numerous discrepancies between brands, both in terms of the markers chosen and the targeted amount of marker. For example, *Panax ginseng* products may claim to be standardized to contain anywhere from seven to 70 percent ginsenosides. Kava (*Piper methysticum*) products may claim to contain anywhere from 30 to 70 percent kavalactones. Similarly, Milk thistle (*Silybum marianum*) products vary in their claimed "standardized" marker content from 30 to 80 percent silymarin or silybin. Some *Echinacea purpurea* products are standardized to a specific citric acid content, while others are standardized to "total phenolic" content.

The latter case of Echinacea products standardized to "total phenolic" content (using chlorogenic acid as a standard) provides a clear example of the "strength contest" waged in the North American marketplace. From the scientific perspective, standardization to the total phenolic content is absurd for several reasons: "phenolics" is an extremely broad and ill defined class of compounds that potentially encompasses almost half of all plant constituents; chlorogenic acid is a ubiquitous plant constituent; and chlorogenic acid does not have immunostimulant activity. Standardizing to "total phenolics" is meaningless, both in terms of producing a consistent product and in terms of potential efficacy. But for the unwary consumer, a product containing four percent total phenolics would likely appear to be much more 'potent' than one containing one percent cichoric acid.

Should all industry members be required to use the same markers and/or the same marker content levels? If so, who should determine the appropriate markers and marker content, and what criteria should be used to make these decisions? While such a requirement might help to protect consumer interests, it would also stifle research and the development of innovative products. The promotion of marker compounds as "active ingredients" is also misleading to the public, as are the escalating marker content claims. Should such claims be restricted to those for which there is substantiating evidence? If so, what level of evidence would be sufficient? Would adoption of the European terminology – differentiating between active principles, pharmacologically active markers and analytical markers – help to clarify the issue?

While pharmacologically active or useful analytical markers have been identified for most (but not all) of the top selling herbs, markers have not been identified for the vast majority of the 3,000 botanicals commonly found in commerce. Thus, for the majority of botanicals, while surrogate markers can be chosen, there are numerous questions that arise:

- Who should be responsible for determining the appropriate markers and marker levels?
- What criteria should be used to determine appropriate markers?
- What criteria should be used to determine appropriate marker content and the permissible range of deviation?

- What criteria should be used to determine whether additional or new markers should be employed?

- How will these standards be reconciled with those of other jurisdictions? (i.e., international harmonization)

- How should the issues of marker stability and bioavailability be addressed?

- Who should be responsible for authenticating and distributing the reference standards for these markers?

Methods Validation

The issue of marker content and standardization claims has unquestionably been the central, almost exclusive, focus of recent discussions on product quality. There is a common misconception that the quantification of marker content is a black and white issue. Many people are not aware that numerous methods can be used – and, more importantly, that the results may vary significantly depending upon the method used. Most manufacturers presently use in-house methods to determine marker content, or they contract this work out to an independent laboratory that may also use an in-house method (i.e., a unique method developed to suit the company's particular needs and capabilities). Considering the multiplicity of methods currently in use, it is not at all surprising from a scientific perspective that there may be significant variations in marker content between brands. Likewise, it is hardly surprising that products that meet their label claim based upon the manufacturers method of analysis may be found to be lacking when other methods are used.

Ideally, to create a level playing field in terms of marker content claims, and to better protect consumer interests, all stakeholders would use the same method. Further, the rigour of the method in question would be validated to ensure that reasonably consistent results could be obtained in spite of differences in equipment, personnel and laboratory operations.

Some stakeholders believe that the solution rests in the industry-wide adoption of one validated method for each botanical and that the first step towards the accomplishment of this goal is the establishment of a methods validation (MV) program. Some of the specific issues and challenges involved in the creation of a MV program include:

- What criteria should be used to select potential methods? (e.g., what is the appropriate balance between scientific robustness and practical considerations such as time and cost?)

- Who should be responsible for selecting and validating methods?

- Who will conduct the validation work and who will pay for it?

- What are the priorities for determining which methods should be developed first?

- What mechanism can be used to ensure that these priorities keep in step with newly emerging concerns?

- What criteria should be used to determine whether new methods should be developed and validated?

There are also several, more global, issues that arise in relation to the creation of a MV program, such as whether the research would be restricted to methods for analyzing raw botanicals, or whether finished products methods would also be targeted. Another issue is the question of whether the MV initiative would be restricted solely to marker analysis or whether methods for assessing other aspects of quality would also be included, since many of the same concerns also apply to identity and purity testing.

Analytical competence is another important issue. Many stakeholders have expressed concerns over this issue and have argued that some mechanism for ensuring analytical competence is needed. The availability of validated methods and even a regulatory requirement for their use would not necessarily result in quality improvements if the labs did not employ the methods correctly and consistently. Variations in sample preparation, poor adaptation of the method to specific equipment or inaccurate calculations are just a few potential causes of discrepancies in analytical results. Before this issue can be addressed however, factual data on the nature and extent of the problem must be obtained. In particular, a scientific study would be essential in order to identify the main causative factors.

There are also a number of issues surrounding the adoption of validated methods – most prominently, the question of how this would be accomplished. Would the use of validated methods be voluntary or would manufacturers making marker content claims be required to use a specific validated method(s)?
Beyond method and lab validation is the challenge of reconciling quantitative analyses with qualitative assessments of product potency. What weight should be given to qualitative versus quantitative evaluations? If marker content claims are not made, is the quantification of the weight of the raw herb or extraction ratio sufficient for assessing potency? If quantitative measures ultimately fail to adequately measure quality, how can qualitative evaluations be effectively employed in the industry?

Current capacity – methods validation

The protocols and procedures for validating analytical methods for other substances are well established and there are numerous labs with the necessary experience in MV, although few of these labs also have experience and expertise in analyzing botanicals. In the US, there are currently two MV projects underway in which Canadians could participate or use as a model.

A methods validation program was initiated in 1998 by the Institute for Nutraceutical Advancement (INA), in collaboration with more than 30 government and industry partners, including some Canadians. To date, the INA has published 20 methods for use in the analysis of 15 botanical ingredients (www.inanetwork.com). More recently, a MV program spearheaded by the Association of Official Analytical Chemists (AOAC) was initiated in 2001, in collaboration

with US government, industry and academic partners. The AOAC established a task group on dietary supplements, in collaboration with the Food and Drug Administration (FDA), the Center for Drug and Evaluation Research (CEDAR), the National Institutes of Health (NIH), the National Institute of Standards and Technology (NIST), the Office of Dietary Supplements (ODS), the Bureau of Alcohol, Tobacco, and Firearms (BATF), the US Pharmacopoeia (USP), the American Herbal Pharmacopoeia (AHP), five trade organizations, and other interested parties (including representatives from Health Canada's Food Research Division and the National Research Council). "AOAC has created this Task Group to identify dietary supplements for which validated methods are most urgently needed and to facilitate the development and validation of these methods, in response to the growing demand for validated methods for dietary supplements." The AOAC has also received a contract from the FDA-NIH to produce validated test methods for Ephedra (ephedrine alkaloids) and aristolochic acid.

It is noteworthy that the US federal government has taken action on this issue. Recognizing the urgent need for quality standards and reference materials, the 2002 Congressional Budgetary Appropriations Committee earmarked two million dollars for the ODS to address the issue of validated methods and reference standards. Dr. Joe Betz joined the ODS in January 2002 to head up this initiative as Director of the Dietary Supplements Methods and Reference Materials Program.

Standardization

The process of standardization was originally introduced to produce more consistent botanical products. Strictly speaking, a standardized product is produced by mixing batches of raw material to achieve the target marker content.[127, 128] In practice, however, most manufacturers use normalization to achieve the target marker content. In normalization, the concentration of product is adjusted by adding excipients or changing the extraction ratio.
In many cases, manufacturers are only concerned with ensuring that the minimum amount of marker specified on the label is present; the products may contain any amount of marker greater than the label claim. This defeats the purpose of standardization: to produce products that are consistent in strength. In other cases, the manufacturer's claim of standardization is based upon the fact that a standard formula or extraction technique is used. As one expert recently remarked, "there are no standards in standardization,"[129] and a standardization claim does not necessarily mean consistent product quality. An industry wide consensus on the precise definition of standardization would seem to be a prerequisite to meaningful discussion of the subject.

The market's emphasis on marker content and standardization has been a boon for unethical businessmen. It is much easier to pass off adulterated materials to companies that only assess marker content. The ambiguity of the term 'standardization' facilitates questionable if not outright fraudulent practices. For example, the strength of an extract is expressed as the extraction ratio: a 10:1 extract means that 10 kilograms of plant material were extracted to yield a total of 1 kilograms of native extract or 10 percent extractives. If only 1 kilogram of extract is obtained from 100 kilograms of plant material, the percentage of extractives is very low (one percent), but the extraction ratio is extremely high (100:1). Such "high strength" extracts can only be achieved by using more selective, less polar solvents that will only extract specific constituents or a particular fraction of the plant's constituents. Thus, while such products have

the appearance of "high potency," they contain only a narrow range of the constituents and are quite possibility lacking in medicinal value. Furthermore, the remaining plant material or marc can then be extracted with more polar solvents to produce an extract that contains many of the typical constituents. In this manner, one batch of plant material can yield two fraudulent products: a "high strength" extract and a "standardized" extract. [130]

To summarize, some of the major issues and challenges in assessing potency are:

- development and validation of bioassays
- designation of the most appropriate markers and marker content
- development of cost-effective validated analytical methods
- analytical competence
- adoption of validated methods: voluntary, pharmacopoeial standards or NHPD product license requirement?
- assessing the potency of products that do not make a marker content claim

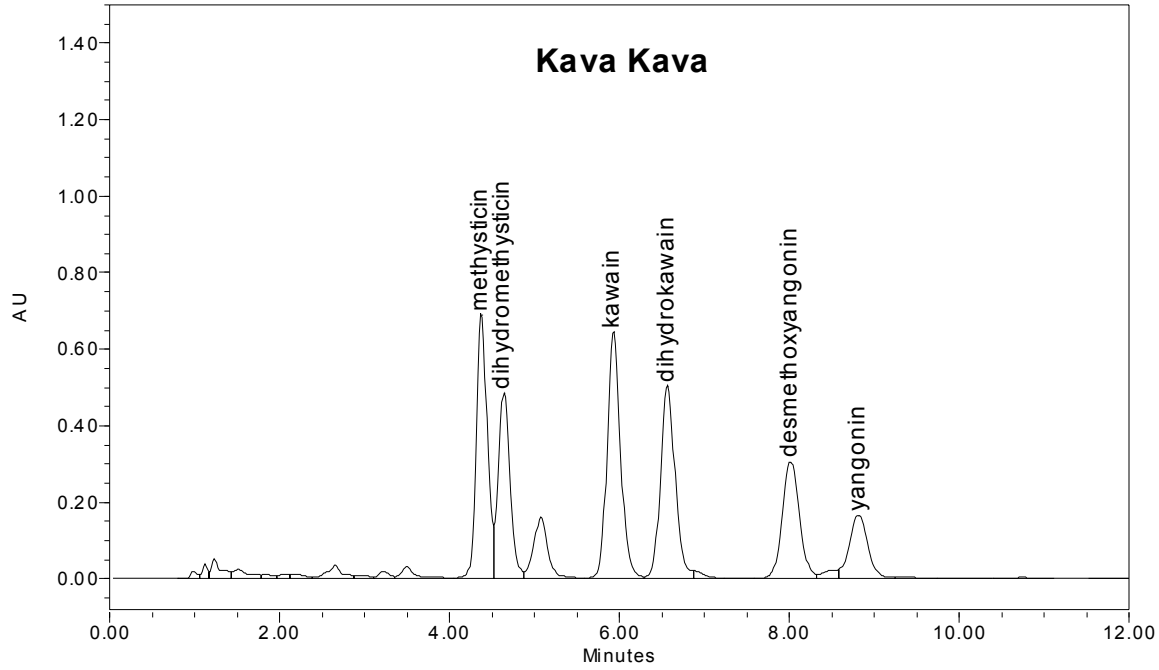
Some of the challenges for scientists conducting research on commercial products are:

- cannot assume the claimed marker content is correct
- markers used are not necessarily pharmacologically active compounds
- products that contain the specified marker content are not necessarily efficacious
- products with the same marker content are not necessarily bioequivalent (of equal potency)
    - the ratio of specific marker compounds may be more important than the total content
    - the content of other important constituents may vary significantly, even though the marker content is the same
- the strength or potency of products with the same extraction ratios are not necessarily the same, unless the same solvent and extraction protocol were used
- research results may not be scientifically valid (reproducible) unless the product has been very well characterized chemically and wherever possible biologically

b. Identity

The literature survey suggests that the failure to adequately ensure the correct botanical identity is one of the most common shortcomings of botanical quality assurance. The primary scientific challenge is to develop validated methods that will reliably discriminate the presence of substitutes, contaminants and/or adulterants. From a practical perspective, the main challenge may be that misidentification is not recognized as a serious risk and/or that the chemical techniques currently used may not be very effective.

Most pharmacopoeias provide written macroscopic and microscopic descriptions, and a TLC (Thin Layer Chromatography) method for confirming the botanical identity of raw and powdered herbs. In practice though, many North American companies rely upon HPLC (High Pressure Liquid Chromatography) analyses. When the HPLC technique is used for identification, the resulting chromatogram is referred to as the "fingerprint." As an example, the HPLC lactone fingerprint for kava (*Piper methysticum*) is shown below:



In general, HPLC analyses of different plant species give characteristic fingerprints for each species, although the relative intensities of the various chemicals present (indicated by the area under each peak) will vary widely depending on many factors, such as growing conditions, plant age, harvesting methods, etc. A key issue in this regard is how much variation in the peak area and the time they come off the column (retention time) should be considered acceptable. How closely must a sample's fingerprint match the typical fingerprint for that species? What deviations are indicative of incorrectly identified material rather than natural infraspecific variation?

In terms of ensuring botanical identity, the greatest limitation of HPLC analysis is that the fingerprint represents only a small portion of the entire spectrum of compounds present in the

herb. Unless considerable care is taken in developing the protocol, the presence of other botanicals, or substitutions with related species, may not be detected. For example, in a study utilizing an HPLC method to assess Dong quai (*Angelica sinensis*, Apiaceae), it was found that although two other angelica species (*A. dahurica* and *A. pubescens*) could readily be distinguished from Dong quai, there were no marked qualitative differences between Dong quai and related species from two other Apiaceae genera (*Ligusticum chuanxiong* and *Levisticum officinalis*).[131] This suggests that manufacturers using HPLC to assess Dong quai would not detect these common substitutes. HPLC analysis cannot be considered a reliable method for assessing identity unless the protocol has been validated to ensure that the results are consistent and that undesirable chemotypes, related species, common botanical adulterants and contaminants may be reliably discriminated. Unfortunately, in practice this is rarely done.

By comparison, Thin Layer Chromatography (TLC) provides a more reliable chemical method for ensuring botanical identity. As a broad spectrum of extracted constituents is represented on the chromatogram, the presence of negative markers and foreign botanicals is usually readily detected. This is the main reason why pharmacopoeias still specify TLC methods for identification. In addition, TLC analysis is quick to perform, easy to learn and does not require expensive equipment, materials and/or supplies. In spite of these advantages, industry members tend to deride TLC as a low-tech, scientifically inferior method.

Other emerging techniques for ensuring identity are capillary electrophoresis (CE) and DNA analysis. Some publications have presented persuasive evidence that CE may provide a superior alternative to HPLC in some cases, by facilitating the reliable discrimination of other species.[132, 133] Similarly, DNA methods for species characterization and adulterant detection have been published.[134, 135] Although DNA analysis is currently considered to be cutting edge technology, its use to assess botanical identity has been largely limited to academia due to the high start-up costs and limited applicability. A genetic library for the species in question, as well as closely related species and common botanical contaminants and adulterants must first be established, which is a costly and time consuming process. For the most part, DNA analysis is only suitable for raw botanicals, as sufficient intact DNA rarely survives the extraction process. In spite of these shortcomings, DNA analysis may be suitable for some species for which identity cannot be reliably established using other techniques. Gene chip technology should eventually result in lower costs.

Organoleptics and microscopy

For raw and powdered botanicals, organoleptic (sensory) assessments and microscopic examination of diagnostic anatomical and histological characteristics are usually the most effective means of ensuring identity – given experienced and competent personnel. Compared to chemical analyses, these methods are very quick and inexpensive. Organoleptics in particular can be extremely accurate. Despite all of the recent advances in analytical technology, the human senses are still superior to chemical techniques in making fine discriminations in taste and aroma. This is evidenced by the fact that machines have yet to replace professional wine, coffee and tea tasters, or professional noses in the perfume industry. An experienced pharmacognosist can accurately identify botanical material and assess its "quality" based upon organoleptic

features, often in a matter of seconds. Until one attains this level of experience, positive reference standards for comparison are essential.

The same provisos apply to microscopic assessments. An experienced practitioner can reliably confirm the identity and purity of a sample and provide a fairly accurate qualitative assessment of its potential strength in a matter of minutes. Again, to gain the necessary experience, one must have access to authenticated reference standards. Physical samples of authenticated powders and common adulterants are preferable, although reference texts such as Jackson and Snowdon[136] are also indispensable resources.

The ability to make accurate organoleptic and/or microscopic assessments is a skill that can only be learned through a great deal of practice under the tutelage of an expert. At the present time, there are no professional educational programs offering training in these techniques.

Certification of botanical identity

Since 1974, the WHO has asserted that the single greatest improvement in botanical quality would be the implementation of a program for the certification of botanical identity. Examination of intact plants enables the most confident botanical identifications and can greatly reduce the need for in-depth expertise at all other points in the distribution chain if the credibility of the certification program is widely recognized. The fact that, after more than 25 years, such a system has not yet been developed, despite the minimal technical requirements, is indicative of the challenges involved. However, the substantial progress made in recent years in establishing organic certification procedures and guidelines, as well as in the area of Good Agricultural (Plant) Practices (GAP/GPP) is very encouraging and suggests that the initiation of a pilot project may become feasible in the near future. To be successful, however, the veracity of the certification must be beyond reproach. The personnel making the identifications must have recognized expertise, the certifier must be an authoritative and respected third party, and the procedures must be stringent, with sufficient safeguards to discourage and detect falsification.

Summary – issues in botanical identity

In spite of the numerous advantages provided by organoleptics, microscopy and TLC, there are several obstacles preventing more widespread use of these techniques, especially the perception that they are unscientific, low-tech methods. These methods are highly accurate, reliable, and inexpensive when employed by an experienced pharmacognosist. The main disadvantage of organoleptics and microscopy is that a significant investment in human resources is required to train personnel, as no professional college or university programs exist. In addition, adjunct methods such as TLC are required for the assessment of extracts. Convincing industry members that these techniques are scientifically sound and highly accurate in the assessment of raw herbs represents a significant challenge. The most significant challenge associated with the use of HPLC to confirm identity is that substitutes may not be readily discriminated. The development of HPLC fingerprints rarely includes validation studies to ensure that closely related species and other chemically similar herbs can be distinguished from the intended herb.

Undoubtedly, the scientific community will continue to develop and improve methods for assessing identity of extracts as new technologies emerge. In addition to the need for method validation, the challenges associated with the use of new, high-tech chemical and genetic methods are their high start-up costs and limited application. The establishment of a botanical identity certification system, as advocated by the WHO, is one potential solution that could alleviate many of the problems associated with botanical identity.

c. Purity

Are the health risks caused by impurities serious enough that purity testing should be mandatory for all NHPs? Although no surveys on Canadian products have been conducted, the general literature, together with the relatively frequent Health Canada warnings, suggests that heavy metal contamination and, in particular, pharmaceutical adulteration are serious problems. Can their occurrence be predicted? Do they occur only in specific sub-categories of products, or are they more widespread? Should products be tested for pesticide residues and microbial load, as well as for heavy metals? Factual data on the occurrence of impurities in products sold on the Canadian market are needed to answer these questions. Furthermore, what analytical methods should be used for purity testing? Perhaps more importantly, what should be the allowable limit for each type of impurity?

For food products, methods for assessing microbial load, heavy metals and pesticide residues in a wide range of matrices are well established. Some European pharmacopoeias include limits for pesticides and heavy metals in botanicals, but Canadian standards for herbal medicines are lacking. In their absence, it is assumed that food standards apply. Are food standards are appropriate for herbal medicines? They are based upon the assumption that the substance may be consumed in unrestricted quantities on a daily basis. Herbal medicines are taken in relatively small quantities. In addition, the processing and extraction procedures that most botanicals are subjected to may ameliorate or even eliminate contaminants that are present in unacceptable levels in the raw material.

There is a significant gap in our knowledge regarding the health risks posed by the various types of impurities, as well as the appropriate standards and testing methods for assessing impurities. Much more research is needed in each of these areas to address the issues associated with product purity.

d. Reference materials

Authenticated standards are an essential prerequisite for any type of scientific assessment of NHPs. However, there are numerous challenges involved in obtaining the necessary reference materials. Few chemical reference standards are readily available. Analysts often must either make their own, have them custom synthesized, or prevail upon the goodwill of their colleagues. One of the most critical issues is that the chemicals may be impure or even incorrectly identified and these defects may often go undetected. Other potential issues in the selection and use of chemical standards are instability, special handling or storage requirements and shelf life. Economics may also be an important factor, as the cost of these standards is often prohibitive for routine analyses. The development of a system to supply affordable chemical reference standards

whose identity and purity have been authenticated by a reputable authority presents a substantial challenge. Moreover, the required reference standards encompass more than pure chemicals, as botanical reference materials are required for accurate identity and purity testing. These include authenticated herbarium voucher specimens, raw and powdered herb samples, and prepared microscopy slides. The fact that private industry has not attempted to fulfill this demand is indicative of the prohibitive economic factors: high start-up costs, low initial demand and lack of official credibility. In particular, a substantial amount of basic research and development would be required.

Current capacity

The basic skills and facilities for developing a reference collection are already in place. For example, most Canadian universities have a herbarium, as do several Agriculture Canada stations. These collections probably already contain many common medicinal plants. These herbaria represent an incredibly valuable but underutilized resource. A survey of their holdings could be conducted to create an electronic inventory of herbal reference materials. The dissemination of this information would facilitate greater use of these existing resources. It would also be useful to survey these institutions to identify areas of taxonomic expertise.

Collaborative agreements with other countries that already have or are also in the process of establishing reference collections (e.g., China, England, the US) would expedite the establishment of the collection and help reduce costs. For example, the internationally recognized Kew Gardens has a large initiative underway to build a reference collection of Chinese medicinal plants in collaboration with many of the world's leading botanical taxonomists. The American Herbal Pharmacopoeia is also working on establishing a reference collection.

In terms of chemical reference standards, there are some industry and academic stakeholders who have experience in producing reference materials. This expertise could be drawn upon in a more formal program to provide authenticated reference materials.

Canada has the basic technical capacity needed to create a reference collection. The fundamental lack is the political and financial support needed to establish the infrastructure and to conduct the necessary research and development. Public funding for Canadian herbaria, for example, is practically nil. The greatest challenge is that this type of work is generally not considered 'real research' eligible for funding from public granting agencies.

e. Quality standards

The issue of quality standards was implicit throughout the preceding discussions. While there may be a consensus on the need for such national standards, the accomplishment of this goal constitutes a significant challenge. Unique Canadian standards could be developed and/or standards from other countries could be adopted; in either case, there are numerous interwoven practical, scientific and legal issues involved. Foremost are questions concerning who should be responsible for establishing these standards, what criteria would be used to set or select the standards, what the scope of the standards should be (potency, identity and purity) and how

flexible the standards should be. International harmonization would have to be taken into consideration as well as potential legal liability issues.

As discussed in the preceding sections, a substantial amount of research is needed to inform the establishment of standards for product potency, ingredient identity and product purity. These wide-ranging research needs include both quality standards and standard methods for:

- bioassays
- markers, marker content and marker ratios
- chemical analyses
- botanical identification
- heavy metals, microbes, pesticide residues and other impurities
- reference materials
- certification of botanical identity
- certificates of chemical analysis and analytical competence

f. Product quality assessment

The first step in any scientific endeavour is to survey and critically evaluate the existing knowledge. In the case of Canadian or even North American product quality, there is only a very small body of evidence on marker content. In addition, these competitive analyses have focused almost exclusively on products purchased from retail outlets, even though sales data[137] clearly show that other types of outlets such as mail order, Internet, direct marketing and buyers clubs compose a substantial portion of the NHP market (~ 50 percent).

As currently conceived, the primary regulatory mechanism for ensuring product quality in the proposed new regulatory framework is the GMP requirements. Will GMP compliance alone be sufficient to ensure product quality? How effective will these new regulations be in improving and/or ensuring acceptable product quality? Physical assessments of product quality are essential for meaningful evaluations of these questions.

There is no epidemiological data on type, severity and/or frequency of quality defects in products on the Canadian market, as an objective, randomized assessment of product quality has not been conducted. The current evidence base is derived primarily from case reports and extrapolations from the international literature. Research is urgently needed to provide a solid scientific basis for rational decision-making and policy development as well as the designation of research priorities. Specifically, this would require a well-coordinated research program to assess the identity, purity and potency of products randomly selected from all segments of the market. There are several academic and industrial labs that have the necessary experience and expertise

to conduct a product quality survey. Although validation tests to ensure the consistency and accuracy of results between labs would have to be conducted, this would also provide an opportunity for participating labs to demonstrate their competence. The project would have to be restricted to herbs for which validated methods and authenticated reference standards were available. Additional research would have to be conducted to identify the common substitutes, contaminants and adulterants for each product, and to assess the effectiveness of the analytical methods in detecting these materials.

g. Education, training and professional experience

The need for education and training in quality assessment is another important issue implicit in the preceding sections. Pharmacognosy was deleted from Canadian post-secondary curricula during the 1960s. Hence, today, researchers new to the field of herbal medicines – and even some experienced scientists – are often not aware of the potential quality issues. For quality assurance personnel, industry members generally have to hire and train individuals with expertise in related fields such as food quality, biochemistry and natural products, or must attract experienced personnel from abroad.

There are numerous post-secondary institutions with the appropriate infrastructure and required facilities. The most significant challenge is the extremely limited number of qualified educators in this field. And even though there is a demand for such programs, there is usually considerable institutional inertia that would need to be overcome before institutions would be willing to make the necessary investments in course development.

8. Summary: common themes, gaps in our knowledge and key issues

From the survey of the literature, important issues have been identified, not only concerning product potency, but also botanical identity and purity. The subject of marker content claims in particular has been dominant in the public eye, although the concerns raised in the media may be an artefact caused by the wide variations in the methods used to assess marker content. In response to this controversy, industry-wide adoption of validated methods and certification of product quality have been the primary focus of many stakeholder discussions.

While marker content is an important issue, some may lose sight of the fact that one first has to deal with the plant – chemical analysis is moot if one does not have the right plant or if the plant material is not pure. The industry's fixation on marker content also facilitates fraudulent practices. The issues of methods, method validation and implementation also arise in relation to identity and purity research. In the case of identity testing, there is also a significant gap between the best scientific approach and the methods used by industry. In the case of purity testing, there is a need for some basic research to determine whether the standard purity tests are reliable in detecting impurities in botanicals, especially finished products.

Three other cross cutting themes that have emerged are the need for authenticated reference materials, national quality standards, and pharmacognosy education and training. The basic skills, expertise and facilities required to address all of these issues already exist, although they

are widely scattered across the country. The most significant gap is the lack of an organizational infrastructure to plan, foster, facilitate and coordinate research. It is also apparent from the literature survey that there is a tremendous gap in knowledge regarding the quality of products on the Canadian market.

Some of the key challenges in bridging these gaps are obtaining consensus on:

- research leaders and leadership roles
- appropriate scope of research programs
- appropriate balance between scientific rigor and practicality
- specific botanical priorities within each area
- most effective strategies for facilitating the accomplishment of research goals

At the present time in Canada, research on product quality is uncoordinated, with quality research projects conducted in isolation and the results often not widely disseminated. Knowledge transfer from academia to industry and government, and information dissemination between industry members is quite limited. Fostering the development of a cohesive quality research network could make significant inroads in addressing this problem, and could generally assist in the successful execution of strategies to close quality research gaps.

Appendix 1 - Funding Strategies

The research budget of the NHPD is currently $1,000,000 per year. While yet to be finalized, current budget plans project that more than half of these funds will be disseminated in collaboration with community partners such as the Canadian Institutes of Health Research (CIHR). The remaining funds have been designated for use by the NHPD to facilitate and support research development and to conduct priority projects.

Both CIHR and the Natural Sciences and Engineering Research Council (NSERC) fund a number of industry partnership grants as well as the traditional academic grants to support new investigators, investigator initiated projects, post-doctoral fellowships and graduate students. Further information on CIHR, NSERC and other support programs is available at the websites listed below.

Canadian Institutes of Health Research
http://www.cihr.ca

Natural Sciences and Engineering Research Council of Canada
http://www.nserc.ca

Industrial Research Assistance Program (IRAP)
http://www.nrc.ca/irap/home.html

Agriculture and Agri-Food Canada
http://www.agr.gc.ca

Matching Investment Initiative
http://res2.agr.gc.ca/research-recherche/industry/mii/ match.html

Research Partnership Program
http://res2.agr.gc.ca/research-recherche/partnership.html

Canadian Adaptation and Rural Development (CARD)
http://www.agr.gc.ca/progser/card_e.phtml

Industry Canada
http://strategis.ic.gc.ca

Listing of provincial funding sources: http://strategis.ic.gc.ca/SSG/tf00070e.html

Health Policy Research Program (HPRP)
http://www.hc-sc.gc.ca/iacb-dgiac/nhrdp/indexe.html

Atlantic Canada Opportunities Agency Program
http://www.acoa.ca/

Western Economic Diversification Canada (WD)
http://www.wd.gc.ca/eng/default.asp

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