



## **Product Quality Stakeholders Meeting**

**March 10<sup>th</sup>, 2009** 1:00 am – 4:00 pm

Calgary Delta Hotel, Aspen Room, Calgary, Alberta, Canada

### **MEETING REPORT**

#### **1. Welcome and Roundtable**

Participants (see Appendix I) were provided with information packages (see Appendix II) welcomed by the facilitator, advised that the information would be compiled into a brief report for Nutri-Net Canada, and the specific meeting objectives given.

Meeting objectives: To present work to date on Product Quality for Natural Health Products and tap into the collective wisdom of the group to assess the feasibility of a Product Quality program in Canada/US.

Participants were asked to give a brief introduction to themselves, followed by a round-table interactive discussion answering the following question, *“From a researcher, consumer and/or industry perspective, my hopes for a Product Quality program are...”*

##### **1.1. Researcher Perspective Summary**

Researchers from industry commented that product quality refers to purity, i.e. pesticides, heavy metals content is within safe limits, the accuracy of the label information on the bioactives and the safety of those bioactives. For a complex bioactive profile, ingredient consistency and standardization is important. Others mentioned that product quality is a critical component to support innovation and that a framework for product quality analyses could be useful to prioritize research activities supporting product quality. An issue highlighted is the absence of programs that train researchers and analysts in the technologies used for defining and assessing quality.

##### **1.2. Consumer Perspective Summary**

Stakeholders felt that consumers want a regulatory system that works in assuring product identity and purity. This is needed to engender trust in regulatory oversight, in laboratory test results and the industry overall. Consumer acceptance requires not only acceptable organoleptic properties but assurance that there is meaningful and accurate information on product labels. There is a need for consumer education on quality assurance and standardization to permit differentiation of products beyond the price point.

##### **1.3. Industry Perspective Summary**

Industry members present represented growers, primary processors, bulk ingredient and finished products manufacturers/distributors. Representation also spanned natural health products, functional foods and pharmaceuticals.

Industry members commented that product quality is critical to capture the true and total value of product and that evidence for quality is essential for Canadian companies to compete globally in international markets. Product quality is necessary for marketing, regulatory compliance and consumer confidence in the safety and efficacy of products. Participants commented that product quality involves the full product chain from production, post-harvest storage and handling, and through the chain of custody from manufacturers to the point of sale. A comprehensive approach to tackle this issue is needed as well as recognition by industry and regulators that the costs for ensuring quality e.g. developing and validating methods will have price consequences.

Understanding analytical needs for identity, purity and safety were highlighted as a priority. The loss of the cultural knowledge foundation for traditional medicines has consequences for identity. Identity issues are compounded by the complexity of the distribution chain which makes “ignorance easy” and compliance and enforcement challenging.

Standards for microbial content were mentioned as an example where standards are not realistic or rationale e.g. the number of colony forming units (CFU) permissible for food is less than 1000 whereas this is even more stringent for cosmetics where permissible CFU is less than 100. With industry trends for organic or natural products, the likelihood of non-compliance with unrealistic, possibly unattainable standards, will increase. A second example illustrating the need to understand the rationale for testing was a discussion on bioactives, the challenges of standardizing products for consistent content and the high level of variability in testing approaches leading to industry and consumer confusion.

The discussion concluded with comments on industry naivety and the need for ongoing education of companies. Companies require information on the basics for identity, purity and other product specification; what type of testing is needed including testing replication, and how to document this information. Quality has to be supported by documented evidence.

## **2. Product Integrity Challenge – Global Industry Perspective Presentation**

A presentation was given, with permission, using material provided by Loren Israelson, Executive Director, United Natural Products Alliance, Salt Lake City, Utah. This emphasized the current product quality issues globally that are affecting the market and the potential for legislation-based responses from the US which will have implications for Canadian exporters. The following one-page synopsis of the PowerPoint was provided in the participants' information packages:

### **PRODUCT INTEGRITY: OUR GREATEST CHALLENGE**

By Loren Israelson, Executive Director, United Natural Products Alliance, Salt Lake City, Utah

#### **The Current Situation**

From Beijing to Baltimore, consumers are wondering why those who grow, make, sell and regulate foods cannot seem to prevent fraud, adulteration, and incompetent regulation. In short, why can't food be safer?

#### **THE PROBLEMS**

##### **1. The "Sushi Economy"**

The global food supply is like a sushi combo plate.  
It comes from everywhere.  
It travels fast.  
It is hard to trace.  
You are not always sure that it's really Yellow Tail.

##### **2. The "Crashing Economy"**

The global recession, coupled with a deep recession in the U.S., has destabilized supply chains and traditional buying relationships.  
Suppliers of raw materials are dumping inventory – some of it expired goods, very low quality, blended down stock and intentionally spiked material to fake lab tests.  
The global food and supplement supply chains are setting themselves up for another melamine or peanut disaster.

#### **What Can Be Done?**

In the U.S., there is very serious talk of legislative reform for food safety. This could include substantial user fees to pay for enhanced inspection, analytical development, certification of food manufacturing suppliers and facilities, mandatory notification to FDA of negative lab results, mandatory recall authority and U.S. government recognition of foreign food safety regulatory systems.  
Many of these ideas will drop out along the way, but chances are significant food safety reform will happen this year or early next year.

#### **Three Greatest Challenges:**

- 1) The intentional spiking of supplement products with active pharmaceutical ingredients (APIs). The clearest example is that of weight loss products sold via the Internet into the U.S. and Canadian markets.
- 2) Total plate count standards. Currently many companies set TPC at 3,000 to 5,000. This is unrealistic. Recently the American Herbal Products Association proposed a TPC of 10 million. I personally agree that, absent pathogens or other disqualifying factors, a TPC of 10 million is practical and sensible. Failure to establish an achievable TPC will lead to the illegal use of irradiation or falsification of paperwork or shopping for labs that give you the results you want. None of these are desirable.
- 3) The continued lack of validated analytical methods, authenticated reference materials and template C of As. The global NHP and DS industry should focus efforts on these three things, which if accomplished would really transform safety, quality and product integrity in Canada, the U.S. and worldwide.

#### **Contact**

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### **3. Product Quality Initiative – Report on Project Activities by Paula Brown**

A comprehensive PowerPoint presentation was given with opportunities for questions and discussion throughout. The following was covered and augmented with reference to materials provided in the participants' information package:

#### **3.1. Lab Proficiency Program**

- 3.1.1. Method validation, reference materials & lab proficiency
  - a brief history of the series of projects undertaken since 1999
  - discussion of the rationale for the NNC Product Quality Initiative and the project work completed
- 3.1.2. Expert Advisory Meetings – Prioritization of NHPs
  - a description of the processes used, their evolution and the current priority list
- 3.1.3. Microbial Load Criteria Project
  - a description of the work undertaken within the NNC Product Quality Initiative and recommendations for next steps

#### **3.2. Product Quality Initiative – Building Business Case for Quality**

- 3.2.1. 2008 Industry Survey
  - the survey used and the summary results were discussed
- 3.2.2. 2008 Workshop Summary
  - the results of the Product Quality Workshop from 2008 were presented

#### **3.3. Engaging Industry & Building Capacity**

- 3.3.1. Next Steps – The five project components from February 18<sup>th</sup>, 2009 Expert Advisory Committee Meeting were discussed briefly
- 3.3.2. Partnership & Funding Opportunities – Open Discussion. This centred on the possible opportunity for a Health and Wellness Science Cluster under Growing Forward and highlighted the need for collaboration with academia, government and industry.

#### **4. Facilitated Discussion using Challenge Wall**

The final component of the workshop attempted to identify the next steps for implementing the business plan for sustained Product Quality Initiative. Participants were asked to answer the following questions with respect to the current product quality initiatives, “What is working now?”, “What is not working?”, “What do we need to fix?” and “What do we need to start doing?”.

Responses were sorted into thematic areas by the workshop facilitator as follows.

##### **4.1. “What is working now?”**

- Canadian regulations for natural health products were highlighted repeatedly as successful and important for prompting industry to raise quality and build a desirable Canadian brand.
- Our Canadian reputation for clean high quality products is increasing our awareness of product quality issues.
- The extent of collaboration across government, industry and academia covering the whole production chain supports product quality understanding and development.
- The identification of the need for validated methods and reference materials as a critical first step to a comprehensive program.
- The processes described leading to laboratory analytical proficiency clearly recognizes the training needs.

##### **4.2. “What is not working?”**

- Inadequate funding for this applied work.
- Poor sector understanding of product quality issues; raw materials and testing decisions are primarily cost driven.
- Lack of expertise, trained analysts and training programs; Current dependence on volunteers for methods validation in AOAC program.
- Lack of enforcement of NHP regulations – improper or no validation of methods, inadequate documentation of testing “labs cannot stand by their numbers”.
- Lack of regulatory framework for foods to have health claims, “functional foods”

##### **4.3. “What do we need to fix?”**

- Long term funding for an integrated quality initiative covering validated methods, reference materials and lab certification. Inconsistent funding for this applied research leads to challenges as momentum is lost. The funding cut to the Natural Health Products

Directorate at Health Canada sends a negative message about the importance of the evidence base for quality.

- Communication
  - industry to researchers and vice versa of product quality issues and needs
  - industry to government and vice versa on the importance of supporting quality initiatives for market access
- Increased partnering across industry in the US and Canada

#### **4.4. “What do we need to start doing?”**

- Highly Qualified Personnel development - Training programs need to be developed for this sector. Academic institutions need to be encouraged to increase programming related to quality for botanicals (e.g. microscopy for identification), natural health products (e.g. pharmacognosy, phytoforensics) and analytical methods.
- Communication campaign
  - For industry throughout the supply chain to build understanding how to select testing laboratories to how to evaluate test results.
  - For the sector at large to understand that quality products are necessary for quality results from clinical trials which are necessary for quality claims on products which are necessary for sales.
  - For government (Agriculture and Agri-Food Canada, Health Canada and the Canadian Food Inspection Agency) about the product quality initiative
- Information repository, e.g. an open source website, for industry to get timely relevant information on methods, validated methods, reference standards and other key information for decisions on methods such as ongoing projects and collaborations.
- Applied research funding targeted to address industry needs such as methods development and validation for adulterants, markers for quality and bioactives.
- Long term product quality program including methods validation, reference material development and laboratory training and proficiency testing to develop official methods and certified testing labs to enable enforcement of use of ‘fit for purpose’, validated methods by industry

## **5. Close**

A formal meeting evaluation was not conducted; however, comments written on the Challenge Wall included positive comments thanking the meeting presenters and participants and thanking Paula Brown and colleagues for their persistence in raising awareness and providing useful resources for industry.



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### **Appendix I – Attendee List**

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## **Appendix II – Contents of Participants’ Package**

### Agenda

Product Integrity: Our Greatest Challenge presentation – Loren Israelson, Executive Director, United Natural Products Alliance, Salt Lake City, Utah. (included in Meeting Summary above)

Nutri-Net Canada: Canadian Product Quality Initiative – Executive Summary

1. Project Summary
2. Project Rationale
3. Project Reports
  - 3.1. Revised Microbial Load Criteria Recommendations
  - 3.2. Development of a National Lab Proficiency Program
    - 3.2.1. Ginseng Quality Assurance Program
    - 3.2.2. Goldenseal Quality Assurance Program
    - 3.2.3. Echinacea Quality Assurance Program
4. Product Quality Initiative Recommendations for 2008/2009
5. List of Appendices
  - Appendix A – NHP Industry Survey on Quality
  - Appendix B – Summary of NHP Survey Results
  - Appendix C – Product Quality Initiative Workshop March 26<sup>th</sup>, 2008 Toronto, ON Summary



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### **AGENDA**

1:00 **Welcome and Introductions**

1:30 **Product Integrity Challenge - Industry Perspective**

2:00 **Product Quality Initiative – Report Project on Activities**

Lab Proficiency Program

- Method validation, reference materials & Lab proficiency
- Expert Advisory Meetings – Prioritization of NHPs

Microbial Load Criteria Project

2:45 **Product Quality Initiative – Building Business Case for Quality**

2008 Industry Survey

2008 Workshop Summary

3:00 **Engaging Industry & Building Capacity**

Next Steps – Disseminate 5 project components from February 18<sup>th</sup>, 2009 Meeting

Partnership & Funding Opportunities – Open Discussion

3:15 **Facilitated Discussion using Challenge Wall:**

- What is working
- What is not?
- What can be improved?
- What needs to be done that is not currently being done

4:00 **Meeting Close**

# NutriNet Project: Canadian Product Quality Initiative

## 1.0 Project Summary

This project was designed to assist industry and regulators address critical issues for this sector; an assessment of current microbial load testing demands; the paucity of validated analytical testing methods; concerns over the variability in analytical test performance and the need to increase industry capacity and improve perceptions of NHP quality. Three subprojects were conducted:

- A. Development of Microbial Load Criteria Recommendations,
- B. Initiation of a National Lab Proficiency Program
- C. Development of a Product Quality Program Business Plan.

## 2.0 Project Rationale

The need to address functional food/natural health product (FFNHP) quality has been widely recognized not only in Canada (Parliamentary Standing Committee on Health, Health Canada, Industry Canada, Agriculture and Agri-Food Canada and NSERC) but also by the White House Commission on Complementary & Alternative Medicine, the US FDA, National Academy of Sciences, AOAC International, and the Medicine Evaluation Agency. Product quality affects market access and growth of this important value-added agri-food industry sector. Market access is impeded by several quality-related factors:

- Low quality products confuse and diminish respect and trust by consumers and regulators. The 'snake-oil' reputation decreases interest, awareness, acceptance and use of high quality products.
- Fraudulent or unsafe products decrease market acceptance and access for Canadian products within Canada and abroad. Media coverage of sub-standard, sub-potent and even adulterated products has diminished the reputation of NHPs and overall industry suffers;
- As a consequence of the above points, healthcare providers, researchers, and regulators continue to dismiss these products as potentially significant contributors to healthcare cost reductions. Although industry stakeholders are aware of these issues and their growing impact; individual industry members do not have the required expertise, organizational and financial resources, or 3rd party credibility.

The objective of this project is to develop a credible, cost-effective approach to address these industry issues. Successful validation of appropriate methods to meet international standards, as well as a fair and equitable approach to laboratory proficiency determinations has been developed.

## 3.0 Project Reports

### 3.1 Revised Microbial Load Criteria Recommendations

The main rationale for microbial load limits for natural health products (NHPs) comes from the understanding that microbial contamination of NHPs can pose a risk to the health of Canada's population. Currently, the criteria for finished or formulated NHPs require meeting purity specifications to comply with the regulations in Canada. The criteria are meant to show adherence to Good Agricultural Practices (GAP) and Good Manufacturing Practices (GMP), whether the product is suitable for the intended purpose, and/or stability of the product (shelf-life). Most importantly, the criteria are used when import of a product into Canada is undertaken and the product's production parameters are unspecified.

A comprehensive literature review to determine the state of the science was conducted. The American Herbal Products Association included a link to this review in their monthly "AHPA Report" for May 2008 referring to it as a significant list of relevant literature (<http://www.connotea.org/user/BCITNRGJamie>) for industry.

The results of the literature review were employed as a guide to design the microbial sampling plan and testing strategy. The American Herbal Products Association volunteered compiled data gathered from member companies to support this project permitting evaluations of baseline data for three botanicals – ginseng, ginger and licorice. Baseline data collection is an important factor for development of appropriate and realistic recommendations of microbial limits. This approach includes four steps to help establish safety risk(s) including hazard identification, exposure assessment, hazard characterization, and risk characterization.

Raw herbs are teeming with mostly harmless environmental bacteria; however pathogens in the environment can be introduced during handling and processing. Of the thousands of known microorganisms present in the environment, the concern is primarily with those with a history of spreading in foods and hence NHPs. Based on this and current industry practice, five specific microbial tests were chosen for inclusion to cover the range of microbial limit purposes, including shelf-life and contamination from locale sources, e.g. from local water sources used or during processing. The purpose of total aerobic count and yeast/mould is to determine the shelf-life and/or spoilage of the NHP. *E. coli* and *Salmonella spp.* testing check whether there is contamination from local environmental reservoirs. Similarly, the test of *S.aureus* is to confirm that processing procedures are not contaminated. The indicator tests for *E. coli*, *Salmonella spp.*, and *S. aureus* are meant to show the presence of the microorganism. It must be emphasized that those tests do not allow the interpretation of whether the strain is pathogenic or not, only that the bacteria is present and that additional tests are required for identification.

The microbial load criteria, as set by the NHPD, does not specify the number of sampling units required to be statistically confident in establishing an acceptable measurement of a NHP lot (or batch) under study. Current sampling plans in use are concerned with two types of related risk: the consumer risk of consuming an unacceptable lot and the producer risk of rejecting an acceptable lot. Consequently, The International Commission on Microbiological Specifications for Foods (ICMSF) was employed as a guide by BCIT to create an appropriate sampling plan for this project. The ICMSF sampling plan was used for each lot analyzed by BCIT in two forms: individual and pooled replicates.

Distinct lots of *Panax quinquefolius* were obtained from growers in Ontario. Every effort was made to acquire raw material from different geographic regions within Canada; however this was not possible within the timeframe of this project. Acquisition of the first 3 lots of *Panax quinquefolius* was delayed by grower participation. In the last month of the project, the initial suite of testing on the original 3 lots of material was concluding, 5 more lots were acquired and are undergoing microbial testing. Once complete, the materials will be pooled, processed and re-assessed and the data made available.

Conducting baseline assessments of botanical raw materials supports the establishment of appropriate (realistic) microbial levels. This is meant to be included in the four steps of hazard identification, exposure assessment, hazard characterization, and risk characterization. However, technical limitations in interpreting data for counts of total aerobic bacteria and yeasts and moulds stymie setting appropriate microbial limits for NHPs. This is a consequence of the fact that many botanicals naturally have bacteriostatic or antimicrobial properties and consequently inhibit assays based on microbial growth. Secondly, having levels set at zero or “absent” means that depending on the sampling plan and the associated sensitivity factor, a “pass” material may still pose a risk. Ultimately, having control of the supply chain by making use of GAP followed by proper handling (GMP) is the best way to mitigate risk of microbial contamination.

Preliminary project results were disseminated at the 5<sup>th</sup> Annual Natural Health Product Research Society of Canada Conference, March 27<sup>th</sup>, 2008 in Toronto, Ontario by Jamie Finley . The American Herbal Products Association included this presentation in their monthly “AHPA Report” for May 2008. The work was also presented in a poster presentation at the AOAC International Annual Meeting, September 21<sup>st</sup> – 24<sup>th</sup>, 2008, Dallas Texas, USA.

### Short Term Recommendations

(1) The control of the supply chain of any NHP should be emphasized to be the top priority to mitigate risk of microbial contamination. Compliance with Good Agricultural Practices is clearly one of the best routes to achieve this, coupled with stringent adherence to Good Manufacturing Practices to keep bacteria from being reintroduced into the product stream and to prevent growth in processed products.

(2) Sampling plans such as those created by the ICMSF should be used to be confident in results obtained from microbial testing. This is especially critical if the supply chain of a NHP is not well understood or unknown. Without appropriate sampling plans, the common specification in various compendia of zero tolerance for pathogens can not be realistically achieved.

### Longer Term Recommendations

(3) Investigation of whether current microbial methods can be validated for NHPs as it is well-known that NHPs do contain anti-bacterial and anti-fungal substances. The inhibition of microorganisms by such substances will prevent a true picture to be obtained even with the recommended sampling plans as suggested by the ICMSF. Alternative methods like PCR or fluorescence-activated cell sorting (FACS) could support demonstration of the validity of current microbial methods and, in some case, could provide more cost effective indicator testing for multiple microbial species.

(4) Ongoing acquisition of baseline data for building an appropriate information base on the expected microbial load for a clean, high quality material. Collaboration with international partners for this recommendation will accelerate this process.

(5) Evaluation of the presence of mycotoxins, natural toxins produced by a number of species of common fungal genera such as *Aspergillus*, *Penicillium* and *Fusarium*. should be conducted. They may occur as natural endophytes in the field or as spoilage microorganisms. Fungal presence may indicate mycotoxin presence, but in many cases the botanical itself can inhibit production. Currently, the burden is placed on the manufacturer to determine whether or not mycotoxins are likely to be a problem in their raw material; however, given increasing product safety scrutiny by regulators, proactive surveys could mitigate industry exposure.

(6) Longer term hazard characterization (dose-response assessment) through analyses of routes of infection, host immunity or tolerance and matrix influence on microbial level and composition. This will require human volunteer studies, use of animal models, and use of survey

### 3.2 Development of a National Lab Proficiency Program

Methods validation for three Natural Health Products of interest to Canadian manufacturers was undertaken. Completion of the validation components is essential to develop a quality assurance testing program that will be open to all Canadian labs willing to register as participants. This will increase capacity amongst laboratories and permit objective, scientifically robust assessments of analytical laboratory proficiency. Participating labs will be required to demonstrate their ability to produce consistently accurate results. The program is an essential prerequisite for the achievement of establishing product quality standards, ensuring quality assurance for both the manufacturer and producer, as well as for objective, scientifically rigorous research of FFNHPs. Refined protocols for method selection and validation, and laboratory proficiency tracking and testing were developed through this NNC-funded project.

For the selected FFNHPs, existing methods were collected and assessed. The most robust and cost-effective method then undergoes a Single Laboratory Validation (SLV), Youden Ruggedness Trial (YRT), and finally a full inter-collaborative study (IS). According to AOAC International multi-laboratory validation is required to archive the highest degree of confidence in performance as required to generate credible, defensible, and reproducible results. Only AOAC® Official Methods are recognized worldwide as authoritative, because of their thorough and rigorous testing and characterization and are cited in the U.S. Code of Federal regulations. According to AOAC International the Collaborative Study process takes 12 months minimum, require 8-10 independent laboratories but upon successful completion of the study are

published in the *Journal of AOAC INTERNATIONAL* and may go through the process to becoming an *Official Methods of Analysis (OMA)*.

It was initially proposed BCIT would undertake Peer-verified Validation as per AOAC International with collaborators in order to develop laboratory-to-laboratory precision criteria; however AOAC has not yet published clear and concise guidelines. Thus, despite the additional labour required for conducting a fully collaborative study, it was determined that this approach was necessary to maintain the integrity of the project. Ultimately the multi laboratory data is a prerequisite to developing the proficiency program. Without going through the process of a full validation the laboratory-to-laboratory method precision would not be determined and hence no statistically proficiency criteria could be established.

BCIT recently participated in an initiative by the National Institute of Standards and Technology (NIST) to establish a Dietary Supplement Laboratory Quality Assurance Program in collaboration with the National Institutes of Health (NIH) Office of Dietary Supplements (ODS). This pilot study employed a proficiency material performance based approach. Subsequent to the study NIST hosted an invitational workshop in Gaithersburg, Maryland, February 21<sup>st</sup>, 2008 to discuss the program results. The major advantage of their program is that study participants are provided feedback regarding their performance relative to expected values and although a summary of results is distributed to all participants, laboratories are identified by code numbers known to them but not to other participants. The program model is based on having proficiency materials, both a known control and unknown are provided to each lab, however no method is provided. The results, which were so scattered a logarithmic scale was required to present all data on a single graph, clearly demonstrate that without provision of methods laboratories are not able to achieve consistent test results.

Based on BCIT's experience with the NIST program, subsequent discussions with NIST and ODS as well as our past experiences dating back to 1999; BCIT has reconsidered the approach being taken for laboratory proficiency testing. Consequently, BCIT's program will adopt elements of NIST's approach, specifically, providing a control and unknown, but will also provide a validated analytical method. In the absence of certified proficiency materials, BCIT will employ well-characterized materials (i.e. for which >10 measurements have been made) for use as control and unknown materials. With the two inter-collaborative studies now completed and all required materials acquired, BCIT can implement a **Quality Assurance Program for Laboratory Proficiency** with minimal additional support (see *Product Quality Initiative Recommendations for 2008/2009*).

The process of identifying botanicals of interest in Canada that also have International relevance was previously devised, and modeled after the NIH process of ingredient ranking (Saldanha *et al.*, *Journal of the AOAC International* Vol. 87:1, 2004; Betz *et al.*, *Anal Bioanal. Chem.*, 2007). The top ranking botanicals in 2004 were determined to be Ginseng, Goldenseal and Echinacea. Following this process, the Expert Advisory Committee (EAC) re-prioritized in 2006, when the top botanicals were determined to be Ginseng, Echinacea, Hawthorn and Cranberry. Based on this, efforts focussed on Ginseng, Goldenseal and Echinacea. It is recommended that re-evaluation of the priority list be conducted (see *Product Quality Initiative Recommendations for 2007/2008*).

As per the project proposal, BCIT undertook development of results validation data and a proficiency testing model for *Panax quinquefolius* (American Ginseng), *Hydrastis canadensis* (Goldenseal), and *Echinacea spp.*; detailed reports on each sub-project are found below.

### 3.2.1 Project B1: Ginseng Quality Assurance Program

There is significant commercial interest globally in North American ginseng (*Panax quinquefolius*). The active secondary metabolites of ginseng species responsible for its medicinal properties are considered to be the triterpene saponins, commonly known as ginsenosides. As such, the major six ginsenosides of interest: Rg<sub>1</sub>, Re, Rb<sub>1</sub>, Rc, Rb<sub>2</sub> and Rd are a common analytical target. These ginsenosides are relatively abundant in the root and rhizome compared to the other parts of the plant. The root and rhizome are commercially ground up to produce a pulverized ginseng powder that can be used as a raw material or as a powdered extract in either powder, tablet or capsule form.

High Performance Liquid Chromatography (HPLC) has been used extensively in the analysis of neutral ginsenosides but not acidic ginsenosides which are the malonylated forms (*m*-Rb<sub>1</sub>, *m*-Rc, *m*-Rb<sub>2</sub> and *m*-Rd) of Rb<sub>1</sub>, Rc, Rb<sub>2</sub> and Rd. These acidic protopanaxadiols (*m*-Rb<sub>1</sub>, *m*-Rc, *m*-Rb<sub>2</sub> and *m*-Rd) can be readily converted to their neutral counterparts by hydrolysis during common extraction procedures; however this hydrolysis is partial and not quantifiable. Consequently, this has resulted in an inability to produce consistent test results from lab to lab and caused frustration for growers, manufacturers, and scientists alike.

In response to the demand for a consistent, reproducible analytical method for Ginseng analysis, AOAC International convened an Expert Review Panel (ERP) in 2005 to decide on a suitable analytical method of analysis to undergo a Single Laboratory Validation (SLV) procedure as per AOAC guidelines. The ERP recommended pursuing a method that resulted in complete hydrolysis of malonyl ginsenosides to prevent further confounding analytical results. The ERP selected commercially available ginseng root, extracts and select dietary supplements to be used to validate the analytical method. Although there are published scientific studies that employ a base hydrolysis step that performs this conversion to assess total ginsenosides of a sample, none had undergone a comprehensive procedure that assures the validity of the method in determining and quantifying ginsenosides.

The purpose of this study was to demonstrate and establish the accuracy, repeatability and ruggedness of an HPLC-UV method for the determination of individual and total ginsenosides in North American ginseng raw materials and finished products. The analytical method selection, assessment and preliminary validation studies were completed in previous pilot projects. Analysis of the preliminary validation studies and Youden Ruggedness Trial (YRT), determined that the method selected was not adequately rugged to pass an SLV, let alone an inter-collaborative study. The Youden trial is a process through which the effect(s) of minute changes in conditions on the analytical outcomes of the method are identified. Specifically, the YRT demonstrated that the validated method was sensitive to changes when extraction solvent volume, extraction solvent composition and sonication time were altered. As such BCIT conducted an additional series of method optimization experiments beginning in November 2007.

These investigated the impact of changing specific method parameters to optimize the extraction efficiency and chromatographic resolution of the method for 8 different matrices. Parameters investigated included modification of the following: extraction solvent type, solvent composition, sonication time, omission of pre-concentration step, amount of base hydrolysis per sample, effects of base hydrolysis on different matrices, residual analysis, mobile phase composition, resolution of each ginsenosides, application of acid and buffered solvents, column temperature, column type and decrease the total elution time. This was intensive and more exhaustive than anticipated, and thus prolonged the study and the whole proficiency program itself.

In December 2007, BCIT conducted a full SLV in support of the new method. The development and optimization of the method were dependent on the availability of certified reference standards and the test samples materials. The acquisition of certified reference materials was a lengthy process due to the scarcity of reference standards available, not to mention the extensive isolation and verification of the reference materials required. Similarly, the collection of the adequate test samples materials was important to ensure that identical lots of each sample was obtained for the SLV, inter-collaborative study (IS) and lab proficiency program (LPP). This ensures all the samples are processed at the same manner, reducing variability (homogeneity issues).

The data generated from the SLV demonstrated that the validated method was fit for its intended purpose. In addition to this study, the Youden Ruggedness Trial (YRT) was repeated conducted on the method to ensure that small deviations in conditions would not have significant impact on analytical results. The results from the SLV and the YRT were completed in January 2008. This is the maximum level of certainty that can be achieved within a single laboratory and is considered to be the first step on the path to becoming an Official Method of Analysis.

While undertaking the SLV, BCIT prepared an Inter-collaborative study protocol template for Ginseng. It is a requirement that any Inter-collaborative study protocol be accepted through AOAC's peer-review process prior to initiating the study. Knowing the time delay can be considerable BCIT had provisional

acceptance of the protocol based on successful SLV completion. This allowed for minimal delay (2 weeks) between SLV completion and the Ginseng Inter-collaborative Study initiation. Without the Dietary Supplement Method Committee's approval of the Ginseng Inter-collaborative Study Protocol (Appendix E) the method cannot proceed through the process to become an Official Method of Analysis. By February 2008 the protocol was approved in full and a total of 13 out of 14 recruited laboratories participated.

Prior to analyzing the test samples, the laboratories were provided with practice samples to complete. The majority of the laboratories encountered minor problems following protocol. This resulted in having to request the laboratories re-test the practice samples until results were deemed acceptable. This caused another delay in the proposed timeline but resulted in very high level of participation with 12 laboratories continuing in the project. As most of the recruited laboratories provide professional analytical contract services in support of environmental, pharmaceutical and food safety industries, all were engaged with other projects and should be commended for their commitment to this project.

To date 11 out of 12 laboratories have submitted their test sample results and the statistical analysis is in the final stages. The majority of the data submitted from the participating laboratories has been compiled and statistically analyzed for potential outliers. Once the collaborative study is completed, an official manuscript will be submitted to the AOAC International Dietary Supplement Method Committee for consideration as Official First Action. The anticipated completion date for the study is June 2008.

All materials and a preliminary study design for a **Quality Assurance Program for Laboratory Proficiency** for analysis of ginseng as been developed and the recruitment of laboratory participants are on-going. Should additional funding become available to support a study coordinator, Ginseng Lab Proficiency Determinations, as well as Goldenseal (see section 4.2.2) could be initiated in the 2008/2009 fiscal year (see *Product Quality Initiative Recommendations for 2008/2010*). With existing funding from the BC Innovation Council, BCIT anticipates completing the first pilot of this new approach to proficiency testing by September 2008; a significant accomplishment of immediate relevance to industry which has been recently confronted with widespread ginseng adulteration issues.

### 3.2.2 Project B2: Goldenseal Quality Assurance Program

The perennial herb (*Hydrastis canadensis*) is a native to southeastern Canada, is frequently found in combination products and has been identified as an important Canadian agricultural commodity. As a consequence of the high value of this crop, there have been issues with economic adulteration by other species, such as Coptis. Consequently, the selection of the method includes a measure to ensure this common adulterant is not present. The addition of the "positive" marker canadine and "negative" marker palmatine differentiates this methodology from the current methods available from sources such as United State Pharmacopoeia. The method and SLV were prepared as a manuscript, accepted for publication in September 2007 and published in January 2008 in *Pharmaceutical Biology*, volume 46, number 1-2, pages 135-144. Building from this previous work, an existing protocol with modifications to maximize the use of collaborative data from participating labs was employed.

Extensive revision and statistical evaluation of laboratory data resulted in the development of an Inter-collaborative Study manuscript. Working with the AOAC International Subject matter expert and statistical advisor, the results of a multi-lab study were approved to be accepted as Official First Action. The inter-collaborative study manuscript was assigned *Official Methods* SM number **2008.04**. A notice of the adopted method was published in the AOAC magazine, *Inside Laboratory Management* April 2008 and will be published in "For Your Information" in the *AOAC Journal*. AOAC staff editors will prepare the manuscript for publication in the *Journal*. The method will be published as part of the collaborative study and will be included in the *Official Methods of Analysis* online at <http://eoma.aoac.org/> and in the next printed edition.

It was noted during this study that the method preparation was not ideal for berberine extraction from raw materials. The SLV and YRT did not demonstrate any significant variation due to extraction parameters; however, when moved to a multi-laboratory scenario the variation become significant. Despite acceptance as Official First Action by AOAC International, it was a marginal pass for raw materials. Thus, while awaiting AOAC deliberations over the statistical data of the collaborative study, BCIT engaged in an

optimization study in March-April 2008. Since this was a significant modification to the original workplan, statistical analysis of the data is not yet complete. It is recommended that the statistical analysis and a matrix extension, which is essentially a matrix specific SLV be re-initiated and completed (see *Product Quality Initiative Recommendations for 2008/2009*).

As described above, the approach to laboratory proficiency testing has been re-designed. The “control” and “unknown” materials have been prepared and will be included in the SLV to ensure >10 measurements are obtained to characterize the “proficiency” materials. Experience has also revealed that laboratories cannot engage in multiple studies simultaneously. Upon completion of the Ginseng Quality Assurance Program, specifically the Ginseng Lab Proficiency testing, Goldenseal Lab Proficiency testing could be conducted in Fall 2008 (see *Product Quality Initiative Recommendations for 2008/2009*).

### **3.2.3 Project B3: Echinacea Quality Assurance Program**

Echinacea products are among the most popular herbal products in North America. This perennial plant and its extracts are commonly used for the treatment and prevention of upper respiratory infections such as cold and flu. Of the various species of Echinacea, three species are commonly traded for medicinal preparations, *Echinacea pallida*, *E. angustifolia* and *E. purpurea*.

Clinical trials investigating Echinacea have yielded mixed results. Both positive and negative studies have been subject of criticism due to methodological flaws. One of the major obstacles identified for conclusive demonstration of the efficacy or non-efficacy of this herb is the lack of adequate chemical and botanical descriptions of the test articles used in the clinical trials. Each of the three species utilized in medicinal formulations contain significantly different chemical compositions. In addition to the chemical distinctions inherent in the species, chemical variability is also present within each of the species. As with many herbal products, variables such as the part of the plant used, the method of extraction and the season of harvest can affect the chemical composition of the plant and the resulting product. It is imperative that researchers investigating Echinacea and its products incorporate a careful evaluation of the phytochemicals in their samples to ensure that meaningful conclusions can be made.

Manufacturers and consumers of Echinacea preparations also face similar issues. Non-standardized material can result in the production of batches of the same product having completely different phytochemical compositions. Misidentification and/or adulteration can also occur. These problems clearly highlight the need for validated analytical methods to ensure product quality and botanical identity.

Although constituent isobutylamides, polysaccharides, glycoproteins and phenolics have been hypothesized as potential active ingredients, most of the published methods for ensuring identity and potency were developed to quantify the phenolic marker compounds. None of these methods have undergone a validation study as per the guidelines by AOAC International. A recent Expert Review Panel (ERP) was convened to review the published methods and determine which would be the most promising method to undergo further investigation. A High Performance Liquid Chromatography (HPLC) method originally developed by the Institute for Nutraceutical Advancement (INA) was considered the most promising candidate. At the time NSF and Midwest Research Institute volunteered to conduct extraction studies and conduct method validation, however this work was not done and both groups were informed that NNC through BCIT had initiated this project.

The investigation of the INA method was initiated. Sample and reference materials were obtained. It was desired that sample materials should reflect the common products available on the marketplace. It was also important to ensure sufficient quantity of identical lots of each sample was obtained for both a single laboratory validation (SLV) and an inter-collaborative study (IS) with 15 participating labs (maximum). Sufficient quantities of chemical reference materials were obtained, such that the same lot could be employed for SLV, inter-collaborative study and proficiency testing. The insistence in identical lots and the large amount of material required resulted in a delay in receipt of some materials as some items were on back order from the suppliers. After receiving the standards, further verification of the materials to determine their purity was conducted.

The original INA method utilized only a single standard from which total phenolics were quantified. The quantification of each phenolic was calculated through the use of response factors. Preliminary work with the method revealed that the response factors yielded neither precise nor accurate results. It was determined that each phenolic compound needed to be quantified using its own standard to ensure precise and accurate results would be obtained. Consequently, additional standards were obtained to allow for a full complement of reference materials to be provided to collaborative study participants.

A series of preliminary experiments on the INA method, using the acquired raw materials and extracts of Echinacea spp., revealed that the method as written had significant shortcomings. In addition to the erroneous results obtained from the use of response factors, poor accuracy and precision of the method could be attributed to sub-optimal extraction procedures and less than ideal chromatography. To address the former, an extraction study was designed and performed and to address the latter, a study to optimize the chromatography of the method designed and performed. This additional experimentation resulted in important revisions to the method.

The Youden Ruggedness Trial (YRT) was performed on the method and demonstrated that the method was robust and suitable for validation studies. An SLV study on the optimized method was performed for analysis of raw materials (root and aerial parts) and extracts as per AOAC International guidelines. The data from the SLV demonstrated the method was fit for its intended purpose. Following completion of the SLV, BCIT intended to conduct an inter-collaborative study and potential participants were recruited. There was resounding consensus from laboratories that only one inter-collaborative study could/should be pursued at a time, as the effort and contribution from the participants is significant. Furthermore, during recruitment of laboratories, a potential confounding analytical issue was raised. The stability of one of the phenolic compounds in extracts was questioned. Further investigations indicated that an enzyme in the Echinacea roots could cause cichoric acid to degrade over time in solution. It was considered prudent that further investigation of this was conducted.

An experiment to examine the extent of degradation and potential methods to circumvent degradation, if present, was developed and initiated. This new information will be incorporated into the SLV protocol developed to evaluate product formulations, by including a set of additional raw materials. Depending on the findings of the degradation experiment, changes to the method may be necessary and thus minor changes to the SLV protocol will occur. Until such time as the method has been finalized and the requisite laboratories are recruited and confirmed, test samples and standards will not be prepared and distributed.

BCIT has obtained all of the materials and is prepared to prepare and distribute them upon completion of the degradation study and SLV, expected to be complete by June 2008. Once this is finalized, an Echinacea Inter-collaborative Study can be scheduled (see *Product Quality Initiative Recommendations for 2008/2009*).

### **3.3 Canadian FFNHP Product Quality Program Business Plan**

Pilot Projects showed commitment by industry through laboratory participation and commitment of funds. These projects have been well-regarded within BC, nationally and internationally. Implementation of NHP regulations and the growing market demand for quality assurance has increased industry interest in validated methods, lab proficiency training and testing. The level of interest, support and commitment by stakeholders in implementing an expanded, formal program is evidenced by participation from various levels of government, academia and industry, representing regional, national and international organizations (e.g. Office Dietary Supplements) in the previous pilot projects.

Formal documentation of market needs and financial support options are being acquired to develop a **Canadian NHP Product Quality Program Business Plan** to continue the program of methods validation/lab proficiency over the long term. To date, an industry survey (**Appendix A**) has been conducted with 14 participants representing ingredient and finished product manufacturers. The results of this survey, provided in **Appendix B**, were disseminated at a Product Quality Workshop in Toronto on March 26<sup>th</sup>, 2008. During this meeting, industry associations representatives, scientists and companies

expressed interest in seeing the survey expanded in scope and provided very specific feedback to NPICenter.

The summary of this workshop can be found in **Appendix C**. The completed business plan is in preparation. Len Monheit of NPICenter was sub-contracted by BCIT to develop a business case to present to industry stakeholders. The success of making a business case for quality initiatives is a key factor in the success of implementing any business plan for the future of this initiative. A review of past (e.g. INA) and existing (e.g. AOAC International, NIST) attempts is being conducted including a SWOT analysis. The business case and preliminary Business Plan will be presented to Industry stakeholders in the coming months. A second workshop is recommended for October 2008 (see *Product Quality Initiative Recommendations for 2008/2009*).

#### **4.0 Product Quality Initiative Recommendations for 2008/2009**

Establish a regular annual review of the botanical priority list for the Canadian Product Quality Initiative, in alliance with international partners.

Formally implement a pilot program, Quality Assurance Program for Laboratory Proficiency, to evaluate the feasibility of long term program.

Further distribute the Executive Summary results of the NutriNet Project Canadian Product Quality Initiative at NNC and other industry meetings, workshops and conferences in hard copy and presentation formats.

Initiate Phase 1 of the Canadian Product Quality Program:

- Hire a part-time Canadian Product Quality Program Co-ordinator to oversee the Program
- Conduct a Quality Assurance Test for Laboratory Proficiency for North American Ginseng using the validated method and proficiency materials developed in 2007/2008.
- Conduct one workshop with the Expert Advisory Committee to review the botanical priority list.
- Conduct a Quality Assurance Test for Laboratory Proficiency for Goldenseal using the validated method and proficiency materials developed in 2007/2008.
- Conduct the an Echinacea Inter-collaborative Study with the proficiency materials developed in 2007/2008 , using the optimized method for phenolic marker compounds once the protocol has been approved by AOAC International
- Conduct a Quality Assurance Test for Laboratory Proficiency for Goldenseal using the validated method and proficiency materials developed in 2007/2008.

#### **5.0 List of Appendices**

Appendix A – NHP Industry Survey on Quality

Appendix B – Summary of NHP Survey Results

Appendix C – Product Quality Workshop Summary

# Appendix A – NHP Industry Survey on Quality

## NPI center Survey of NHP Companies for BCIT's Product Quality Initiative

1. Are your client's quality related expectations of you:

rising  
falling  
staying the same

How do you know?

2. Do you actively measure this? How?

To your organization, is quality control \_\_\_\_\_ as it was in previous years?

as important  
more important  
less important

3. What % of your staff operate in QC and QA?

4. Has this increased/decreased in the past 3 years?

5. How have your QC/QA related expenses fared in the past three years relative to sales?

stayed the same  
increased at a greater rate  
increased at a lesser rate  
decreased at a greater rate  
decreased at a lesser rate  
decreased while sales have increased  
increased while sales have decreased

6. Do you perform all of your testing in house or use contract analytical services?

7. If testing is performed in-house, do you follow any validation protocols? If using contract analytical services, does the laboratory provide documentation to support their method validation?

8. What kind of analytical QC testing do you perform?

Identity?  
Purity?  
Strength or analyte concentration?

9. Do you or the contract laboratory use reference materials (botanical voucher specimen) for analysis?

10. What do you do when a reference material is not available: \_\_\_\_\_  
Do you purchase analytical standards for instrument calibration?  
If so, where do you buy them?

11. How do assess purity of these standards?

12. What do you do when a chemical calibration standard is not available: \_\_\_\_\_

13. Rate the following as resources you might use for analytical method development, where 1 is least helpful, 10 is most helpful

USP/NF

EP (European Pharmacopoeia)

Ph EU

AHP

Other Compendia, please specify: e.g Japanese Pharmacopoeia, Pharmacopoeia of the People's Republic of China\_ \_\_\_\_\_

AOAC Official methods

Journal of the AOAC

Other Journal publications (such as Journal of Ag Food Chemistry?)

Search Engines:

Pubmed

Other search engines

Other resources:

INA MVP

ODS IBIDS (Bibliography of literature publications in DS)

AOCS Methods

USDA Methods

Forums and blogs: Specify \_\_\_\_\_

Tradeshows/conferences: specify \_\_\_\_\_

14. How significant is access to the community of NHP analytical scientists to your QA/QC program?

Critical

Valuable

Occasionally helpful

Rarely helpful or N/A

15. How frequently does your organization interact with external analytical scientists?

Frequently

Often

Rarely

Never

We would interact more if: \_\_\_\_\_ -

16 Are you or your Clients aware that AOAC International has an Official Methods program for dietary supplement and raw material testing?

17. To which compendia or authority do you reference your method selections? validation protocols?

18. How many lots of ingredients do you typically fail per year?  
What % of lots does this represent?

19. What is the (range? Or typical?) cost to reject an ingredient batch?

20. Do you feel ingredient quality is:  
getting poorer  
staying the same  
getting better?  
What are your observations based on?

21. What is the single, most significant thing adversely impacting quality in the marketplace?  
lack of validated and specific analytical methods  
lack of reference materials (certified reference materials or botanical voucher specimens) and chemical calibration standards  
lack of willingness to pay the price to properly validate methods to ensure rigor  
cost of reference materials and standards for instrument calibration

**BRANCH:** Ingredient Manufacturer

22. Do you feel quality and quality control of ingredients are 'appropriately' valued?

if no, What would it take for your clients to ascribe 'full' value?

23. What specifications do you use for your ingredients?

- 1) Compendial
- 2) In house
- 3) Other external (e.g. supplier specifications)
- 4) Other? Specify:

24. Do you have proprietary specifications for your ingredient(s)?  
Provide an example

25. Can a general commercial analytical lab test your product(s) to your specifications?

26. Have you tested (or had tested) competitor product? If yes, How did it test against your specifications?

27. Is there a minimum quality standard for the categories of ingredients you supply? If yes, what is it:\_\_\_\_\_. If no, Do you believe a minimum quality standard is possible for the categories of ingredients you supply?

28. Do you supply ingredients directly for clinical trials?

29. Have you been asked to expand product characterization for the materials you provide?

## **BRANCH 2: Finished Products Manufacturer**

30. How many lots of finished products do you reject per year? What %

31. For what % of your ingredient suppliers have you been dealing with for:

<1 year

1-3 years

3-5 years

5-10 years

>10 years

32. What is the average cost of a failed finished product batch?

33. Do you request pre-shipment samples? If yes, have you ever found variability or quality issues when comparing pre-shipment samples and production quantities?

34. Do you hold raw material inventory in quarantine pending testing? If yes, who pays freight costs associated with rejected materials?

35. Have you ever been in a potential conflict with an ingredient supplier over quality and test results of incoming ingredients? If yes, how was the conflict resolved?

36. Are industry Certificates of analysis adequate? If no, what areas are they typically deficient?

37. Have you ever tested and found a discrepancy in a C of A? If yes, what action did you take?

38. Do you have proprietary specifications for your product(s)?  
Provide an example

39. Can a general commercial analytical lab test your product(s) to your specifications?

40. Have you tested (or had tested) competitor product? How did it perform against its' specifications and/or label claim? How did it perform against your specifications?

41. Do you believe a minimum quality standard is possible for the categories of products you supply?

42. Do you supply products directly for clinical trials? If yes, Have you been asked to expand product characterization for the materials you provide?

**ALL back from branches:**

43. How much do you invest in quality on an annual basis? (Invest as separate from R&D)

44. What is your single largest quality-related expenditure?

45. Is there a portion of this expenditure that you think can be spent on a third-party venture, perhaps government supported?

B if yes, what %?

46. What tasks would you consider outsourcing?

47. Are there adequate qualified personnel available 'out there' to support your QA/QC needs? In which areas are there not?

48. Are there adequate training resources to develop QA/QC personnel? Which areas are deficient?

49. What is industry's biggest quality related need?

Thank you for your time and responses. NPIcenter and BCIT appreciate your contribution.

## **Appendix B – Summary of NHP Survey Results**

### **BCIT Product Quality Initiative: Survey Overview By Len Monheit, President & Editor, NPIcenter**

As we began preparing the business case report for the Nutrinet product quality initiative, we began to see signals that there was more transparency emerging along the value chain and that companies appeared more willing to share quality-related experiences with an objective body or group, intent on understanding quality, the cost of quality, and perhaps developing systems, tools and resources to allow industry to better self-police and to allow higher quality ingredient and finished product companies to differentiate themselves.

We therefore initiated a small-scale branched survey covering ingredient and finished product companies, discussing experiences and practices including sourcing, Certificates of Analysis, useful resources, deficiencies, perceived needs and changing behaviors and practices. In the small scale selection of companies for the survey, we leveraged existing relationships to get access to senior Quality Assurance and Regulatory personnel (typically VP or Senior Director) who were specifically asked to complete the survey. In select cases, our strongest relationships were asked to pass along the survey link to senior staff. One organization, (a Canadian ingredient company) felt unable to complete the survey as they felt it inadequately presented responses for them as an ingredient manufacturer who completely outsourced testing. In this and related cases, modification to survey questions with a focus on this type of operation would be recommended as next steps.

In general, we were pleased with the response and apparent openness of companies to discuss behaviors and experiences in this format. Of course, the results must be considered with agendas and individual company beliefs in mind. We were able, to a large part, to obtain the feedback, by leveraging NPIcenter relationships, and by guaranteeing the non-disclosure of individual responses except for non-attributed comments, and the disclosure for report purposes of aggregate responses. Almost all companies appeared interested in further dialogue about individual and aggregated responses, indicating to us that the level of frustration and exasperation at poor quality practices and poor quality value reaching a tipping or 'action' point, and perhaps the market was ready to really differentiate based on quality.

Significantly, all felt the survey to be worthwhile and would like further input. Other stakeholders presented with survey results or of knowledge of the survey have asked to participate or to expand survey scope.

## **The survey itself:**

There are a total of 14 respondents, of which 5 are ingredient companies, 9 are finished product manufacturers.

Of the ingredient companies, one is based in Canada, one is based in Europe, the other three are headquartered in the United States. Two ingredient participants have significant operations in China, all five have some sales activity in Canada, although for one, it is quite minimal. All five can be considered 'category leaders'.

On the finished product side, three are Canadian manufacturers selling to retail/pharma representing small, (1) and mid-to large (2). Two are US-based brand manufacturers with a strong Canadian line presence. One is a US-practitioner-based line with minimal Canadian market presence. Two are US-based direct marketers with strong presence in Canada in the same distribution channel. The final company is a leading retail brand/manufacturer operating in the US only.

The finished product manufacturers represent small companies (1), mid-size (3) and large (4).

The survey findings were presented in aggregate format at the workshop held March 26<sup>th</sup> in Toronto. Attendees included North American trade association representatives, leading scientists with expertise and interest in analytical and quality-related issues, and industry.

Specific findings:

- Are your client's quality-related expectations of you...

86% responded rising.

- Do you actively measure this?

64% responded yes.

- To your organization, is quality control \_\_\_\_\_ as it was in previous years?

43% responded more important

- How have your QC/QA related expenses fared in the past three years relative to sales?

57% responded increasing.

- For testing performed in house,

71% responded they used validation protocols

- Do you audit third party labs?

29% said no.

- All companies except one use reference materials
- 40% of companies do not currently purchase analytical standards
- All are aware of the AOAC method validation program.
- How many lots of ingredients do you typically fail per year?

Responses ranged from 0 to over 300 (5% of all lots).

- What is the typical cost to reject an ingredient batch?

Specific responses indicated up to over \$15000.

- No respondent felt that ingredient quality is getting poorer with about equal distribution feeling it was either improving or staying the same.
- Most ingredient companies felt that ingredient quality is not adequately valued.
- All ingredient companies had tested competitor product; most finding it poorer.
- Finished product manufacturers responded they were rejecting up to over 200 lots per year, and average costs of failed batches ranged from under \$5000 to \$75,000 per batch
- All companies in the survey have been dealing with ingredient companies for over 5 years.
- All manufacturers reported that they had been in a potential conflict with an ingredient supplier over quality and test results of incoming ingredients.
- All manufacturers reported that they felt that industry Certificates of Analysis are inadequate.
- All had tested and found a discrepancy in a C of A.

Several of the survey responses relate directly to the establishment of the business case for quality and future work as might be anticipated in an evolved or continuing product quality initiative. Some of the responses, such as a general lack of perceived need for outsourced services argue against readiness at this time for industry to appreciate its own needs and deficiencies in light of new GMPs and quality requirements, and so a broad-based education and communication platform is most likely also required.

## **Appendix C – Product Quality Workshop Summary**

### **Product Quality Initiative Workshop: Building a Sound Business Case**

March 26<sup>th</sup>, 2008, Toronto, ON, Canada

#### **Meeting Summary**

Prepared by J. H. Cardellina II, ODS, NIH

For at least a decade, the herbal natural health products/dietary supplement industry has repeatedly been embarrassed by reports, in both the scientific literature and the mainstream news media, that significant numbers of products in the marketplace do not contain the correct botanical or the correct or stated amount of the ingredient botanical(s). Despite this withering fire from its detractors, the industry has, in general, appeared reluctant to take appropriate steps to ensure the quality and content of its raw materials and products.

Following an evaluation of preliminary results of a Nutrinet survey of industry leaders and marketing managers on issues related to product quality initiatives, a workshop was convened in conjunction with the 5<sup>th</sup> Natural Health Products Research Conference in Toronto in March, 2008. A group of trade association representatives and expert scientists from various disciplines critical to botanical quality issues met to review the current state of affairs and lay the groundwork for building a business case for a quality initiative by the industry.

The preliminary survey results were used to stimulate and focus the discussion. Some of the survey results were quite telling, even if they represent a rather small sampling. In the area of analytical laboratories and services, the following data are relevant:

- 100% of respondents were aware of the AOAC Methods Validation Program;
- respondents reported 5-30% of company personnel were involved in QA/QC; but
- 30% of respondents used only contract analytical services for QA/QC;
- 20% did not audit contract labs [Len: is this 2/3 of those using contract services, i.e., 20 of the same 30% in the bullet above? Or is it 20% of the 30% = 6% of the total?]; and
- 20% of those using in house analytical laboratories did not validate methods.

Useful insight also emerged from questions about ingredient supplies:

- 0-300 lots (average ~2%) fail QA/QC;
- the cost of failing an ingredient lot ranges from \$1000-15000;
- 45% said ingredient quality was constant, while 33% felt it was improving; and
- 0.2-4M dollars is spent annually on quality.

Respondents also identified the following needs for the industry:

- good, meaningful specifications for raw materials;
- suppliers who meet those standards;

- certified laboratories; and
- risk management.

The central challenge in the discussion was defining drivers or selling points for a convincing business case. Three possible approaches were considered:

1. Fear of Failure. This selling point emphasizes the negative. Given the uncertain supply sources and pipelines in several parts of the world, questionable certificates of authenticity and/or analysis, and repeated instances of contaminated, adulterated or incorrect botanical raw materials or extracts, the case for a quality initiative might play on a company executive's fear that his/her company could be implicated in such an imbroglio. While many workshop attendees felt that this was, logically and rationally, a sufficient justification for a product quality initiative, it is clear that the numerous episodes that have already been publicized have apparently not been sufficient drivers for the captains of this industry. The group felt that, at least in the US, the advent of cGMPs might be a driver for a quality initiative, but this would fall under this approach.
2. Risk Management. This is a slightly more positive variant of the first concept. Instead of focusing on failure, though, this approach is an emphasis on avoidance of failure and minimization of risk and subsequent potential liability to a company. If a company undertakes steps to ensure the quality and integrity of its botanical ingredient supply chain, it will reduce, or actually eliminate, the possibility of an inferior or substandard finished product. In turn, the company reduces substantially its risk of adverse events related to its products and ensuing liability issues.
3. Grow Market Share. This positive view of a quality initiative holds that a company that consistently produces a quality product will present consumers with safe and efficacious goods. This should contribute significantly to increases in market share of a company's products. Despite the positive approach, this point may be the weakest argument, given market data showing that consumers are largely driven by price in choosing botanical products.

An important aspect of any business case for a quality initiative would have to consider and compare the (certain) cost of such an initiative versus the cost of product 'failure' (possible for any given company, but not certain in any case). Two related corollary questions are:

- What is the gain from or advantage of a quality initiative, i.e., what is the effect on the bottom line?
- How can consumers be made to perceive the differences in product quality? This speaks to price-driven consumer decisions.

After a spirited, broad discussion of the many issues or considerations relevant to any quality initiative, the attendees divided into two groups charged with developing some specific steps to take or potential components of an action plan. The first group identified three issues critical to any such plan:

1. *Consumer Education.* Quality-committed companies will need a mechanism to differentiate their products from others to consumers.
2. *Laboratory Certification.* With all the discussion of the need for validated analytical methods and certified reference standards, coupled with the results of the survey, the group felt that the industry could use -draft standards and an education program to educate industry laboratories on sampling, sample preparation and analytical methods. Such standards could also guide auditing of contract laboratories by client companies.
3. *Supply Chain.* The discussants felt strongly that any quality initiative would have to include a capability to trace the supply chain of botanical ingredients back to the fields in which they grew.

The other group focused on the need to bring QA/QC units in the industry up to speed. A two stage education program was recommended, with the first stage consisting of web-based training programs and guidance; this would be followed up by short courses conducted by expert third parties. The web-based material could be developed from the ODS Analytical Program experience, and the training might best be accomplished by veteran contract laboratory personnel. The group went so far as to consider sources of funding for this project, and recommended considering the dairy industry model.

The group briefly discussed what steps to take next:

1. The results of the full industry survey need to be evaluated, organized, disseminated and discussed, particularly as they reflect on the concept of an industry initiative on quality.
2. All the trade associations need to buy into this initiative; that accomplished, a more detailed role for those associations needs to be defined.
3. Perhaps most important, a second meeting, one focusing on industry representatives (marketing, management) will be needed to promote the initiative and gauge the industry's response and level of enthusiasm. A planning teleconference with trade association representatives would seem the best approach to organize the next meeting.