Overview
The United States Pharmacopeial Convention (USP) held the 2020 USP Dietary Supplements (DS) Stakeholder Forum (SF) on May 28, 2020. For the first time, the event was held in an all-virtual format due to the COVID-19 pandemic. The DS SF brought together leaders from industry, regulatory agencies, and USP to exchange information, gather input from stakeholders, address stakeholder questions and concerns, and ultimately improve USP standards. There were more than 250 attendees, and they were able to participate by submitting comments and questions for the speakers in real-time. Dr. Holly Johnson of the American Herbal Products Association served as Chair of the SF.

Response to COVID-19 Pandemic
In the first session, speakers discussed Dietary Supplements and the COVID-19 Pandemic. Dr. Phillip Nguyen and Dr. Hellen Oketch of USP gave an overview of the USP Response to the Public Health Crisis. USP adapted quickly to the pandemic so the organization could deliver on its public health mission. For example, USP responded to the shortage of hand sanitizer, an essential product, by developing a Hand Sanitizer Toolkit that industry and other stakeholders can use to produce their own hand sanitizer for their staff. USP is providing the Toolkit as a free resource, available on its website.

USP is working on a variety of initiatives to address the critical issue of supply chain vulnerability. For example, efforts have included supporting the production of quality medical products needed in the pandemic, mitigating supply chain problems through standard-setting, and addressing the public health need for transparency regarding the risk of shortages.

Within the DS community, USP is offering support by streamlining the website for the Dietary Supplements Compendium and investigating which new DS monographs would be most useful to stakeholders. The Chair and other attendees agreed to provide suggestions for new monographs, and the Chair noted that consumer demand has increased for products marketed for immune health.

The first session also included a Panel Discussion, Supplement Industry Experiences, Priorities, Gaps, and Needs for Public Standards. The panelists represented five national trade associations for the DS industry:
- Mr. Michael McGuffin, American Herbal Products Association (AHPA)
- Dr. Jay Sirois, Consumer Healthcare Products Association (CHPA)
- Mr. Steve Mister, Council for Responsible Nutrition (CRN)
- Dr. Daniel Fabricant, Natural Products Association (NPA)
- Mr. Loren Israelsen, United Natural Products Alliance (UNPA)

The panelists described many challenges that their member companies are experiencing. Companies are trying to determine how they can 1) respond to supply chain problems such as difficulty getting raw materials, 2) keep production up while demand is rising and production lines are moving slower for worker safety, 3) ensure that DS retailers are recognized as essential businesses, and 4) decide whether a product lot should be quarantined if an employee was ill while working on the production line.

Panelists raised some additional questions, such as how can a company qualify a new supplier without making an in-person visit, and what are the implications of the US Food and Drug Administration (FDA) announcement that the agency is currently suspending inspections. All five panelists said their member companies are very concerned about protecting their employees from COVID-19. Companies want information and guidance on how to screen their staff, provide good-quality personal protective equipment (PPE), and modify their operations to reduce risk.
**Pyrrolizidine Alkaloids as Contaminants**

The second session, *Contaminants – Pyrrolizidine Alkaloids*, featured three speakers with expertise on this topic. Dr. Sandeep Putty of USP explained that pyrrolizidine alkaloids (PAs) occur naturally in over 6,000 plant species, and many PAs are toxic to the liver as well as the lungs and blood vessels if the individual’s exposure is prolonged. Various DS products can contain PAs as contaminants, even if the main ingredients in the DS do not contain PAs naturally. Dr. Troy Smillie explained that most herbs and teas used in DS products do not naturally contain PAs, but they can become contaminated with nuisance plants that do contain PAs. This can happen during harvesting when the plant species get mixed together inadvertently; this can be reduced or prevented if farmers use Good Agricultural Collection Practices.

The third speaker, Mr. James Neal-Kababick, noted that regulators and scientists recognized the need for PA standards in 2000. However, 20 years have passed, and the FDA has not produced any PA standards or official methods for PA analysis. USP plans to develop a general chapter that would explore the current limits for PAs set by regulatory authorities. For instance, the World Health Organization has recommended minimizing exposure to toxic, unsaturated PAs, and several European countries have set maximum thresholds of 1 microgram of PAs daily. The lack of reference standards is a significant challenge in the work on PAs, and more research is needed to determine the levels of PAs that consumers are currently obtaining from the diet.

During the Question & Answer session, speakers made the following points:

- **PA testing requirements:**
  - The European Union (EU) is proposing PA testing of DS products. In the US, it is vital to keep in mind that DS Good Manufacturing Practices (GMPs) state that products need to be free from reasonably anticipated contaminants. PAs are reasonably anticipated contaminants.
  - Required PA testing will probably start with the EU member states, but will not stop with the EU. Other countries will look at PAs too because they will see that this issue is important.

- **Plans for USP standards:**
  - The USP informational general chapter on PAs is expected to be submitted to PF in Q3/4 2020.
  - Shortly after submission of the informational general chapter is submitted, USP plans to develop a second general chapter to provide methods of analysis as a tool for the DS community.
  - In the long term, USP plans to develop PA reference standards to support its general chapter(s).

**Standards for Hemp and Cannabidiol**

In the third session, *Standards and Information for Hemp and Cannabidiol (CBD)*, attendees heard from three speakers. First, Dr. Robin Marles, Chair of the USP Botanical Dietary Supplements Expert Committee, noted that the DS industry is facing some major challenges because there are no public standards for foods and DS that contain hemp. Also, it is important to differentiate hemp products from cannabis products containing more than 0.3% tetrahydrocannabinol (THC). FDA has determined that products containing CBD or THC cannot be marketed as DS, despite the presence of these CBD containing products in the market. A major concern is that the quality of these products varies greatly, and other concerns include pesticide residues, microbial load, and the need for accurate labeling of hemp and CBD products.

USP recently published an article on cannabis inflorescence in the *Journal of Natural Products*; the article provides comprehensive, detailed information including quality parameters, with open access. USP has an Expert Panel on cannabis and is currently considering the idea of forming a second cannabis Expert Panel; the new panel would potentially perform a comprehensive, evidence-based safety review of oral CBD.

Dr. David Sommer described the experience of his company, Bluebird Botanicals, with developing hemp specifications. They sent hemp samples to various labs for testing but found that this was costly. Identity testing is necessary, and chain of custody is important, he noted. Ms. Laura Eder of Mile High Labs noted that USP could help level the playing field by publishing standards. Consistent use of nomenclature and analytical methods would be helpful as well. Ms. Eder also made the points that hemp as a starting material is variable, and companies are only as good as the lab they use for testing their product.

During the Question & Answer session, speakers made the following points:

- Testing of raw materials and products
When testing raw material for botanicals, one can take a “family of monographs” approach. Cannabis inflorescence is the bud of the plant, the source material. If you test this, you will need less testing later on. This approach works very well with many botanicals. If the bud meets the specification, you are in good shape after that.

When testing a hemp supplement, if it is oil-based, the carrier oil may make up more than 90% of the product. The oil has to be held to the same standard as the hemp.

**Nomenclature**
- The challenge is that many terms, such as broad-spectrum and full-spectrum, are widely used in industry but are interpreted in various different ways.
- It is important to find out if there is any consensus on the meaning of a term, and then standardize what it means.

**Specifications and Quality Control**

In the fourth session, *Specifications: How Industry Interprets USP’s Standards in Monographs, and Regulatory Requirements*, attendees heard three speakers who discussed the need for a strong quality control program. Dr. Stephen Andruski of USP focused on DS quality considerations. He noted that there are disconnects between the monographs and industry utilization of monograph methods. Starting with raw materials, a DS company may base their specification on a Certificate of Analysis (CoA), but industry needs to be critical of what the supplier is telling them. He suggested that companies use the USP monograph as a way of judging the CoA. Companies should insist on buying materials that comply with the USP monograph, he added.

Ms. Larisa Pavlik, a former FDA investigator, emphasized that companies should have written specifications in place. One of the top five reasons for citations issued by the FDA in the past four years was the lack of a finished product specification. The most common mistake that companies make, she added, is to interpret “purity” as indicating microbiology results. Actually, purity is the amount of the element/molecule of interest among the other substances. Mr. Robert Durkin of Arnall Golden Gregory LLP noted that quality has to be built into a product, beginning with the starting materials and continuing through all the steps in the manufacturing process. He described a Production and Process Control System as a means to achieve quality.

During the Question & Answer session, speakers made the following points:

- **Dosage form performance characteristics:**
  - Performance requirements vary from product to product. The intent is to use a quality test to show that the product is the same from batch to batch and that the materials in the product are actually getting released into the body and absorbed.

- **Monograph acceptance ranges:**
  - The acceptance ranges are based on the idea that the product is formulated to 100%. Companies use method variability and say that 98% is acceptable. Analytical variability is captured. You should formulate at over 100% to be sure you hit 100%.
  - If a firm claims compliance with USP, they have to meet the monograph requirements if the company does not want their product to be misbranded. If they want to aim for over 100%, it has to be planned, not by accident.

- **FDA’s distinction between the terms “valid” and “validated”:**
  - A company needs to use a method that is valid based on scientific principles, i.e., the method can accomplish what it is expected to do. The method has to be valid but not validated.

**Clean Labeling and Quality Metrics**

In the fifth session, Dr. Gabriel Giancaspro of USP described the concept of a “clean label” on food products and explained that the clean-label concept is consumer language, not a scientific term. The term is ill-defined, but it reflects the preference of some consumers for ingredients with familiar names, often words that sound “natural” rather than artificial or chemical. While consumers may think that an ingredient sounds harmful, it may be GRAS (generally recognized as safe), Dr. Giancaspro noted.

Dr. Barry Ritz of Atrium Innovations explained that consumers are looking for clean labels on DS bottles as well, and this means they are avoiding ingredients such as MSG, high-fructose corn syrup, gluten, sodium benzoate, and artificial flavors, colors, and sweeteners. The clean label concept aligns well with third-party verification, Dr. Ritz said, but he noted that the available certification programs fall short of covering the comprehensive needs of a clean-label
certification. Dr. Giancaspro added that USP wants to hear from stakeholders about this issue as well as any other issues affecting the DS community. As USP continues to revise and update its standards, the organization wants to know what the DS community needs.

During the Question & Answer session, speakers made the following points:
  o A stakeholder interpreted, FDA has zero-tolerance for pesticides in DS, and if action levels are exceeded, the FDA may issue a warning.
  o There is also a huge debate on what is meant by “zero” since the limit of detection (LOD) varies according to the method used. In the past, the LOD was typically one part per million (ppm), but now the analyses can measure smaller and smaller quantities.

  • Clean label concept in relation to standards:
    o The clean label would have to be GMP compliant and the labeling accurate. The concept means that the manufacturer has done everything it can to avoid ingredients that are not needed.

**Conclusion**
Throughout the SF meeting, USP expressed interest in hearing about stakeholder concerns, challenges, and feedback. USP is dedicated to serving the DS community by providing useful quality standards and offering a forum for discussion and collaboration. In closing, USP encouraged all stakeholders to send in their questions, comments, and suggestions at any time to us at DietarySciStaff@usp.org