Applying Modern Toxicology to Botanical Dietary Supplements

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SOT Webinar
23 April 2020
Outline

• Background on the Botanical Safety Consortium (BSC)
• Goals and Objectives
• Structure and management
• Next steps and opportunities
Conflict of interest

No conflicts of interest to declare
Botanicals are complex

- Plants are chemical factories
  - 28,187 plant species recorded as being of medicinal use*
    - Very few (16%) cited in regulatory publications
  - Secondary metabolites exhibit a broad range of bioactivities
  - Many bioactive constituents from plants have been exploited by humans for use as pesticides, pharmaceuticals, or consumer products

Botanical products are variable

<table>
<thead>
<tr>
<th>Source material</th>
<th>Processing</th>
<th>Finished product</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plant part (aerial, root, whole plant, leaf, seed)</td>
<td>Extraction process*</td>
<td>Manufacturing process*</td>
<td>Dose (use pattern)</td>
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<tr>
<td>Climate</td>
<td>Solvents</td>
<td>Excipients</td>
<td>Length of dosing</td>
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<tr>
<td>Soil conditions</td>
<td>Adulteration</td>
<td>Combination with other botanicals</td>
<td>Life-stage</td>
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<tr>
<td>Season</td>
<td>Contamination</td>
<td>Adulteration</td>
<td>Disease-state</td>
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<tr>
<td>Plant maturity</td>
<td>Storage/shipping conditions</td>
<td>Contamination</td>
<td>Nutritional status</td>
</tr>
<tr>
<td>Contaminants</td>
<td></td>
<td>Storage/shipping conditions</td>
<td>Background genetics</td>
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<tr>
<td>(mold, pesticides, metals)</td>
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<td>Co-exposures</td>
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<tr>
<td>Co-harvested materials (other plants, soil)</td>
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<tr>
<td>Adulteration</td>
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</tbody>
</table>

*Proprietary

**Notes:**
- Manufacturing process includes extraction process and other proprietary processes.
- Storage/shipping conditions can affect the stability and safety of the final product.
- Contaminants can come from various sources, including harvested materials and manufacturing processes.
- Co-exposures refer to potential interactions between the botanical product and other substances or conditions.

**Images:**
- Peak from the extraction process.
- Manufacturing equipment.
- Finished product (capsules).
- Botanical safety consortium logo.

**Background Information:**
- Genetics can influence the composition and properties of botanicals.
- Co-exposures can affect the efficacy and safety of botanical products.
- Source materials can be influenced by environmental factors such as climate and soil conditions.
- Plant maturity can affect the quality and efficacy of the botanical product.
- Contaminants, such as mold, pesticides, and metals, can be present in source materials and during processing.

**Manufacturing Process:**
- The extraction process involves isolating active compounds from the botanical material.
- Solvents are often used to facilitate extraction.
- Adulteration and contamination can occur during extraction.

**Finished Product:**
- Manufacturing processes involve further processing of the extracted compounds.
- Excipients are added to improve the physical properties of the final product.
- Combination with other botanicals can affect the final product's efficacy and safety.
- Storage/shipping conditions are crucial for maintaining product quality.

**Exposure:**
- Dose and use pattern are critical for determining the appropriate dosage and frequency.
- Length of dosing affects the duration of treatment.
- Life-stage considerations are important for pediatric and geriatric populations.
- Disease-state influences the selection of botanical products.
- Nutritional status can interact with botanical products, affecting absorption and efficacy.
- Background genetics can influence individual responses to botanical treatments.
- Co-exposures can interact with botanical products, requiring careful consideration.

**Key Points:**
- Botanical products are variable due to factors throughout the product lifecycle.
- Understanding these variables is crucial for ensuring the safety and efficacy of botanical products.
- Standardization and regulation of botanical products are necessary to address these variables.

**Additional Resources:**
- More comprehensive information on botanical product variability can be found in various scientific journals and regulatory guidelines.
- Professional organizations, such as the Botanical Safety Consortium, provide resources and guidelines for the safe use of botanical products.

**References:**
- [Botanical Safety Consortium](https://www.botanicsafety.org)
- [Regulatory Guidelines for Herbal Medicines](https://example.com/regulations)
Consumption is widespread*

- ~18% of adults in the U.S. used non-vitamin, non-mineral dietary supplements in the past 12 months according to the 2012 National Health Interview Survey
- U.S. sales of botanicals topped 8 billion dollars in 2017
- Recommended doses can be in the range of 100s - 1000s mg per day

A System Built for Single Chemicals

- Drugs and pesticides are the most highly regulated industries
- Our toxicity testing, safety evaluation, and risk assessment processes were built around and optimized for single chemicals
- How do botanicals compare to drugs and pesticides?

**Drugs**
- Simple and consistent
- Regulatory structure aimed at ensuring safety
- Assumed to be harmful until proven safe
- Biological activity is associated with the constituent

**Botanicals**
- Complex and variable
- Regulatory structure aimed at ensuring access
- Assumed to be safe until proven harmful
- Biological activity is associated with the whole mixture
Safety concerns

• The label may not reflect the content!
  • Efficacy-driven adulteration
  • Economic adulteration
The Problem…

• Limited botanical safety assessment toolkit and framework
  1) Compile history-of-use data.
  2) Are there significant safety gaps?
  3) If no, safety substantiation is complete.
  4) If yes, proceed with traditional in vivo toxicity testing (cost, time, and ethical concerns)

• Lack of global consensus regarding what constitutes sufficient safety substantiation for a botanical

• Global botanical safety requirements are diverse and varied

• Very little toxicity data on most botanicals currently on the market
"...as with other commodities that the agency regulates, it's critical that FDA continue to work closely with our partners in industry to achieve our primary goal of protecting public health and safety. As the dietary supplement industry develops new products and ingredients, advances new delivery systems and innovates in other ways, the FDA must do more to leverage its existing resources and authorities to evaluate these products. This requires collaborative research and a shared understanding. I'm pleased to announce that we've recently created the Botanical Safety Consortium, a public-private partnership that will gather leading scientific minds from industry, academia and government to promote scientific advances in evaluating the safety of botanical ingredients and mixtures in dietary supplements. This group will look at novel ways to use cutting-edge toxicology tools, including alternatives to animal testing, to promote the goals of safety and effectiveness we share with consumers and other stakeholders."
FDA Announces Convening of the Botanical Safety Consortium

Constituent Update

November 14, 2019

The U.S. Food and Drug Administration (FDA) announced today that the Botanical Safety Consortium (BSC) has formally been convened. This milestone is the result of a Memorandum of Understanding (MOU) that was recently signed between the FDA, the National Institutes of Health’s National Institute of Environmental Health Sciences, and the Health and Environmental Sciences Institute (HESI). This MOU establishes the framework for the BSC.

The BSC was originally announced in the FDA’s February 2019 statement on the agency’s new efforts to strengthen regulation of dietary supplements through modernization and reform. The Consortium’s mission is to provide a forum for scientists from government, academia, consumer health groups, industry, and non-profit organizations to work collaboratively to generate a sound scientific basis for integrating existing safety data and the latest toxicology tools to evaluate botanical safety in dietary supplements. With the execution of the MOU, specific guidelines for membership and participation in the BSC will be established by early 2020.
Mission of the Botanical Safety Consortium

To enhance the botanical safety toolkit and bring clarity to botanical dietary ingredient assessments for manufacturers and regulators.
Botanical Safety Consortium Objectives

1. Engage with a broad group of global stakeholders to leverage the best scientific approaches.
2. Establish the appropriate levels of chemical characterization for complex botanical substances.
3. Identify pragmatic, fit-for-purpose in vitro & in silico assays to evaluate botanical safety.
4. Evaluate the application of these tools via comparison to the currently available safety information.
5. Integrate these tools and approaches into a framework that will facilitate robust evaluation of botanical substances.
**Strategy**

- **Identify Botanical Candidates**
  - Develop a list of botanical reference substances that have available safety information
  - Create a reference substance library

- **Substance Characterization**
  - Utilize non-targeted and targeted analytical approaches and chemometrics for adequate characterization
  - Develop strategies to address variability between botanical substances for safety assessment

- **Identify Suitable Approaches & Assays**
  - Identify suitable in vitro/in silico assays that are within the identified domain of applicability for botanicals

- **Evaluation of Library**
  - Evaluate the botanical reference substances in a battery of selected in vitro/in silico assays
  - Perform suitable data analysis
  - Compare the results from the testing battery to existing animal and human safety data

- **Reporting**
  - Make data publicly available
  - Provide recommendations based on learnings
Botanical Safety Consortium Structure
Botanical Safety Consortium Structure

**General Public:** Open to all. Access to materials via the website and the opportunity to attend the Annual Meeting.

**Steering Committee:** This group is comprised of the overall consortium chairs, liaisons from the Technical Working Groups, and two at-large members from the Stakeholder Council.

**Stakeholder Council:** Comprised of interested parties that provide a justification statement (private sector must provide a financial contribution.) Members receive an invitation to the Annual Meeting and will be placed on a distribution list for quarterly newsletters and webinars. Members will also be able to submit feedback and project ideas.

**Technical Working Groups:** These members are selected from the Stakeholder Council via an application process reviewed by the Steering Committee and appropriate existing Technical Working Group members.
Inaugural Steering Committee

Cynthia Rider
NIEHS / NTP

Cara Welch
FDA/ODSP

Joe Dever
Amway

Dan Marsman
Procter & Gamble

James Griffiths
CRN

Stefan Gafner
ABC

Michelle Embry
HESI

Connie Mitchell
HESI
Technical Working Groups

• Chemical analysis
• Priority endpoints/systems to evaluate
  • Genotoxicity
  • Hepatotoxicity
  • Developmental and reproductive toxicity
  • Systemic toxicity
  • Cardiotoxicity*
• Data analysis

Selected based on:
• Severity of associated disease (e.g., genotoxicity and cancer, cardiotoxicity and heart disease)
• Adverse event reporting and research on botanicals (e.g., hepatotoxicity)
• Building bridges with current gold standard - animal safety data (e.g., in vitro systemic toxicity vs repeat dose in vivo)
• Availability of alternative assays to measure effects in that system

*To be formed later in 2020
Technical Working Groups

- Developmental and Reproductive Toxicity (DART)
- Genotoxicity
- Cardiotoxicity
- Hepatotoxicity / ADME
- Systemic Toxicity

Chemical Analysis
Data Analysis
Technical Working Groups – Current status

- Formation of teams of experts for each of the focus areas
  - Balance of industry, government, and academic scientists
  - Global representation, where possible
- Refining goals and objectives
- Reviewing the state of the science on botanicals research in each of the key areas
What the BSC is.....and is not....

- Focused on *in vitro* and *in silico* approaches
- Dedicated to advancing the science of botanical safety evaluation
- Aimed at providing recommendations for tools and technologies that are useful in evaluating botanical safety

- Focused on generating new *in vivo* toxicity data
- Involved in regulatory decisions or guidance
- Aimed at developing additional testing requirements for botanical products
1st BSC (virtual) Annual Meeting
29 May 2020
9:00 – 12:45 (US Eastern)

Meeting Objectives:

- Provide information on the structure, mission, objectives, and strategy of the BSC
- Share an overview of the current Technical Working Group (TWG) plans
- Recruit new BSC members
- Solicit input into current scientific challenges and opportunities related to botanical dietary supplement safety

Visit www.botanicalsafetyconsortium.org to register!
Agenda

9:00  Introductions & Objectives
     Michelle Embry, HESI

9:15  Botanical Safety: Discovering Common Struggles, Needs, and Solutions
     Dan Marsman, Procter & Gamble

9:35  The BSC as a public-private partnership: HESI’s involvement in the BSC
     Connie Mitchell & Michelle Embry, HESI

10:05 Research on Botanical Safety at the National Toxicology Program
     Cynthia Rider, NIEHS / NTP

10:25 The Modernization of FDA’s Dietary Supplement Program: the Botanical Safety Consortium
     Cara Welch, USFDA CFSAN

10:45 What are the objectives of the BSC and how does it plan to meet them?
     Jim Griffiths, CRN

11:00 Botanical Ingredient Characterization; a tale of more than one thousand and one compounds
     Stefan Gafner, ABC

11:30 Avengers Assemble! A Day in the Life of the BSC Technical Working Groups
     Joe Dever, Amway

12:00 Conclusions

12:15 Open discussion / Q&A

12:45 Adjourn
BSC Timeline

**Late April**
- SOT Webinar
- Continued recruitment of members

**Late May**
- Survey literature for suitable assays and already tested botanicals
- Annual Meeting!

**August**
- Development of detailed timelines for working groups
- Coordination between groups to share information
- Potential development of publications
- Update webinar for Stakeholders
- ICSB Meeting – Oxford, MS

**November**
- Perform scoping / in silico work to prioritize in vitro assays
- Exploratory / method development work as needed

**May**
- Working group objectives refined
- Additional experts contacted
- Continued membership recruitment

**June → July**
- Perform scoping / in silico work to prioritize in vitro assays
- Exploratory / method development work as needed

**Sept → October**
- Finalize list of candidate assays and botanicals

**2021**
- Initiate in vitro assay work with botanicals library
Thanks to Cynthia Rider & Joe Dever for slides