Development of a Consensus Approach for Botanical Safety Evaluation.

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Introduction

Continued interest in botanicals in a variety of consumer care products, coupled with a strong desire to eliminate animal testing, presents some unique challenges for this category of ingredients. There are various approaches for safety assessment of botanicals intended for use in food/dietary supplements, from reliance on capturing adverse events via post-market surveillance, to tiered approaches building an assessment based on existing data and new data generated specifically to meet safety assessment needs. For example, critical data endpoints that are often lacking may include raw material characterization, developmental and reproductive toxicity, genotoxicity/carcinogenicity testing, and/or ADME considerations (including herb-drug and herb-herb interactions).

To expand on the topic of botanical safety assessments, a scientific session entitled, “Botanical safety evaluation in the era of alternatives,” was held at the 53rd Congress of the European Societies of Toxicology (Eurotox) held in Bratislava, Slovakia (September 10-13, 2017). This session was followed by a Roundtable Event which built on the approach elements shared bypresenters during the scientific session. The intent of the roundtable was to review the decision tree (Figure 1) approach for botanical evaluation which was shared in the scientific session. The roundtable panel and participants were used to address the objectives below:

- Discuss and provide perspective on the decision tree approach (i.e., is there agreement in the key elements that are needed to build a robust botanical safety evaluation)
- Highlight and debate any vulnerabilities in the decision tree approach
- Share additional perspectives to ensure this end-to-safety approach is sufficient and actionable

Key Elements of Botanical Safety Decision Tree Approach

Following accurate identification and advanced multi-detector analytical characterization of botanical raw materials, in-silico approaches can be used to address safety data gaps and inform need for further studies based on the following:

- Similarity comparisons to commonly consumed foods or botanicals with a well-established safety profile
- Systematic evaluation for toxicity data utilizing structure-activity relationships as necessary
- Comparison to established thresholds of toxicological concern (TTC) in absence of data
- Where safety endpoint gaps are identified which cannot be resolved without in-vitro or in-vivo studies, the botanical compositional data are critical to inform on study design

During the Roundtable event, and based on the above objectives, a number of consensus statements were developed and aligned upon and are presented in this poster.

Decision Tree Approach – Botanical Safety Evaluation

Technical Rationale

CONSENSUS STATEMENT # 1: Critical to the safety evaluation of a botanical is clarity on the identity of the plant and plant part, along with an understanding of the constituents, method of botanical preparation and extraction, and final daily dose.

- Characterization; how much?
- Relevance to the market (is the test ingredient relevant to what is in marketplace)
- Whole vs. isolated active principle (deconstructionist approach vs. whole extract)
- Understanding contamination (chemical, biological, process-related)

CONSENSUS STATEMENT # 2: When applying a weight of evidence approach, evaluate the relative robustness of a review/evaluation, which could range from high to low dependent on the source and quality of the review and supporting references, the scientific quality of the studies that have been conducted, and data sources supporting history of use.

- Peer-reviewed scientific literature (assess objective reporting) with anecdotal evidence
- Traditional use and anecdotal reports, single case reports (potentially subjective reporting)

CONSENSUS STATEMENT # 3: The safety of a botanical cannot be judged based solely on a history of food use unless it can be demonstrated that a comparable composition is ingested on a regular basis across a broad geographic and demographic populations.

- "Sufficient similarity" or phytoequivalence approach (e.g. does test article represent other available products with similar labels). What needs to be true from the human use experience to be considered as sufficiently similar.
- Botanicals as dietary supplements; Dietary supplements as food (first assumption = low risk)

CONSENSUS STATEMENT # 4: In the assessment of a botanical, it is misleading to assume that a history of human use addresses all aspects of safety.

- Traditional "History of Use" vs. Significant "History of Use" (breath and depth of exposure)
- Geographic and demographic population(s) (homogeneity vs. heterogeneity)
- Comparison to use as a food vs. medicinal product (dietary intake)

CONSENSUS STATEMENT # 5: Integration of in-silico approaches broadens the dataset and may provide information on structural alerts that suggest the potential for certain biological properties.

- Tiered approach (progress systematically)
- Test systems to mimic biology (physiological relevance)
- Predictive power
- Evolution of understanding

CONSENSUS STATEMENT # 6: In the absence of toxicity data, threshold of toxicological concern (TTC) is a worst case risk assessment tool that can be applied to individual constituents to support their safety.

- Chemical fingerprinting coupled with short term assessment of biological similarity (comparison of novel formulations to those with comprehensive toxicity data)

CONSENSUS STATEMENT # 7: The application of TTC to a botanical product needs to consider dose addition, which is relevant if assessing constituents in the same chemical class and/or with a common mode of action.

- TTC depends upon chemistry (common mode of action)
- Compounds of same/similar "class" – additive for TTC
- Compounds with different (or unidentified) "class" – non-additive for TTC

CONSENSUS STATEMENT # 8: There is a requirement for guidance on how to generate and interpret ADME-related data on complex botanical mixtures. This guidance will include how to incorporate Physiologically-based pharmacokinetic (PBPK), and other kinetic models, to extrapolate to in vivo-relevance.

- Identify marker constituents to extrapolate across in-vitro, in-vivo animal and human clinical
- Include consideration of interaction potential (Herb-Drug and Herb-Herb)
- Use of advanced intestinal and hepatic models and/or co-cultures
- Use of molecular docking and other in-silico approaches

Conclusion and Action Items

The series of consensus statement presented above were developed by roundtable participants to provide perspective on the proposed decision tree methodology for botanical safety evaluation. Key elements needed to build a robust botanical safety evaluation were evaluated and discussed. These consensus statements provide a useful and pragmatic approach to evaluate botanicals for safe human use by determining dietary intake levels, sufficient safe margins of exposure from existing safety information, and/or establishing safe exposure thresholds via TTC/SAR approaches. Additionally, critical areas and data gaps were identified as opportunities for future focus including better context on history of use, systematic assessment of weight of considerations, and guidance on evaluating ADME parameters of botanical constituents.

References

2. Little, J. et al. In silico approaches to safety of botanical dietary supplement ingredients utilizing constituent-level characterization. Food and Chemical Toxicology 107 (2017) 418-429

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