REAGAN-UDALL FOUNDATION FOR THE FDA

Botanical Drug Development

Learnings from Expert Discussions

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What are botanical products?

- Botanicals are products that include plant materials, algae, macroscopic fungi, and combinations thereof.
- Botanical products may be classified as a food (including a dietary supplement), drug/biologic, medical device, or cosmetic.
- Botanical drug products (BDPs) may be available as a powder, tablet, capsule, elixir, topical, injection, or solution (e.g., tea).
- Plant-based medicines have been used for millennia, and the long-standing history of use provides a meaningful starting point in drug discovery.

How are BDPs regulated?

- In the U.S., botanical drug products (BDPs) are regulated as drugs when they are intended to diagnose, cure, mitigate, treat, or prevent disease in humans.
- While many botanicals have extensive histories of human use and inherently heterogenous makeups, further evidence is needed to demonstrate safety and efficacy for specific therapeutic indications.
- In recognition of these unique considerations, the U.S. Food and Drug Administration (FDA) published "Botanical Drug Development: Guidance for Industry" in December 2016.
- The guidance outlines recommendations related to characterization, quality control, clinical investigation, and regulatory considerations for BDPs.

About the Project

Background

Despite increasing interest in plant-based medicines, the inherent heterogeneity of botanicals creates unique challenges in research, product development, and regulatory review. The Reagan-Udall Foundation for the FDA, in collaboration with FDA, engaged botanical drug development experts to characterize these challenges and identify potential solutions.

How Information Was Gathered

- Initial background research
- Interviews
- Invitation-only roundtable
- Other correspondences

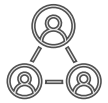
Who Participated

Consultants, former regulators, product developers and manufacturers, researchers, and standards developers

Key Themes

Discussants agreed that BDPs present meaningful scientific and public health opportunities but face distinct and persistent challenges.

The priority challenges and potential solutions identified by discussants were concentrated in these areas:



Education and engagement

Investment and funding

Production and quality standards

Regulatory process

Research design and implementation

Key Themes: Education and Engagement

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- There is a need for increased education and collaboration across stakeholders, including regulators, industry, and investors.
- Discussants highlighted the specific value of FDA and other health agencies using public messaging to signal BDP development as a priority.
- Confusion persists around differences between dietary supplements and drug development requirements.
- Discussants identified the opportunity for increased engagement between FDA and BDP developers to discuss adequacy of trial designs, tolerance for variation, and areas of adaptability in standard drug requirements.

Key Themes: Investment and Funding

Discussants noted that securing funding is a major barrier, and in their experience, investors are more deterred by the perceived regulatory risks and high costs associated with botanical drugs, compared to non-botanical drugs.

A few discussants noted that the windows of data and marketing exclusivity also discourage investors from getting involved.

Discussants suggested that longer patent/market exclusivity protections might incentivize more companies to take on the unique risks of botanical drug development (e.g., biologics receive 12 years).

Key Themes: Production and Quality Standards

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Discussants noted that BDPs face unique challenges in achieving batch-to-batch uniformity due to natural variation in raw plant materials.

Discussants highlighted the importance of and challenges in achieving Good Agricultural and Collection Practices (GACPs) and observed that long-term relationships with growers can help ensure consistent raw material quality.

Some discussants articulated a need to better define and educate stakeholders on the use of marker compounds versus active ingredients when/if suppliers change.

Discussants highlighted opportunities to strengthen pharmacopeial standards and improve alignment between FDA and standard-setting bodies.

Key Themes: Regulatory Process

Discussants emphasized that while the current regulatory pathway is functional, its application varies significantly across different review divisions.

Discussants felt that implementation of botanical guidance for specific applications was inconsistent and failed to account adequately for the multi-component nature of BDPs. With a botanical drug, the entire drug substance is considered active unless proven otherwise. Discussants expressed that reviewers were not taking this into consideration and were instead treating BDPs like small molecules or combination products.

External stakeholders perceive a lack of BDP-specific knowledge within FDA review divisions and advocate for providing additional training for reviewers or bringing in more specialized experts.

The lack of regulatory predictability and consistency directly discourages product development and external investment.

Key Themes: Research Design and Implementation

- Consistent with other areas of drug development, discussants noted the need for additional engagement with FDA to align on early phase trial approaches, appropriate endpoints, expectations about validation, and adoption of innovative trial designs (e.g., platform trials).
- Researchers and sponsors can consider opportunities to improve documentation for research and regulatory purposes.
  - Ensure that informed consent and other participant materials clearly communicate botanical origin, compositional complexity, known vs. unknown constituents, and differences from traditional use
- Educate Institutional Review Boards (IRBs) on best practices for evaluating research with complex mixtures, considerations for batch variability, and how botanical drugs differ from dietary supplements.

Potential Opportunities and Actions

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- Improve consistency and transparency in regulatory processes, including clearer communication and expectations
- Expand internal FDA expertise in botanical products
- Incorporate real-world evidence to inform fit-for-purpose BDP development programs
- Identify and apply appropriate quality frameworks to address batch-to-batch variability and ensure reproducibility
- Acknowledge the importance of botanical drug products to help catalyze investment and innovation
- Enhance collaboration with external organizations to support standards development and data sharing
- Increase education and outreach to align understanding across the development ecosystem

About the Foundation

The Reagan-Udall Foundation for the FDA is an independent 501(c)(3) organization created by Congress "to advance the mission of the FDA to modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety."

The Foundation works to advance regulatory science, support development and dissemination of reliable information, and facilitate engagement and information exchange.