Docket No. FDA-2026-N-9550

BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON

ADVANCING DEVELOPMENT OF BOTANICAL DRUG PRODUCTS; REQUEST FOR INFORMATION

November 3, 2026

Prefatory remarks

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA members include companies doing business as growers, importers, processors, manufacturers, and marketers of herbs, herbal products, and other dietary supplements. AHPA serves its members by promoting the responsible commerce of such products, including conventional human foods, dietary supplements, health and beauty products, animal products, botanical drugs, and other products.

The United States Food and Drug Administration (FDA) currently defines "Botanical Drug Products" (BDPs) as drug products that include or may be derived from plant materials, algae, macroscopic fungi, or combinations thereof and that are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans. FDA has primarily articulated its understanding of the BDP category and its regulatory treatment through nonbinding industry guidance.

The agency first released final industry guidance comprehensively addressing the BDP category in 2004.[1] This guidance was intended to encourage the clinical study of BDPs and submission of new drug applications for them by providing guidance to sponsors looking to submit investigational new drug applications (INDs) for BDPs as well as to distinguish circumstances in which BDPs would more appropriately come to market via the OTC drug monograph pathway. As a part of this guidance, FDA described evidentiary challenges and opportunities presented by the BDP category and articulated special review and evidentiary standards applicable to BDPs, particularly in the context of INDs for phase 1 and 2 clinical studies. A subsequent revision finalized in 2016[2] greatly streamlined the guidance and made numerous revisions to reflect industry experience and questions.

Despite the issuance of this guidance and associated policies, only four prescription BDPs have been approved in the decade following the last update to the guidance. The small number of BDP approvals may be attributed to (a) the limited appeal of BDPs to the investment community[3]; (b) often with the encouragement of FDA staff, applicants'

[1] FDA, Guidance for Industry, "Botanical Drug Products" (Issued June 9, 2004).

[2] FDA, Guidance for Industry, "Botanical Drug Development" (Issued December 29, 2016).

[3] In the experience of at least some AHPA members, potential investors do not consider BDPs sufficiently viable opportunities and are much more interested in what they perceive to be technologically advanced

expending limited resources on collecting data that may not prove truly necessary to support the application, such as mechanism of action data; (c) lack of clarity by applicants and FDA staff regarding how to appropriately control batch-to-batch reproducibility; and (d) applicants' choices of therapeutic targets.[4]

In mid-2026, in service to a grant from the agency, the Reagan-Udall Foundation held a closed stakeholder roundtable to identify challenges in BDP development and identify opportunities to accelerate the same. A public document of outcomes from the roundtable[5] identified overarching issues in the consistency of FDA review which were intensified when applied to the complexities of multi-ingredient BDPs.

On September 4, 2026, FDA released a request for information[6] (the RFI) seeking comments on the agency's efforts to advance the development of botanical drug products. The RFI consists of eleven wide-ranging questions seeking input on challenges and opportunities in BDP development, current BDP research and development practices, and potential agency actions, including revisions to the current guidance, that would facilitate a greater flow of approvals for safe and effective BDPs.

AHPA's members are engaged in the commerce of herbs and herbal products, including the development of BDPs. AHPA members support the structure of the current BDP guidance and associated review policies. AHPA believes that the principal obstacles to greater BDP development are rooted in a lack of knowledge and the limited visibility of BDP opportunities to relevant stakeholders positioned to resource their development.

General Comment

To begin with, AHPA generally agrees with the current FDA guidance on BDPs. AHPA members appreciate the flexibility and practicality of the guidance as written. AHPA notes that FDA's current approach to BDPs provides opportunities for applicants to take

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fields such as biologics or AI-driven drug discovery. Investors often do not understand the advantages or market opportunity for BDPs.

[4] For example, a topical genital warts BDP that discolors the skin may have limited commercial prospects. In other cases, companies have chosen endpoints too expensive to study without the backing of a major pharmaceutical company or other outside investor.

[5] Reagan-Udall Foundation for the FDA, "Botanical Drug Development: Learnings from Expert Discussions."

[6] FDA, Advancing Development of Botanical Drug Products; Request for Information, 91 Fed. Reg. 56,887 (September 4, 2026).

advantage of available historical information about a botanical, especially with respect to safety, to accelerate the development and approval process.

AHPA is aware that other commenters to the RFI have proposed creation of a Traditional Herbal Drugs category. AHPA believes that the creation of such a category would require an act of Congress vesting FDA with new approval and regulatory authorities. AHPA further believes that, if such a category is created: (a) it must be clearly differentiated from the existing BDP category; (b) the existing pathway to market under the current BDP guidance should not be altered; (c) creation of such a category must not in any way prevent or circumscribe the ability of traditional herbal practitioners to create their own therapeutic herbal products and formulas for use in individualized patient care; and (d) creation of such a category must not in any way supplant, limit, or impose new requirements on the existing categories of health-promoting foods, including dietary supplements and foods bearing health claims.

Q 2b. Challenges of chemically complex botanical drugs

AHPA believes that one of the biggest challenges in developing chemically complex BDPs is the persistent assumption in both the scientific and regulatory communities that chemical reproducibility is necessary and desirable in order to ensure a safe and reproducible therapeutic benefit, and therefore chemical reproducibility must be demonstrated in a properly controlled BDP.

This position assumes that, when given a chemically-reproducible dose of drug, day after day and year after year, a patient's body will respond in a reproducible way day after day and year after year. However, the body's physiology may change in response to the drug, which can result in either attenuation of the body's response (therapeutic failure) or exacerbation of toxic effects (safety failure).

Traditional herbal practitioners typically find this to be less of a problem than occurs in modern medicine. Herbal products normally contain a variety of phytochemicals that bind to a variety of different receptors or otherwise stimulate a variety of different physiologic pathways, thereby enhancing efficacy and making therapeutic failure less likely. This also enhances safety insofar as the various phytochemicals working synergistically achieve a therapeutic benefit despite each individual phytochemical being present at a lower level than would otherwise be required. The various phytochemicals may also act in antagonistic ways, thereby enhancing safety.[7] The

[7] For example, ephedra herb contains both compounds that raise blood pressure, such as ephedrine and pseudoephedrine, and compounds that lower blood pressure, such as ephedranines A and B.

levels of these phytochemicals are inherently variable in the botanical, and yet herbalists routinely achieve reliable therapeutic benefits even from crude, unprocessed herbs.

The complex suite of phytochemicals present in any given species are the result of long-term evolutionary pressures; plants produce phytochemicals for their own important purposes such as deterrence of herbivory or resistance to microorganisms. Therefore, it is relatively rare to see wholesale changes in the phytochemical profile of a plant, especially when it is grown under reasonably reproducible conditions.

While there are circumstances where the levels of individual phytochemicals or classes of constituents are of overriding importance to the safety and efficacy of a BDP, such as with the levels of opiate alkaloids in a poppy-derived BDP, in many cases AHPA believes FDA should apply greater flexibility with respect to issues of reproducible phytochemistry.

Q 2a. FDA has not adequately cultivated its botanical expertise

AHPA has concerns about a lack of transparency regarding the participant roster of the Reagan-Udall Foundation roundtable and the associated interests driving its findings; however, the roundtable summary identified valid concerns regarding a lack of BDP-specific knowledge among FDA reviewers. Other findings also communicated difficulties with the review process that stemmed from insufficient agency familiarity with the differences between botanical ingredients and highly purified synthetic compounds. The roundtable concluded that the agency's "internal expertise" needed expansion.

AHPA shares this sentiment. While individual staff within the agency may be highly familiar with botanicals or expert with particular phytochemicals, botanical ingredients, or BDPs, agency reviewers and other participants in the approvals process do not share this level of comfort with botanical ingredients or their history, composition, or evidence. The wide range of considerations and complexities applicable to botanicals requires a greater sustained base of support for personnel with BDP-specific expertise.
As with other resourcing difficulties, the agency has visibly struggled to maintain a critical mass of knowledge that would consistently and adequately inform BDP application development feedback and subsequent reviews.

Q 3a. FDA must make lasting commitments to botanical expertise

While BDPs exist within well-developed regulatory categories, these products and the associated guidance remain a "special case" outside the daily experience of the general drug approval pathways.

AHPA notes that many of the challenges of agency literacy in the treatment of botanical ingredients are not limited to the BDP setting; problems regarding the treatment of multi-ingredient botanical products, such as the appropriate and limited use of marker compounds, are also experienced in the treatment of other regulated product categories, including dietary supplements, animal health products, and conventional foods. Institutional botanical expertise can help the agency serve its public health mission in these areas as well, regardless of regulatory distinctions.

The construction of institutional botanical knowledge, rather than incidental experience or temporary attention, is ultimately necessary for the smooth functioning of BDP application reviews. AHPA recommends that FDA staff include experts in pharmacognosy, the foundational scientific discipline in botanical drugs, and also individuals trained in the use of herbs for disease treatment, such as certified herbalists, Ayurvedic practitioners, and Traditional Asian Medicine practitioners. Such experts are best positioned to understand what is necessary to ensure safety and therapeutic efficacy.

AHPA recommends an all-routes approach to expertise development that both values the development of personnel with specialized botanical expertise as well as the full integration of BDP-specific considerations in general procedural training. In this regard, botanical ingredients offer one strong advantage: humanity has a long history of study and training regarding these products, and there are many external sources of expertise upon which the agency can draw for both staffing and education purposes.

Q 2a. Botanical substances often require comprehensive standardization; chemistry testing should be de-emphasized where appropriate

Some BDPs are highly concentrated extracts consisting primarily of one or another class of compounds (e.g., catechins or triterpenes). Such preparations can often be adequately standardized on the basis of chemistry alone.

In contrast, other BDPs are much less processed and may contain many different classes of compounds, perhaps even the full spectrum of constituents natively present in the plant. Such products require a consistent manufacturing process applied to a consistent botanical raw material – i.e., comprehensive standardization – to achieve a consistent BDP that delivers the expected therapeutic safety and efficacy. Simply measuring one or another phytochemical, or even one or another class of

phytochemicals, cannot substitute for comprehensive control over the raw material and the manufacturing process.[8]

Therefore, AHPA agrees with FDA's current "totality of the evidence" approach to ensuring the reproducibility of chemically complex BDPs. Furthermore, AHPA would discourage FDA from requiring applicants pursuing approval of chemically complex BDPs to focus on product chemistry except where a single phytochemical or class of phytochemicals really does represent the majority of the BDP's intended therapeutic benefit and/or where other evidence of reproducible potency, such as bioassay data, are not available.

AHPA would also suggest that the level of effort the agency requires an applicant to devote to analyzing and controlling product reproducibility through either chemistry testing or bioassay testing should be tailored depending on the intended use of the BDP. AHPA believes that, in certain cases, it would be appropriate to approve BDPs without any such data and rely entirely on consistent raw material sourcing combined with consistent manufacturing processes to ensure BDP consistency. This could apply, for example, to BDPs intended to treat minor or self-limiting health conditions or BDPs whose effects are readily perceptible to the patient, especially where the botanical drug substance comprises the majority of the final dosage form such that dosage weight or volume can be used to assess content uniformity.[9]

Q 3d. FDA should permit alternatives to animal models for safety evaluations

AHPA commends the agency's commitment to the Botanical Safety Consortium[10] (BSC). Established in 2019 as a joint commitment by FDA, the National Institute of Environmental Health Sciences, and the Health and Environmental Sciences Institute, the BSC brings together regulators, academics, and private stakeholders to identify and develop assays to confirm the safety of botanicals. While the BSC's work is largely

[8] For further discussion of standardization, see AHPA's Standardization of Botanical Products: White Paper (2001) and Use of Marker Compounds in Manufacturing and Labeling Botanically Derived Dietary Supplements (2001).

[9] From a purely pragmatic standpoint, AHPA notes that in many cases no chemical analyses are actually necessary in order to deliver a therapeutically reliable herbal drug. Millennia of human experience have demonstrated that simply harvesting, preparing, and consuming (or applying) a botanical from the wild is sufficient to achieve a reliable health effect. AHPA has members that routinely treat their own health conditions using "botanical drugs" harvested straight from their yard; and herbal practitioners worldwide routinely achieve positive health outcomes using crude, unprocessed botanicals.

[10] Botanical Safety Consortium, https://botanicalsafetyconsortium.org/, accessed October 13, 2026.

oriented toward the application of new approach methodologies for safety evaluation of botanicals in dietary supplements, methods developed and validated by the BSC are certainly applicable to BDP development as well.

AHPA recommends that FDA continue its support for the BSC and consider further opportunities to develop or support institutions to address development of alternatives to animal testing. AHPA encourages FDA to allow the use of validated non-animal methods, where appropriate and available, for evaluation of BDP safety.

Q 2a. The BDP category lacks stakeholder visibility

At root, the slow movement of BDP development is a matter of market incentives and information. Drug development investment can at times be possessed with deep inertia; the greatest reason for a lack of BDP approvals may well be a lack of BDP approvals. In the experience of AHPA members involved in BDP development, one simple problem compounding this inertia is that potential sponsors must be educated on BDPs from first principles. To the degree that investors are aware of BDPs, they may share the agency's perception that such products are a more complicated (and therefore riskier) special case of drugs – not recognizing the work FDA has done to facilitate the development of these products or the inherent advantages of BDPs compared to other types of drugs. For example, candidate BDPs have a much lower risk of failing to receive approval due to safety issues than single-entity chemicals, and they have a lower risk of safety failure than novel small-molecule drugs.

FDA could do more to communicate the opportunities that the current BDP guidance represents for potential supporters. Other than publishing the guidance itself and promotional pages that accompanied the RFI, the agency maintains two primary websites dedicated to informing the public about BDPs. The first is a single website[11] titled "What is a Botanical Drug Product?" that answers the question, directs readers to the guidance, and offers very limited additional context. The second is an FAQ on BDP[12] development that does provide some useful stakeholder information; it is not presently linked from any other FDA page relating to BDPs, and it does not link to the BDP guidance document.

[11] FDA, "What is a Botanical Drug?", https://www.fda.gov/about-fda/cder-offices-and-divisions/what-botanical-drug, accessed October 13, 2026.

[12] FDA, "Frequently Asked Questions on Botanical Drug Product Development", https://www.fda.gov/about-fda/cder-offices-and-divisions/frequently-asked-questions-botanical-drug-product-development, accessed October 13, 2026.

Q 3c. FDA should actively communicate the utility of BDPs and their development

Much as FDA could benefit from greater institutional knowledge of botanical substances, all parties to the BDP market would benefit from greater publicity attached to the product category.

AHPA encourages the full redevelopment of existing public-facing website material relevant to BDPs to ensure that all information and that all pages are accessible from each other in a consistent manner that communicates their respective purposes with a minimum of redundancy. As a part of this revision process, FDA should create a website that specifically summarizes the elements of the BDP development process with a target audience of potential development sponsors in mind.

Summary

AHPA greatly appreciates the opportunity to present comments on this Request for Information. AHPA staff and counsel will make themselves available at any mutually convenient time to further address any of the topics addressed herein. Please feel free to contact AHPA if clarification or additional discussion is needed on the issues raised in these comments.

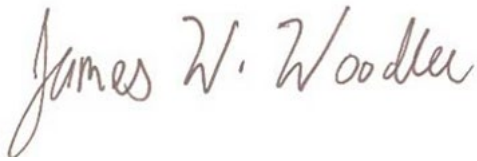
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