



## Botanical Drug Review

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It's no secret that nature has many healing powers. This includes botanical products, which are finished, labeled products that contain plant-derived ingredients. In the case of botanical drug products, as with all medicines, there are benefits as well as risks. It is FDA's role to formally assess whether the benefits of botanical products outweigh the risks and can be marketed as drugs in the United States.

Botanical products may be classified as foods, dietary supplements, drugs, medical devices, or cosmetics, depending on their "intended use." A product's "Intended use" is established by, among other things, its advertising, labeling, and circumstances surrounding its distribution. For example, a botanical may be regulated as a:

- *Food* if it is used for food and consumed primarily for their taste, aroma, or nutritive value.
- *Dietary supplement* if it is labeled as a dietary supplement and otherwise meets the

definition of a [dietary supplement as defined in the Dietary Supplement Health and Education Act \(DSHEA\) of 1994.](#)

- *Drug* if it is intended for use in the diagnosis, cure, mitigation, or treatment of disease in humans. Botanical drug products often have unique features (e.g., complex mixtures, lack of a distinct active constituent(s), and substantial prior human use). Fermentation products, products derived from animals or minerals, highly purified substances, and materials derived from botanicals that are genetically modified with the intention of producing a single molecular entity are not considered botanical drug products.

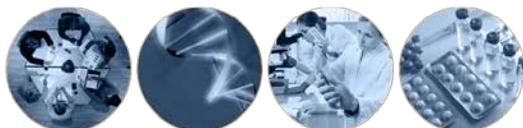
### Regulation of Botanical Drugs

In order to market a botanical drug product within the U.S., a company must follow the appropriate regulatory procedures. A botanical drug product may be marketed in the United States under either an over-the-counter (OTC) drug monograph or an approved new drug application (NDA).

**OTC Drug Monograph:** The [OTC drug review](#) is a three-phase public rulemaking process resulting in the establishment of standards (monographs or non-monographs) for an OTC therapeutic drug category. The monographs represent regulatory standards for the marketing of non-prescription drug products not covered by NDAs. These standards provide the marketing conditions for some OTC drug products including the active ingredients, labeling, and other general requirements. For a botanical drug substance to be included in an OTC monograph, there must be published data establishing a general recognition of safety and effectiveness, including the results of adequate and well-controlled clinical studies. A manufacturer would also need to submit a petition in accordance with [21 CFR 10.30](#) and [330.10\(a\)\(12\)](#), or a Time and Extent Application in accordance with [21 CFR 330.14](#) to amend the monograph to include a botanical drug substance. Several botanical drug substances (e.g. psyllium and senna) are included in the OTC drug review and witch hazel is currently marketed under a monograph.

**NDA:** Under current regulations, if there is no marketing history in the U.S. or a foreign country for a botanical drug product, if available evidence of safety and effectiveness does not warrant inclusion of the product in an OTC drug monograph, or if the proposed indication would not be appropriate for nonprescription use, the manufacturer must submit an NDA to obtain FDA approval to market the product for the proposed use. An NDA for a botanical drug could seek approval for either prescription or OTC use, depending on the indication and characteristics of the product and whether it is safe for use outside of the supervision of a practitioner licensed by law to administer it.

An NDA must contain substantial evidence of effectiveness derived from adequate and well-controlled clinical studies, evidence of safety, and adequate chemistry, manufacturing, and controls (CMC) information. The format of an NDA submission and the requirements for its various sections are set forth in [21 CFR 314](#) and discussed in several [CDER guidances](#).



**INDs for Botanical Drugs:** If there is insufficient information to support an NDA for a botanical drug, the sponsor may need to first develop the product further under an investigational new drug (IND). In general, an IND is required under section 505(i) of the Act and [21 CFR 312](#) when a botanical product is studied in the U.S. for a drug use, even if such study is intended solely for research purposes. Under [21 CFR 312.22](#), an IND must contain sufficient information to demonstrate that the drug product is safe for testing in humans and that the clinical protocol is properly designed for its intended objectives.

**CMC Information:** Because botanical drug products have certain unique characteristics, CMC documentation that should be provided for botanical drugs will often be different from that for synthetic or highly purified drugs, whose an active constituent(s) can be more readily chemically identified and quantified.

**CMC and Toxicology Information to Support Initial Studies:** Many botanical products are legally available in the U.S. as dietary supplements and are widely available outside of clinical trials. Therefore, to support initial clinical trials, the nonclinical pharmacology and toxicology information that must be provided under 21 CFR 312.22(b) for legally available botanical products with no known safety issues may be markedly reduced compared to that expected for synthetic or highly purified new drugs that are not legally marketed and for which there is no prior human experience.

**Combination Drug Regulations:** Botanical drug products that are derived from a single part of a plant, or from a single species of alga or macroscopic fungus are not considered to be fixed-combination drugs within the meaning of [21 CFR 300.50](#) and [330.10\(a\)\(4\)\(iv\)](#). Consequently, they do not have to meet the requirements for combination drugs, principally the need to demonstrate that each component or active constituent makes a contribution to the claimed effects. Botanical drugs composed of multiple and easily separable parts of a single species of plant (e.g., flowers and bark of a woody plant), or of parts from different species of plants algae, or macroscopic fungi, currently are subject to the combination drug requirements. However, FDA is considering revising its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances.

#### CDER's Botanical Drug Review Experience

CDER established the [Botanical Review Team](#) in 2003, published a [Guidance for Industry: Botanical Drug Products](#) in 2004, and recently revised and published in 2015 a draft [Guidance for Industry: Botanical Drug Development](#). The draft guidance provides additional recommendations on quality, nonclinical, clinical, and other unique aspects associated botanical drug development. In this guidance, FDA described a "totality-of-evidence" approach that overcomes the limited ability to characterize the entire botanical mixture or its active components by available analytical techniques. In addition to conventional CMC data, this totality of the evidence approach considers other information including raw material control, clinically relevant bioassay(s), and other data generated based on a multiple-batch and multiple-dose clinical trial of the botanical product. The available evidence is used to ensure that the quality consistency of the botanical product is sufficient to ensure therapeutic consistency. The degree of reliance on these other data for ensuring consistency of quality depends on the extent that the botanical mixture can be characterized and quantified.

Since the publication of the botanical Guidance in 2004, over 400 botanical product INDs have been submitted to the Office of New Drug (OND) at CDER for clinical investigation as treatments for various diseases, such as cancer, infectious diseases, and arthritis, just to name a few. Two NDAs have been approved for marketing botanical products as prescription drugs in the US: Veregen (sinecatechins), a topical drug for the treatment of genital and perianal warts and Fulyzaq (crofelemer), an oral drug for the treatment of HIV/AIDS related diarrhea. These two NDA approvals show that new therapies derived from complex botanical mixtures can be developed to meet modern FDA standards of quality, safety, and efficacy as new drugs.

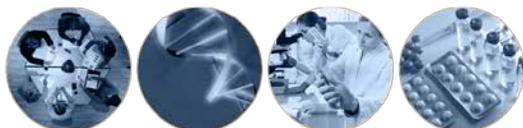
Thanks again for tuning in!

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CDER Small Business and Industry Assistance

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This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.



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