
Guidance for Industry

Botanical Drug Products

Draft Guidance

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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U.S. Department of Health and Human Services
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TABLE OF CONTENTS

I	INTRODUCTION	1
II	BACKGROUND	1
III	GENERAL REGULATORY APPROACHES	2
A.	MARKETING UNDER OTC MONOGRAPH VERSUS APPROVED NDA.....	3
B.	CMC INFORMATION FOR BOTANICAL DRUG PRODUCTS.....	4
C.	CMC AND TOXICOLOGY INFORMATION TO SUPPORT INITIAL STUDIES	4
D.	APPLICABILITY OF COMBINATION DRUG REGULATIONS	5
IV	MARKETING A BOTANICAL DRUG UNDER AN OTC MONOGRAPH	5
V	MARKETING A BOTANICAL DRUG UNDER AN NDA	6
VI	INDS FOR BOTANICAL DRUGS	6
A.	IND INFORMATION FOR DIFFERENT CATEGORIES OF BOTANICALS	6
B.	BASIC FORMAT FOR INDs.....	7
VII	INDS FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES OF LAWFULLY MARKETED BOTANICAL PRODUCTS	12
A.	DESCRIPTION OF PRODUCT AND DOCUMENTATION OF HUMAN USE.....	12
B.	CHEMISTRY, MANUFACTURING, AND CONTROLS (§ 312.23(A)(7)).....	13
C.	PHARMACOLOGY/TOXICOLOGY INFORMATION (§ 312.23(A)(8)).....	15
D.	BIOAVAILABILITY	16
E.	CLINICAL CONSIDERATIONS.....	16
VIII	INDS FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES OF NONMARKETED BOTANICAL PRODUCTS	16
A.	DESCRIPTION OF PRODUCT AND DOCUMENTATION OF HUMAN USE.....	16
B.	CHEMISTRY, MANUFACTURING, AND CONTROLS (§ 312.23(A)(7)).....	18
C.	PRECLINICAL SAFETY ASSESSMENT.....	23
D.	BIOAVAILABILITY.....	24
E.	CLINICAL CONSIDERATIONS.....	24
IX	INDS FOR PHASE 3 CLINICAL STUDIES OF ALL BOTANICAL PRODUCTS	24
A.	DESCRIPTION OF PRODUCT AND DOCUMENTATION OF HUMAN EXPERIENCE.....	25
B.	CHEMISTRY, MANUFACTURING, AND CONTROLS (§ 312.23(A)(7)).....	25
C.	PRECLINICAL SAFETY ASSESSMENT (INCLUDING PRE-NDA).....	31
D.	BIOAVAILABILITY AND DRUG-DRUG INTERACTIONS	34
E.	CLINICAL CONSIDERATIONS.....	35
	DEFINITIONS	36

Guidance For Industry¹

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I. INTRODUCTION

This guidance explains when a botanical drug may be marketed under an over-the-counter (OTC) drug monograph and when FDA approval of a new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355(b), is required for marketing. In addition, this document provides guidance to sponsors on submitting investigational new drug applications (INDs) for botanical drug products, including those botanical products (or *botanicals*) currently lawfully marketed as foods and dietary supplements in the United States.

This guidance also discusses several areas in which, because of the unique nature of botanicals, FDA finds it appropriate to apply regulatory policies that differ from those applied to synthetic, semisynthetic, or otherwise highly purified or chemically modified drugs (including antibiotics). (This latter group of drug substances is referred to in this guidance as *synthetic* or *highly purified* drugs.) In particular, the guidance states that applicants may submit reduced documentation of preclinical safety and of chemistry, manufacturing, and controls (CMC) to support an IND for initial clinical studies of botanicals that have been legally marketed in the United States as dietary supplements or cosmetics without any known safety concerns.

II. BACKGROUND

Botanical products are finished, labeled products that contain vegetable matter as ingredients.² The FD&C Act characterizes a product primarily based on its intended use. For a botanical product, the intended use may be as a food (including a dietary supplement), a drug (including a biological drug), a

¹This guidance has been prepared by working groups in the Medical Policy, Pharmacology and Toxicology, and Complex Drug Substances Coordinating Committees in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance document represents the Agency's current thinking on botanical drug products. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

²*Botanical product* and other terms used in this guidance are defined in the Glossary for use in this guidance only; these definitions may not be appropriate in other contexts.

medical device (e.g., gutta-percha), or a cosmetic as shown by, among other things, the product's accompanying labeling claims, advertising materials, and oral or written statements (21 CFR 201.128).

For the purposes of this document, the term *botanicals* includes plant materials, algae, macroscopic fungi, and combinations thereof. It does not include fermentation products such as products fermented with yeast, bacteria, and other microscopic organisms, even if previously approved for drug use or accepted for food use in the United States, nor does it include highly purified or chemically modified substances derived from botanical sources, such as paclitaxel, because these substances can readily be fully characterized. This guidance addresses only those botanical products that are regulated by CDER.

Although this guidance does not address drugs that contain animals or animal parts (e.g., insects, annelids, shark cartilage) and/or minerals, either alone or in combination with botanicals, many scientific principles described in this guidance may also apply to those products. When a drug product contains botanical ingredients in combination with either (1) a synthetic or highly purified drug or (2) a biotechnology- or other naturally-derived drug, this guidance only applies to the botanical portion of the product.

III. GENERAL REGULATORY APPROACHES

Many botanical products are used widely in the United States and are often marketed as dietary supplements. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), an orally ingested product that meets the definition of a "dietary supplement" under section 201(ff) of the FD&C Act may be lawfully marketed using a statement that (1) claims a benefit related to a classical nutrient deficiency disease (and discloses the prevalence of the disease in the United States), (2) describes how the product is intended to affect the structure or function of the human body, (3) characterizes the documented mechanism by which the product acts to maintain such structure or function, or (4) describes general well-being from consumption of the product (section 403(r)(6)(A) of the FD&C Act, 21 U.S.C. 343(r)(6)(A)).

The manufacturer must have substantiation that such statement is truthful and not misleading (section 403(r)(6)(B) of the FD&C Act, 21 U.S.C. 343(r)(6)(B)). In addition, the statement must contain, prominently displayed and in boldface type, the following: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" (section 403(r)(6)(C) of the FD&C Act, 21 U.S.C. 343(r)(6)(A)).³

FDA has issued regulations defining the types of statements that can be made concerning the effect of a dietary supplement on the structure or function of the body under section 403(r)(6)(a) of the FD&C Act (65 FR 1000; January 6, 2000). The regulations distinguish these statements from the types of statements that require prior approval as drug claims under section 201(g)(1) of the FD&C Act, 21 U.S.C. 321(g)(1), or prior authorization as health claims under section 403(r)(1)(B) and (r)(5)(D) of the FD&C Act.

³Section 403(r)(6) also imposes a notification requirement in connection with the permitted claims.

A dietary supplement statement of the type described above may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases (section 403(r)(6) of the FD&C Act, 21 U.S.C. 343(r)(6)). A botanical product is a drug under section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), if it is intended for use in diagnosing, mitigating, treating, curing, or preventing disease (except for a product marketed with certain health claims under sections 201(g)(1) and 403(r) of the act). Such a drug product must be marketed under an approved NDA⁴ unless the product is excluded from the definition of a *new drug* under section 201(p) of the FD&C Act. Certain products that FDA determines are *generally recognized as safe and effective* in accordance with section 201(p) may be marketed under FDA's OTC drug monograph system.

A. Marketing Under OTC Monograph Versus Approved NDA

A botanical drug product may be marketed in the United States under (1) an OTC monograph or (2) an approved NDA or ANDA. A botanical product that has been marketed in the United States for a material time and to a material extent for a specific OTC drug indication may be eligible for inclusion in an OTC monograph codified in 21 CFR Parts 331-358. The manufacturer would need to submit a petition to amend the monograph to add the botanical substance as a new active ingredient in accordance with 21 CFR 10.30.

Under current regulations, if there is no marketing history in the United States for a botanical drug product,⁵ if available evidence of safety and effectiveness does not warrant inclusion of the product in an OTC 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 (sections 201(p) and 505 of the FD&C Act). 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. If existing information on the safety and efficacy of a botanical drug product is insufficient to support an NDA, new clinical studies will be needed to demonstrate safety and effectiveness.⁶

⁴Under section 505(j) of the FD&C Act, 21 U.S.C. 355(j), a botanical drug product may also be marketed under an abbreviated new drug application (ANDA). An applicant may submit an ANDA for a botanical drug product that is the same drug for the same indication as a previously approved drug product. The *generic* version of the previously approved drug would have to be both pharmaceutically equivalent and bioequivalent to such drug. For information on the submission of ANDAs, see FDA regulations in 21 CFR Parts 314 and 320 as well as Agency guidance documents.

⁵FDA has issued a proposed rule that would establish additional criteria and procedures by which conditions may become eligible for inclusion in the OTC drug monograph system (64 FR 71062, December 20, 1999). Among other things, the proposed rule addresses how FDA would consider *foreign* marketing data in determining whether a drug has been used under particular conditions to a material extent and for a material time (as required under section 201(p) of the FD&C Act) to qualify for inclusion in an OTC drug monograph. Statements in this guidance are subject to changes implemented through that rulemaking.

⁶See 21 CFR 312.20 (concerning requirement for an IND).

When a final OTC drug monograph is published for a specific use of a botanical drug, any person can market a product containing the same substance and for the same use, provided the labeling and other active ingredients (if present) are in accord with all relevant monographs and other applicable regulations. In contrast, when a product is approved under an NDA, the approval is specific to the drug product that is the subject of the application (the applicant's drug product), and the applicant may be eligible for marketing exclusivity for either 5 years (if it is a new chemical entity) or 3 years from the time of approval, even in the absence of patent protection. During the period of exclusivity, FDA will not approve, or in some cases even review, certain competitor products unless the second sponsor conducts all studies necessary to demonstrate the safety and effectiveness of its product. Therefore, if a person who wishes to market a botanical drug product that is not included in an existing OTC monograph desires marketing exclusivity for the product, they should seek approval of an NDA rather than petition the agency to amend a monograph. Appendix A contains a schematic showing different regulatory approaches that can be taken for marketing botanical drug products in the United States, including OTC monograph and NDA procedures.

B. CMC Information for Botanical Drug Products

Botanical drug products have certain unique characteristics that should be taken into account in the application of FDA regulations and guidance. Botanical drugs are derived from vegetable matter and are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, even the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, the CMC documentation that should be provided for botanical drugs will be different from that for synthetic or highly purified drugs, whose active constituents can be more readily chemically identified and quantified. For example, active constituents in a botanical drug might not need to be identified during the IND stage or in an NDA submission if this is shown to be infeasible. In such circumstances, FDA will rely instead on a combination of other tests (e.g., spectroscopic or chromatographic fingerprints, chemical assay of characteristic markers, and biological assay), controls (e.g., strict quality controls of the botanical raw materials and adequate in-process controls), and process validation (especially for the drug substance) to ensure the identity, purity, quality, strength, potency, and consistency of the botanical drug.

C. CMC and Toxicology Information to Support Initial Studies

Many botanical products are legally available in the United States as dietary supplements. Given the wide availability of such products outside of clinical trials, it is important to assess the effectiveness of such products. The preclinical pharmacology and toxicology information that should be provided for legally available botanical products with no known safety issues during initial clinical trials may be markedly reduced (in most cases, additional toxicology and CMC data will not be required) 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 (see 21 CFR 312.22(b)).

D. Applicability of Combination Drug Regulations

Botanical drug products that are derived from a single part of a plant (e.g., leaves, stems, roots, seeds), or from an alga or macroscopic fungus (e.g., a mushroom), are not considered to be fixed-combination drugs within the meaning of 21 CFR 300.50 and 330.10(a)(4)(iv). Consequently, they would not have to meet the requirements for combination drugs, principally the need to demonstrate that each component or active ingredient makes a contribution to claimed effects.

Botanical drugs composed of multiple parts of a single plant species, or of parts from different plant species, currently are subject to the combination drug requirements. However, FDA intends to propose revisions to its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances.

IV. MARKETING A BOTANICAL DRUG UNDER AN OTC MONOGRAPH

A botanical product that has been marketed in the United States (but see footnote 5) for a material time and to a material extent for a specific OTC indication may be eligible for consideration in the OTC drug monograph system. Currently, there are several botanical drugs, including cascara, psyllium, and senna, that are included in the OTC drug review. For a botanical drug substance to be included in an OTC monograph, there must be published data establishing general recognition of safety and effectiveness, including results of adequate and well-controlled clinical studies. Requirements related to safety, effectiveness, and labeling for drugs to be included in an OTC drug monograph are set forth in 21 CFR Part 330.

A request to amend an OTC monograph to include a botanical substance should be submitted by citizen petition in accordance with 21 CFR 10.30 and 330.10(a)(12). There should be publicly available quality standards for such a botanical substance in the *United States Pharmacopeia* (USP).⁷ In the absence of a USP monograph, the petitioner should propose suitable quality standards for inclusion in the OTC monograph and simultaneously propose adoption of those standards in the USP.

An OTC drug monograph does not ordinarily contain CMC information for a drug product beyond the names of the active ingredients (i.e., the drug substances). However, tests and specifications for a botanical drug product, including its corresponding botanical raw materials and botanical drug substances, should be made part of the OTC monograph either directly or by cross-reference. In addition, FDA regulations on current good manufacturing practices (CGMPs) apply to all OTC drug monograph products, including botanical drug products (see 21 CFR 330.1(a)).

⁷However, a botanical drug's conformance to the standards of the USP or any other official compendium does not establish that the botanical is safe, effective, and not misbranded for its intended use as a drug.

For further information on the OTC monograph approach to marketing a botanical drug substance, sponsors are encouraged to contact CDER's Division of Over-the-Counter Drug Products (HFD-560).

V. MARKETING A BOTANICAL DRUG UNDER AN NDA

Any botanical drug product that is not generally recognized as safe and effective for its therapeutic claims is considered a *new drug* under section 201(p) of the FD&C Act. Section 505(a) of the Act requires any person wishing to market a botanical drug product that is a new drug to obtain FDA approval of an NDA or ANDA for that product. According to section 505(d) of the Act and 21 CFR 314.50, an NDA must contain substantial evidence of effectiveness derived from adequate and well-controlled clinical studies, evidence of safety, and adequate CMC information. The format of an NDA submission and the requirements for its various sections are set forth in 21 CFR Part 314 and discussed in several CDER guidance documents.

VI. INDs FOR BOTANICAL DRUGS

If available information is insufficient to support an NDA for a botanical drug, the sponsor will need to develop further data. If the sponsor wishes to conduct clinical trials in the United States to support an NDA, it will have to submit an IND under section 505(i) of the FD&C Act and 21 CFR Part 312. An IND is also required when a botanical product is studied for a drug use (see 21 U.S.C. 321(g)), 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.

A. IND Information for Different Categories of Botanicals

Under 21 CFR 312.22(b), the amount of information that must be submitted in an IND for a particular drug product depends on, among other things, the novelty of the drug, the extent to which it has been studied previously, the drug product's known or suspected risks, and the developmental phase of the drug. Sections VII and VIII of this guidance describe the information that a sponsor should provide in an IND for initial (i.e., phase 1 and phase 2) clinical studies of a botanical drug. As noted above, for botanicals legally marketed under the DSHEA, there will often be very little new CMC or toxicologic data needed to initiate such trials, as long as there are no known safety issues associated with the product and it is used at approximately the same doses as those currently or traditionally used or recommended. When properly conducted, these early investigations, including controlled effectiveness trials in phase 2, should allow a determination of whether there is a clinical effect worth pursuing and will provide a more systematic evaluation of safety than previously available. Should a botanical drug product show promise of effectiveness in such early trials, the potential for wider use for particular purposes will create a need for greater assurance of product quality and consistency and for expanded (i.e., phase 3) clinical studies of safety and effectiveness (21 CFR 312.22(b)). IND information appropriate for expanded clinical studies of botanical drugs is discussed in section IX.

The IND sponsor of a botanical product that has been previously marketed but *not* in the United States should provide certain additional information to assist FDA in determining the safety of the product for use in initial clinical studies (section VII). Such additional information is appropriate under 21 CFR 312.22(b) because these products are not already marketed in the United States, and evidence of safety is needed before patients should be exposed to them.

This guidance also addresses the type of information that should be provided in INDs for initial studies on botanical products that have not been lawfully marketed anywhere or have known safety issues (section VIII). In contrast to botanical products that have been marketed in some form without any known safety issues, considerably less information may be available on the safety of a new botanical product that has not been marketed anywhere as a food or dietary supplement and has not been tested as a drug in humans. Consequently, it is appropriate that, under § 312.22(b), sponsors of INDs for initial trials of botanical products that have not previously been lawfully marketed anywhere, or for which there are known safety issues, should provide certain additional information to FDA.

The information to be provided in an IND for a botanical drug product is illustrated schematically in Appendix B and discussed in this section and sections VII-IX below. CDER reviews INDs and NDAs based on the clinical indication being sought for labeling. FDA encourages sponsors of INDs for initial studies of botanical drugs to seek input from CDER review divisions to ensure that the appropriate information is submitted and that the clinical protocols are well designed. Many guidance documents specific to certain indications or dosage forms are also available from the respective review divisions.

FDA will place an IND on clinical hold (i.e., an order issued by the Agency to delay a proposed clinical study) if it finds that the IND does not contain sufficient information required under 21 CFR 312.23 to assess the risk to subjects of the proposed studies (21 CFR 312.42(b)(1)). However, the lack of any specific item of information listed in § 312.23 for a phase 1 study will not necessarily be grounds for a clinical hold. Possible grounds for a clinical hold are set forth in 21 CFR 312.42(b) and discussed in CDER's guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (November 1995).

B. Basic Format for INDs

The format and general requirements for IND submissions are stated in 21 CFR 312.23 and discussed in several CDER guidance documents, including the phase 1 guidance referenced above. These requirements are summarized below, with guidance on the type of information that sponsors of botanical drug products should provide under particular provisions:

1. Cover Sheet (see § 312.23(a)(1))

2. *Table of Contents (see § 312.23(a)(2))*
3. *Introductory Statement and General Investigational Plan (see § 312.23(a)(3))*
4. *Investigator's Brochure (see § 312.23(a)(5))*
5. *Protocol (§ 312.23(a)(6))*

This section requires information on protocols for planned studies. In general, clinical evaluation of botanical drug products for safety and effectiveness does not differ significantly from evaluation of synthetic or highly purified drugs. For study results to be interpretable, clinical studies should be well designed and carefully executed. A sponsor need not differentiate the clinical effects of each molecular entity in a botanical product derived from a single part of a plant (see section III.D, Applicability of Combination Drug Regulations). Even where the components of a combination product must be studied, initial controlled studies could be used to evaluate the entire combination product. For additional information on the clinical development of new drugs, see the CDER guidance *Format and Content of the Clinical and Statistical Sections of an Application* (July 1988) and other guidances related to the submission of applications involving specific drug classes and diseases.

Clinical studies of botanical products may pose special problems associated with the incorporation of traditional methodologies, such as selection of doses and addition of new botanical ingredients based on response, that will need to be resolved. In almost all cases, credible studies will be randomized, double-blind, and placebo-controlled (or dose-response). For most conditions potentially treated by botanical drugs (generally mildly symptomatic), active control equivalence designs would not be credible.

For botanical as well as for synthetic or highly purified drugs, absolute safety does not exist for any therapeutic intervention, and any risk should be assessed in light of potential clinical benefits. For more comprehensive information on safety evaluations, see other CDER guidance documents. As for synthetic or highly purified drugs, safety data on newly developed botanicals are mostly derived from controlled efficacy trials and — for chronic indications — long-term, open-label extensions. For chronic conditions, exposures of at least 6-12 months' duration are usually appropriate (see ICH guidance *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995)).

Section VII.E of this guidance provides recommendations on the protocol design of initial clinical trials for botanical products legally marketed under the DSHEA. Sections VIII.E and IX.E provide information on the design of initial clinical trials for nonmarketed

botanical drug products and for expanded studies on all botanical drug products, respectively.

As with any clinical study, appropriate human research subject protections must be followed, including submission of the protocol to an institutional review board (IRB) and receipt of proper informed consent (see 21 CFR Parts 56 and 50). The consent form should describe what is or is not known about the product to be studied and should acknowledge any lack of additional chemical or toxicological characterization.

6. *Chemistry, Manufacturing, and Controls (§ 312.23(a)(7))*

The requirements for the content and format of the CMC section of an IND are stated in 21 CFR 312.23(a)(7)(iv)(a)-(e). These regulations require documentation of the drug substance, drug product, placebo, labeling, and an environmental analysis.

Plant materials used in the production of botanical drug products often are not completely characterized and defined or are prone to contamination, deterioration, and variation in composition and properties. In many cases, the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, unlike synthetic or highly purified drug products, it may be difficult to ensure the quality of a botanical drug by controlling only the corresponding drug substance and drug product. To ensure that a botanical drug product is made consistently with good quality, the sponsor should have, in addition to final product testing, appropriate quality controls for the botanical raw materials and adequate in-process controls during manufacturing and final process validation, especially for the drug substance.

As noted in section III.C, sponsors of initial clinical trials on botanical products that have been legally marketed as dietary supplements and that do not have safety issues can submit less CMC information than should be provided for later studies and for studies on products not previously marketed. Section VII.B describes the CMC information that should be submitted for initial trials on previously marketed botanicals.

Sponsors should submit additional CMC information for initial studies on nonmarketed botanical products and marketed botanicals with safety issues (see section VIII.B) and for expanded trials on all botanical products (see section IX.B). Additional guidance (not specific to botanical drugs) on the submission of CMC information in INDs and marketing applications can be found in other CDER guidance documents.

In the initial stage of clinical studies on a botanical drug, it is generally not necessary to identify the active constituents or other biological markers or to have a chemical identification and assay for a particular constituent or marker. Identification by chromatographic fingerprinting and strength by weight can be acceptable alternatives. Attributes for lot or batch release testing should be determined as the clinical study

progresses, although appropriate limits for batch use need not be established until later in phase 3 studies. Batch analyses on clinical lots should be submitted as they become available to demonstrate the batch-to-batch consistency and to help establish appropriate limits for fingerprinting. When possible, efforts should also be made to identify active constituents during phase 3 studies.

A single formulation (i.e., one in which the components or ingredients and composition of the drug substance and drug product are kept constant) and a single-dosage form should be used throughout the different stages of the clinical trials. More important, the IND sponsor should, to the extent possible, obtain sufficient quantities of the botanical drug product in a single batch from a single source of the botanical drug substance and/or raw materials to sustain the initial clinical trials. This is especially true if the sponsor does not have access to the manufacturing and controls information on the botanical drug substance and finished product. Unless the sponsor is equipped to conduct quality assurance testing from batch to batch, using a single batch or source of product is the best way to eliminate any possible product differences or batch variations during the clinical trial. In addition, sufficient quantities of the botanical raw material and drug substance from the same batch should be retained for future chemical and/or pharmacological/toxicological testing. It is equally important to obtain the botanical drug product from a source willing to provide FDA with detailed manufacturing and controls information when needed, or as clinical evaluation of the product progresses. These factors are crucial if the sponsor intends to pursue FDA approval for a drug claim for the botanical product.

Botanical raw materials may sometimes be dispensed at clinics on an *as needed* or *by prescription* basis and subsequently prepared by patients themselves at home. These practices should be avoided during clinical trials if at all possible because data related to such use may not be reliable due to variability of preparation among patients. When absolutely necessary, dispensing in such a manner may be considered for initial clinical studies. But as clinical trials are expanded, the botanical drug product should be produced in a controlled manner by an established manufacturer to ensure the validity and reliability of data.

If previously available preclinical and/or clinical data are provided or referenced in the IND, a comparison should be made among the botanical drug products used in the referenced studies, those to be used in the proposed trials, and (if appropriate) the products intended for marketing (including their corresponding botanical raw materials, drug substances, and formulations).

If a synthetic or highly purified drug or a biotechnology- or other naturally derived drug is added to a botanical drug product, the CMC data for this added substance should be described or cross-referenced according to FDA regulations and guidances. Animal parts (e.g., insects, annelids, shark cartilage) or minerals that are combined with the

botanical in a drug product should be accompanied by additional manufacturing and controls information specific to these materials.

CMC information on a botanical raw material, drug substance, and/or drug product may be submitted by the sponsor as part of the IND or by the manufacturer (if different from the sponsor) in a drug master file (DMF). A DMF is a submission from a manufacturer to FDA that may be used to provide confidential information on a human drug (21 CFR 314.420(a)). The information contained in a DMF may be used by cross-reference to support an IND or NDA and is reviewed by FDA only when authorized by the manufacturer. However, the sponsor relying on information in a DMF should have adequate acceptance testing for receipt of raw material, drug substance, or drug product from the DMF holder.

7. Pharmacological and Toxicological Information

The content and format for pharmacological and toxicological information to be provided in an IND are stated in 21 CFR 312.23(a)(8). Preclinical pharmacology and toxicology studies are useful in guiding early clinical studies and in predicting the potential toxicity of a new drug. Traditional herbal medicines or currently marketed botanical products, because of their extensive though uncontrolled use in humans, may require less preclinical information to support initial clinical trials than would be expected for synthetic or highly purified drugs. When early clinical studies are to be conducted with a botanical product that is not currently lawfully marketed in the United States, but is prepared, processed, and used according to methodologies for which there is prior human experience, sufficient information may be available to support such studies without standard preclinical testing. After initial clinical studies, further pharmacology and toxicology studies of a botanical drug would generally be needed prior to later phases of clinical development and prior to approval for marketing. Sections VII.C, VIII.C, and IX.C provide details on the pharmacological and toxicological information that should be provided in clinical trials on botanical drugs.

8. Previous Human Experience With the Product

Under 21 CFR 312.23(a)(9), an IND sponsor must submit information about previous human experience with an investigational drug. Because many botanical products have been marketed or tested in clinical studies (although such studies often involve few patients), this information should be included in an IND to assist FDA in its overall assessment of the safety of the product. Sections VII.A, VIII.A, and IX.A of this guidance provide additional recommendations on the submission of information on previous human experience with a botanical product.

VII. INDS FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES OF LAWFULLY MARKETED BOTANICAL PRODUCTS

This section provides more detailed guidance on the submission of certain types of information for INDS for initial clinical studies on botanical products that have been lawfully marketed and that do not raise safety issues (for drugs with known safety concerns, see section VIII). This section also notes where additional information should be provided when an IND is for a botanical product that has been marketed in one or more foreign countries but not the United States.

A. Description of Product and Documentation of Human Use

1. Description of Botanicals Used (§ 312.23(a)(3)(i))

The following information should be provided for *each* of the botanical raw materials used as ingredients in a botanical drug product:

- Common or usual names of the plant, alga, or macroscopic fungus
- Synonyms (e.g., Latin, Greek, English, Spanish, Chinese)
- Name of variety, species, genus, and family, including the name of the botanist who first described the species or variety, if known
- Chemical class of the active constituent (the chemical constituent that is responsible for the claimed pharmacological activity or therapeutic effect) or characteristic marker (a chemical constituent used for identification and/or quality control purposes), if known

2. History of Use (§ 312.23(a)(3)(ii), (9))

The sponsor should include information found in historical sources (e.g., books of medical practice in Ayurveda, traditional Chinese medicine, Unani, Sida) and scientific literature about the prior human use of the botanical product, and each of its ingredients, in traditional foods and drugs. The literature should be provided in English (and in its original language, if other than English).

3. Current Marketed Use (§ 312.23(a)(3)(ii), (9))

The sponsor should include information about the nature and extent of the current worldwide use of the botanical product, and each of its ingredients, in foods and drugs, including evidence concerning its marketing experience in the United States and/or foreign countries. For a foreign-marketed botanical product, the sponsor should provide data (if available) that verify its safe human use, including official proof of the annual sales

volume, an estimate of the size of the exposure population, and the rate of adverse effects.

B. Chemistry, Manufacturing, and Controls (§ 312.23(a)(7))

Outlined below is the CMC information that should be submitted, in accordance with 21 CFR 312.23(a)(7), in an IND to support a phase 1 or phase 2 clinical trial on a botanical product that is currently lawfully marketed without any known safety issues in the United States and/or a foreign country. Literature references and relevant official compendia or published standards should be provided wherever possible.

1. Botanical Raw Material

The information discussed in section VII.A.1 should be provided for all currently lawfully marketed products. A certificate of authenticity signed by a trained botanist should be provided, if available, for each botanical raw material in a product that is only marketed outside the United States.

2. Botanical Drug Substance

The type of *manufacturing process* (e.g., pulverization, decoction, expression, aqueous extraction, or ethanolic extraction) should be provided, if available. This is especially important where more than one process exists in the literature on which the safety of the botanical drug substance is based.

3. Botanical Drug Product

A botanical drug product is manufactured from a botanical drug substance by adding one or more excipients, mixing, blending, granulating, tableting, encapsulating, or performing other dosage form-specific procedures, followed by packaging. When packaged without further processing, a botanical drug substance is considered the drug product. The following information should be provided for a botanical drug product:

- a. A *qualitative description* of the finished product, including the dosage form, route of administration, names of all ingredients (i.e., botanical drug substance and excipients), and a statement that the product is not adulterated with potent, toxic, or addictive botanical substances, synthetic or highly purified drugs, or biotechnology- or other naturally derived drugs.
- b. The *composition or quantitative description* of the finished product (i.e., the quantity of the botanical drug substance) expressed in terms of amount per dosage unit. This information should be provided in tabulated form.

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Example for a single-herb botanical drug product:

<u>Component</u>	<u>Amount per 1-g tablet</u>
Senna leaf extract (1:8 powdered aqueous extract)	250 mg

Example for a multi-herb botanical drug product:

<u>Component</u>	<u>Amount per 1-g tablet</u>
A 1:5 powdered, aqueous extract from 1:1 mixture of <i>Forsythia suspensa</i> Vahl. flowers and <i>Lonicera japonica</i> Thunb. fruits	600 mg

- c. If available, the *manufacturer's certificate of analysis* for the study product or *authorization to allow FDA to cross-reference* its previous submission for the relevant CMC information. If this information is unavailable for a foreign-marketed product, the sponsor should perform *quality testing* on the product according to the recommendation listed under section VIII.B.3.e, a heavy metal analysis, and an animal safety test, if applicable, and should provide the *test results* in the IND. The study product should be from a single source and, where feasible, from a single batch. A product sample from the batch to be used in the clinical study should be retained for possible future testing by FDA.

4. *Placebo*

The components of any placebo used should be described.

5. *Labeling*

The following labeling information should be provided:

- a. A copy of the container label and the immediate outer carton label of the marketed product to be used in the clinical study.
- b. A mock or printed representation of the proposed container label that will be provided to the investigators in the proposed clinical study. It should contain the following information: protocol number; patient number; sponsor's name; product name or code number; strength and/or potency; recommended storage conditions; lot number; and (as required under 21 CFR 312.6) the statement,

"Caution: New drug — Limited by Federal law to investigational use." In a placebo-controlled clinical trial, both the study drug and the placebo should be properly labeled to protect the integrity of the blinded study.

6. *Environmental Assessment or Claim of Categorical Exclusion*

A claim for categorical exclusion from the requirement for preparation of an environmental assessment (EA) ordinarily can be made for an IND (21 CFR 25.31(e)).

C. **Pharmacology/Toxicology Information (§ 312.23(a)(8))**

1. *All Marketed Botanical Products*

To support initial clinical trials (phase 1 and phase 2) of a botanical drug product, previous human experience and available animal toxicity data concerning the clinical formulation and the individual botanical ingredients within the formulation should be provided to support the proposed use. As noted in section VI.A, initial studies for U.S.-marketed products may generally be conducted without further pharmacologic/toxicologic testing. Nevertheless, available information should be provided. A database search should be conducted, when feasible, to identify information relevant to the safety and effectiveness of (1) the final formulation of the intended commercial botanical drug product, (2) the individual botanical ingredients, and (3) the known chemical constituents of the botanical ingredients.

An integrated summary of available data from medical and toxicological databases (e.g., Medline, Toxline, TOMES, RTEC) should be submitted for review. Using the information gathered from this literature, the sponsor should address, as appropriate for the proposed study, the following issues concerning the botanical drug product: (1) general toxicity; (2) target organs or systems of toxicity; (3) teratogenic, carcinogenic, or mutagenic potential of any botanical ingredient in the product; (4) relationship of dosage and duration to toxic responses; and (5) pharmacological activity.

2. *Foreign-Marketed Botanical Products*

For the reasons discussed in section VI, for a botanical product with which there is some foreign marketing experience, but which is not marketed in the United States, in addition to information listed above, the sponsor should provide data that support safe human use and should include the annual sales volume, an estimate of the size of the exposure population, and available data on the rate of adverse effects. The nature of preclinical pharmacology/toxicology information needed before a sponsor conducts an initial clinical study will be determined on a case-by-case basis depending on the indications, dose proposed, and available supporting safe human experience.

D. Bioavailability

Depending on the complexity of the botanical drug product to be studied, pharmacokinetic and pharmacodynamic information may be helpful in the design and interpretation of clinical studies. Botanical products often consist of more than one chemical constituent. In some cases, a product's active moieties may not be known, and standard pharmacokinetic measurements to demonstrate systemic exposure to a product in animals and/or humans may be infeasible. However, when feasible a sponsor should attempt to monitor the blood levels of known active ingredients, representative markers, or major chemical constituents in a botanical drug product.

E. Clinical Considerations

The initial clinical trial for a botanical product marketed under the DSHEA should ordinarily be a well-controlled study capable of demonstrating effectiveness. Because the product is marketed and the dose thought to be appropriate and well tolerated is known, there should be little need for pilot or typical phase 1 studies, and uncontrolled observations are unlikely to be useful. Sponsors are therefore strongly encouraged to initiate more definitive trials early in the development program to determine whether a botanical preparation has efficacy for one or more claimed indications. If there is doubt about the best dose of the product tested, a randomized, parallel, dose-response study may be particularly useful as an initial trial.

Regarding the safety of the drug, a botanical preparation lawfully marketed in the United States will be considered acceptable for at least short-term (e.g., up to several months) use in clinical trials. For foreign marketed botanical products, safety considerations will be based on available CMC, pharmacology, and toxicology information, as well as indications, dose proposed, and available data supporting safe human use.

VIII. INDs FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES OF NONMARKETED BOTANICAL PRODUCTS

This section discusses the type of information that should be provided in INDs for initial trials of botanicals that have not previously been lawfully marketed in the United States or elsewhere or that have known safety issues.

A. Description of Product and Documentation of Human Use

In addition to the information outlined in section VII.A.1-2, the following should be provided for each raw material contained in a botanical product not lawfully marketed in either the United States or other countries:

1. Description of Botanicals Used (§ 312.23(a)(3)(i))

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- Morphological and anatomical description (including gender, if applicable) and a photograph of the plant or plant part, alga, or macroscopic fungus used
- Natural habitat and geographical distribution of the plant, alga, or macroscopic fungus
- Current sources of the plant, alga, or macroscopic fungus, including its geographical location and whether it is cultivated or harvested from the wild
- A statement indicating whether the species is any of the following:
 - Determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora;
 - Entitled to special protection under some other Federal law or international treaty to which the United States is a party;
 - The critical habitat of fauna that have been determined to be endangered or threatened

2. *History of Use (If Any) (§ 312.23(a)(3)(ii), (a)(9))*

- Method of preparation, processing, and formulation
- Routes, schedules, and doses of administration
- Medical claims
- Contraindications and adverse events that have been associated with use in humans and animals
- Traditional geographical areas and populations in which such use occurred
- A description of the similarities and/or differences between the traditional preparation and the proposed clinical formulation

3. *Current Investigational Use (If Any) (§ 312.23(a)(3)(ii), (a)(9))*

- Proposed therapeutic claim and dose regimen (mg/kg/dose and dose/day)
- All available information in the literature both in support of and in opposition to the proposed therapeutic claim

B. Chemistry, Manufacturing, and Controls (§ 312.23(a)(7))

Outlined below is the CMC information that should be submitted, in accordance with 21 CFR 312.23(a)(7), in an IND to support a phase 1 or phase 2 clinical trial using a botanical product that is not currently lawfully marketed in the United States or a foreign country, or for which there are known safety issues.

1. Botanical Raw Material

A botanical drug substance can be derived from one or more botanical raw materials. The following recommendations apply to each individual botanical raw material used.

The botanical raw material should be described as outlined in sections VII.A.1 and VIII.A.1. If the botanical raw material has no documented history of use, the IND sponsor should so indicate. Proper identification by trained personnel of the plant, plant parts, alga, or macroscopic fungus used, including organoleptic, macroscopic, and microscopic examination, should be provided. If more than one variety or source of a given species is used, each should be specified. A voucher specimen of the plant or plant parts should be retained for each batch.

In addition, the following items should be provided if available:

- Certificate of authenticity
- Name and address of the grower and/or supplier
- Harvest location and harvest time
- Collection, washing, drying, and preservation procedures
- Handling, transportation, and storage

2. Botanical Drug Substance

The following information should be provided for all botanical drug substances, regardless of whether they are prepared from one or more botanical raw materials:

- a. A *qualitative description* of the drug substance, including the name, appearance, physical and chemical properties, active constituent (if known), biological activity (if known), and clinical indication (if known) of each botanical raw material. If the active constituent, biological activity, and/or clinical indication is unknown, the IND sponsor should clearly so state. In the case of a multi-herb substance, the sponsor should state whether the drug substance is

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prepared by combining individually processed botanical drug substances or by processing combined botanical raw materials.

- b. The *quantitative description (strength)* of the drug substance. Historically, the strength of a botanical drug substance is expressed simply as the absolute weight of the processed substance. The batch size and the yield of the process, relative to the botanical raw material, should also be indicated. Furthermore, where the active constituents or other chemical markers are known and measurable, the amount in which they are present in the botanical drug substance should be declared. For a multi-herb substance, its composition should be expressed in terms of the relative ratio of the individually processed botanical drug substances or of the botanical raw materials before processing, whichever is appropriate.
- c. The name and address of the drug substance *manufacturer* (processor)
- d. The type of *manufacturing process*, as described in section VII.B.2
- e. The *quality control tests* performed on each batch of the drug substance and the available test results. These tests should include, but need not be limited to, the following attributes:
 - Appearance
 - Chemical identification by spectroscopic or chromatographic fingerprints. Examples of spectroscopic methods include ultraviolet, infrared, and Fourier transformed infrared. Examples of chromatographic methods include high performance liquid chromatography (HPLC), HPLC with diode array detection, thin layer chromatography (TLC), 2-dimensional-TLC, and gas chromatography.
 - Chemical assay (or assay) for active constituents or characteristic markers, if available
 - Assay for biological activity (or biological assay), if available
 - Strength by weight (equivalent to botanical raw material)
 - Heavy metals
 - Microbial limits
 - Animal safety test, if applicable

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A chemical assay and/or assay for biological activity should be performed if the botanical drug substance is considered potent (i.e., highly active), toxic, addictive, or to have abuse potential (e.g., ephedra or marijuana).

- f. A description of the *container* in which the botanical drug substance is to be stored and/or shipped
- g. Available *stability data* on the drug substance. The sponsor should develop stability-indicating analytical methods and conduct stability studies as the IND progresses.
- h. The *container label*, which should reflect the qualitative and quantitative description of the botanical drug substance, as discussed above, and recommended storage conditions. Examples of labeling for single- and multi-herb substances are shown below:

Single-herb substance:

- Expressed in terms of yield:
Senna, 10 kg, equivalent to 80 kg of dried leaves
or
Senna, 10 kg, 1:8 (w/w) powdered extract of dried leaves
- Expressed in terms of chemical markers or active constituents:
Senna, 10 kg, contains 2 kg of hydroxyanthracene glycosides (sennosides), calculated as sennoside B

Multi-herb substance:

- Prepared by combining individually processed botanical drug substances:
Lonicera japonica Thunb. and *Forsythia suspensa* Vahl., 6 kg, containing 3 kg of *Lonicera japonica* Thunb. 1:4 solid extract and 3 kg of *Forsythia suspensa* Vahl. 1:6 solid extract
- Prepared by processing combined botanical raw materials:
Lonicera japonica Thunb. and *Forsythia suspensa* Vahl., 6 kg, a 1:5 powdered extract prepared from 15 kg of *Lonicera japonica* Thunb. and 15 kg of *Forsythia suspensa* Vahl

3. *Botanical Drug Product*

The following information should be provided:

- a. A *qualitative description* of the finished product (see section VII.B.3.a)
- b. The *composition, or quantitative description*, of the finished product (i.e., the name and quantity of the botanical drug substance and of each excipient (if any), expressed in terms of amount per dosage unit and amount per batch). This information should be provided in tabulated form. A quantitative description of the drug substance should be provided as described in section VIII.B.2.h.

Example:

<u>Component</u>	<u>Amount per tablet</u>	<u>Amount per batch</u>
Senna	250 mg (equivalent to 2000 mg dried leaves)	10.0 kg (equivalent to 80.0 kg of dried leaves)
Excipient 1	100 mg	4.0 kg
Excipient 2	10 mg	0.4 kg

- c. The name and address of the *manufacturer* of the finished drug product
- d. A description of the *manufacturing process*. (If the botanical drug substance is filled and packaged directly as the finished product without the addition of excipients and further processing, items b, c, and d will not apply.)
- e. A list of the *quality control tests* performed on each batch of the drug product and the available test results. These tests should include, but need not be limited to, the following attributes:
 - Appearance
 - Chemical identification by spectroscopic or chromatographic fingerprints
 - Assay for active constituents or characteristic markers, if available
 - Assay for biological activity (or biological assay), if available
 - Strength by weight (of drug substance)
 - Microbial limits
 - Other attributes specific to the dosage form of interest

A chemical assay and/or assay for biological activity should be performed if the botanical drug substance is considered to be potent (i.e., highly active), toxic, addictive, or to have abuse potential.

- f. A description of the *container/closure* in which the drug product is to be packaged
 - g. Available *stability data* on the drug product. The sponsor should develop stability-indicating analytical methods (using markers when feasible) and conduct stability studies as the IND progresses.
- 4. *Placebo (see section VII.B.4)*
 - 5. *Labeling (see section VII.B.5)*

Additionally, a quantitative description of the drug substance per dosage unit (as described in section VIII.B.2.h and 3.b) should be provided. An example of a quantitative description for a multi-herb botanical drug product is shown below:

BRAND X. 100 tablets. Each 1-g tablet contains:
300 mg of *Lonicera japonica* Thunb. 1:4 solid extract and
300 mg of *Forsythia suspensa* Vahl. 1:6 solid extract

6. *Environmental Assessment or Claim of Categorical Exclusion*

A claim for categorical exclusion from the requirement for preparation of an EA ordinarily can be made for an IND (21 CFR 25.31(e)). However, FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21 CFR 25.21; 40 CFR 1508.4). CDER will evaluate INDs on a case-by-case basis when the drug or biological product is derived from wild plants or animals to determine whether the extraordinary circumstance provision in 21 CFR 25.21 is applicable. FDA encourages early consultation with the Agency on environment-related aspects of a requested action, especially one that involves harvesting a wild species, to ensure that planning and decisions reflect environmental values, avoid delays later in the process, and avoid potential conflicts (21 CFR 25.10(b) and 25.10(c)). For additional information see 21 CFR Part 25, 40 CFR Parts 1500-08, and the CDER/CBER guidance for industry on *Environmental Assessment of Human Drug and Biologics Applications* (July 1998). An environmental assessment or a claim for categorical exclusion should be provided as required under 21 CFR 25.15(a).

C. Preclinical Safety Assessment

1. Traditional Preparations

Preclinical pharmacology and toxicology studies are particularly important in establishing the safety of a new botanical drug for which there is no current marketing experience. The information is used for assessing the botanical drug's risk-to-benefit ratio, guiding early clinical studies, and predicting potential toxicity.

Because of their extensive though uncontrolled use in humans, there may be sufficient information on traditional herbal medicines to support initial clinical studies without standard preclinical testing. Therefore, such products may require different preclinical safety information under 21 CFR 312.23(a)(8) than that expected for synthetic or highly purified drugs for which there is little experience.

A traditional herbal preparation, which may have evolved over time, generally has the following characteristics: (1) It meets official compendia or other published standards in terms of the botanical identity and plant part used for each botanical raw material; (2) in the case of a multi-herb substance, it is composed of the same formulation as a historical formula, with the amount of each botanical ingredient falling within the range of traditional usage; (3) it is prepared by the same processing methodology as traditionally used; and (4) it is used in the traditional manner in terms of therapeutic indication, route and schedule of administration, and quantities or doses.

For initial clinical studies on a botanical drug product that is not currently lawfully marketed in the United States or elsewhere but is prepared, processed, and used according to methodologies for which there is prior human experience, sufficient information might be available to support the studies without standard preclinical testing. In general, the considerations listed under section VII.C are applicable. When the initial clinical study for such a drug shows promising results and further clinical development of the drug is intended, pharmacology and toxicology studies carried out prior to the later phases of the clinical trials may be needed to support a risk-benefit assessment and to identify potential toxicities not readily detected in clinical studies (see section IX.C below).

2. Others

For a botanical product that is not prepared according to a traditional methodology, the extent of variation from the traditional formulation, preparation, or processing should be described in full detail. The nature of preclinical pharmacology/toxicology information needed before conducting an initial clinical study (in addition to that described under section VII.C) will be determined on a case-by-case basis, depending on the indications,

extent of safe human experience, and safety concerns about the new formulation, preparation, or processing methodology used.

D. Bioavailability

As stated in section VII.D, a botanical product's active constituents may be unknown, and standard pharmacokinetic measurements to demonstrate systemic exposure to a product in animals and/or humans may be infeasible. However, when feasible a sponsor should attempt to monitor the blood levels of known active constituents, representative markers, or other major chemical constituents in a botanical drug product. Because there is less human use experience with botanical products that have never been lawfully marketed than with those that have been, a sponsor of a drug that has not been lawfully marketed should consult FDA's guidance on *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro* (April 1997) to assess potential drug-drug interaction when a clinical study includes co-administration with another drug.⁸

For a botanical product that is prepared according to traditional methodology, the nature of clinical pharmacology information needed should be determined on a case-by-case basis, depending on the indications, extent of human experience, target patient population, and projected length of clinical use.

E. Clinical Considerations

In general, initial clinical investigations of nonmarketed botanical preparations are the same as those of marketed products (see section VII.E). Because of the lack of current marketing experience, however, greater concerns could exist about toxicity. Therefore, FDA will seek greater assurance of the safety of the product for initial clinical trials in the United States. Such assurance may be provided in the form of additional chemical analysis and/or additional toxicology data. It may also be helpful to provide documentation of the product's previous safe human use by referencing literature and/or pharmacopoeias.

IX. INDs FOR PHASE 3 CLINICAL STUDIES OF ALL BOTANICAL PRODUCTS

When conducting expanded (i.e., phase 3) clinical studies on a botanical drug product, an IND sponsor is expected to provide more detailed information on CMC and preclinical safety than when conducting a phase 1 or phase 2 study (21 CFR 312.22(b), 312.23(a)(7)(i), 312.23(8)). The better definition of the product will ensure an ability to apply data from trials to a well-controlled, reproducible substance. The additional toxicology data is needed to support wider use. This additional information should be provided regardless of whether the product is currently lawfully marketed in the United States or elsewhere as a dietary supplement.

⁸In addition, FDA has published a draft guidance on *In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling* (November 1998).

For phase 3 clinical studies of a botanical product, the following information should be provided in accordance with § 312.23:

A. Description of Product and Documentation of Human Experience

See sections VII.A and VIII.A for guidance on how to describe the botanical product and human experience with it.

B. Chemistry, Manufacturing, and Controls (§ 312.23(a)(7))

To support phase 3 clinical trials using a botanical product, regardless of its marketing experience in the United States or other countries, the following CMC information should be provided unless already submitted in the IND for phase 1/phase 2 studies on the product:

1. Expanded Clinical Studies

a. Botanical raw material

- A *description* of the botanical raw material as outlined in sections VII.A.1 and VIII.A.1. If the botanical has no documented history of use, this should be indicated. Proper identification by trained personnel of the plant, plant parts, alga, or macroscopic fungus used, including organoleptic, macroscopic, and microscopic examination, should be provided. If more than one variety or source of a given species is used, they should be blended in a fixed proportion in a consistent manner. A voucher specimen of the plant or plant parts should be retained for every batch. In addition, a certificate of authenticity and information on the grower and/or supplier, growing conditions (including pesticides used), harvest location, harvest time, preservation procedures, handling, and shipping should be provided.
- A chromatographic fingerprint of each botanical raw material and the *chemical identity* of the active constituents or characteristic markers in the botanical raw material
- The name and address of the botanical raw material *manufacturer* (processor)
- A description of the *preparation* of the botanical raw material, including collection, washing, drying, preservation, and/or detoxification and preservation procedures. Equipment and quantity used, temperature employed, processing time, in-process controls, and yield should be specified.
- The *quality control tests* applied by the botanical raw material supplier, including the following specifications:

- Botanical identification
- Chemical identification by spectroscopic or chromatographic fingerprint
- Chemical identification for active constituents or characteristic markers if active constituents are not known
- Assay for active constituents or characteristic markers if active constituents are not known
- Biological assay, if available
- Heavy metals
- Microbial limits
- Residual pesticides, including parent pesticides and their major toxic metabolites
- Adventitious toxins (e.g., aflatoxins)
- Foreign materials and adulterants
- A specimen of the botanical raw material retained as the *reference standard* for use in identification, fingerprinting, and other comparative and noncomparative tests
- A *certificate of analysis* for a representative batch of the botanical raw material
- A description of the *storage conditions*, including the container/closure system and temperature
- b. Botanical drug substance
 - A *qualitative and quantitative description* of the drug substance and the name and address of the *manufacturer* (see section VIII.B.2.a-c).
 - A *chemical identification* for the active constituents or characteristic markers in the drug substance, if possible. If the chemical identity is unknown, a representative chromatographic fingerprint may suffice.
 - Appropriate *specifications* (tests, methods, and acceptance criteria) for the botanical raw material, similar to the list of quality control specifications in section IX.B.1.a, established by the botanical drug substance manufacturer. Upon receipt

of each batch of the raw material and its certificate of analysis, the manufacturer should, at a minimum, conduct an identification test and assay.

- A description of the *manufacturing process* for the botanical drug substance. The description should include the quantity of botanical raw material, equipment, solvents, temperature/time for mixing, grinding, extraction and/or drying, yield, and in-process controls. The yield of the process, expressed as the amount of the extract relative to the amount of the original botanical raw material, should also be indicated. If more than one botanical raw material is introduced to produce a multi-herb substance, the quantity of each raw material and the sequence of addition, mixing, grinding, and/or extraction should be provided. If a multi-herb substance is prepared by combining two or more individually processed botanical drug substances, the process leading to each botanical drug substance should be described separately.
- The *quality control tests*, including, but not limited to, the following specifications:
 - Appearance
 - Chemical identification by spectroscopic or chromatographic fingerprints
 - Chemical identification for the active constituents or, if unknown, the characteristic markers
 - Chemical assay for the active constituents, or the characteristic markers if the active constituents cannot be determined. If several botanical raw materials are combined to produce a multi-herb substance and a quantitative determination of each individual active constituent or marker is infeasible, a joint determination can be carried out for several active constituents or markers.
 - Biological assay
 - Strength by weight
 - Residue on ignition
 - Water content
 - Residual solvents
 - Heavy metals
 - Microbial limits
 - Animal safety test, if applicable
 - Residual pesticides
 - Radioisotope contaminants, if applicable
 - Adventitious toxins (e.g., aflatoxins)

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- Endogenous toxins (e.g., pyrrolizidine alkaloids)
 - Other attributes specific to the botanical raw materials from which the drug substance is derived
-
- A description of all *test methods* and, where appropriate, their validation reports
 - A description of the batch of botanical drug substance designated as the *reference standard* for use in fingerprinting and other comparative tests
 - Test results for a representative batch (i.e., *batch analysis*)
 - A description of the *container and closure* used to package the botanical drug substance
 - Sufficient *stability data* on the drug substance to support its safe use during clinical studies.
 - Stability-indicating analytical methods should be established.
 - Information on the *container label* as described in section VIII.B.2.h.
- c. Botanical drug product
- A *qualitative description and the composition* of the dosage form and the name and address of the *manufacturer* (see section VIII.B.3.a-c)
 - Appropriate *acceptance specifications* established by the botanical drug product manufacturer for the botanical drug substance, similar to the quality control tests in section IX.B.1.b. Upon receipt of each batch of the drug substance and its certificate of analysis, the manufacturer should, at a minimum, conduct an identification test and assay.
 - A description of the *manufacturing process*, without the actual batch record. The description should include weighing, mixing, blending, sieving, in-process controls, and other processes, as appropriate.
 - The *quality control tests*, including, but not limited to, the following specifications:
 - Appearance
 - Chemical identification by spectroscopic or chromatographic fingerprints

- Chemical identification for the active constituents or, if unknown, the characteristic markers
 - Chemical assay for active constituents or, if unknown, the characteristic markers
 - Biological assay
 - Strength by weight
 - Residual solvents
 - Microbial limits
 - Adventitious toxins (e.g., aflatoxins)
 - Other attributes specific to the dosage form of interest
- A description of all *test methods* and, where appropriate, their validation procedures
 - Test results for a representative batch
 - A description of the *container and closure* used to package the finished product
 - Sufficient *stability data* on the drug product to support its safe use during clinical studies. Stability-indicating analytical methods should be established.
- d. Placebo (see section VII.B.4)
- e. Labeling (see sections VII.B.5.b for investigational labels and VIII.B.5 for quantitative description)
- f. EA or claim of categorical exclusion (see section VIII.B.6)

2. *End-of-Phase 3 Clinical Studies and Pre-NDA Considerations*

By the end of the phase 3 clinical trial, as the sponsor prepares to submit an NDA, the following objectives should be reached:

- a. Adequate controls for *botanical raw materials* should be established.

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- b. The *manufacturing process* should be finalized and validated, and *in-process controls* should be established. An executed batch record should be available.
- c. *Batch-to-batch consistency* should be demonstrated for the botanical drug substance and drug product based on results from all chemical, physical, and biological tests on all relevant batches. All chemical constituents present in the drug substance batches should be qualitatively and quantitatively comparable based on spectroscopic and/or chromatographic fingerprinting.
- d. Appropriate *specifications* (i.e., a list of test attributes, analytical methods and test procedures, and acceptance criteria), including identification and assay for active constituents, identification and assay for characteristic markers, and/or biological assay, should be established to control the quality of the drug substance and product. Both the active constituents and the biological assay should be clinically relevant. If the identity of the active constituents is not known or a suitable assay cannot be developed, the characteristic markers should be demonstrated to be clinically relevant by direct or indirect correlation to the clinical outcome.
- e. *Analytical methods and test procedures* should be properly validated. Analytical methods used for fingerprinting should be capable of detecting as many chemical constituents as possible. Multiple fingerprints, using a combination of analytical methods with different separation principles and test conditions, may be useful. Additionally, the analytical methods in combination should be able to demonstrate the mass balance of the test sample.
- f. A suitable *reference standard* for each of the botanical raw materials, drug substances, and drug product should be established and retained.
- g. *Stability-indicating analytical methods* should be developed to monitor the stability of the drug substance and drug product. The stability of a botanical drug substance or product generally should not be based entirely on the assay of the active constituents, assay of the characteristic markers, or biological assay, because degradants formed during storage from other chemical constituents in the botanical drug substance or product should also be controlled. An analytical method capable of detecting these degradants (such as a chromatographic fingerprint) should be established through exploratory studies by subjecting the drug substance and drug product to stress conditions.
- h. A comparison of the similarities and/or differences in CMC among the preclinical, clinical, and intended commercial products should be made regarding raw materials, drug substance, and drug product.

- i. The manufacturing and testing facilities for the drug substance and drug product should be ready for FDA inspection to determine if they are in conformance with CGMPs as set forth in 21 CFR Parts 210 and 211. A satisfactory inspection is necessary for NDA approval.
- j. Preparation should be underway for submission in the NDA of either an EA or a claim for categorical exclusion from the requirement for preparation of an EA (21 CFR 25.15(a)). Classes of NDAs that are categorically excluded and, therefore, ordinarily do not require preparation of an EA are listed in 21 CFR 25.31. However, FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21 CFR 25.21; 40 CFR 1508.4). The Agency regards the submission of an NDA for a drug derived from plants taken from the wild as an extraordinary circumstance requiring the submission of an EA. See section VIII.B.6 for additional information.

Applicants are encouraged to discuss with the review division any CMC issues regarding a botanical drug prior to the preparation and submission of an NDA.

C. Preclinical Safety Assessment (including Pre-NDA)

To support safety for expanded clinical studies or to support marketing approval of a botanical drug product, toxicity data from standard toxicology studies in animals may be needed. A botanical product submitted for approval for marketing as a drug will be treated like any other new drug under development. Previous human experience may be insufficient to demonstrate the safety of a botanical product, especially when it is indicated for chronic therapy. Systematic toxicological evaluations could be needed to supplement available knowledge on the general toxicity, teratogenicity, mutagenicity, and carcinogenicity of the final botanical product. Depending on the indication (e.g., target patient population, disease to be treated), route of administration, and duration of recommended drug exposure, the timing of these animal studies in relation to concurrent clinical trials and other requirements for preclinical animal studies can vary.

The following are points to consider in preparing a preclinical pharmacology/toxicology development plan for a botanical drug product that is intended to be used in large-scale human trials or to support an NDA. If questions arise during any stage of the clinical development of a botanical drug, sponsors are encouraged to consult the appropriate review division in CDER.

1. Repeat-Dose General Toxicity Studies

The primary objective of long-term, repeat-dose toxicity studies in animals is to identify the target organs and/or systems for toxicity and the threshold doses for producing toxic effects. The studies provide information valuable for designing long-term clinical studies

at safe doses with appropriate monitoring for predicted adverse reactions. Existing literature on the animal toxicity of a botanical drug product is often limited to single-dose (acute) toxicity studies. These studies may be inadequate to support the conclusion that a botanical drug product is *nontoxic* for multiple administrations because they were not designed to monitor the usual parameters of toxicity (e.g., clinical pathology and histopathology) or take into consideration the effect of more frequent dosing.

To support expanded clinical trials, repeat-dose toxicity of a drug product should usually be evaluated in two mammalian species (one of which is a non-rodent) by employing sufficiently high doses to produce a toxic effect or by using a maximum feasible dose. If possible, the drug should be tested using the same formulation and route of administration as proposed for clinical use. Animal studies should be of a duration at least equal to that of the clinical trial (usually a minimum of two weeks). General animal toxicity studies need not exceed 6 months of testing in a rodent species and 9 months testing in a non-rodent species. For additional information on the timing of animal toxicity studies in relation to clinical trials, see the International Conference on Harmonisation (ICH) guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (November 1997).

2. Nonclinical Pharmacokinetic/Toxicokinetic Studies

In the development of a new drug that is a single molecular entity, pharmacokinetic studies are often carried out to demonstrate systemic exposure and to relate exposure levels to toxicities in both animals and humans. Because botanical products usually consist of more than one chemical constituent, standard pharmacokinetic measurements to substantiate the systemic exposure of a botanical drug product in animals may be technically infeasible. However, monitoring major or representative chemical constituents in a botanical drug product can provide valuable information regarding systemic exposure. Depending on the complexity of the botanical drug product to be studied, pharmacokinetics could be helpful in the design and interpretation of toxicity studies. For additional information on toxicokinetic evaluations, see the ICH guidances *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies* (March 1995), and *S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies* (March 1995).

3. Reproductive Toxicology

Reproductive toxicology studies, such as those on fertility/reproductive performance, teratology, and prenatal/perinatal development in animals, provide information on the potential of a botanical drug product to produce toxicity during the different stages of reproductive and developmental processes. In the absence of documentation on reproductive toxicity in humans or animals, these tests should be conducted prior to expanded clinical trials. For detailed information regarding reproductive toxicology,

sponsors should refer to the ICH guidances *S5A Detection of Toxicity to Reproduction for Medicinal Products* (September 1994), and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility* (April 1996).

4. Genotoxicity Studies

Information on the potential of a botanical drug product to produce genetic toxicity should be obtained as early as possible, preferably before the initiation of human clinical trials. A complete assessment of genetic toxicity may be needed prior to expanded clinical trials. A standard battery of tests is defined in the ICH guidances *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (April 1996), and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (November 1997).

If the tests chosen indicate that a drug is devoid of genetic toxicity, additional studies may not be needed. If one or more test results are positive, the sponsor may need to carry out additional genotoxicity tests in consultation with the appropriate CDER review division.

5. Carcinogenicity Studies

Carcinogenicity studies may be needed to support marketing approval of a botanical drug, depending on the duration of therapy or any specific cause for concern. The toxicity profile of the botanical drug product and the indication and duration of the intended use may influence the need for carcinogenicity studies and their timing relative to clinical development (see ICH guidance *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996)). Draft protocols for carcinogenicity studies should be submitted to the appropriate review division and the CDER Carcinogenicity Assessment Committee for review and concurrence prior to the initiation of such studies to ensure the acceptability of dose selection and study design. Study types should be in accordance with the ICH guidance *S1B Testing for Carcinogenicity of Pharmaceuticals* (February 1998). Doses used should be chosen according to the principles outlined in the ICH guidances *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals* (March 1995), and *S1C(R) Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on a Limit Dose and Related Notes* (December 1997).

6. Special Pharmacology/Toxicology Studies

A general evaluation of pharmacological activity on organs and/or systems is often performed during new drug development. This evaluation can be accomplished using established in vitro and in vivo assays of broad specificity that screen for the modes and

sites of action of the botanical drug. When significant and unique toxicities to certain organs and/or systems are evident, the sponsor should provide further explanation of the mechanism of toxic actions, if necessary by performing additional in vitro or in vivo studies.

7. Regulatory Considerations

Preclinical toxicity studies conducted as part of botanical drug development and intended to support safety must be in accordance with regulations governing good laboratory practices under 21 CFR Part 58. To the extent possible, a botanical drug substance tested in animals should be prepared and processed in the same manner, and the botanical drug product should have the same formulation, as the product intended for human use. Both the drug substance and the drug product should be made with batch-to-batch consistency. If changes occur in the drug substance or product during clinical development, bridging toxicity studies might be needed.

D. Bioavailability and Drug-Drug Interactions

The general requirements for, and criteria for waiver of, in vivo bioavailability data in an NDA, described in 21 CFR 320.21 and 320.22, are applicable to botanical drug products. These data should be obtained from properly designed in vivo bioavailability studies during the IND stage. The type of bioequivalence study that is appropriate for a specific botanical drug product is based on the following: (1) information on the active constituent, if known; (2) the complexity of the drug substance; and (3) the availability of analytical methods. FDA may, for good cause, waive or defer the in vivo bioavailability study requirement if a waiver or deferral is compatible with the protection of the public health (21 CFR 320.22(e)).

Because there could be more than one active constituent in a botanical drug product or the active constituent may not be identified, it could be difficult or impossible to perform standard in vivo bioavailability and pharmacokinetics studies by measuring, as a function of time, the concentration of the active moiety, active ingredients, or active metabolites in whole blood, plasma, serum, or other appropriate biological fluid, or by measuring the excretion of the active moiety or active metabolites in urine. In some cases, it may be possible to measure an acute pharmacological effect as a function of time using an appropriate biological assay method. If this is not possible, the bioavailability and pharmacokinetics of a botanical drug could be based on clinical effects observed in well-controlled clinical trials.

Interactions with other commonly used medicines, either synthetic/highly purified or botanical, may occur with botanicals and should be investigated extensively. This may include characterization of the metabolic enzymes and/or pathway affected by the drug.⁹

⁹See CDER draft guidance on *In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling* (November 1998)).

Where possible, the effects of impaired clearance (renal or hepatic) on the drug's pharmacokinetics should be examined. This is easiest when the active substance(s) are known, but even if they are not, knowledge of the major constituents should make it possible to determine the effects of impaired clearance. Dose-response information may indicate the proper level of concern about impaired excretion.

As with synthetic and/or highly purified drugs, pharmaceutical and biopharmaceutical studies for botanical drug products are important for product quality control, batch comparison, and linkage between different strengths. These studies may involve, for example, in vitro dissolution testing, in situ drug absorption testing, in vitro-in vivo correlation studies, or in vitro percutaneous absorption/penetration testing, depending on the indication and formulation of the botanical product.

E. Clinical Considerations

Expanded studies of botanicals have the same purposes as expanded studies of synthetic drugs, including further evaluation of dose-response for favorable and unfavorable effects and evaluation of long-term effectiveness, different populations, different stages/severity of disease, and drug-drug interactions.

DEFINITIONS

The following definitions are intended for use in this guidance only and may not be appropriate in other contexts.

Active Constituent: The chemical constituent in a botanical raw material, drug substance, or drug product that is responsible for the intended pharmacological activity or therapeutic effect

Botanical Product; Botanical: A finished, labeled product that contains vegetable matter, which may include plant materials (see below), algae, macroscopic fungi, or combinations of these. Depending in part on its intended use, a botanical product may be a food, drug, medical device, or cosmetic.

Botanical Drug Product; Botanical Drug: A botanical product that is intended for use as a drug; a drug product that is prepared from a botanical drug substance. Botanical drug products are available in a variety of dosage forms, such as solutions (e.g., teas), powders, tablets, capsules, elixirs, and topicals.

Botanical Drug Substance: A drug substance derived from one or more plants, algae, or macroscopic fungi. It is prepared from botanical raw materials by one or more of the following processes: pulverization, decoction, expression, aqueous extraction, ethanolic extraction, or other similar process. It may be available in a variety of physical forms, such as powder, paste, concentrated liquid, juice, gum, syrup, or oil. A botanical drug substance can be made from one or more botanical raw materials (see Single-Herb and Multi-Herb botanical drug substance or product). A botanical drug substance does not include a highly purified or chemically modified substance derived from natural sources.

Botanical Ingredient: A component of a botanical drug substance or product that originates from a botanical raw material

Botanical Raw Material: Fresh or processed (e.g., cleaned, frozen, dried, or sliced) part of a single species of plant or a fresh or processed alga or macroscopic fungus

Chromatographic Fingerprint: A chromatographic profile of a botanical raw material or drug substance that is matched qualitatively and quantitatively against that of a reference sample or standard to ensure the identity and quality of a batch and consistency from batch to batch

Cosmetic: An article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, or an article intended for use as a component of any such article, except that such term does not include soap (21 U.S.C. 321(i))

Dietary Supplement: "[A] product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or

other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E); (2) means a product that (A) is intended for ingestion in a form described in section 411(c)(1)(B)(i) [of the FD&C Act]; or complies with section 411(c)(1)(B)(ii); is not represented for use as a conventional food or as a sole item of a meal or the diet; and is labeled as a dietary supplement; and (3) does (A) include an article that is approved as a new drug under section 505 or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262) and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless [FDA] has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f); and (B) not include (i) an article that is approved as a new drug under section 505, certified as an antibiotic under section 507, or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), or (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless [FDA], in [its] discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act" (21 U.S.C. 321(ff)).

Dosage Form: A pharmaceutical product type, for example, tablet, capsule, solution, or cream, that contains a drug ingredient (substance) generally, but not necessarily, in association with excipients

Drug: "[M]eans (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) [of the FD&C Act] or sections 403(r)(1)(B) and (r)(5)(D), is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement" (21 U.S.C. 321(g)(1)).

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body (21 CFR 314.3(b))

Drug Product: The dosage form in the final immediate packaging intended for marketing

Food: The term *food* means (1) articles used for food or drink, (2) chewing gum, and (3) articles used for components of such articles (21 U.S.C. 321(f)).

Formulation: A formula that lists the components (or ingredients) and composition of the dosage form. The components and composition of a multi-herb botanical drug substance should be part of the total formulation.

Marker: A chemical constituent of a botanical raw material, drug substance, or drug product that is used for identification and/or quality control purposes, especially when the active constituents are not known or identified.

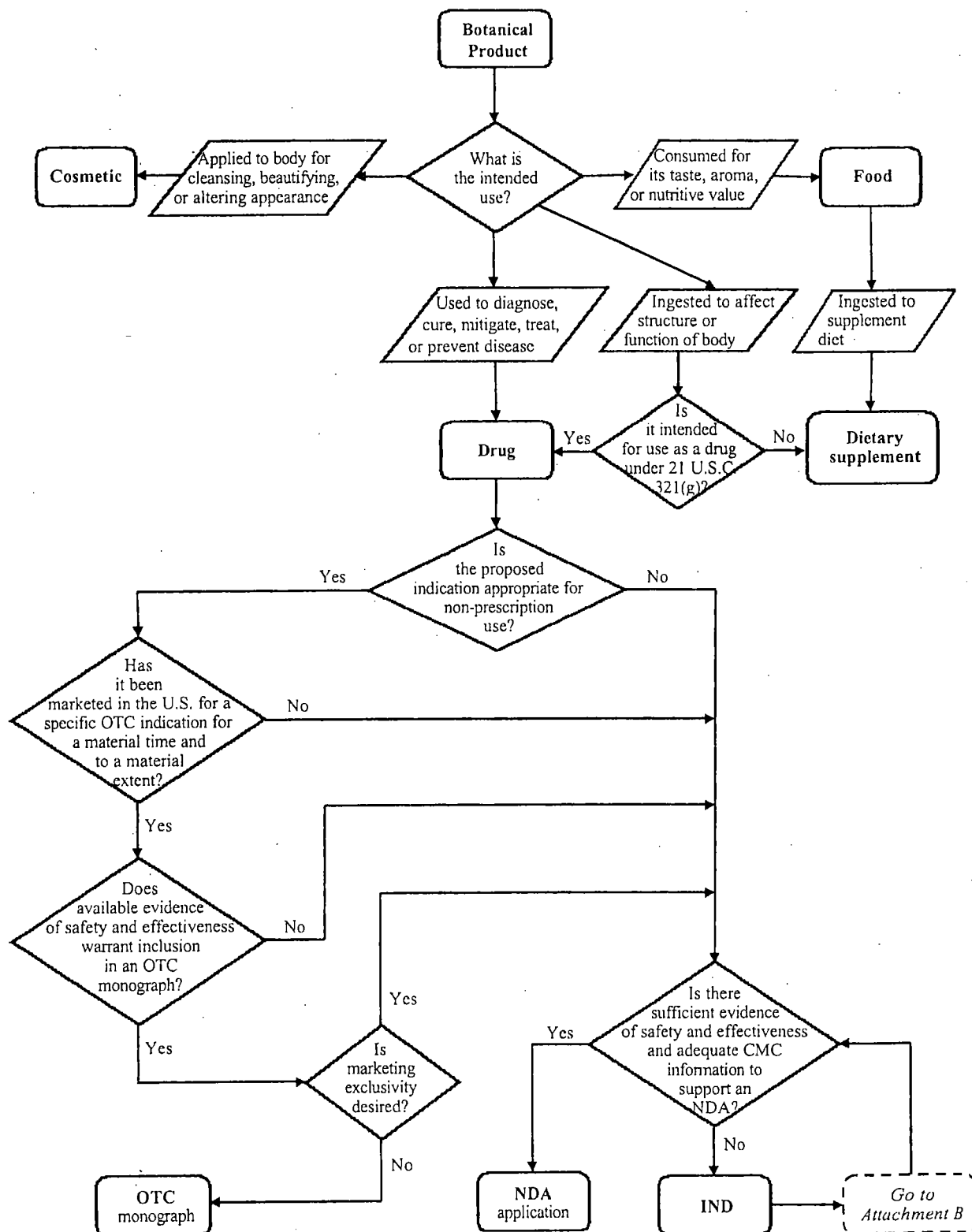
Multi-Herb (Botanical Drug) Substance or Product: A botanical drug substance or drug product that is derived from more than one botanical raw material, each of which is considered a botanical ingredient. A multi-herb botanical drug substance may be prepared by processing together two or more botanical raw materials, or by combining two or more single-herb botanical drug substances that have been individually processed from their corresponding raw materials. In the latter case, the individual single-herb botanical drug substances may be introduced simultaneously or at different stages during the manufacturing process of the dosage form.

Plant Material: A plant or plant part (e.g., bark, wood, leaves, stems, roots, flowers, fruits, seeds, berries, or parts thereof) as well as exudates

Single-Herb (Botanical Drug) Substance or Product: A botanical drug substance or drug product that is derived from one botanical raw material. Therefore, a single-herb substance or product generally contains only one botanical ingredient.

ATTACHMENTS

ATTACHMENT A: REGULATORY APPROACHES FOR A BOTANICAL PRODUCT



ATTACHMENT B: IND FOR A BOTANICAL DRUG PRODUCT

