Botanical Drug Development
Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/CMC
Revision 1

Botanical Drug Development

Guidance for Industry

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the Center for Drug Evaluation and Research's (CDER's) current thinking on appropriate development plans for botanical drugs to be submitted in new drug applications (NDAs) and specific recommendations on submitting investigational new drug applications (INDs) in support of future NDA submissions for botanical drugs. In addition, this guidance provides general information on the over-the-counter (OTC) drug monograph system for botanical drugs. Although this guidance does not intend to provide recommendations specific to botanical drugs to be marketed under biologics license applications (BLAs), many scientific principles described in this guidance may also apply to these products.

This guidance specifically discusses several areas in which, due to the unique nature of botanical drugs, the Agency finds it appropriate to apply regulatory policies that differ from those applied to nonbotanical drugs, such as synthetic, semi-synthetic, or otherwise highly purified or chemically modified drugs, including antibiotics derived from microorganisms. Because this guidance focuses on considerations unique to botanical drugs, policies and recommendations applicable to both botanical and nonbotanical drugs are generally not covered in this document; readers should refer to other FDA guidance documents for appropriate information.

This guidance revises the Guidance for Industry on *Botanical Drug Products* issued in June 2004. After it has been finalized, this guidance will replace the June 2004 guidance. The general approach to botanical drug development has remained unchanged since that time; however, based on improved understanding of botanical drugs and experience acquired in the reviews of NDAs and INDs for these drugs, specific recommendations have been modified and new sections have been added to better address late-phase development and NDA submission for botanical drugs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

[1] This guidance has been prepared by a working group composed of staff from the Office of Pharmaceutical Quality, Office of New Drugs, Office of Translational Sciences, and Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

For the purposes of this document, the term *botanicals* means products that include plant materials, algae, macroscopic fungi, and combinations thereof. It does not include:

- Products that contain animals or animal parts (e.g., insects and annelids) and/or minerals, except when these are a minor component in a traditional botanical preparation.
- Materials derived from botanical species that are genetically modified with the intention of producing a single molecular entity (e.g., by recombinant DNA technology or cloning).
- Products produced by fermentation of yeast, bacteria, plant cells, or other microscopic organisms, including plants used as substrates, if the objective of the fermentation process is to produce a single molecular entity (e.g., antibiotics, amino acids, and vitamins).
- Highly purified substances, either derived from a naturally occurring source (e.g., paclitaxel) or chemically modified (e.g., estrogens synthesized from yam extracts).

If the botanical material is derived from traditional cultivation or breeding techniques (e.g., not genetic engineering), or if fermentation is part of the manufacturing process to produce a product that is a natural mixture consisting of multiple active constituents,[2] then appropriate provisions in this guidance will apply.

When a drug product contains a botanical drug substance in combination with either a (1) synthetic or highly purified drug or (2) biotechnology-derived or other naturally derived drug, this guidance can generally be applied to the botanical portion of the product.

III. GENERAL REGULATORY APPROACHES

A botanical product may be a food (including a dietary supplement), drug (including a biological drug), medical device, or cosmetic under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Whether an article is a food, drug, medical device, or cosmetic depends on its intended use,[3] which is established by, among other things, its labeling, advertising, and the circumstances surrounding its distribution.[4]

[2] Active constituents are the chemical constituent(s) in a botanical drug substance that contribute significantly to a botanical drug's intended pharmacological activity or therapeutic effect.

[3] See 21 USC 321(f)(1), (g)(1)(B) and (C), (h)(2) and (3), (i), (ff).

[4] See 21 CFR 201.128.

If a botanical product is intended for use in diagnosing, curing, mitigating, or treating disease, it is a drug under section 201(g)(1)(B) of the FD&C Act and is subject to regulation as such. If a botanical product is intended to prevent disease, it is also a drug under section 201(g)(1)(B). There are a number of exceptions to the drug classification, including an exception for when a food product bears a health claim that is authorized in accordance with section 403(r)(1)(B) of the FD&C Act (21 USC 343(r)(1)(B)); such a product is not a drug solely because its labeling contains such a claim. The recommendations in this guidance are for botanical drugs only.

A. Marketing of Botanical Drugs under OTC Drug Monographs

Any drug that does not fall within the definition of a prescription drug in section 503(b)(1) of the FD&C Act is a nonprescription or OTC drug. A botanical drug that has been marketed 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.[5] Currently, several botanical drug substances (e.g., psyllium and senna) are included in the OTC drug review, and witch hazel is currently marketed under an OTC drug monograph. To be included in an OTC drug monograph, a botanical drug must generally be recognized as safe and effective based on the standards for safety and effectiveness set forth in 21 CFR 330.10(a)(4).

A request to amend an OTC drug monograph to include a botanical drug substance may be submitted by a citizen petition in accordance with 21 CFR 10.30 and 330.10(a)(12) or a Time and Extent Application (TEA) in accordance with 21 CFR 330.14.[6] To be included in an OTC drug monograph, a botanical drug substance must be recognized in an official United States Pharmacopeia and National Formulary (USP-NF) drug monograph that sets forth its standards of identity, strength, quality, and purity.[7] Therefore, a request for a botanical drug substance to be included in an OTC drug monograph should include a reference to the applicable USP-NF drug monograph. In the absence of such a USP-NF drug monograph, the request should include a proposed standard for inclusion in an article to be recognized in an official USP-NF drug monograph, as described in 21 CFR 330.10(a)(2). Considering the complexity of botanical drugs, there are challenges to this approach. Interested parties (e.g., a botanical drug manufacturer) should contact the Division of Nonprescription Drug Products in CDER's Office of New Drugs/Office of Drug Evaluation IV for additional information about the OTC drug monograph approach to marketing a botanical drug.

B. Marketing of Botanical Drugs under NDAs

Any person who wishes to market a new drug in the United States must submit an NDA and obtain Agency approval prior to marketing the new drug product for the proposed use (see

[5] See 21 CFR Part 330.

[6] 21 CFR 330.14 sets forth criteria and procedures by which OTC drugs initially marketed in the United States after the OTC drug review began and OTC drugs without any U.S. marketing experience can be considered in the OTC drug monograph system. Basic information to be provided in the TEA includes a detailed description of the botanical drug substance, as set forth in 21 CFR 330.14(c)(1)(ii).

[7] See 21 CFR 330.10(a)(2) and 330.14(i).

sections 201(p) and 505 of the FD&C Act). FDA may approve a drug product containing such a drug substance for OTC sale pursuant to an application submitted under section 505 of the FD&C Act. Accordingly, an applicant could seek marketing approval for a botanical drug under section 505 of the FD&C Act for either prescription or OTC use.[8]

Because of the heterogeneous nature of a botanical drug and possible uncertainty about its active constituents, one of the critical issues for botanical drugs is ensuring that the therapeutic effect for marketing drug product batches is consistent. In general, therapeutic consistency can be supported by a "totality of the evidence" approach, including the following considerations:

- Botanical raw material control (e.g., agricultural practice and collection).
- Quality control by chemical test(s) (e.g., analytical tests such as spectroscopic and/or chromatographic methods that capture the active or chemical constituents of a botanical drug substance) and manufacturing control (e.g., process validation).
- Biological assay (e.g., a biological assay that reflects the drug's known or intended mechanism of action) and clinical data (for details regarding use of clinical data in ensuring therapeutic consistency, see Section VI(F)(1) of this guidance under Study Design of Multiple Batch Analyses and Section VI(F)(2) of this guidance under Dose-Response Effect).

Section VII of this guidance describes recommendations for submitting NDAs, including instructions for submitting information to support therapeutic consistency for botanical drug products, and discusses post-marketing issues for botanical drug products.

IV. BOTANICAL DRUG DEVELOPMENT UNDER INDS

To develop information to support either an NDA or an OTC monograph for a botanical drug, interested parties may need to develop data by, among other things, conducting clinical investigations.

Section 505(i) of the FD&C Act and 21 CFR Part 312 require clinical investigations in which a drug is administered to human subjects to be conducted under an IND (unless exempt under § 312.2(b)). To determine whether a proposed study would be exempt from the IND requirements, a sponsor[9] (or sponsor-investigator of an individual investigator-initiated study) should consult the Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards on *Investigational New Drug Applications (INDs)—Determining Whether Human*

[8] See section 503(b)(1) of the FD&C Act.

[9] In this guidance, "sponsor" refers to anyone who submits an IND and "applicant" refers to anyone who submits an NDA.

Research Studies Can Be Conducted Without an IND.[10] If a sponsor is uncertain, we recommend that the sponsor contact the appropriate Office of New Drugs (OND) review division for advice about whether the IND regulations apply.

Pre-IND, end-of-phase 1, end-of-phase 2 and 2A, pre-phase 3, and pre-NDA consultations[11] are strongly encouraged for the sponsor of a botanical drug to assess the adequacy of existing information for an IND submission or an NDA, obtain advice regarding the need for additional studies, ensure that clinical protocols are properly designed, and allow discussion of the initial or overall development plan. The sponsor should submit all available information to the appropriate OND review division in accordance with the content and format requirements outlined below.

The format and content requirements for IND submissions are provided in § 312.23 and discussed in several FDA guidance documents.[12] In general, an IND must contain sufficient information to demonstrate that the drug is safe for testing in humans and that the clinical protocol(s) is properly designed for its intended objectives. While these general requirements are applicable to botanical drug INDs, botanical drugs have certain unique characteristics that may affect the information necessary to be provided in an IND. Botanical drugs are generally heterogeneous mixtures. As such, their chemical constituents often are not well defined; in some cases, their active constituents are not identified and their biological activities are not well characterized. However, certain botanical drugs may have been used in humans prior to submission, which may provide some indication of their safety. The unique characteristics of such botanical drugs could have significant impact on their development program (e.g., quality control and clinical study design). Sections V and VI below provide recommendations for IND submissions that consider these unique characteristics.

V. INDS FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES

Under § 312.22(b), the amount of information that must be submitted in an IND for a particular drug depends on several factors, including the extent of prior human experience and past clinical studies, the drug's known or suspected risks, and the developmental phase of the drug. For example, a botanical dietary supplement marketed under the Dietary Supplement Health and Education Act of 1994 (DSHEA) that has no known safety issues often would require less chemistry, manufacturing, and controls (CMC) or toxicological data to initiate early-phase studies than would a botanical product that is newly discovered, has not been marketed, or has known safety issues. For most botanical drugs, detailed CMC information (e.g., data on comprehensive characterization of the drug substance) may not be warranted for early-phase

[10] CDER updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] See the Guidance for Industry on *Formal Meetings Between the FDA and Sponsors or Applicants* and the Guidance for Industry on *End-of-Phase 2A Meetings*.

[12] Examples of related guidance documents include the 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* and the Guidance for Industry on *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information*.

development (Phase 1 and Phase 2 clinical studies); however, gathering of CMC data should be initiated during these phases because such preliminary information should be submitted prior to initiating Phase 3 studies.

Every botanical drug has unique considerations, and the Agency encourages a sponsor to seek input from the appropriate OND review division before formally submitting an IND. We recommend that the clinical development of a botanical drug take a stepwise approach so that raw material control considerations, analytical characterization data, and early-phase study results can assist in the design of late-phase studies. However, botanical drug substances used in various stages of development may differ in some characteristics (e.g., chemical composition), as there could be possible changes in agricultural practice and collection for botanical raw material(s) and/or manufacturing process conditions as a result of process optimization. Therefore, bridging studies may be needed to justify these differences. The sponsor should request input from the appropriate OND review division so the review division can evaluate any changes in the botanical drug substance during development and provide guidance (e.g., on the type of bridging studies that may be needed).

To comply with the requirements outlined in 21 CFR 312.23, the sponsor should specifically address the following issues unique to botanical drugs in the IND submission. We recognize that some aspects of the following quality control strategy may not be completed until Phase 3 studies; nonetheless, all available information should be provided:

A. Description of Product and Documentation of Prior Human Experience

1. Description of Botanical Raw Materials Used and Known Active Constituents or Chemical Constituents (§ 312.23(a)(3)(i))

Provide the following general information for each of the botanical raw materials used as the source of the botanical drug substance in a botanical drug product:

- Scientific name of the plant species according to international binomial nomenclature convention, including the genus name, the specific epithet, and the name of the botanist who described the species.
- Synonyms, especially those used in recent publications of scientific studies related to the species.
- Subspecific rank (subspecies, variety, and form) and cultivars, if applicable.
- Family name.
- Botanical parts used (e.g., aerial parts, roots, rhizomes, flowers, and/or leaves) as the botanical raw material(s).
- Common or usual names of the plant, alga, or macroscopic fungus in English and other languages (e.g., Chinese or Spanish), especially the languages of the region in which the species and the raw materials have medicinal or other significance.

- Active constituents identified as individual compounds or chemical classes, if known. If active constituents are not known, chemical constituents that have been identified (e.g., those can be used as a characteristic profile for identification and quality control purposes).

2. Prior Human Experience (§§ 312.23(a)(3)(ii),(a)(9))

Under § 312.23(a)(9), a sponsor must submit information about prior human experience with the investigational drug, if available. Many botanical drugs have been previously marketed or tested in clinical studies. Where clinical studies have been conducted, the study reports should be submitted in the IND with a critical review of the data quality and the data's relevance to the proposed use. The botanical drug's marketing history also should be described. In particular, it should include documentation of the annual sales volume, an estimate of the size of the exposure population, and rates of adverse effects, as well as provide references to compendia and publications (e.g., books of medical practice in Ayurveda, traditional Chinese medicine, Unani, Sidha, and other herbal medicine and pharmacognosy textbooks). For botanical drugs only available in foreign markets, the information's reliability and relevance to the proposed clinical study should be justified. A sponsor planning to support its IND with a well-designed and well-conducted foreign clinical study or studies not conducted under an IND should refer to § 312.120 and related FDA guidance documents.[13] Any literature that is submitted should be provided in English (and in its original language, if other than English).[14]

In addition to a thorough review of the past human experience with the botanical drug, the sponsor should also present information to bridge the past experience with the current proposed investigation. This information may include a:

- Description of the amount of raw material or traditional preparation that is equivalent to the dose proposed in the IND study,

- Comparison of the identity of the investigational botanical drug with traditional preparations described in the literature, and/or

- Comparison of the clinical settings in which the drugs have been used with the setting(s) in which they are proposed to be used.

The Agency will determine the relevance of prior human experience with traditional preparations to the assessment of botanical drugs' safety in clinical studies proposed under INDs on a case-by-case basis.

[13] Examples of related guidance documents include the Guidance for Industry and FDA Staff on *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions* and the Guidance for Industry on *E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data: Questions and Answers*.

[14] See § 312.23(c).

B. Chemistry, Manufacturing, and Controls

The amount of CMC information to support clinical studies conducted under an IND depends on a number of factors, including the botanical drug's marketing history and the phase of development. The use of botanical drugs in foreign markets may provide useful human experience; however, the relevance of such experience to determining the amount of CMC information needed for early-phase clinical studies depends on the integrity of the control measures and the quality of the foreign manufactured botanical drug. Provided below is an overview of the CMC information that is recommended to support early-phase clinical studies for a botanical drug. More detailed CMC information will be warranted to proceed into late-phase clinical studies (see Section VI).

1. Botanical Raw Materials (§ 312.23(a)(7)(i))

A botanical drug substance can be derived from one or more botanical raw materials of the same or different plant species. The following recommendations apply to each individual botanical raw material used.

For raw material control, trained personnel should identify the plant species, plant parts, alga, or macroscopic fungus used via methods including organoleptic, macroscopic, and microscopic examination. This identification should be done against a voucher specimen (i.e., reference specimen). If more than one variety of a given species is used, each variety should be specified. The botanical raw material supplier and drug substance manufacturer for each batch should retain and store under appropriate conditions a sample of the plant, plant parts, or other botanical materials. These samples can be used to further verify identity, if needed. The sponsor should provide the following information:

- Identification of the plant species, plant parts, alga, or macroscopic fungus used.
- A certificate of authenticity.
- Whether the plant species is:
  - 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,[15]
  - Entitled to protection under some other federal law or international treaty to which the United States is a party, and/or

[15] See www.fws.gov/international/laws-treaties-agreements/us-conservation-laws/endangered-species-act.html.

- In a critical habitat that has been determined to be endangered or threatened.

- The following items for each grower and/or supplier, if available:

  - Name and address,

  - Description and characterization of the plant species, as well as varieties and cultivars (if applicable), and botanical identification (macroscopic and microscopic),

  - Harvest location (e.g., by global positioning system (GPS) coordinates), growth conditions, stage of plant growth at harvest, and harvest time/season, and

  - Post-harvest processing (e.g., washing, drying, and grinding procedures); control of foreign matter (i.e., inorganic and organic contaminants such as soil, insects, and algae/fungus); preservation procedures; handling, transportation, and storage conditions; tests for elemental impurities; microbial limits; tests for residual pesticides, including parent pesticides and their major toxic metabolites; and tests for adventitious toxins (e.g., aflatoxins), foreign materials, and adulterants.

2. Botanical Drug Substance (§ 312.23(a)(7)(iv)(a)*)*

The sponsor should provide the following information for the botanical drug substance, regardless of whether it is prepared from one or more botanical raw materials:

- Qualitative description of the drug substance. It should include the name, appearance, active constituents, physicochemical properties, biological activity, and any prior clinical use of each botanical raw material used to prepare the drug substance. If the active constituents, biological activity, and/or prior clinical use are unknown, the application should clearly state this. For a multi-plant drug substance, the application should state whether the drug substance is prepared by combining individually processed botanical drug substances or processing combined botanical raw materials.

- Quantitative description of the drug substance. The strength of a botanical drug substance should generally be expressed as the absolute dry weight of a processed botanical substance. The batch size and yield of the process relative to the botanical raw material should be provided. When the active constituents or other chemical constituents are known and measurable, the amount in which they are present in the botanical drug substance should be declared. The composition of multi-plant drug substances, in terms of the relative ratio of the individually

processed botanical drug substances or of the botanical raw materials before processing (as applicable), should be expressed.

- Name and address of the drug substance manufacturer (i.e., processor).

- Description of the manufacturing process. The description should include each process step (e.g., pulverization, decoction, expression, aqueous and/or ethanol extraction), the quantity of botanical raw material, solvents, temperature and time for extraction and/or drying, and in-process controls. The yield of the process, expressed as the amount of the original botanical raw material relative to the amount of the extract, should be indicated. If more than one botanical raw material is introduced to produce a multi-plant substance, the quantity of each raw material and the sequence of addition, mixing, grinding, and/or extraction should be provided. If a multi-plant substance is prepared by combining two or more individually processed botanical drug substances, a separate description of the process leading to each botanical drug substance should be provided.

- Quality control tests performed on each batch of the drug substance, analytical procedures that were used, available test results, and proposed acceptance criteria. The quality control tests should include, but are not limited to, tests for the following attributes:

  - Appearance.

  - Strength by dry weight (equivalent to botanical raw material).

  - Chemical identification for the active constituents, if known, or the chemical constituents.[16] In general, the sponsor should use the best available analytical technology to address the issue of analytical resolution. When the resolution is inadequate in one particular method, multiple methods should be used to provide complementary data for adequate chemical identification and quantification.

  - Quantification for the active constituents, if known, or the chemical constituents. If several botanical raw materials are combined to produce a multi-plant substance and a quantitative determination of each individual active or chemical constituent is infeasible, a joint determination can be made for several active or chemical constituents. When multiple active or

[16] The characteristic profile of chemical constituents can be determined based on spectroscopic and/or chromatographic methods. Examples of spectroscopic methods include ultraviolet, infrared, Fourier transformed infrared, mass spectroscopy, and liquid chromatography–mass spectrometry (LC-MS). Examples of chromatographic methods include high performance liquid chromatography (HPLC), gas chromatography (GC), thin layer chromatography (TLC), and capillary zone electrophoresis.

chemical constituents are known, they should be chemically characterized and their relative amounts should be defined.

- Biological assay. If the active constituents are not known or quantifiable, a biological assay should be developed, prior to initiation of Phase 3 studies, to assess drug substance batch potency and activity relative to a reference standard (see Section VII.B.2.d).

- Mass balance. Methods should be developed to quantify other classes of compounds (e.g., lipids or proteins) that contribute to the mass balance of the botanical substance, prior to initiation of Phase 3 studies (see Section VII.B.2.e).

- Tests for residual pesticides as outlined in USP <561> and for any pesticides routinely used in the countries of origin of botanical raw materials.

- Tests for elemental impurities, residual solvents, and radioisotope contamination, if applicable.

- Tests for microbial limits and viral load.

- Tests for adventitious toxins, such as aflatoxins.

- Available stability data. The sponsor should develop stability-indicating analytical methods and conduct stability studies as the IND progresses.

*3. Botanical Drug Product (§ 312.23(a)(7)(iv)(*b*))*

The sponsor should provide the following information for a botanical drug product:

- Qualitative description of the drug product. It should include the dosage form, route of administration, names and functions of all ingredients (e.g., botanical drug substance, other drug substances, and excipients), and a statement declaring if the botanical drug substance is combined with other drug substances (e.g., a highly purified, biotechnology-derived, or other naturally derived drug substance).

- Composition or quantitative description of the drug product expressed in terms of amount per dosage unit and amount per batch. The sponsor should provide this information in tabular form (see example on next page).

Component	Amount per Tablet	Amount per Batch
A 5:1 powdered, aqueous extract from 1:1 mixture of *Forsythia suspensa* Vahl. fruits and *Lonicera japonica* Thunb. flowers	600 mg	24.0 kg
Excipient 1	100 mg	4.0 kg
Excipient 2	10 mg	0.4 kg

- Manufacturer's certificate of analysis for the drug product or authorization for the Agency to cross-reference the manufacturer's previous submission or drug master file (DMF) for the relevant CMC information. If this information is unavailable for a foreign-marketed product, the sponsor should perform quality testing on the drug product. In addition to those tests, elemental impurities analysis and, if applicable, an animal safety test, should be performed. The sponsor should provide these test methods and results in the IND. A product sample from each batch to be used in clinical studies should be retained for possible future testing by the Agency and/or sponsor.

- Stability data to support the use of a botanical drug product for at least the length of the clinical study. As development continues, stability studies in line with International Conference on Harmonisation (ICH) guidelines[17] should continue to generate data in support of the proposed expiration dating period.

Although generally discouraged, it may be permissible in unusual cases to augment levels of individual active constituents in a botanical drug product to achieve batch-to-batch consistency in the therapeutic effect. In general, this approach would only be appropriate in situations in which the active constituents in the drug substance are known and there is a substantial natural variation in the concentrations of these active constituents in the botanical raw material (e.g., due to changes in growing conditions over time that cannot be controlled). In such cases, limited amounts of the purified active constituents could be added to meet the specification for a benchmark drug substance. The target levels for active constituents should not exceed levels that occur naturally. The sponsor should consult with the Agency in advance concerning the appropriateness of augmenting levels of active constituents in a specific case and the process for determining the specification for the benchmark drug substance.

4. Placebo (§ 312.23(a)(7)(iv)(c))

Use of certain botanical materials in the placebo to mask the identity of active drug may be necessary, but such botanical substances should not have any known pharmacological activity because that will make the clinical data difficult to interpret. The Agency understands that for some botanical drugs, it may be difficult to create a placebo with the identical taste, odor, and

[17] See ICH *Q1A(R2) Stability Testing of New Drug Substances and Products*.

appearance of the active drug. It may be acceptable for these attributes in the placebo to be subtly different from those of the botanical drug if the investigators and study subjects cannot differentiate the active drug from the placebo and blinding of the clinical study can be maintained. The sponsor is encouraged to consult with the appropriate OND review division regarding the use of such a placebo in clinical studies.

5. Environmental Assessment or Claim of Categorical Exclusion (§ 312.23(a)(7)(iv)(e))

A claim of categorical exclusion from the requirement for preparation of an environmental assessment (EA) can ordinarily be made for an IND (21 CFR 25.31(e)); however, additional information should be provided in the IND to support a claim for a categorical exclusion for a botanical drug product.[18]

C. Nonclinical Pharmacology/Toxicology

The amount of nonclinical information recommended to support Phase 1 and Phase 2 clinical studies with botanical products will depend on the extent of previous human use and the design of the proposed clinical studies. Examples are provided below:

- For a botanical drug that is currently lawfully marketed in the United States as a dietary supplement, initial clinical studies may be allowed to proceed without further nonclinical pharmacological/toxicological testing provided that the previous use is similar to the proposed use. Nevertheless, literature and other available information related to the safety of the drug should be provided.

- For a botanical drug that is not currently lawfully marketed in the United States, if it is administered using the route (e.g., topically or orally) and prepared, processed, and used according to methodologies for which there is extensive prior human experience, sufficient information may be available to support initial clinical studies without additional nonclinical pharmacological/toxicological testing.

- Regardless of whether a botanical drug is currently lawfully marketed in the United States, if the anticipated exposure in the proposed clinical studies exceeds that in the prior human use (e.g., higher doses or a longer duration), an additional nonclinical pharmacological/toxicological assessment is warranted to adequately address the difference between the prior human use and the proposed clinical studies.

- For nontraditional routes of administration of a botanical drug (e.g., if a drug

[18] See the Guidance for Industry on *Environmental Assessment of Human Drug and Biologics Applications* (*Environmental Assessment Guidance*).

traditionally has been used only topically and the sponsor is proposing it be used orally), additional pharmacological/toxicological information may be warranted to support this difference before initial clinical studies.

- For a new botanical drug for which extensive prior human use is not available, a more extensive nonclinical pharmacological/toxicological assessment is warranted. This assessment would be similar to that for nonbotanical drugs (e.g., synthetic drugs), and recommendations would follow appropriate ICH and FDA guidances.

If formal, nonclinical studies have not been performed for the IND submission, the sponsor should conduct a literature search to identify any publicly available information pertaining to the safety of the following:

- Final formulation of the intended commercial botanical drug product,
- Botanical substance(s) of the drug product, and
- Known active or chemical constituents of the botanical substance.

Under § 312.23(a)(8)(ii), an integrated summary of available data from medical and toxicological literature (e.g., Medline and Toxline) should be submitted for review. The following issues should be addressed in the original IND for review:

- General toxicity,
- Target organs or systems of toxicity,
- All data suggesting adverse genetic or reproductive effects of any constituents of the botanical substance,
- Relationship of dosage and duration to toxic responses, and
- Pharmacologic effects reported for the whole botanical substance and its individual active constituents.

For botanical drugs that have been previously marketed only outside of the United States, the sponsor should provide additional data to verify and document the safety of prior human use.

D. Clinical Pharmacology

The Agency recognizes the technical challenges in determining standard pharmacokinetic measurements of systemic exposure because a botanical drug product often consists of more than one chemical constituent and the active constituents may not be identified. However, a sponsor should attempt to measure the blood levels of known active constituents or major chemical constituents in a botanical drug product using a sensitive analytical method to achieve the same objectives of Phase 1 and 2 clinical pharmacology studies for nonbotanical drugs. Examples of these objectives are provided below:

- Assess drug absorption, distribution, metabolism, and excretion,

- Assess the dose-response or exposure-response relationship for desirable and undesirable effects,

- Address pharmacokinetics in specific populations (e.g., the elderly or patients with hepatic or renal impairments), and

- Provide information from in vitro studies to evaluate the potential for interactions with drugs or other botanicals (e.g., contribution of enzymes and transporters to drug disposition, inhibition, and induction potential on drug metabolizing enzymes), and evaluate potential for QT interval prolongation.

An approach based on a pharmacodynamic or clinical endpoint may be appropriate if no quantifiable active or chemical constituents are available for in vivo pharmacokinetic or in vitro studies.

E. Clinical Considerations

The clinical evaluation of botanical drugs in early-phase clinical studies does not differ significantly from that of synthetic or highly purified drugs in such studies (see 21 CFR 314.126). Botanical drug products currently marketed as dietary supplements under DSHEA generally would not require typical Phase 1 tolerability studies if sponsors can provide adequate justification for the relevance of the prior human use. The sponsors of such drug products are strongly encouraged to initiate well-controlled and more definitive clinical studies in order to explore the therapeutic effect early in the development program. If there is uncertainty about the dose selection, a clinical dose-response study may be necessary to determine the optimal dose for Phase 3 clinical studies. As is generally the case with all drugs, safety data should be collected during these early-phase clinical studies.

If an IND of a botanical drug product includes only foreign marketing experience, no prior human experience, or known safety issues, the sponsor should provide additional early-phase clinical data before initiating larger-scale, late-phase clinical studies. To mimic the use in traditional practice, when the preparation is simple (e.g., decoction), botanical raw materials are sometimes dispensed at clinical study centers and subsequently prepared by patients at home. This practice should be applied cautiously in clinical studies because it may introduce potential variability to safety and efficacy data. The sponsor is encouraged to discuss this issue with the appropriate OND review division.

VI. INDS FOR PHASE 3 CLINICAL STUDIES

A. General Regulatory Considerations in Late-Phase Development

During the Phase 3 development, further ongoing characterization of the botanical drug product will ensure drug substance quality and, therefore, the validity and reliability of the clinical data that are generated. Given the more extensive exposure in late-phase clinical studies, additional toxicology data are warranted to support safe human use and facilitate the design of clinical

safety evaluations. This additional information should be provided regardless of prior marketing history.

Batch-to-batch variations (e.g., a variation in chemical composition) are known to exist in different batches of the botanical drug substances. Therefore, it would be of both scientific and regulatory interest to learn the impact of such variations on the therapeutic effect of botanical drug products. The sponsor should consider what evidence will be needed to support that the variations observed in botanical drug substance batches do not cause any meaningful differences in the therapeutic effect. One approach is to use multiple batches of the botanical drug product (i.e., each manufactured by using a different batch of the drug substance) in the Phase 3 clinical studies and to examine the clinical effects across these drug product batches (see Section VI.F for further discussion). This type of investigation would help the sponsor better understand which variations are clinically relevant, and, if clinically relevant, what range of variability can be tolerated to consistently maintain a botanical drug product's identity, efficacy, and safety. Such an improved understanding would aid in setting acceptance criteria for a clinically relevant specification.

If previously available nonclinical and/or clinical data in the earlier phases of development are provided or referenced in the IND, the sponsor should provide a comparison of the investigational botanical drug product to be used in the IND and the botanical drug product(s) used in the referenced studies (e.g., chemical identification and quantification of active or chemical constituents in the drug substance, drug product composition and formulation). Likewise, when the source and manufacturing process of the botanical raw material, drug substance, or drug product are changed during development, the sponsor should provide a comparison of the previous and new sources and manufacturing processes, because seemingly minor changes in the source and/or process may result in a meaningful difference in the clinical effects and raise the question about the applicability of earlier pharmacological, nonclinical, and clinical data.

If there is uncertainty about whether different batches of the drug substance are similar, bridging studies (e.g., chemical identification and quantification of active or chemical constituents in the drug substance, biological assay, and/or other nonclinical studies) may be warranted to demonstrate that the drug substances used in various stages of development are sufficiently similar to justify reliance on previous nonclinical and clinical testing results. Sufficient quantities of the botanical raw material and drug substance from the different batches should be retained for future chemical characterization and/or pharmacological/toxicological testing.

The sponsor should also refer to Section VI.G below regarding the applicability of the fixed-dose combination rule to the investigational botanical drug.

Phase 3 studies should provide pivotal support for an NDA submission. Thus, it is important that the sponsor reviews Section VI of this guidance regarding the information recommended for botanical-specific contents in an NDA submission to ensure that the necessary information will be collected with appropriate technologies and well-designed studies during this phase.

B. Description of Product and Documentation of Prior Human Experience

This information should have been submitted to the IND in support of Phase 1 and Phase 2 clinical studies in accordance with § 312.23. See Section V.A of this guidance for details.

C. Chemistry, Manufacturing, and Controls

To support Phase 3 clinical studies of a botanical drug product, the sponsor should provide information under the same categories outlined in Section V.B in accordance with § 312.23; however, more detailed information should be provided to support these studies, as described below.

1. Botanical Raw Material

To ensure quality and therapeutic consistency, it is important to select representative raw material batches (i.e., raw material from three or more representative cultivation sites or farms) for the manufacturing of the clinical drug substance for multiple batch Phase 3 studies. The sponsor should establish large growing regions with three or more cultivation sites or farms whose locations are purposefully selected to be representative of the regions for each of the botanical raw materials following the principles of Good Agricultural and Collection Practices (GACP).[19] This will help reduce the likelihood of an insufficient supply of the botanical raw material post-NDA approval.

The sponsor should provide information on additional work performed to characterize the botanical raw material(s) (e.g., chemical identification of each botanical raw material by a spectroscopic or chromatographic method, and authentication of each botanical raw material by a DNA fingerprinting method as necessary), updates on the quality control tests and analytical procedures applied by the botanical raw material supplier, and the proposed acceptance criteria, with the goal of working toward final development in preparation for an NDA submission.

2. Botanical Drug Substance and Drug Product

For the drug substance and drug product, the sponsor should provide updates (as necessary) on additional work conducted to improve characterization of the botanical drug and its active constituents. The sponsor should establish specifications (with interim acceptance criteria) that can be finalized during the NDA review based on the results of Phase 3 clinical studies. In addition, pharmaceutical development of the drug substance and drug product should be well advanced so that no significant changes of the botanical raw material(s) and manufacturing processes will be needed during Phase 3 clinical studies to support the marketing application. For

[19] See the World Health Organization's "WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants" at http://whqlibdoc.who.int/publications/2003/9241546271.pdf and the European Medicines Agency's "Guideline on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin" at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003362.pdf.

example, a robust manufacturing process for the drug substance and drug product should be established and demonstrated to ensure that the clinical study materials and the to-be-marketed materials are consistent, so bridging studies may not be necessary to support the marketing application (see Section V).

D. Nonclinical Safety Assessment

Toxicity data from standard toxicology studies in animals should generally be provided to support late-phase clinical studies.[20] A botanical drug product in Phase 3 clinical studies will generally be assessed with the same overall nonclinical review standards as any other new drug under development in accordance with § 312.23(a)(8).

Certain changes in formulation could affect whether previously performed pharmacology or toxicology studies are applicable to the new formulation, and in some cases may warrant the submission of nonclinical bridging studies. The sponsor should discuss all proposed formulation changes with the appropriate OND review division to determine whether the changes would warrant bridging or other types of studies.

The sponsor should consider the following points when preparing a nonclinical pharmacology/toxicology development plan for a botanical drug product that is intended to be used in Phase 3 clinical studies. If questions arise during any stage of botanical drug product development, the sponsor is encouraged to consult the appropriate OND review division.

1. General Pharmacology/Toxicology

In general, for late-phase clinical studies, the recommendations for general pharmacology/toxicology assessment of botanical drugs are no different from those for nonbotanical drugs.[21] Doses used in toxicology studies should follow the principles in ICH *M3(R2).*

The sponsor should reach agreement with the appropriate OND review division about the methods it plans to use for arriving at acceptable dose levels in safety pharmacology (see ICH *S7A* and *S7B*)[22] and toxicology studies. In principle, the highest dose used in toxicology studies should produce some measurable toxicity. This toxicity information can be used to inform safety monitoring during human studies.

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[20] See the ICH joint safety and efficacy guidances at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065006.htm and the ICH safety guidances at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065007.htm.

[21] See ICH *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.*

[22] See ICH *S7A Safety Pharmacology Studies for Human Pharmaceuticals* and *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.*

2. Nonclinical Pharmacokinetic/Toxicokinetic Studies

Because a botanical drug product usually consists of more than one chemical constituent, it may be technically challenging to use standard pharmacokinetic measurements to substantiate the systemic exposure of a botanical drug in animals. Monitoring representative chemical constituent(s) in a botanical drug product using a sensitive analytical method can provide information regarding systemic exposure. If feasible, chemical constituents of a drug product that contribute to toxicity or pharmacology should be assessed in the pharmacokinetic/toxicokinetic studies. The sponsor should also attempt to determine the metabolic fates of these chemical constituents. Pharmacokinetic/toxicokinetic information collected during the toxicity studies may help the sponsor to interpret the studies' outcomes.[23]

3. Reproductive Toxicology

For most botanical drug products, prior human experience may be a less reliable indicator of reproductive safety than are specialized animal toxicology studies. In the absence of documented reproductive safety data in humans or animals, reproductive toxicology studies are normally conducted per recommendations provided in ICH guidelines (same as for nonbotanical drugs).[24]

4. Genotoxicity Studies

A complete assessment of genetic toxicity may be warranted prior to Phase 3 clinical studies if these assessments have not been conducted earlier. See ICH *S2(R1)* for the definition of a standard battery of genotoxicity tests.[25] Interpretation of the results of this standard battery of tests and the determination of the need for additional tests should be no different for botanical and nonbotanical drugs.[26]

5. Carcinogenicity Studies

Carcinogenicity studies are typically submitted with an NDA. To meet this goal, dose range finding studies and the carcinogenicity studies should generally be conducted during the IND phase. The indication and duration of the intended use of the botanical drug product will influence the need for carcinogenicity studies and their timing relative to clinical development.[27] Protocols for carcinogenicity studies should be submitted to the Agency for review under Special Protocol Assessment[28] and for concurrence prior to the initiation of such studies to ensure that the dose selection and study design are acceptable. In particular, these protocols should identify

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[23] See ICH *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies* and *S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies.*

[24] See ICH *S5A Detection of Toxicity to Reproduction for Medicinal Products*, *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*, and ICH *M3(R2)*, supra note 21.

[25] See ICH *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*.

[26] See § 312.23(a)(8)(ii)(*a*).

[27] See *Environmental Assessment Guidance*, supra note 18. Also, see ICH *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* and *S1B Testing for Carcinogenicity in Pharmaceuticals.*

[28] See the Guidance for Industry on *Special Protocol Assessment*.

the rationale for selecting the high dose for the carcinogenicity study.[29]

6. Other Toxicity Studies

In general, recommendations for special pharmacological/toxicological studies (e.g., studies that are used to identify potential biomarkers or provide mechanistic understanding) for botanical drugs are not different from those for nonbotanical drugs.[30]

7. Regulatory Considerations

Nonclinical pharmacological and toxicological studies that the sponsor conducts as part of botanical drug development and to support safety should generally be performed in accordance with regulations governing good laboratory practices under 21 CFR Part 58. Both the botanical drug substance and drug product should be manufactured to achieve adequate batch-to-batch consistency as outlined in this guidance's CMC sections. If changes occur in the botanical drug substance or botanical drug product during clinical development, nonclinical bridging studies may be needed to comply with 21 CFR 312.23(a)(8)(ii)(*a*).

E. Clinical Pharmacology

To support Phase 3 clinical studies of a botanical drug product, regardless of its marketing experience in the United States or other countries, the sponsor should provide the dose selection rationale (including a description of the human pharmacokinetic and pharmacodynamic relationships for both efficacy and safety, if available). This information should be provided in addition to the information recommended in Section V.D. It may be useful for the sponsor to perform clinical trial simulations prior to conducting Phase 3 clinical studies, if feasible. The sponsor is encouraged to meet with the Agency to reach agreement on the sponsor's planned clinical pharmacology development programs prior to Phase 3.

F. Clinical Considerations

Phase 3 clinical studies of botanical drugs have the same purpose as Phase 3 clinical studies of nonbotanical drugs. Many general and therapeutic area-specific guidance documents are available on the FDA Drugs guidance web page.[31] Special considerations for Phase 3 clinical studies of botanical drugs are summarized as follows:

1. Study Design for Multiple Batch Analyses

Analyses of batch effects on clinical endpoints (i.e., batch effect analyses) should be considered when drug product batches exhibit variations (e.g., a variation in chemical composition), potentially affecting clinical outcomes. These are additional analyses beyond the standard

[29] See ICH *S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals*.
[30] See *Environmental Assessment Guidance*, supra note 18.
[31] See www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

primary efficacy analyses usually performed. Standard analyses involve comparing a control group to a treatment group composed of subjects pooled across different batches. The batches that are chosen should be representative of the marketing batches and should not be too homogenous. The goal of these analyses is to quantify potential heterogeneity in clinical outcomes for subjects who receive different batches in the study. This is in principle similar to other types of subgroup analyses.[32]

If batch effect analyses are warranted, the sponsor should design clinical studies to facilitate these analyses, pre-specify in the protocols how these analyses will be carried out, discuss with the appropriate OND review division the pre-planned models for these analyses, and present the results of these analyses in the clinical study report. Batch effect analyses are usually exploratory, with no formal requirement of control of the Type I error rate. The remainder of this section provides more details on our recommendations for clinical study design, as well as modeling and presentation of clinical study results, to accommodate batch effect analyses.

Randomization of subjects to different batches in each site is highly recommended to facilitate batch effect analyses. For instance, a study of three different batches is conceptually similar to a study with three different randomized dosage groups and one control group. If subjects are not randomized to different batches, a direct comparison of clinical outcomes in different batches can be confounded by other effects. For example, if drug products supplied to any given site are only from one batch rather than from multiple batches, then a direct comparison of clinical outcomes in different batches is confounded with site effects on clinical outcomes.

The sponsor should also ensure that subjects randomized to a certain batch group receive study drug from the same batch for the duration of the study. In situations where this may not be possible, the batch effect analyses may only be able to estimate a batch sequence effect.

With regard to modeling and presentation of results from batch effect analyses, the sponsor should include summary tables and/or forest plots displaying estimates and confidence intervals of clinical outcomes or treatment effect by batch, describe the pre-planned models used to generate these results, assess possible heterogeneity of clinical outcomes in subjects that receive different batches, and describe the statistical measures of heterogeneity and statistical tests of homogeneity used. In addition, the sponsor should provide a summary of the subjects' baseline characteristics by batch to explore possible imbalances in the subjects' baseline characteristics between batches and identify possible confounders of batch effect on clinical outcomes.

2. Dose-Response Effect

Another approach to show that clinical response to a botanical drug will not be affected by variations of different batches is to demonstrate that the drug's effect on clinical outcomes is not sensitive to dose, while also demonstrating that the studied doses are more effective than placebo or control, or not inferior to active treatment. If a randomized, multiple-dose, parallel group

[32] See Section 5.7 of ICH *E9 Statistical Principles for Clinical Trials.*

design, Phase 3 study demonstrates a similar treatment effect across multiple doses, concerns about the impact of variability in chemical composition across batches may be diminished. Therefore, to facilitate the Agency's evaluation of the effects of doses on clinical outcomes, the sponsor should summarize the results of different doses on clinical outcomes, including estimates and confidence intervals of treatment effects by dose displayed in tables and/or forest plots, in the clinical study report.

3. Clinical Studies of Botanical Drugs for Serious Conditions

While extensive anecdotal human experience for some botanical drugs may exist, not knowing the active constituent(s) and/or mechanisms of action may cast doubt on the drug's presumed efficacy. Lack of scientifically reliable and relevant data to support efficacy may raise ethical concerns for clinical studies evaluating the botanical drug alone, especially for serious conditions. In these cases, an "add-on to standard care versus standard care" design is preferred to a "stand-alone versus control" design in clinical studies for serious conditions. However, add-on designs present the possibility of an adverse interaction between the standard of care and the botanical drug. If such an interaction is possible and strong evidence is available to support the presumed efficacy of the botanical drug alone, alternative designs (e.g., adding a third arm of botanical drug alone) should be considered.

4. Other Study Design Issues

When the rationale for developing certain botanical drug products is based on prior clinical experience in alternative medical systems (e.g., Ayurveda, traditional Chinese medicine, Unani, Sidha, and other herbal medicine and pharmacognosy textbooks), the sponsor may propose to incorporate traditional practices into their clinical protocols. For example, patients may be selected or grouped based on alternative medical theory or practice and treated with specific botanical regimens accordingly, or the final dosage form may be prepared by individual patients according to traditional Chinese or Indian methods.

These unconventional measures should be considered individually and could be acceptable if they will help ensure or enhance the therapeutic effect for an acceptable indication and can be described and translated into practical instructions for use in the labeling for patients and healthcare providers in the United States. The sponsor contemplating such approaches should consult with the appropriate OND review division.

G. Applicability of Combination Drug Regulations

For a fixed-combination drug product, current regulations require sponsors to demonstrate each component's contribution toward overall efficacy and/or safety.[33] However, these regulations generally do not apply to naturally derived mixtures, such as those found within a single botanical raw material. Botanical drug products derived from a single botanical raw material are

[33] See §300.50 and 330.10(a)(4)(iv).

generally not considered fixed-combination drugs because the entire botanical mixture generally is considered to be the active ingredient.

Botanical drug products derived from multiple botanical raw materials are currently considered fixed-combination drugs. However, the Agency recognizes that demonstrating each botanical raw material's contribution to efficacy and safety in a product with multiple botanical raw materials may not always be feasible. The Agency is currently reviewing the requirements for fixed-combination drugs and how they should be applied to botanical drug products.

Until the Agency issues further guidance or policy specific to the application of these regulations to fixed-combination botanical drug products, nonclinical data from animal disease models or pharmacological in vitro assays may be useful to show the contribution of individual components[34] to the claimed effects.

VII. NDAS FOR BOTANICAL DRUG PRODUCTS

The pre-NDA meeting is of particular importance for botanical drug products, given their unique characteristics and considerations. The pre-NDA meeting should be held sufficiently in advance of (e.g., more than 2 months before) the planned NDA submission to allow the applicant enough time to meaningfully respond to the Agency's feedback. In accordance with the Prescription Drug User Fee Act (PDUFA V) performance goals,[35] the Agency and applicant will agree on the content of a complete application for the proposed indication(s) at the pre-NDA meeting. Agreements and discussions will be summarized at the conclusion of the meeting and reflected in the Agency's meeting minutes.

Submission requirements for an NDA for a botanical drug product are generally no different from those for other drug products. For instructions and advice on submitting NDAs (applicable to all drug products), the applicant should refer to existing Agency regulations and FDA guidances. The applicant should submit an NDA for a botanical drug product in the Electronic Common Technical Document (eCTD) format.[36] Issues specific to NDAs for botanical drug products are discussed in this section. Refer to previous sections of this guidance for details on data to be acquired and the studies to be conducted to collect such data during the IND process.

A. Description of Product and Documentation of Prior Human Experience

All information provided in the IND should be submitted in the NDA. Refer to Sections V.A.1 and 2. If more recent human experience exists for the botanical drug (e.g., based on a similar

[34] In this context, a component refers to a mixture derived from a specific botanical raw material.

[35] See *PDUFA Reauthorization Performance Goals and Procedures for Fiscal Years 2013 through 2017* at http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

[36] For information about a Common Technical Document (CTD), see the Guidance for Industry on *M4: Organization of the CTD*. For information about an Electronic Common Technical Document, see the FDA web page eCTD Basics and Getting Started.

drug product marketed in foreign countries), an updated summary also should be provided in the NDA.

B. Quality Control

Because the drug substance's active constituents may not be unequivocally identified, the technical challenges for quality control are to determine a botanical drug's identity and ensure its consistency of strength. A botanical drug product's quality control should consider a totality-of-the-evidence approach as outlined in Sections III.B and VII.F. It should extend to the raw material(s) and may require additional measures such as biological assays and/or information on the effect of variations on clinical outcomes from a multiple batch clinical study.

1. Botanical Raw Material

A botanical drug product's quality control should start with the raw material(s) and should be described in the NDA. Specific information on medicinal plants (e.g., verification of authenticity with morphology, macroscopic and microscopic analysis, and chemical analysis), agricultural practices (e.g., growing, harvesting, and storage conditions), geographic locations, and collection and processing methods should be identified. The applicant should establish GACP and summarize the related procedures for each of the botanical raw materials when submitting an NDA. The general GACP principles established by the World Health Organization (WHO), European Medicines Agency (EMA), or the regulatory body of the botanical raw material growing region should be referenced. DNA fingerprinting may be warranted in cases of complicated taxonomy and when identification issues related to the botanical raw material exist. For example, if multiple related plant species have been used to produce a particular botanical raw material, the DNA fingerprint may provide more plant-specific characteristics for identification than would other methods. In addition, the applicant should describe approaches used to minimize contamination, deterioration, and variations. The same methods should be used to collect and process the raw material(s) for manufacturing the botanical drug substance tested during early-phase clinical studies and the drug substance tested during late-phase clinical studies. Making changes to these collection and processing methods during clinical development could change the chemical profile of the drug substance in the resulting botanical drug product and may warrant bridging studies to justify reliance of previous clinical testing results. Also see Sections V.A.1 and B.1.

2. Botanical Drug Substance and Drug Product

a. Identity

Because of inherent difficulties in characterizing all chemical constituents in botanical drugs, establishing their identity relies not only on chemical characterization of molecules in the mixture, but also on other aspects, including control of the raw material(s) at the medicinal plant level, characterization of relative potency and activity by a biological assay, and/or clinically relevant specifications based on results of the multiple-batch clinical studies. Nevertheless, the applicant should evaluate the current and emerging technologies and develop orthogonal

analytical methods to provide adequate identification and quantification of the active or chemical constituents in a botanical drug. When the active constituents are not known and the botanical mixture cannot be fully characterized, the applicant may then select a characteristic profile of chemical constituents (which shows sensitivity to changes in the quality of the raw material(s) and/or manufacturing conditions for drug substance and product) for identity testing.

b. Chemical Characterization

The multiple analytical methodologies used for chemical characterization of the botanical drug should be fully described in the NDA. The NDA should include all chemical tests performed to qualitatively and quantitatively characterize active or chemical constituents, as well as provide data to address mass balance.

c. Manufacturing Processes

The applicant should provide information about all of the sites that will be used to manufacture the drug substance and drug product for commercial distribution. These should be the same manufacturing sites that produced the drug substance and drug product used in Phase 3 clinical studies, to provide consistency. Changes in manufacturing sites should be avoided, especially during late-phase clinical development. The NDA should include full manufacturing information, including manufacturing equipment used, in-process controls, and testing.

The drug substance and drug product manufacturing processes should be finalized, and in-process controls and testing should be established.

d. Biological Assay

In cases where chemical testing alone may not be sufficient to ensure quality and thus therapeutic consistency, the applicant should include a biological assay in the release specifications and stability protocols for the botanical drug substance and/or drug product. A biological assay that reflects the drug's known or intended mechanism of action is preferred.

Because results from a biological assay are inherently more variable than most of the chemical assays, the batch potency and activity should be measured relative to a suitable reference standard or material; results should be expressed in units of activity calibrated against the reference standard or material. The applicant should incorporate system suitability criteria and quality controls to ensure that the assay will perform in a reproducible and predictable manner.

At the time of the NDA submission, the biological assay should be appropriately validated. At a minimum, the validation should demonstrate accuracy, precision, specificity, linearity, and range.

When the same botanical drug product is intended for multiple indications, the applicant should consult with the appropriate OND review division regarding whether it is necessary to develop a separate biological assay for each indication.[37]

e. Specifications

The experience and data accumulated during the development of a botanical drug should form the basis for setting clinically relevant specifications. Analytical procedures should be properly validated. In addition, when multiple orthogonal methods are used, the totality of the data from all analytical procedures should be able to demonstrate the mass balance in the test sample on the basis of the different classes of chemicals and, if appropriate, among the individual constituents detected within a chemical class.

The following tests on the drug substance should be included, if possible (see § 312.23(a)(7)):

- Amount by weight of each known chemical constituent,
- Area percentage of each unknown peak,
- Relative Retention Time (RRT) of each unknown quantifiable peak,
- Amounts by weight of total lipids and individual fatty acids,
- Amounts by weight of total amino acids and individual amino acids,
- Total amount by weight of simple carbohydrates,
- Total amount by weight of complex carbohydrates,
- Amounts by weight of total vitamins and individual vitamins, and
- Ash content (see USP <561 >, Articles of Botanical Origin).

If a biological assay is needed for quality control, the mass balance should be evaluated in conjunction with the biological assay.

f. Stability

The applicant should develop, validate, and use stability-indicating analytical methods and/or a biological assay to monitor the stability of the botanical drug substance and drug product. The applicant also should perform stress stability studies to identify degradation products in the drug substance and drug product, assess the potential toxicity, and provide adequate control of these degradation products. A retest period for a drug substance and an expiration dating period for a botanical drug product should be established based on data from stability studies designed according to the scientific principles described in ICH *Q1A(R2)*.[38]

[37] See ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* and USP *Biological Assays <1032>: Design and Development of Biological Assays* and USP *<1033>: Biological Assay Validation*.

[38] See ICH *Q1A(R2)*, supra note 17.

g. Drug Master File

CMC information about the botanical raw material and/or drug substance may be submitted as part of the IND, NDA, or a drug master file (DMF). However, if the applicant relies on information in a DMF, the applicant should have adequate acceptance testing (e.g., chemical identification test and biological assay) before accepting the raw materials and/or drug substance received from the DMF holder for further processing or for direct use in humans.

h. Naming Consideration

Regulation at 21 CFR § 299.4(d) encourages the applicant to contact the United States Adopted Name (USAN) Council for designation of an established name. When deriving an established name for the botanical drug substance, the USAN Council will base its consideration on a common similar pharmacological action or common structural type for the active or chemical constituents in the mixture.[39]

The corresponding International Nomenclature body (the INN Expert Committee) does not grant INNs for mixtures, so a botanical drug substance will not be granted an INN.

i. Current Good Manufacturing Practices

Because of a botanical drug's heterogeneous nature and uncertainty in its defined active constituents, control of botanical raw materials—including their storage conditions and processing methods—are of particular importance in the manufacture of a botanical drug substance. The applicant should provide sufficient information about the quality of the starting material in the application and should not rely solely on quality control of the finished product for a botanical drug product. The manufacturing of botanical drug substance should be in compliance with current good manufacturing practices (CGMPs). In some cases, compliance with both GACP and CGMPs may be warranted to cover the way in which the botanical raw material is grown, collected, processed, and stored. The applicant should designate and document the rationale for the point at which production of the drug substance begins and is encouraged to contact the appropriate review division in the Office of Pharmaceutical Quality to reach agreement on this aspect.

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[39] If a drug substance submitted to the USAN Council for naming is closely related to a compendial article (i.e., USP/National Formulary (NF)), compliant with the current USP/NF monograph, or purified to a different extent than required in the monograph, the USAN Council has three basic options in naming the substance:

1) Vote "No USAN," stating that the substance is already compendial and has a compendial name;
2) Vote to adopt the compendial name as USAN (in some cases, the name is NF and the monograph concerns use as an inactive ingredient), and the USAN would provide an official name for the substance for use as an active drug substance; or
3) Vote to adopt a name different from the compendial name. This might be done if the origin of the botanical raw material or level of purification or manufacturing results in a different mode of action, clinical indication, or safety, efficacy, or pharmacokinetics profile.

j. Environmental Assessment

Environmental assessment (EA) requirements for NDA approval are described in 21 CFR §§ 25.30, 25.31, and 25.40. 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.[40]

C. Nonclinical Safety Assessment

Pharmacology and toxicology requirements for an NDA for a botanical drug would be substantially the same as those for a nonbotanical drug. For example, carcinogenicity studies are generally submitted with an NDA. Standard guidance documents are available on the FDA Drugs guidance web page.[41] The applicant should work closely with the Agency on all regulatory issues relating to pharmacology and toxicology studies needed during the IND process. Possible exceptions to normal drug development recommendations should have been initially discussed with the Agency by the end of Phase 2, and general agreements should be reached by the end of Phase 3 studies and captured in pre-NDA meeting minutes in accordance with PDUFA V performance goals.

D. Clinical Pharmacology

The general requirements for in vivo bioavailability data in an NDA (described in § 320.21) are applicable to botanical drugs (See Section V.D and VI.E). The type of bioavailability study that is appropriate for a specific botanical drug product is based on the following: (1) information on the active constituents, if known; (2) the complexity of the drug substance; and (3) the availability of sensitive analytical methods. Because there could likely be more than one chemical constituent in a botanical drug or the active constituents may not be identified, standard in vivo bioavailability and pharmacokinetic studies that measure the blood or urine concentration of the active moieties or active metabolites may be difficult or impossible to perform. Documentation of the methods evaluated and the reason for their abandonment should be provided. As an alternative, it may be reasonable to measure an acute pharmacological effect as a function of time using an appropriate biological assay method. Well-controlled clinical studies that establish the botanical drug's safety and efficacy may be considered acceptable for measuring bioavailability when other methods are not possible.

The general criteria for granting a waiver of in vivo bioavailability data in an NDA, described in § 320.22, are applicable to botanical drug products. The Agency 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 (see § 320.22(e)).

The applicant should refer to existing regulations and FDA guidance documents for further instructions on the format and content of the clinical pharmacology sections of NDAs.

[40] See *Environmental Assessment Guidance*, supra note 18.

[41] See www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

E. Clinical Evidence of Efficacy and Safety

The overall requirements for demonstrating a botanical drug product's efficacy and safety are the same as those for other drug products. The applicant should refer to existing regulations and FDA guidance documents for further instructions on the format and content of the clinical sections of NDAs. See also Sections VI.F and G.

F. Evidence to Ensure Therapeutic Consistency

One of the key challenges for manufacturers of a botanical drug product is to ensure that different marketing batches, with their variations, have the therapeutic effect consistent with those of the batches used in the Phase 3 clinical studies. Given the heterogeneous nature of botanical drug products, chemical testing alone may not be sufficient for quality control and therefore for ensuring therapeutic consistency. As outlined in Section III.B, quality control of botanical drug products should take into consideration the three following aspects: (1) botanical raw material control, (2) quality control by chemical tests and manufacturing control, and (3) biological assay and clinical data. These different aspects of the quality control should be viewed collectively. For example, the amount of data needed from (1) and/or (3) (biological assay) could depend on the extent to which the molecules in a botanical mixture are characterized based on the chemical testing in (2). The applicant should provide an integrated assessment of the above three quality control aspects to demonstrate that the commercial botanical drug product batches will have the therapeutic effect consistent with those observed in the pre-marketing clinical testing.

The quality information should be collected from the clinical studies conducted during drug development, as discussed under different sections earlier in this guidance. All available data should be summarized and an integrated evaluation should be presented in the NDA in a botanical drug-specific section entitled "Assurance of Therapeutic Consistency" under Module 2.3.P.2 (Pharmaceutical Development).

1. Raw Material Control

Refer to Section VII.B.1.

2. Quality Control by Chemical Tests and Manufacturing Control

Refer to Section VII.B.2.

3. Biological Assay(s) and Clinical Data

While the raw material control and other CMC measures will help establish the identity and ensure the quality of the botanical drug products, information on correlations between such quality parameters and the pharmacological activity or clinical effect may be warranted in certain cases to ensure that variations in raw materials and drug substance will not affect a botanical drug product's therapeutic consistency. Examples of such information are as follows:

a. Biological Assay

As noted above, a biological assay is an important method by which to measure a botanical drug's potency and activity. While the biological assay should be as closely related to the drug's presumed mechanism of action as possible, other less relevant assays may also be considered and evaluated in individual cases. Also see Section VII.B.2.

b. Clinical Data

Dose-response data (see Section VI.F.2): If the clinical effects are not sensitive to dose (but are still superior to the placebo control group), it can reasonably be assumed that the variations within the established specifications probably will not affect the therapeutic consistency of drug products.

Multiple batch clinical data (see Section VI.F.1): Clinical studies in which subjects are randomized to receive different drug product batches can be used to assess treatment-by-batch interactions. Lack of significant interaction could provide confidence that therapeutic effects will be independent of drug batches within the established specification.

G. Postmarketing Considerations

Because of the importance of having a stable source of the botanical raw material and consistent manufacturing process for the botanical drug substance, any changes made post-approval (e.g., change in agricultural sites, agricultural and collection practice, and/or processing methods) should be assessed carefully to determine if drug product batches produced after such a proposed change would be sufficiently similar (pharmacologically and/or therapeutically) to batches produced before such a change. For botanical drug products, the effect of changes may not be easily evident. Additional studies (e.g., assessment of potency and activity using biological assays and/or other in vivo bridging studies) may be necessary. The Agency will determine the amount of data required on a case-by-case basis, taking into consideration a number of factors including, for example, the nature and extent of the changes and the extent of characterization of the active or chemical constituents in the mixture.