POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Review of Botanical Drug Products

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PURPOSE

- This MAPP describes the review process for investigational new drug applications (INDs) and new drug applications (NDAs) for botanical drug products and the role of the Botanical Review Team (BRT). These policies and procedures are intended to ensure quality and consistency in the review of these products.

- This MAPP does not include the review of over-the-counter drug monographs and ANDAs for botanical drug products.

- This MAPP describes policies, process, and procedures specific to botanical drug products. Unless otherwise mentioned, all other policies, process, and procedures follow CDER standards for review and regulatory action.

BACKGROUND

- Botanical drug products often have unique features (e.g., complex mixtures, substantial prior human experience, such as with traditional medical systems and/or lack of a distinct *active constituent(s)*[1]). These unique features require special consideration during the review process.

[1] See the Definitions section.

- CDER published a revised FDA guidance for industry on *Botanical Drug Development* (botanical guidance)[2] to consider these unique features and to facilitate the development of new therapies from botanical sources.

- CDER established a Botanical Review Team (BRT) to help manage the unique features and review issues associated with botanical drug products. The BRT ensures quality and consistency in the review of botanical drug products by acting as an advisory resource to all review divisions and offices in the Office of New Drugs (OND) and other review disciplines at CDER.

POLICY

1. General

- CDER review divisions have the same review responsibilities for INDs and NDAs for botanical drugs, including taking regulatory actions, as for non-botanical drug products.

- The BRT, located in the Office of Pharmaceutical Quality's (OPQ) Immediate Office, is a designated member of the OPQ review team and reviews pre-IND meeting requests, INDs (e.g., original submissions and amendments), NDAs (e.g., original submissions and supplements), citizen petitions (CPs), and pharmacy compounding consult requests involving botanical drugs.

- The BRT provides a pharmacognosy review (including an analysis of previous human experience and of the phytochemical ingredient profile) for all original IND and NDA submissions.

- The BRT collaborates with other review disciplines to ensure consistency of the review process for botanical drug products, including a totality of the evidence approach as described in the botanical guidance.

- For submissions, meetings, inquiries and other matters regarding botanical drugs that require participation by the BRT in OPQ as described in this MAPP, there will be a lead from the BRT designated.

2. Application Review

- The reviews of pre-IND meeting requests, INDs, and NDAs completed by the various review disciplines, including reviews provided by the BRT, will be

[2] The cited guidance represents the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

managed according to current CDER practices.

- The OPQ regulatory business project managers (RBPMs) manage meeting requests, regulatory submissions, and other inquiries that are solely related to chemistry, manufacturing, and controls (CMC) and facility issues.

- BRT reviews:

    - For original NDAs, the BRT will be part of the OPQ (or quality assessment) review team and their review will be incorporated into the OPQ integrated quality assessment.

    - For original INDs, including the 30-day safety review, the BRT will provide a stand-alone review document that will be uploaded into the electronic document system and routed to the assigned review team using established review timelines.

    - The BRT will additionally review the following:

        - Pre-IND meeting packages and related submissions
        - IND amendments
        - Postapproval NDA supplements
        - CPs
        - Pharmacy compounding consults that are relevant to the BRT review responsibilities (e.g., submissions that may impact quality, safety related to prior human experience, and therapeutic consistency of botanical drug products)
        - Submissions for which the quality assessment team requests BRT input

- The **CMC and biopharmaceutics team members** aligned with the OND review division that was assigned the application will conduct the review of CMC and biopharmaceutics information. This will include the drug substance and drug product manufacturing processes, controls, and testing (e.g., physical, chemical, biological assay testing, and dissolution). The Office of New Drug Products (ONDP) and the Office of Process and Facilities (OPF) in OPQ will also designate one or more botanical drug experts from their offices, as needed, to ensure quality and consistency in the CMC review of botanical drugs across divisions in ONDP and OPF.

- The **clinical pharmacology review team members** aligned with the OND review division that was assigned the application will conduct the clinical pharmacology review of botanical drug submissions. The clinical pharmacology review will be performed by the Office of Clinical Pharmacology (OCP) in the Office of Translational Sciences. OCP will also designate one or more botanical experts, as

needed, to ensure quality and consistency in the clinical pharmacology review of botanical drugs across divisions of OCP**.**

- The **nonclinical pharmacologist/toxicologist** in the OND review division will conduct the nonclinical pharmacology and toxicology reviews of botanical drug submissions. OND will also designate one or more botanical experts, as needed, to ensure quality and consistency in the nonclinical pharmacology and toxicology reviews of botanical drugs.

- The **clinical reviewers from OND and the statistical reviewers** from Office of Translational Sciences (OTS) will conduct reviews of the efficacy and safety of botanical drug products.

3. Postapproval Activities

- For all botanical drug-related postapproval activities involving questions of quality, clinical safety, or efficacy, the responsible review division will include the BRT in the review team and the BRT will, when appropriate, contribute to the review.

- Procedures for postmarketing surveillance of botanical drug products are the same as the procedures for non-botanical drug products.

RESPONSIBILITIES AND PROCEDURES

1. Communication, Inquiries, Meetings, and Materials

a) General information

- In general, the assigned OND regulatory project manager (RPM) will coordinate all communications with sponsors/applicants of botanical drug INDs and NDAs. However, the OPQ RBPMs, when appropriate, coordinate communications with sponsors/applicants with regard to meeting requests, regulatory submissions, and inquiries related to CMC and facility issues.

- If any discipline determines that a product was not identified by the FDA as a botanical drug product when it should have been, the assigned project managers (the OND RPM and the OPQ RBPM) are notified. The RPM or the RBPM then updates membership of the review team to include the BRT.

b) Inquiries related to botanical products

- General inquiries that are strictly facility/product quality in nature, but do not reference a specific application should be sent to the OPQ-Inquiries mailbox

(CDER-OPQ-Inquiries@fda.hhs.gov). The Botanical Team Leader will then be consulted to draft the response in collaboration with other review disciplines when appropriate.

- For inquiries regarding a specific application:
    - Facility/product quality inquiries should be sent to the assigned RBPM.
    - Non-CMC inquiries related to a specific application should be sent to the assigned OND RPM.
    - The assigned OND RPM or OPQ RBPM will inform other review disciplines, including the BRT, of relevant inquiries.

c) Meeting requests and background information

- The OND RPM or OPQ RBPM will invite the BRT to attend all internal and sponsors/applicants meetings.
- The BRT will provide applicable written responses to sponsor/applicant questions in the meeting package, information requests, and verbal responses at the meetings.

2. IND/NDA Review Disciplines

a) CMC and Biopharmaceutics Reviewers

1) The **CMC and biopharmaceutics reviewers in ONDP and OPF** are responsible for:

- Reviewing the CMC and biopharmaceutics information following the current FDA botanical drug guidance and other applicable regulations, policies, and FDA guidance documents.
- Reviewing information pertaining to the botanical drug substance/drug product manufacturing process, controls, and testing (i.e., physical, chemical, and biological assay testing). The review of this information, along with recommendations from the clinical review team on the impact of different product batches on the clinical response, will be used to develop specifications that will help ensure acceptable product quality.
- Participating in review team meetings and meetings with sponsors/applicants.

- Providing microbiology reviews of information supporting validation of sterility for sterile botanical drug products.

2) The **CMC and biopharmaceutics secondary reviewers** are responsible for:

- Conducting secondary CMC and biopharmaceutics reviews to ensure the consistency of quality information.

- Keeping the ONDP and OPF Branch Chiefs and Division Directors informed of botanical drug-related issues.

- Participating in review team meetings and meetings with sponsors/applicants, as appropriate.

- Ensuring that policies relating to CMC and biopharmaceutics issues for botanical drug products are applied consistently.

3) The **ONDP and OPF Botanical Experts (if identified)** are responsible for:

- Serving as expert consultants, as needed, on botanical-related CMC and facility issues.

- Advising staff regarding policies for botanical-related CMC and facility issues.

b) Clinical Pharmacology Reviewer

1) The **clinical pharmacology reviewer from OCP** is responsible for:

- Reviewing the clinical pharmacology information in accordance with the FDA botanical drug guidance, and other applicable regulations, policies, and guidance documents.

- Participating in review team meetings and meetings with application sponsors/applicants.

2) The **clinical pharmacology team leader** is responsible for:

- Conducting secondary clinical pharmacology reviews.

- Keeping the OCP Division Director informed of botanical drug-related issues.

- Participating in review team meetings and meetings with sponsors/applicants, as appropriate.

- Ensuring that policies relating to clinical pharmacology for botanical drug products are applied consistently.

3) The **OCP Botanical Expert** (**if identified**) is responsible for:

- Serving as an expert consultant, as needed, on botanical drug issues.

- Advising staff regarding policies and requirements for botanical drug products and their development.

c) Nonclinical Pharmacology/Toxicology Reviewer

1) The **nonclinical pharmacology/toxicology reviewer** is responsible for:

- Reviewing, in consultation with the OND Nonclinical Botanical Expert as necessary, nonclinical pharmacology/toxicology information in accordance with the FDA botanical drug guidance and other applicable regulations, policies, and guidances.

- Determining pharmacology/toxicology study requirements for botanical drug products for the different stages of drug development according to Center policies for botanical drug products.

- Participating in review team meetings and meetings with sponsors/applicants.

2) The **nonclinical pharmacology/toxicology team leader** is responsible for:

- Conducting secondary pharmacology/toxicology reviews.

- Participating in review team meetings and meetings with sponsors/applicants, as appropriate.

- Ensuring, in consultation with the Pharmacology/Toxicology Coordination Committee (PTCC) and the Associate Directors or PTCC Dietary Supplement Subcommittee as necessary, consistent application of botanical drug policies and requirements.

3) The **OND Nonclinical Botanical Expert** (**if identified**) is responsible for:

- Serving as a consultant, as needed, on nonclinical pharmacology/toxicology botanical issues.

- Providing advice on policies and requirements for development of botanical drug products.

d) Clinical Reviewer

1) The **clinical reviewer** is responsible for:

- Conducting reviews of clinical efficacy and safety, in collaboration with an assigned statistical reviewer, of all botanical drug applications, in accordance with the above policy/procedures and general CDER standards for application review.

- In collaboration with an assigned statistical reviewer, interpreting clinical dose-response data generated from human experience with multiple batches of the drug product with respect to dose-response relationships and the impact of different drug product batches (manufactured by different batches of the drug substance) on clinical response.

2) The **cross-discipline team leader** for NDAs is responsible for:

- Conducting secondary clinical reviews for NDAs and ensuring that the totality-of-evidence has been reviewed by the review team.

- Participating in review team meetings and meetings with sponsors/applicants.

- Keeping the division director and office director, as needed, informed of botanical drug-related issues.

- Consulting and collaborating with other review disciplines, as needed, on botanical drug-specific issues encountered either before or after NDA approval.

e) Assigned Regulatory Project Manager or Regulatory Business Project Manager

- The OPQ RBPMs and the OND RPM are each responsible for ensuring that botanical product IND and NDA submissions that they manage are appropriately identified and that the BRT is included in the review team. For reviewer assignment purposes in the appropriate electronic system, the primary botanical reviewer name should be added to the drug product

review team, until the botanical team task is added to the electronic system. Otherwise, the responsibilities of the RPM or RBPM remain the same as for non-botanical INDs and NDAs, including, but not limited to:

- Managing submissions to the review division and meeting requests involving botanical drugs.

- Serving as the primary point of contact for communications between sponsors/applicants of botanical drug applications and the FDA.

- Ensuring that submissions are circulated to and assigned for review, as appropriate, to the review team, including the BRT.

- Scheduling and facilitating application-related meetings (both internal and external) and recording minutes of the meetings.

4. Botanical Review Team

a) The **botanical reviewer(s) in the BRT** is responsible for:

- Evaluating the identity of the various medicinal plants used in botanical drug products, including, but not limited to, the binomial species name, plant parts, geographical growth location(s), harvest season(s), and cultivation conditions. This can include conducting in-depth research of the phytochemical ingredient profile of each plant species and evaluating the pharmacological actions of key known ingredients that are relevant to the proposed indication.

- Evaluating raw material characterization and control for INDs and NDAs, as well as combination and consistency issues for a botanical product derived from extracts of multiple botanical raw materials.

- Evaluating previous human experience of plant species, botanical raw materials, extracts, and commercial products, especially those used in traditional medicine, that are the subject of botanical drug INDs and NDAs, including the following:

    - Assessing the historical uses of the plant species, botanical raw materials, and extracts proposed in the application with respect to their traditional indications, preparations, formulations, and recommended daily doses.

    - Comparing previous human experience with information from clinical trials of the botanical drug product conducted and submitted in the IND or NDA.

- Evaluating prior human experience information to support safety during early phase IND development.

- Evaluating safety and consistency issues for botanical products derived from multiple botanical raw materials that have significant previous human experience for such combinations.

- Performing collaborative reviews of IND and NDA applications (including pre-IND meeting packages, pre- and postapproval CMC only submissions), CPs, and pharmacy compounding consults for botanical drug products.

- Considering and recommending how the provisions in the FDA botanical drug guidance, applicable laws, regulations, policies, and guidance documents, will be applied to the review of botanical drug applications, CPs, and pharmacy compounding consult requests.

- Participating as a team member at internal meetings and meetings with sponsors/applicants.

- Participating, along with the other reviewers from OPQ (e.g., ONDP and/or OPF staff), in pre-approval inspections of good agricultural and collection practice related sites and drug substance manufacturing facilities, as needed.

b) The **team leader of the Botanical Review Team** in OPQ is responsible for:

- Serving as, or designating his or her BRT member to serve as, a co-Application Technical Lead of an OPQ review or quality assessment team to integrate, in collaboration with other review disciplines, information based on the totality-of-evidence approach in NDAs and assess the sufficiency of this information in ensuring the consistency of product quality.

- Overseeing the BRT's review of regulatory submissions.

- Convening and leading BRT meetings.

- Ensuring that drug products classified as botanical drugs meet the definition of botanical drugs as stated in the current FDA botanical drug guidance.

- Ensuring that the policies stated in the current FDA botanical drug guidance are applied consistently to botanical drug product development and review.

- In collaboration with the review division, conducting a secondary review of botanical drug information in IND and NDA submissions, and recommending

regulatory action(s) to the review division director or office director, as appropriate.

- Participating in discussions with review divisions and sponsors on the clinical development programs of botanical drug products.

- Participating as the BRT secondary reviewer in the collaborative review of botanical INDs, NDAs, and CPs and pharmacy compounding consult requests for botanical drug products.

- Signing off on BRT reviews.

REFERENCES

1. Federal Food, Drug, and Cosmetic Act, 21 USC 301 et. seq.
2. Dietary Supplement Health and Education Act of 1994, 21 USC 321(ff)
3. 21 CFR 10.20, 10.30, 312, 314, 330
4. 21 USC 321
5. FDA guidance for industry *Botanical Drug Development*, 2016 (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm458484.pdf)

DEFINITIONS

- **Active constituents:** The chemical constituent(s) or components(s) in a botanical drug substance that contribute significantly to a botanical drug's intended pharmacological activity or therapeutic effect.

- **Botanical drug product:** A product that is used as a drug and that contains as ingredients vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof. Botanical drug products may be available as (but are not limited to) solutions (e.g., teas), powders, tablets, capsules, elixirs, topicals, or injectables. For the purposes of this MAPP, fermentation products and highly purified (or chemically modified) botanical substances are not considered botanical drug products. See the botanical guidance for a more comprehensive definition of botanical drug products. Allergenic extracts and vaccines that contain botanical ingredients are regulated by the Center for Biologics Evaluation and Research under section 351 of the Public Health Service Act.

- **Dietary supplement:** A product (other than tobacco) intended to supplement the diet by increasing the total dietary intake that bears or contains one or more of the following dietary ingredients: (1) a vitamin; (2) a mineral; (3) an herb or other botanical; (4) an amino acid; (5) a dietary substance for use by humans to supplement the diet by increasing the total dietary intake; or (6) a concentrate, metabolite,

constituent, extract, or combination of any ingredient described in (1) through (5) above. (See 21 U.S.C. 321(ff), the Dietary Supplement Health and Education Act of 1994 (DSHEA), and the botanical guidance for details.)

- **Drugs** (as defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)):

  (A) articles recognized in the official United States Pharmacopoeia [USP], official Homeopathic Pharmacopoeia 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 humans or other animals; and

  (C) articles (other than food) intended to affect the structure or any function of the body of humans or other animals, except for dietary supplements that may be lawfully marketed with such claims under DSHEA; and

  (D) articles intended for use as a component of any articles specified in clauses (A), (B), or (C).

  A botanical drug product that is marketed in the United States with a claim of diagnosing, mitigating, treating, curing, or preventing disease is a drug under section 201(g)(1)(B) of the FD&C Act.

- **Pharmacognosy:** The study of drugs of natural origin, specifically, those derived from plants, animals, and microorganisms. Pharmacognosy today represents a highly interdisciplinary science. Its scope includes the study of physical, chemical, biological, and pharmacological properties of drugs and drug candidates of natural origin and botanical or herbal medicines, as well as the search for new drugs from natural sources.

EFFECTIVE DATE

This MAPP is effective November 30, 2016.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
6/7/04	Initial	N/A
5/2/12	Recertified	Minor changes
4/23/14	N/A	Transferred from OND to OPS

11/30/16	Rev. 1	Changes reflect the OPS reorganization to OPQ
12/30/16	N/A	Updated guidance reference