

OFFICE OF NEW DRUGS

Review of Botanical Drug Products

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PURPOSE

- This MAPP describes the review process in the Center for Drug Evaluation and Research (CDER) for investigational new drug applications (INDs) and new drug applications (NDAs) for botanical drug products. These procedures are intended to ensure quality and consistency in the review of these products.
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BACKGROUND

- Botanical drug products often have unique features (e.g., complex mixtures, lack of a distinct *active ingredient*, substantial prior human uses). These special features require consideration during the review processes.
 - CDER has issued a guidance for industry on *Botanical Drug Products* (referred to as the Botanical Guidance in this MAPP) to take these features into consideration and to facilitate development of new therapies from botanical sources. The guidance also addresses how prior human experiences may be used in preliminary safety assessment.
 - To enhance quality and consistency in the review of botanical drug products, CDER established the Botanical Review Team to serve as a resource to all review divisions and offices in OND in reviewing and evaluating INDs and NDAs for botanical products.
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REFERENCES

- Federal Food, Drug, and Cosmetic Act (the Act)
 - Dietary Supplement Health and Education Act of 1994 (DSHEA)
 - 21 CFR 10.20, 10.30, 312, 314, 321, 324, 330, 331-358
 - Guidance for Industry: *Botanical Drug Products* (the Botanical Guidance)
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DEFINITIONS

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 products. Allergenic extracts and vaccines that contain botanical ingredients are regulated by the Center for Biologics Evaluation and Research (CBER) under section 351 of the Public Health Service Act (42 U.S.C. 262).

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). See also DSHEA and the Botanical Guidance for details.)

Drugs: As defined in section 201(g)(1) of the 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 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 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.

POLICY**General**

- The Botanical Review Team (Botanical Team) located in the ODE V Immediate Office will participate in the review of botanical drug applications as members of the review team and serve as botanical experts for the Agency.
- To maintain consistency, participation by the Botanical Team in the review and decision-making processes is mandatory for all botanical pre-IND, IND, and NDA submissions.
- The review divisions have the same primary responsibility for all botanical drug products as for nonbotanical drug products.
- For botanical applications, both INDs and NDAs, the Botanical Team will be informed of all regulatory actions issued by the designated review division through routing in the Division File System (DFS). The Botanical Team will enter their reviews in DFS and route to the assigned division review team.
- A botanical drug product can be marketed in the United States under an over-the-counter (OTC) monograph or under an approved NDA or abbreviated new drug application (ANDA). Policies regarding the review of OTC monographs and ANDAs for botanical products are outside of the scope of this MAPP.

Botanical Team

- The Botanical Team consists of a team leader, project manager, medical officer(s), and pharmacognosist(s).
- For all botanical submissions, the Botanical Team will conduct pharmacognosy (see Definitions) reviews throughout the IND and NDA process. The pharmacognosy reviewer will be under the immediate office of ODE-V and report to the leader of the Botanical Team. The scope of the pharmacognosy review is defined in the section on Procedures and Responsibilities below.
- In addition to the pharmacognosy review, the Botanical Team may also conduct a botanical-specific medical review when indicated and, after consult with experts in other disciplines, provide comments on all botanical-related issues in a comprehensive botanical report.
- For issues related to specific applications, the Botanical Team will not have direct contacts with the sponsors. All communications will be transmitted through the review division project management staff.
- The Botanical Team may respond directly to general inquiries related to the Botanical Guidance/MAPP and other relevant policies.

Application Review

- The assigned review division will manage the reviews by various disciplines, including the ones provided by the Botanical Team according to this MAPP.
- The current chemistry team supporting the review division that was assigned the application will conduct the chemistry review of botanical submissions. The Office of New Drug Chemistry (ONDC) will also designate one or more botanical experts to serve as consultants only as needed by the review division CMC reviewer and Botanical Team to ensure quality and consistency in the CMC review of botanicals across divisions.
- The review team supporting the review division that was assigned the application will conduct the clinical pharmacology and biopharmaceutic review of botanical submissions. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) will also designate one or more botanical experts to serve as consultants only as needed for the discipline reviewer and Botanical Team to ensure quality and consistency in the clinical pharmacology and biopharmaceutical review of botanicals across divisions.
- The pharmacologist in the review division (who will be assigned by his/her team leader and report to his/her team leader for secondary reviews) will conduct the pharmacology and toxicology reviews of botanical submissions. One or more expert pharmacology reviewer(s) specializing in botanical products will be designated by the Office of the New Drugs (OND) Associate Director for Pharmacology/Toxicology to serve as consultant(s) as needed to the discipline reviewer and the Botanical Team to ensure quality and consistency in the pharmacology and toxicology reviews of botanicals across divisions.
- The review division will process and manage requests for pre-IND consultation from sponsors on the development of botanical products according to existing administrative procedures for nonbotanical drugs. The Botanical Team will be notified by the review division and will provide written reviews for such requests or verbal comments at the meetings.

Postapproval Activities

- For all botanical drug-related postapproval activities involving the review division, the Botanical Team will be notified and, when appropriate, provide a collaborative review.
- Otherwise, the procedures for postmarketing regulatory maintenance of botanical drug products are the same as the current procedures for nonbotanical products.

RESPONSIBILITIES AND PROCEDURES

1. Document and Communication Flow

a) General information

- In general, the Botanical Team and review divisions will inform each other of all communications and regulatory deliberations/actions related to botanical

applications, including petitions and Time and Extent Applications (TEAs) for botanical products for OTC marketing.

- Inquiries on general botanical questions will be directed to the Botanical Team project manager.
- The assigned project manager in the review division will coordinate communications with sponsors of botanical INDs.
- The Botanical Team reviewers and project manager are members of the application review team.

b) Inquiries on specific botanical IND/NDA submissions:

- All inquiries will be referred to the assigned project manager in the review division.
- The project manager in the review division will inform the Botanical Team of the inquiries.
- The Botanical Team will communicate with the sponsors through the project managers in the review division.

c) Inquiries on general botanical-related issues:

- All inquiries will be referred to the project manager or team leader of the Botanical Team.
- The Botanical Team may consult with designated expert reviewers in each relevant discipline.
- If the discussion is relevant to any specific botanical drug application, the Botanical Team will direct the sponsor to the review division immediately.

d) Meeting requests and background information:

- The review division project manager will ensure that the Botanical Team members receive the appropriate number of copies of the submissions.
- The review division will invite the Botanical Team to attend all internal premeetings and meetings with sponsors.

e) IND/NDA submissions and review activities:

- The review division will ensure that the Botanical Team receives a review copy of submissions.
- The Botanical Team will be included in review team meetings as they are full members of the review team.
- The review division will invite the Botanical Team to participate in the preparation of advisory committee meetings.

2. Review Division

a) Chemistry, Manufacturing, and Control (CMC) information review responsibilities:

- 1) The **chemistry reviewer co-located in the review division** is responsible for:
 - Reviewing, in consultation with the ONDC Botanical Expert as necessary, CMC information in accordance with the Botanical Guidance and other applicable regulations, policies, and guidances.
 - Participating in review team meetings and meetings with application sponsors.

- Requesting microbiology review of information supporting validation of sterility for sterile botanical products.
- 2) The **chemistry team leader** is responsible for:
 - Conducting secondary CMC reviews.
 - Keeping the ONDC Division Director informed of botanical-related issues.
 - Participating in review team meetings and meetings with sponsors, as appropriate.
 - Ensuring that policies relating to CMC issues for botanical products are applied consistently.
 - 3) The **ONDC microbiology reviewer** is responsible for:
 - Upon request from the chemistry reviewer, reviewing information supporting validation of sterility for sterile botanical products.
 - Advising on application of policies regarding sterility issues of botanical products.
 - 4) The **ONDC Botanical Expert** is responsible for:
 - Serving as the expert consultant as needed to the review teams on botanical CMC issues.
 - Advising on application of policies regarding botanical CMC issues.
- b) **Clinical pharmacology/biopharmaceutics information review responsibilities:**
- 1) The **clinical pharmacology/biopharmaceutics reviewer co-located with the review division** is responsible for:
 - Reviewing, in consultation with the OCPB Botanical Expert as necessary, clinical pharmacology and biopharmaceutics information in accordance with the Botanical Guidance and other applicable regulations, policies, and guidances.
 - Participating in review team meetings and meetings with application sponsors.
 - 2) The **clinical pharmacology/biopharmaceutics team leader** is responsible for:
 - Conducting secondary clinical pharmacology/biopharmaceutics reviews.
 - Keeping the OCPB Division Director informed of botanical-related issues.
 - Participating in review team meetings and meetings with sponsors, as appropriate.
 - Ensuring that policies relating to clinical pharmacology and biopharmaceutics for botanical products are applied consistently.
 - 3) The **OCPB Botanical Expert** is responsible for:
 - Serving as the expert consultant as needed to the review team on botanical issues.
 - Advising on the application of botanical policies and requirements for drug development.
- c) **Nonclinical pharmacology and toxicology (pharm/tox) information review responsibilities:**
- 1) The **pharm/tox reviewer** is responsible for:

- Reviewing, with consultation with the OND pharm/tox Botanical Expert as necessary, nonclinical pharm/tox information in accordance with the Botanical Guidance and other applicable regulations, policies, and guidances.
 - Determining pharm/tox requirements for botanical products for the different stages in drug development according to center policies for botanical products.
 - Participating in review team meetings and meetings with application sponsors.
- 2) The **pharm/tox team leader** is responsible for:
- Conducting secondary pharm/tox reviews.
 - Participating in review team meetings and meetings with sponsors, as appropriate.
 - Ensuring, in consultation with the Pharm/Tox Committee on Botanicals as necessary, consistent application of botanical policies and requirements.
- 3) The **OND pharm/tox Botanical Expert** is responsible for:
- Serving as consultant as needed on nonclinical pharm/tox botanical issues.
 - Advising on the application of botanical policies and requirements for drug development.
- d) **Medical/Statistical information review responsibilities:**
- 1) The **medical reviewer/team leader/co-located statistical reviewer in the review division** are responsible for:
- Conducting clinical and statistical reviews of the botanical applications, as for nonbotanical products, in accordance with the above policy/procedures and general CDER standards for application review.
 - Consulting and collaborating with the Botanical Team on all botanical-specific issues encountered in the medical/statistical reviews.
- e) **Project Manager responsibilities:**
- 1) The **project manager in the review division** is responsible for:
- Ensuring that botanical INDs and NDAs are identified appropriately.
 - Managing botanical applications, submissions to the division, and communications between sponsors of botanical applications and the FDA.
 - Notifying the Botanical Team project manager of the receipt of new botanical INDs/NDAs, subsequent submissions to INDs/NDAs, and petitions and TEAs for botanical products for OTC marketing.
 - Ensuring that submissions are circulated to and assigned for review, as appropriate, to the Botanical Team.
 - Keeping the Botanical Team informed of new botanical applications and submissions to them.
 - Scheduling and facilitating application-related meetings (internal and external) that involve the Botanical Team and recording minutes of the meetings.

3. Botanical Review Team in ODE-V

- a) The **project manager of the Botanical Team** in ODE-V is responsible for:
- Managing and coordinating responses to all review requests and other

- communications addressed to the Botanical Team.
 - Distributing submissions/technical copies received from the review division to the reviewers on the Botanical Team.
 - Serving as the point of contact with the review division.
 - Acting as liaison to the Office of Counter-Terrorism and Pediatric (OCTAP) Drug Development and/or initiating consults, when appropriate.
 - Scheduling internal Botanical Team meetings and meetings with the review divisions on non-application review issues.
 - Coordinating and leading Botanical Team meetings, together with the Botanical Team leader.
 - Recording and distributing the Botanical Team internal meeting minutes.
 - Ensuring accurate tracking of botanical applications and monitoring data entry for botanical submissions in COMIS.
 - Serving as point of contact for inquiries on the Botanical Guidance, related policies, and MAPP.
- b) The **team leader of the Botanical Team** in ODE-V is responsible for:
- Guiding the Botanical Team's review activities and convening team meetings.
 - Ensuring that products classified as botanical meet the definition of botanicals stated in the Botanical Guidance.
 - Ensuring that the policies stated in the Botanical Guidance are applied consistently to botanical product development and review.
 - In collaboration with the review division, conducting a secondary review of the initial IND submission and recommending regulatory action(s) to the specific subject matter review division director.
 - Participating in discussions with review divisions and sponsors on clinical development of botanical drug products.
 - Participating in the collaborative review of botanical INDs, NDAs, and petitions and TEAs for botanical products, as a Botanical Team secondary reviewer.
- c) The **medical officers of the Botanical Team** in ODE-V are responsible for:
- With assistance from the Botanical Team's pharmacognosist, conducting a review on the history of clinical use for a botanical product.
 - Assessing the quality of existing human data for a botanical drug.
 - Based on the pharmacognosy review (see below), comparing previous human uses of a botanical preparation and those proposed in the IND, in consultation with the review division if necessary.
 - Considering applications and development plans according to the Botanical Guidance and other applicable laws, regulations, policies, and guidances; and making appropriate recommendations.
 - In collaboration with the review division, assessing the risk/benefit of the initial development plan in the IND.
 - Under the Botanical Team leader's guidance, participating in discussion with the review division and sponsors on clinical development of botanical drugs.
 - Perform collaborative reviews of applications, petitions, and TEAs for botanical products.

- d) The **pharmacognosy reviewer in the Botanical Team** is responsible for:
- Evaluating the identities of the various medicinal plants used in botanical drug products.
 - Reviewing the pharmacology of botanical drug products.
 - Assessing the historical uses of botanical drug products.
 - Considering and recommending how the provisions in the Botanical Guidance, and related laws, regulations, policies and guidances, will be applied to botanical applications, petitions, and TEAs.
 - Participating as a team member at internal meetings and meetings with the sponsor/applicant.
 - Providing written reviews to the review division project manager by the review goal agreed upon by the review team.
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EFFECTIVE DATE

This MAPP is effective upon date of publication.