CMC Requirements for Herbal Drug Products

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Objective

- To identify differences in requirements for botanical drug products compared with the requirements for new drugs based on FDA's new chemistry guidance document *Botanical Drug Products,* June 2004.
- To identify areas where additional information will be required to support both Phase III trials, and ultimately the submission and approval of an NDA.

Methods

Step 1: Determine if botanical product meets the definition of a drug based on "intended use" under the FD&C Act.

Step 2: For clinical studies, determine phase of investigation IND is intended to support and amount of CMC information that will be needed as shown in Table 1.

Table 1. Considerations for Amount of Information Needed in an IND

Parameter	Issue
Novelty of drug	Extent previously studied
Safety	Drug product's known or suspected risks
Marketing Status	Whether legally marketed in the US under DSHEA
Marketing History	Whether legally marketed outside US
Development phase of drug	Data requirements may vary

Step 3: Determine if product meets combination drug regulations

- Not considered fixed combination drugs if from single part of plant (leaves, stems, roots or seeds) or from a single species of algae or macroscopic fungi
- Considered combination drug if composed of multiple parts of a single species, or of parts of different species of plant, algae, or macroscopic fungi

Step 4: For marketing, determine if

- Product meets or can meet OTC monograph
- Will require approved NDA or ANDA

Evaluation

The extent of CMC information required for an IND for a botanical drug product depends on information already known and the phase of clinical investigation the IND is intended to support as follows:

- Extensively studied with large body of data
- Legally marketed in US under DSHEA
- Phase I, II, and Phase III studies to be conducted
- Novel Drug
- Legally marketed outside US
- Botanical product has known or suspected risks

Key differences in requirements for botanical drugs as compared to other new drugs include:

- Not essential to identify active constituent(s)
- FDA may rely on combination of tests and controls to ensure identity, purity, quality, strength, potency and consistency of drug substance and drug product testing

Provide the information listed in Table 2 for the plant or plant part, algae, or macroscopic fungi if the botanical has not been previously marketed or has known side effects.

Table 2. CMC Information Required for Nonmarketed Botanical Products and Products With Known Safety Concerns

Material	Information Required
Botanical Raw Material	Identification by trained personnel Certificate of authenticity List of all growers and/or suppliers
Botanical Drug Substance	Qualitative and quantitative description Name and address of manufacturer Description of manufacturing process Quality control tests performed Description of container/closure system Available stability data Container label
Botanical Drug Product	Qualitative description of finished product Composition of finished product Name and address of manufacturer Description of manufacturing process List of quality control tests performed Description of container/closure system Available stability data Placebo Labeling Environmental Assessment or claim of categorical exclusion

Results

Key FDA draft recommendations are summarized below:

- Use a consistent formulation for both drug substance and dosage form throughout the clinical trials, unless this proves impossible.
- Determine the parameters and specifications for batch or lot release testing as the clinical studies progress.
- Retain sufficient quantities of the botanical raw material and drug substance from the same batch for future chemical and physical characterization.
- Include historical and scientific information (and its source) or prior human use of the botanical product and each of its ingredients in traditional foods and drugs.
- Identify the harvest location, growth conditions, stage of plant growth at harvest time, collection/washing/drying and preservation procedures, and handling, transportation, and procedures.
- Provide quantity and sequence of addition, mixing, grinding or extraction if more than one botanical raw material is introduced to produce a multi-herb substance.

Conclusions

- Botanical drug products have unique characteristics that need to be taken into account due to their complex nature and potential lack of knowledge of their active constituent(s).
- Botanical products that are legally marketed in the US may have reduced CMC requirements for initial (Phase I and II) clinical studies.
- Amount of CMC data required to support Phase III studies and NDA/ANDA is consistent with other new drug products.
- Assurance of identity, purity, strength, potency and consistency of drug substance and drug product may require:
  - Multiple tests such as spectroscopic and/or chromatographic fingerprints, chemical assays, biological assays for drug substance and drug product
  - Raw material and process controls
  - Process validation
- Development of a combination botanical drug product can be a challenge.