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Botanical Drug Development and Quality Standards

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Outline

- What are botanical drugs?
- Scientific challenges in botanical drug development and evaluation
- FDA approach for evaluating botanical drug applications

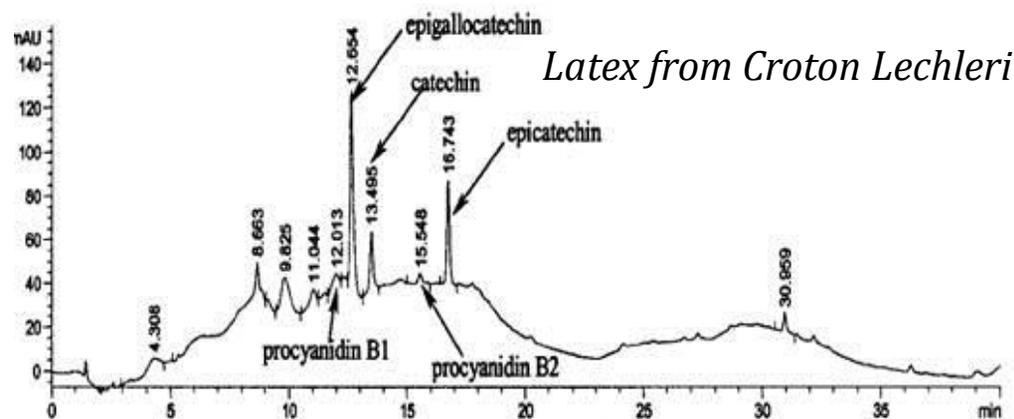
What are the botanical drugs?

- The term *botanical* means products that include plant materials, algae, macroscopic fungi, or combinations thereof.
 - It excludes highly purified drug substances, products containing animals or animal parts and or minerals, materials derived from genetically modified botanical species, and fermentation products
- Botanical drugs may be available in various forms, including solutions, powders, tablets, capsules, topicals, or injectables.
- Two FDA-approved botanical NDAs:
 - Veregen and Fulyzaq



Botanical Drug Characteristics

- Botanical drugs are heterogeneous mixtures that contain:
 - Multiple chemical components
 - Potentially more than one chemical component that contributes meaningfully to the mixture's physiological or pharmacological action



- Chemical components in a botanical mixture and their biological activities are generally not well characterized.

Unique Characteristics of Botanical Drugs

- Botanical drugs exhibit batch-to-batch variations in properties (e.g., chemical composition).
 - Natural variability at the plant and raw material levels
 - Greater than the variability typically observed in non-botanical drugs (e.g., chemically synthesized and purified drug molecules)
- Many botanical drug candidates have previous human-use experience.
 - Dietary supplements in the U.S.
 - Herbal medicines (e.g., Europe)
 - Traditional medicines (e.g., China)

Challenges

- Botanical drugs are complex
 - Multiple chemical components
 - Not well-defined active component(s)
 - Natural variations
- CDER generally considers the entire mixture as the active ingredient (API) for botanical drugs
 - Regulations on fixed combination drugs do not apply to the botanical mixture derived from a single botanical raw material
- Botanical products intended to be marketed as drugs in the United States are expected to meet the same standards as non-botanical drugs for **quality**, **safety**, and **efficacy**.
 - A conventional CMC approach for small-molecule drugs (mainly based on chemical testing) is generally insufficient for quality control of botanical products.
 - Information on prior human use may provide some indication of the safety profile of botanical products.
 - Level of clinical efficacy and safety requirements is the same for botanical and non-botanical drugs.

FDA approach to evaluation of botanical drugs

- Encourage research and development of botanicals as new drugs
- CDER Botanical Review Team
- 2004 FDA Guidance for Industry: Botanical Drug Products
- 2015 FDA Draft Guidance for Industry: Botanical Drug Development

CDER Botanical Review Team

- Established in 2003
 - Previously under the Office of New Drugs
 - Transferred to the Office of Pharmaceutical Quality in 2013
- Provides scientific expertise on botanical issues to the review staff
- Ensures consistent interpretation and implementation of the Botanical Guidance and related policies
- Consolidates experiences in regulatory review of botanical applications and compiles information on the status of botanical drug submissions for agency management

Pharmacognosy Review by CDER Botanical Review Team

- Medicinal plant biology
 - Identification, potential misuses of related species
- Prior human experiences
 - Mostly in traditional medicine/complementary and alternative medicine (CAM) systems, such as traditional Chinese medicines
 - Evidence of prior and current uses
 - Extensive review of past experiences and current uses
 - Documentation of marketing history (volume of sales, adverse events, etc.)
 - All types of old data be considered and reviewed to determine relevance
- Pharmacology of botanical drugs
 - Old theories and practices and new testing
- Product quality
 - Ensuring quality and therapeutic consistency based on integrated *totality-of-evidence* approach

BRT Current Members



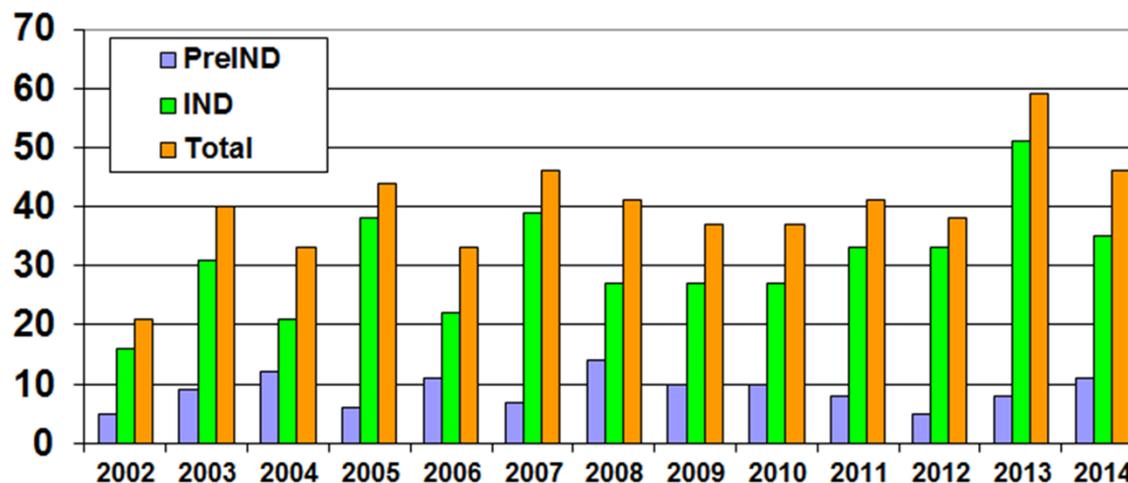
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2004 FDA Botanical Guidance: Key Principles

- Information on prior human use may substitute for animal toxicology studies
 - Non-clinical evaluation may be reduced or delayed for certain botanical products entering phase 1 and 2 trials
- Flexible CMC approach is emphasized
 - Identification of active components in a botanical mixture may not be necessary
 - But relevant chemical marker(s) needed for quality control
 - Further purification generally not needed
 - But additional control of botanical raw material needed
- The level of overall clinical efficacy/safety requirements is the same for botanical and non-botanical drugs for NDA approval
 - The risk/benefit analysis approach will be the same

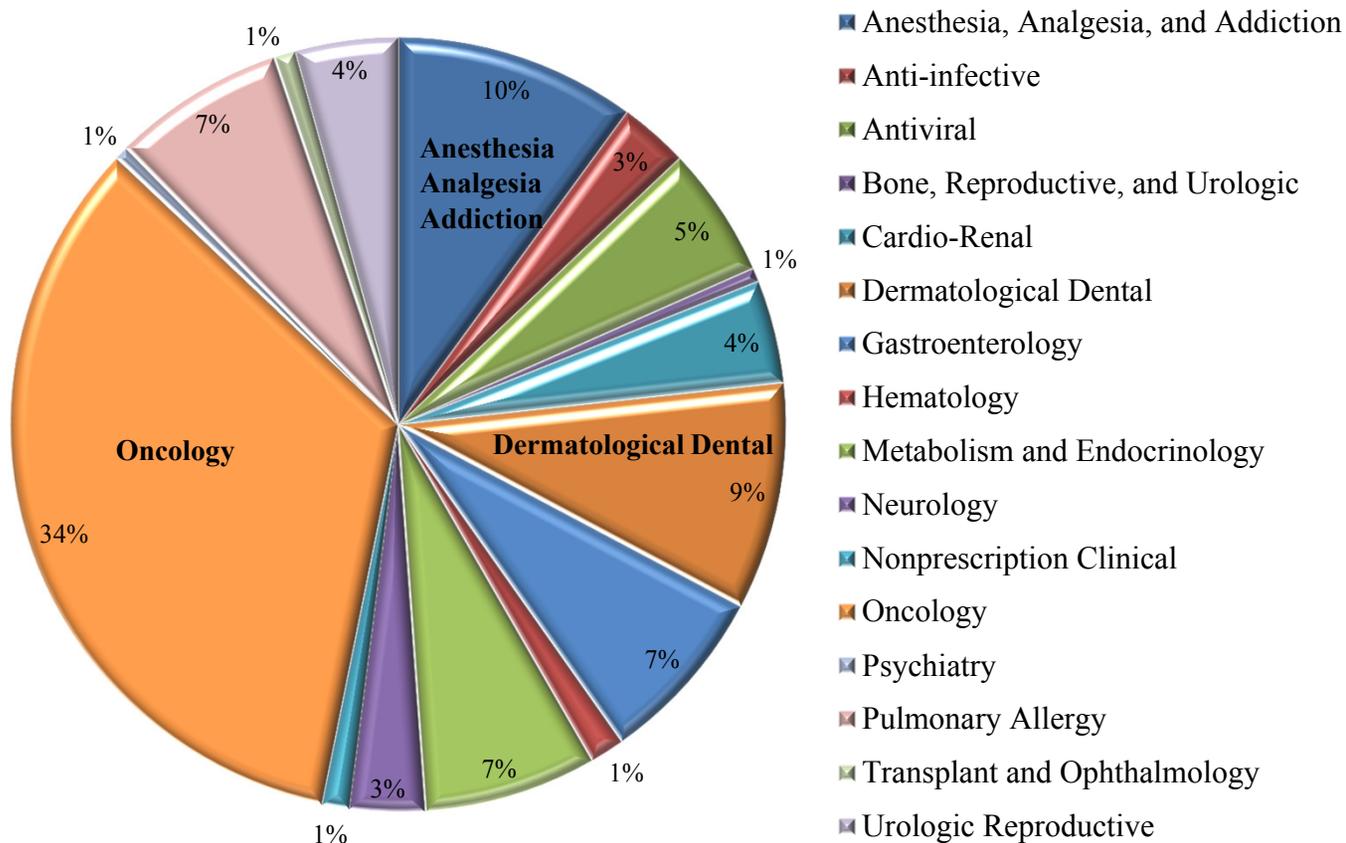
Botanical Applications in CDER

- Up to 2014
 - More than 600 pre-INDs/INDs
 - Approx. 1/3 commercial, 2/3 research
 - 2/3 single botanical raw material, 1/3 multiple botanical raw materials
 - Majority in phase 2, and a handful of them in phase 3
 - Two NDAs approved



Botanical Applications in CDER

IND Review Distribution

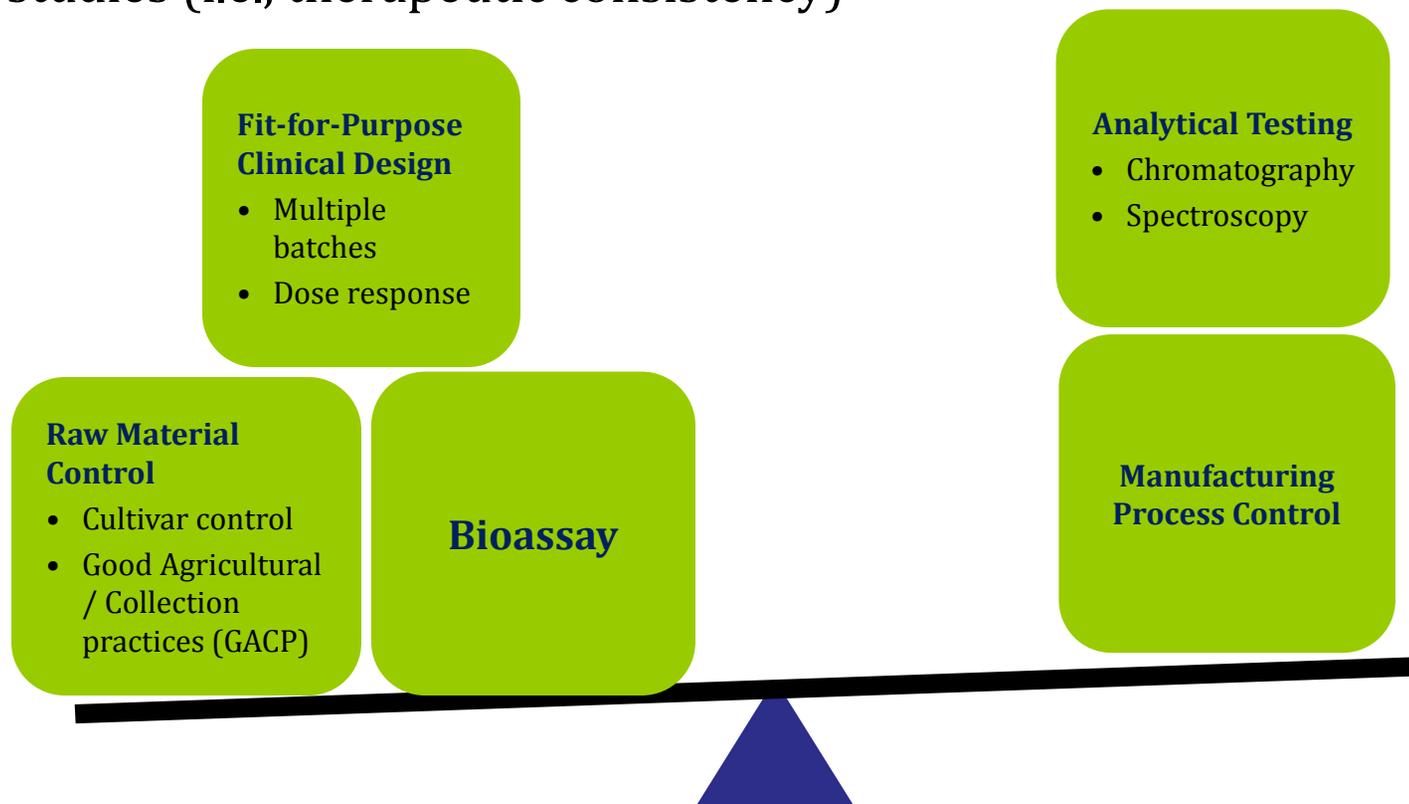


2015 FDA Draft Botanical Guidance

- Revises the final FDA Botanical Guidance issued in 2004
 - The recommendations for early-phase trials remains the same
- Provides additional specific recommendations to better address late-phase development and NDA submission for botanical drugs
 - Veregen approved in 2006
 - Fulyzaq approved in 2012
- Recommends an integrated (the so-called *totality of evidence*) approach to ensure the consistency of quality and thus therapeutic effects of botanical drug products for approval and marketing

Integrated Approach to Quality Control of Botanical Drugs

- To ensure that marketed product batches deliver a therapeutic effect consistent with that observed for product batches tested in clinical studies (i.e., therapeutic consistency)



Case Study: Fulyzaq

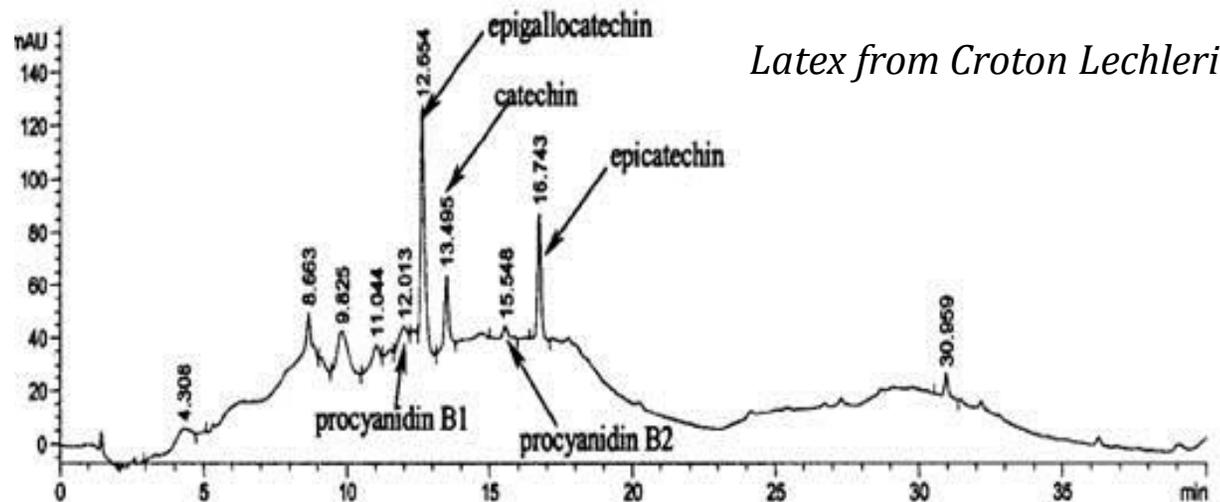
- The 2nd botanical NDA (approved on December 31, 2012)
- Delayed-release oral tablet containing 125 mg crofelemer
- Crofelemer, a botanical drug substance derived from the crude plant latex of *Croton lechleri* (*Dragon's Blood*)



- 1st FDA approved drug for symptomatic relief of noninfectious diarrhea in patients with HIV/AIDS on antiretroviral therapy

Crofelemer Structure

- An oligomeric proanthocyanidin mixture primarily composed of (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin monomer units linked in random sequence



- Multiple analytical methods collectively provide extensive information on the structural signatures of crofelemer (e.g., the composition of proanthocyanidin oligomers)
- These analytical methods were ultimately considered insufficient to support the characterization of quality control of this complex mixture

Additional Data to Support Therapeutic Consistency of Fulyzaq

- Botanical raw material control
 - Implementation of Good Agricultural and Collection Practices (GACP)
 - Restriction of harvesting botanical raw material to specific eco-geographic regions (EGRs)
 - **Reduces the variability at the plant and raw material levels**
- Bioassay
 - Based on well-known mechanism of action (i.e., crofelemer targets and controls dual intestinal chloride channels: cAMP-stimulated cystic fibrosis transmembrane conductance regulator Cl⁻ channel and the calcium-activated Cl⁻ channel)
 - **Potentially provides more flexibility for the manufacturer to make postapproval changes (e.g., expansion of EGRs to increase and diversify the botanical raw material supply)**

Additional Data to Support Therapeutic Consistency of Fulyzaq

- Dose-response clinical data generated based on multiple batches
 - The drug's effects were not sensitive to the tested doses in a range of 125 – 500 mg bid
 - The estimated drug concentrations in the GI tract after oral dosing of 125 mg bid are several-fold higher than the concentrations used to saturate the targeted chloride ion channels
 - Multiple batch data did not reveal noticeable clinical differences among drug product batches manufactured from different drug substance batches
 - **Natural variations observed in crofelemer were unlikely to have significant impact on the efficacy of Fulyzaq**

Lesson Learned from Botanical NDAs

- Approval of botanical NDAs is possible
- Practical approach for quality control of botanical products can be developed
 - Raw material controls required
 - Clinical relevant specifications for drug substance/product can be established if multiple batches are used in the pivotal clinical trials
 - Other data, e.g., from bioassay and/or multiple-batch, dose response clinical trials, may be needed, in conjunction with conventional CMC data, to help ensure therapeutic consistency
- Clinical trials of botanical drugs are no more difficult than non-botanical drugs

Lesson Learned from Botanical NDAs

New therapies from old medicines

Shaw T Chen, Jinhui Dou, Robert Temple, Rajiv Agarwal, Kuei-Meng Wu & Susan Walker

Although new botanical drugs pose many challenges for both industry and the FDA, approval of the first botanical prescription drug shows they can be successfully met.



Green tea leaves are the source for sin catechins, the active ingredients of Veregen—the first botanical product to be approved as a prescription drug by the FDA.

<http://www.nature.com/nbt/journal/v26/n10/pdf/nbt1008-1077.pdf>

Evolution of traditional medicines to botanical drugs

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Botanicals constitute an important source for new drugs (1, 2). To facilitate botanical drug development, the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) established the Botanical Review Team in 2003 and published its first *Guidance for Industry: Botanical Drug Products* in 2004 (3). This guidance represents FDA's thinking and provides recommendations on quality, nonclinical, clinical, and other unique aspects associated with botanical new drug development through the investigational new drug (IND) and new drug application (NDA) processes. From 2004 to 2013, CDER received over 400 botanical IND applications and pre-IND meeting requests (Table 1). Most of the INDs were allowed to enter phase 2 clinical trials for evaluation of preliminary safety and efficacy of the investigational botanical products in patients. FDA approved the first botanical NDA for Veregen (sin catechins) in 2006 (4, 5) and the second botanical NDA for Fulyzaq (crofelemer) in 2012 (6, 7). These two NDA approvals show that new therapies

generated by... The degree of consistency in botanical medicine is an integrated part of the NDAs.

Veregen

Veregen (topical treatment) (4, 5). It contains a substance that is an extract of green tea (Theaceae). 95% by weight is a tea component called epigallocatechin gallate (Figure 1A) (6). For FDA approval, these products were established and controlled by the FDA.

Science 2015 Jan 16;347(6219 Suppl.):S32-4

http://www.sciencemag.org/site/products/collection/nbooks/TCM_Jan_16_2015_high%20res.pdf

Challenges of Developing Products from Multiple Botanical Raw Materials

- A botanical mixture from one plant species is not considered as a fixed combination drug
 - The mixture as a whole is considered as the active ingredient
- Number of INDs for botanical products derived from multiple botanical raw materials is increasing
- FDA currently considers botanical products derived from multiple botanical raw materials as fixed-combination drugs
 - However, FDA recognizes that demonstrating each botanical raw material's contribution to the efficacy of a product with multiple botanical raw materials may not always be feasible
- FDA is looking into the requirements for fixed-combination drugs to accommodate the practical issues of botanical products