BOTANICAL DRUG PHARMACOLOGY/TOXICOLOGY: IND TO NDA

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GENERAL TOPICS

- Unique Aspects of Botanical Drugs
- Pharmacology/Toxicology Requirements for IND
- Pharmacology/Toxicology Requirements for NDA
- Approved Green Tea Extract as Example
REGULATORY DEFINITION OF BOTANICAL DRUG

• Consists of vegetable materials (plant, algae, fungi or combinations of these)
• Available as solution (tea), powder, capsule, tablet, elixir, topical, injectable, inhalable
• Drug: Intended to diagnose, cure, mitigate, treat or prevent disease
UNIQUE ASPECTS OF BOTANICAL DRUGS

Challenges:

- Extracts and complex mixtures; variable composition
- Chemical constituents not always defined
- Active constituents may not be identified
UNIQUE ASPECTS OF BOTANICAL DRUGS

Benefits:

• Many have substantial history of human use (e.g., Dietary supplement, Ayurvedic medicine, marketed ex-us)

• Published or historical safety and/or efficacy information
GUIDANCE FOR INDUSTRY: BOTANICAL DRUG PRODUCTS

FDA:

- Addresses amount/type of information necessary to support US clinical trials
- Differentiates legally available botanical products with no known safety issues vs. synthetic or highly purified NCE without prior human experience
NONCLINICAL TESTING FOR BOTANICAL DRUG TRIALS

At IND Stage, Nonclinical Pharmacology/Toxicology May Be Reduced or Delayed Based On:

• Phase of trial
• Indication
• Dose
• Duration

NOT Less Stringent; Relies on Different Data
WAIVER/DELAY OF PHARMACOLOGY/TOXICOLOGY

Documentation For Early Trials (Phase I/II):

• Evidence of previous human experience
• Extensive literature search for human safety data
  ➢ Document daily human consumption ≥ proposed trial dose
  ➢ Document duration of existing human use ≥ proposed trial duration
WAIVER/DELAY OF PHARMACOLOGY/TOXICOLOGY

- Traditional Formularies or Prior/Current Marketing Experience (e.g., Dietary Supplement, Food)
  - Equivalency of amount of each botanical used in raw form relative to dose form in proposed clinical trial (i.e., extraction ratio)
  - Volume of sales (if only ex-US marketed)

[Adapted from K-M Wu, CDER, FDA, American Society of Pharmacognosy, August 5, 2006]
WAIVER/DELAY OF PHARMACOLOGY/TOXICOLOGY

- Available Nonclinical Safety Data
  - Data from toxicologic databases (RTECS, Toxline, TOMES)
  - Extensive literature search (Medline)
  - Address as appropriate for the proposed study, general toxicity, target organs, teratogenicity and mutagenic/carcinogenic potential and pharmacologic activity
WAIVER/DELAY OF PHARMACOLOGY/TOXICOLOGY

When Feasible, Database Search Should Address the Safety and Effectiveness of:

- Final formulation of the commercial product
- Individual botanical ingredients
- Known chemical constituents of the botanical ingredients
DECISION TREE BASED ON MARKETING AND SAFETY ISSUES

For US Marketed Botanicals With No Known Safety Issue:

Previous human experience may be sufficient to establish safety to undertake Phase I/II clinical trial. Trial with non-oral route may require nonclinical testing.
For Botanicals with Known Safety Issue (*i.e.*, Serious and/or Possible Life-Threatening Effects):

- Nonclinical studies may be appropriate to establish safe dose and characterize toxicity
- Such studies may be required early in development
NONCLINICAL TESTING REQUIREMENTS FOR PHASE III TRIALS AND NDA

No Differentiation Between Botanical and Traditional Drugs

Standard Nonclinical Toxicology Tests Required Based on the Indication (Population, Disease), Route, and Duration
NONCLINICAL TESTING REQUIREMENTS FOR PHASE III TRIALS AND NDA (cont.)

- Repeat-dose studies in two mammalian species (one non-rodent) at sufficient dose to produce toxicity and of duration equal to Phase III trial (ICH M3). For ≥9 month non-rodent, follow guidance (ICH S2B)

- Genotoxicity studies usually required unless published GLP data available (follow ICH S2B); recommended at IND stage
Reproductive toxicology studies usually required unless published GLP data or compelling previous human experience (follow ICH S5A/B, M3)

Carcinogenicity studies not needed for some short-term indications (see ICH S1A); to be determined by CAC
NONCLINICAL TESTING REQUIREMENTS FOR PHASE III TRIALS AND NDA (cont.)

- Toxicokinetic studies to support systemic exposure using markers or known active ingredients
- Safety pharmacology using established screens for modes/sites of action

[Adapted from K-M Wu, CDER, FDA, American Society of Pharmacognosy, August 5, 2006]
COMMON FDA IND REVIEW ISSUES

• Proposed dosing and duration of proposed trial exceeds traditional/historical use
• Claims of “non-toxic” and lack of information on target organ of toxicity
• Equivalency to amount of raw botanical/day in traditional practice/use not addressed

[Adapted From K-M Wu, CDER, FDA, American Society Of Pharmacognosy, August 5, 2006]
GREEN TEA EXTRACT NDA APPROVED BY FDA

Veregen™ (Kunecatechins)

Green Tea Extract (Polyphenon® E) Ointment, 15% (Providing 112.5 mg Catechins/Day)

First Botanical NDA Approval; Indicated for Treatment of External Genital and Perianal Warts (Condylomata acuminata) in Immunocompetent Patients
VEREGENTM
DRUG SUBSTANCE

Partially Purified Fraction of Water Extract of Leaves From Camellia Sinensis (L.) O Kuntze

Contains 8 Catechins (85–95% by Weight), Plus Gallic Acid, Caffeine, Theobromine, and Undefined Constituents

Epigallocatechin Gallate (EGCG) is the Major Catechin (55%)
VEREGEN™ PACKAGE
GENERAL CATECHIN STRUCTURE

EGCG: $R_1 = H$, $R_2 = G$
FDA REVIEW OF VEREGEN™ NDA

Considered Relatively Simple Botanical Derived From a Single Part of a Single Plant, Containing a Class of Well-studied Components as Active Ingredients

Scope Of NDA Review Expanded to Include Assurance That Marketed Botanical Product has Efficacy and Safety Observed With Clinical Trial Batches (Control Not Addressed in Guidance)
CHEMISTRY AND MANUFACTURING CONTROLS

NDA:

Specifications Based on HPLC Fingerprint (Presence, Not Amount) as Discussed in Guidance; Activity Considered to be from Entire Mixture

Biological Assays (DPPH Antioxidation, EGFR and LOX Inhibition) as Proposed in Guidance Were Dose-dependent, But Did Not Differentiate Drug Substance Lots
CHEMISTRY AND MANUFACTURING CONTROLS

**FDA:**

- To reduce variability of raw materials, marketed batches limited to drug substance from same cultivars and farms. Future changes must be approved by FDA

  - Two major varieties of *Camellia sinensis (L.) O Kuntze* (var. *Sinensis* and var. *Assamica*) have species-level differences in catechin amounts and ratios

  - Environmental factors and agricultural practices influence quality of raw material
FDA:

- Acceptance criteria for marketed drug product based on clinical batches: ±10% of lower (efficacy) and higher (safety) amounts of each component

  - Botanical review team considering changing suggestion in guidance that one clinical batch of product be used in trials because multiple batches allow examination of consistency
FDA REVIEW OF VEREGEN™ NDA

PHARMACOLOGY

- Antioxidant *in vitro*
- Inhibition of enzymes involved in carcinogenesis and inflammation *in vitro*
- Inhibition of HPV-associated cervical cancer cell growth and E7 production *in vitro*, but not *in vivo*
- Immunomodulatory (effect on cytokine release)
- 200 publications on pharmacology and safety in NDA

FDA: Mode of action is unknown, although label does refer to anti-oxidative activity
GREEN TEA CATECHIN ACTIVITY IN SUPPLEMENTS AND FOOD

You heard us. A single serving of Hershey’s® Special Dark® chocolate has a higher capacity of antioxidants than two cups of green tea. And Hershey’s® Special Dark® also has the added bonus of being rich, delicious, mildly sweet, never bitter — dark chocolate. It looks like dreams do come true.

Enjoy in moderation.
FDA REVIEW OF VEREGEN™ NDA
TOXICOLOGY

NDA:

Battery of standard nonclinical toxicology studies conducted based on intended topical drug

FDA:

Extensive human oral experience with green tea beverage (high intake ~1 g catechins/day from 20 cups tea), supplements & traditional Chinese medicine did not raise safety concerns but did not provide significant information on safety and efficacy of topical product.
FDA REVIEW OF VEREGEN™ NDA
GENERAL TOXICOLOGY

Rat: 3 month oral and topical
Dog: 3 month oral
Minipig: 9 month topical
Transgenic mice: 28 day

Target organs in rat orally were GI tract, liver, pancreas and lymphoid tissues. No systemic toxicity in minipigs topically
FDA REVIEW OF VEREGEN™ NDA
LOCAL TOLERANCE

Rat: 28 day intravaginal
Rabbit: 7 and 28 day topical
Minipig: 28 day topical, 9 day intravaginal
Repeat-dose epicutaneous
Local lymph node assay

Severe local irritation topically to rabbit. Strong local irritation when applied to rat and minipig vaginal mucosa (unintended route); potential for contact sensitization
Genotoxicity panel (UDS, Ames, micronucleus, transgenic mouse, MLA)

Transgenic mouse: 56 day oral mutagenicity
Knock-out mouse: 6 month oral carcinogenicity

Only MLA positive
FDA REVIEW OF VEREGEN™ NDA
FERTILITY/EMBRYO-FETAL TOXICITY

Rat: combined mating and embryo-fetal, intravaginal; developmental, oral; pre- and postnatal, intravaginal

Rabbit: developmental, oral; embryo-fetal, SC

No substantial effects. SC administration in rabbits resulted in reduced fetal weights and delayed skeletal ossification. Pre- and postnatal intravaginal resulted in increased parturition complications in F0 dams and stillbirths
MARKET EXCLUSIVITY FOR BOTANICAL DRUGS

Marketing approval for traditional drug specific to the NDA product; also true for botanicals

Eligible for 5 years marketing exclusivity from approval as for traditional drug

CFSAN and CDER compliance monitor false drug claims for related non-drug products
CONCLUSIONS

Nonclinical pharmacology/toxicology requirements may be modified in timing, sequence and/or extent based on uncontrolled human experience to expedite early clinical trials (IND)

At pivotal trial/NDA, botanical drug not different from traditional drugs

Regulatory approach to unique issues of botanicals evolving; seek input from review division
CONCLUSIONS

It's not easy bein' green....
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CAC</td>
<td>FDA Carcinogenicity Assessment Committee</td>
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<tr>
<td>CDER</td>
<td>FDA Center for Drug Evaluation and Research</td>
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<td>CFSAN</td>
<td>FDA Center for Food Safety and Applied Nutrition</td>
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<tr>
<td>DPPH</td>
<td>2,2-Diphenyl-2-picrylhydrazyl hydrate (stable free radical)</td>
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<td>E7</td>
<td>Oncogenic protein expressed after infection with certain HPVs</td>
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<tr>
<td>EGCG</td>
<td>Epigallocatechin gallate</td>
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<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
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<td>FDA</td>
<td>US Food and Drug Administration</td>
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<td>GI</td>
<td>Gastrointestinal</td>
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<td>GLP</td>
<td>Good Laboratory Practices</td>
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<td>HPLC</td>
<td>High performance liquid chromatography</td>
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<td>HPV</td>
<td>Human papilloma virus</td>
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<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<td>IND</td>
<td>Investigational New Drug application</td>
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<td>LOX</td>
<td>Lipoxygenase</td>
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<td>MLA</td>
<td>Mouse lymphoma assay</td>
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<td>NCE</td>
<td>New chemical entity</td>
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<td>NDA</td>
<td>New Drug Application</td>
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<td>RTECS</td>
<td>Registry of Toxic Effects of Chemical Substances (RTECS) is a compendium of data extracted from the open scientific literature. The data are recorded in the format developed by the RTECS staff and arranged in alphabetical order by prime chemical name. Six types of toxicity data are included in the file: (1) primary irritation; (2) mutagenic effects; (3) reproductive effects; (4) tumorigenic effects; (5) acute toxicity; and (6) other multiple dose toxicity. Specific numeric toxicity values such as LD50, LC50, TDLo, and TCLo are noted as well as species studied and route of administration used. For each citation, the bibliographic source is listed thereby enabling the user to access the actual studies cited. No attempt has been made to evaluate the studies cited in RTECS. The user has the responsibility of making such assessments.</td>
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<tr>
<td>SC</td>
<td>Subcutaneous (route of administration)</td>
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<td>TOMES</td>
<td>The TOMES® System includes treatment guidelines for acute chemical exposures, evacuation procedures, personal protection data, and chemical disposal information. It is made up of three integrated databases of fully reviewed, referenced information—MEDITEXT®, HAZARDTEXT®, and INFOTEXT®.</td>
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<tr>
<td>UDS</td>
<td>Unscheduled DNA synthesis</td>
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ATTACHMENT B: INFORMATION TO BE PROVIDED IN AN IND FOR A BOTANICAL DRUG

IND for a Botanical Drug Product

General principles, format and contents (Sec. VI)

- Initial clinical trial of a marketed botanical product with no known safety issues (Sec. VII)
- Initial clinical trial of a nonmarketed botanical product or a marketed botanical product with known safety issues (Sec. VIII)
- Expanded clinical trial of any botanical product (Sec. IX)

- Documentation of use; limited CMC information; previous human experience may be sufficient to support safety
- More documentation of use and more CMC information than in Sec. VII
- Same documentation of use but more detailed CMC information than in Sec. VIII; standard nonclinical toxicology studies may be needed

Is the product a traditional preparation?

- No
- Yes

- If the product is marketed only outside the U.S., additional CMC and nonclinical safety information may be needed (Sec. VII.B.1., B.3.c., & C.2)
- Previous human experience may be sufficient to support safety (Sec. VIII.C.1)
- Additional nonclinical safety information may be needed (Sec. VIII.C.2)
References


