Regulatory Requirements from FDA and USP monographs for Botanical Products

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Regulatory Status-GMP

• 1994 DSHEA empowered FDA to come up with GMPs for DS *modeled after* Food GMPs

• 1997 ANPR: Industry proposal, very similar to USP <2750>
  • *FDA asked questions*

• 2003 GMP Proposed Rule

*Major Issues for Industry:*
  • Supplier Applicability
  • Q.C. Units
  • 100% testing of ingredients and final products
GMP Implementation

- 2007 FDA published the final rule
- 2008 became effective for companies with more than 500 employees
- 2009 became effective for companies with less than 500 but more than 20 employees
- 2010 became effective for companies with less than 20 employees
The positive of the GMP for DS

• Provide standards for products, processes, and people

• Supports overall quality of the finished product under the premise that Quality is built into the manufacturing process

“Quality means that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition, and limits on contaminants, and has been manufactured, packaged, labeled and held under conditions to prevent adulteration under 402(a)(1-4), of the FFD&CA”
HACCP for Consistent Manufacturing

• Manufacturers must establish adequate controls over the production process and specifications for their product to ensure that they “consistently and reliably manufacture what [they] intend.”

• “Focus of CGMP is on process controls to ensure that the desired outcome is consistently achieved, and not on the inherent safety of the ingredients used, which is matter of other statutes.”
100% Identity Testing for Dietary Ingredients

• 100% Identity testing is required for every *dietary ingredient*, unless an FDA exemption is obtained pursuant to the petition procedure in the accompany Interim Final Rule.

• Interim Final Rule allows for exemption of 100% identity testing for a dietary ingredient, once the manufacturer demonstrates that using a proposed sampling plan, would be no material diminution of the assurance provided by 100% identity testing.
Certificate of Analysis from Suppliers

• Acceptable as proof of compliance with specifications established for Components for:
  – Every test except Identity for Dietary Ingredients
  – Every test including Identity for non-Dietary Ingredient components.

A manufacturer must "qualify" its supplier, periodically reconfirm the findings in the Certificate of Analysis, and have knowledge of the tests upon which the Certificate relied.
Use of Reference Materials

• The rule requires calibration of analytical equipment, for which reference materials are needed.

• GMPs gives freedom to manufacturers to set their own Reference Materials

• However, supports (but not require) the use of Compendial Reference Standards where they are available.
Manufacturers decide on standards for quality

- Manufacturers decide their own specifications for identity, quality, strength, composition and absence of contaminants for:
  - Components (Dietary ingredients and others)
  - In Process materials
  - Finished dietary supplements

- Manufacturers decide how to qualify their suppliers in order to avoid 100% testing of components (condition to accept certificate of analysis)
Manufacturers decide standards for quality

• No Common or minimum requirement for quality

• Specifications for similar articles can vary widely from manufacturer to manufacturer

• Consumers would not know if two products containing similar ingredients and similar labels are subjected to a different set of quality parameters

• “Standards without standardization” …Roger Williams
Other Concessions of the GMPs

• Complete finished batch testing: one measure is allowed as a proxy for the complete quality.

• Specific microbiological/toxicity testing protocols and reference standards: manufacturers have the flexibility and responsibility to set their own.

• Performance Testing: There are no requirements for testing dissolution or disintegration of oral solid dosage forms.

• Expiration date: No need to perform stability studies.
To improve the health of people around the world through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.
How USP helps GMP

Official Documentary Standards

New Publications with Authorized Information

Compendial Reference Materials

Verification Services
Federal Food, Drug, and Cosmetic Act
Sections 201 (g) and (j), 501(b), 502(g)
*Official compendia* standards FDA enforceable for all drugs.
*Conformance generally not optional.*

Dietary Supplement Health & Education Act (DSHEA)
Section 403(s)(2)(D) of the FD&C Act
A dietary supplement represented as conforming to *Official Compendia* specifications shall be deemed misbranded if it fails to do so.

*Conformance is optional.*
USP Dietary Supplements Admission Policy

Class A: Admitted into the Compendia
Articles for which the available evidence does not indicate a serious risk to health* or other public health concern that precludes inclusion of a quality monograph into the compendia.

Class B: Not admitted into the Compendia
Articles for which the available evidence indicates a serious risk to health* or other public health concern that precludes inclusion of a quality monograph into the compendia.

*Serious risk to health means that the use of the article could:
(A) result in: (i) death; (ii) a life—threatening experience; (iii) inpatient hospitalization; (iv) a persistent or significant disability or incapacity; or (v) a congenital anomaly or birth defect; or
(B) require, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under subparagraph (A).

USP Admission Criteria and Safety Classification for Dietary Supplements Guideline.
Two Volumes:

- **Volume 1: Monographs and General Chapters from USP-NF and FCC**

- **Volume 2: Supplemental information**
  - Safety Admission Reviews
  - Dietary Intake Tables
  - Regulatory Framework
  - Verification Program Documents
  - Guidances
  - Photographic section with chromatograms
Quality Determination

- Compendial Standards: Monographs Containing Specifications
  - Identity
  - Content or Composition
  - Purity
  - Performance
  - Absence of Contaminants

- Consistent with GMPs for DS
Specifications

• Tests
  – One test may not be enough to describe a quality attribute

• Analytical Procedures
  – Validation science, validation data

• Acceptance Criteria
  – Data analysis, statistics, metrology

• Compliance determination
2012 Edition

Two Volumes:

- **Volume 1: Monographs and General Chapters from USP-NF and FCC**

- **Volume 2: Supplemental information**
  - Safety Admission Reviews
  - Dietary Intake Tables
  - Regulatory Framework
  - Verification Program Documents
  - Guidances
  - Photographic section with chromatograms
Macroscopic and Microscopic Descriptions

**Bacopa**

**BOTANIC CHARACTERISTICS**

**a. Macroscopic Description**

1. General appearance: Dry mixtures of broken leaves and stems, with majority of leaves detached.
2. Stems: Cylindrical, 1–1.5 mm in diameter, glabrous, with longitudinal wrinkles, long internodes, and root at nodes.
3. Leaves: Simple, opposite, sessile or short-petiolate, oblong-obovate or spatulate, 0.6–0.3 to 0.9–2.5 cm in length, (2.5)–3 to 5–(8) mm in width, apex round, margin entire, midrib indistinct.
5. Odor and taste: Hay-like; bitter.

**Fig. 1 Dried stems and leaves of Bacopa monnieri (L.) Pennell**

**b. Microscopic Description**

1. Transverse section of *Bacopa monnieri* stem

**Fig. 2 Microscopic features of transverse section of Bacopa monnieri stem**

- A. Sketch
- B. Illustration of transverse section

1. Epidermis
2. Cortex: Broad, composed of parenchymatous cells, with large intercellular space.
3. Endoderms: Single layer of subrounded, subsquare or subrectangular cells.
4. Phloem: Relatively narrow, continuous.
5. Xylem: Vessels radially arranged alternated with uniseriate medulary rays.
6. Phloem: Broad, composed of parenchymatous cells, with distinct intercellular space.
Powder Microphotographs Chemical Structures

**Chemical Characteristics**

a. Chemical Structures

- **Jujubogenin**
  
  \[
  \text{Compound:} \quad \text{Bacopside A1} \\
  \text{Jujubogenin isomer of Bacopasaponin C} \\
  \text{R1} = [\beta-D-Glc(\beta1-3)-\alpha-D-\text{L-Ara}(\beta1-2)-\alpha-D-\text{D-Glc}(\beta1-3)+\alpha-L-\text{Ara}(\beta1-2)] \\
  \]

- **Pseudojujubogenin**
  
  \[
  \text{Compound:} \quad \text{R2} = [\alpha-L-\text{Ara}(\beta1-2)-\beta-D-Glc(\beta1-3)-\alpha-L-\text{Ara}(\beta1-2)] \\
  \]

**Fig. 4** Microscopic features of powder of *Bacopa monnieri* leaf and stem


**Fig. 5** Constituents of *Bacopa monnieri* (L.) Pennell stem and leaves

1. Non-glandular hairs: Bicellular, conical, slightly curved, 12–22 µm in diameter; the basal cell relatively long, walls thickened, tiny protuberances presented on the surface; the apical cell relatively short, with sharp apex and thin wall; yellowish-white when observed under the polarized light microscope.

2. Glandular scales: Head mostly 4-8-celled, subrounded or elliptical in top view, 30-50 µm in diameter; stalk short.

3. Epidermis of leaf: Cells subrounded, subrectangular or irregular in surface view, with wavy anticlinal walls; stomata anomocytic or diacytic.

4. Fibers: Slender, straight or slightly curved, single or in bundles; yellowish-white when observed under the polarized light microscope.

5. Starch granules: Mainly simple granules, subrounded or oval, 4-15 µm in diameter; compound granules occasionally found, composed of 2-3 granules; black and cruciate in shape when observed under the polarized light microscope.

6. Vessels: Mainly spiral vessels, reticulate vessels occasionally present, 5-29 µm in diameter; bright white when observed under the polarized light microscope.
TLC and HPLC chromatograms

**USP Centella asiatica Identification B**

Fig. 8 Typical HPTLC chromatograms

- **Track assignment:**
  1. USP Asaticoside RS, USP Bacipoxide A, RS, asatic acid, and bacacine (with increasing Rf); 2. USP Powdered Bacopa Extract RS (5 μL); 3. USP Powdered Bacopa Extract RS (10 μL); 4. bacopa stems and leaves (commercial sample); 5. bacopa stems and leaves (commercial sample); 6. Centella asiatica aerial parts (commercial sample)

**Sample solutions:**
- sonicate 0.5 g in 5 mL of methanol for 10 min and centrifuge
- Standard solutions: In methanol, 1 mg/mL
- Plate: HPTLC, SI 60 F254, 2-10 μm
- Developing solvent: Methylene chloride, methanol, and water (14:6:1)
- Relative humidity: 33%
- Saturation time: 20 min with filter paper
- Application volume: 4 μL or as indicated above
- Detection: Derivative, heat at 120° for 3 min, and examine under daylight
- Derivatization reagent: 10% sulfuric acid in methanol

**Note:** Bacopa monnieri and Centella asiatica may be substituted for each other in commerce, particularly samples originating from India, since they share the same Ayurvedic names (brahmi or mandukaparni) based on their geographical sources in India. Generally, Bacopa monnieri is called brahmi in south India and mandukaparni in north and west India, whereas Centella asiatica is mandukaparni in south India and brahmi in north and west India.

**Content of triterpene glycosides**

Fig. 9 Typical chromatogram of Powdered Bacopa Extract RS, Standard solution B

**Solutions preparation:** according to the monograph
- Column: Restek Pinnacle DB C18, 250 mm x 4.6 mm, 5 μm
- Mobile phase: 0.14 g anhydrous potassium dihydrogen phosphate and 0.5 mL phosphoric acid in 1 L of water (Solution A) and acetonitrile (Solution B)
- Elution: gradient program, see below
- Flow rate: 1.5 mL/min
- Column Temperature: 25°C
- Injection volume: 20 μL
- Detection: UV, 205 nm

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70</td>
<td>30</td>
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<td>26</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>
FDA’s Botanical Drug Guidance

Guidance for Industry
Botanical Drug Products

Copies of this Guidance are available from:

Division of Drug Information (HFD-240),
Office of Training and Communications,
Center for Drug Evaluation and Research (CDER),
Food and Drug Administration
5600 Fisher’s Lane, Rockville, MD 20857, (Tel) 301-827-4573

Internet at http://www.fda.gov/cder/guidance/index.htm

Final guidance published on 06/09/2004

Other CDER guidance*

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2004
Botanical Drug Product:

A product that contains as ingredients vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof, that is *used as a drug*. It may be available as (but not limited to) a solution (tea, e.g.), powder, tablet, capsule, elixir, topical or injectable.

Excluded: fermentation products, highly purified [or chemically modified] botanical substances, genetically modified plants, allergenic extracts and vaccines which contain botanical ingredients
Botanical “active ingredients”

- The definition differs from “the molecules of the highly purified drugs”
  - Parts of medicinal plants, extracts, fractions,...
- Identification at molecular level is NOT required in the Botanical Guidance
  - Almost impossible to identify all
  - Nor is mechanism required
- Data on the active entities (or major chemical groups) and their effects helpful
Botanical Applications in CDER, FDA (as of December 31, 2012)

- Total of 550 pre-INDs/INDs
  - 430 INDs (2/3 active); 120 pre-INDs
  - 53 in 1990-’98, 497 in 1999-2012, ~3-4 per month
- Approx. 1/3 commercial, 2/3 research
- 2/3 single herb, 1/3 multiple herbs
- Mostly phase 2, and a few in Phase 3
- Two NDAs submitted and approved
of § 312.23(a)(7)(iv), the sponsor should have, in addition to final product testing, appropriate quality controls for the botanical raw materials. The manufacturing process should be well defined, with adequate in-process controls, especially for the drug substance.
# Support of Therapeutic Consistency for Botanicals

<table>
<thead>
<tr>
<th>pre-CMC</th>
<th>(Conventional) CMC</th>
<th>post-CMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Conventional Pharmacognosy</td>
<td>• Core Pharmacognosy</td>
<td>• Pharma-cognosy</td>
</tr>
<tr>
<td>– GACP</td>
<td>– Chromatography</td>
<td>– Bioassay</td>
</tr>
<tr>
<td>• Plant biology</td>
<td>– Spectroscopy</td>
<td>“Fit-for-Purpose Clinical Design”</td>
</tr>
<tr>
<td>• Raw material Process</td>
<td>Manufacturing Process control</td>
<td>– Clinical data from multiple batches</td>
</tr>
<tr>
<td>• Medicinal use</td>
<td></td>
<td>– Dose-response</td>
</tr>
<tr>
<td>• Misuse</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CMC requirements

Not necessary to identify the active constituents in the initial stage. Identification by fingerprint of unknowns is suitable.

If possible, active constituents are identified in phase 3.

Attributes for batch to batch consistency should be set in Clinical stages to define acceptance criteria for fingerprint.

DMF acceptable in support of IND and NDA provided ID and Assay are suitable.

Consistency should be maintained through the different clinical phases, samples should be retained.
Veregen, the 1\textsuperscript{st} Botanical NDA and a BRT Publication

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.

On October 31, 2006, the US Food and Drug Administration (FDA) approved the new drug application (NDA) for marketing of Veregen (sinecatechins), a topical treatment for perianal and genital condyloma. Unlike most small-molecule drugs that comprise a single chemical compound, Veregen, an extract of green tea leaves, contains a mixture of known and possibly active compounds. It is the first new botanical prescription drug approved since the publication of the FDA’s industry guidelines for botanical drug products\textsuperscript{1} in June 2004. The approval shows that new therapies from natural complex mixtures can be developed to meet current FDA standards of quality control and clinical testing. In recent years, interest in further development of herbal or botanical drug products derived from traditional preparations has been increasing steadily. Between 1982 and 2007, more than 350 botanical investigational new drug (IND) applications and pre-IND

![Green tea leaves are the source for sinecatechins, the active ingredients of Veregen—the first botanical product to be approved as a prescription drug by the FDA.](image-url)
FDA NEWS RELEASE
For Immediate Release: Dec. 31, 2012

FDA approves first anti-diarrheal drug for HIV/AIDS patients

Fulyzaq is the second botanical drug approved by the agency

Derived from the red sap of the Croton lechleri plant.
A botanical drug product is often a complex mixture … with varying degrees of purification.
The safety and efficacy of Fulyzaq were established in a clinical trial of 374 HIV-positive patients, …

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333701.htm
Chemical Structures of Tea Catechins and Proanthocyanidins

Crofelemer Proanthocyanidins
\[ n = 1-28 \quad R = H \text{ or } OH \]
1000s+ of oligomer analogs

Common catechins in Proanthocyanidins
- 4 catechins in both tea and crofelemer
- About a dozen catechin monomers in tea

<table>
<thead>
<tr>
<th>Flavan-3-ols</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afzelechin</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>Epiafzelechin</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>Catechin</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>Gallocatechin</td>
<td>OH</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>Epigallocatechin</td>
<td>OH</td>
<td>OH</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
</tr>
</tbody>
</table>
## Therapeutic Consistency for Two Botanical NDAs

### NDA-21902 sinecatechins (Veregen)

<table>
<thead>
<tr>
<th>pre-CMC</th>
<th>(conventional) CMC</th>
<th>post-CMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cultivated species with multiple cultivars on farms</td>
<td>Control of 8 catechins by weight % of semi-purified substance 55-72% EGCg unknown HPLC minor peaks also controlled</td>
<td>same efficacy with 2 doses; No bioassay</td>
</tr>
</tbody>
</table>

### NDA-202292 crofelemer

<table>
<thead>
<tr>
<th>pre-CMC</th>
<th>(conventional) CMC</th>
<th>post-CMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 wild species with no commercial cultivation</td>
<td>Oligomers of different lengths from 4 catechin monomers – MS, NMR of drug substance – HPLC of oligomers and – Acid hydrolysis for monomer info</td>
<td>same response with 3 doses (and multiple lots); Bioassay</td>
</tr>
</tbody>
</table>
## Veregen and Fulyzaq: The BRMs

<table>
<thead>
<tr>
<th>Veregen (Sinecatechins) Ointment</th>
<th>Fulyzaq (Crofelemer) Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried tea leaves (Green tea)</td>
<td>Red latex (Dragon’s/Tree’s blood)</td>
</tr>
<tr>
<td><em>Camellia sinensis</em></td>
<td><em>Croton lechleri</em></td>
</tr>
<tr>
<td>Cultivated in farms in China</td>
<td>Wild collection from South America; Variations of proanthocyanidins unknown</td>
</tr>
<tr>
<td>Variation of catechins in tea</td>
<td></td>
</tr>
<tr>
<td>varieties/cultivars well-known</td>
<td></td>
</tr>
<tr>
<td>Renewed machine or manual harvest</td>
<td>Trees felled, latex collected manually</td>
</tr>
<tr>
<td>2\textsuperscript{nd} only to water as a soft drink; No traditional use recorded for genital warts</td>
<td>No. 1 herb in Peru for diarrhea and wound healing</td>
</tr>
</tbody>
</table>
## Veregen and Fulyzaq – The BDSs

<table>
<thead>
<tr>
<th>Sinecatechins</th>
<th>Crofelemer</th>
</tr>
</thead>
<tbody>
<tr>
<td>“The drug substance as a whole is the active component”</td>
<td>Proanthocyanidin oligomers with degree of polymerization (DP) 3-14 (30) as the major “active” molecules</td>
</tr>
<tr>
<td>8 Catechin monomers: Individually purified and fully characterized, well resolved by HPLC</td>
<td>Total proanthocyanidin oligomers assayed, but individual oligomers or groups (e.g., trimers, tetramers, etc) not separated</td>
</tr>
<tr>
<td>Major catechin (EGCG) : 55-72% Other minor components controlled</td>
<td>Acid hydrolysis : Average monomer units (~7) in oligomer and mean MW (1700-2500) Catechin, EC, GC, EG ratios</td>
</tr>
<tr>
<td>Unknown mechanisms of actions No bioassay</td>
<td>Known mechanisms of action reported Required bioassay(s) for consistency</td>
</tr>
</tbody>
</table>
Fulyzaq (Crofelemer): Pharmacology and Mechanisms of Action

Herbal medicine as an oral anti-diarrheal agent
Products of dragon’s blood marketed as dietary supplements
Inhibition of two types of intestinal chloride channels
   The calcium activated chloride channels (CaCC)
   The cAMP stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels
Action site: luminal surface of intestine
Fulyzaq: Ensuring Quality and Therapeutic Consistency for Approval

Pre-CMC control
- Latex of a single plant
- Identification *Croton lechleri* by morphological characteristics with no known serious misuse issues
- GACP & defined Eco-geographic regions to minimize variations

Post-CMC support
- Clinical relevant bioassay(s)
- Clinical response apparently insensitive to dose or lot variations
- Extensive human use to treat diarrhea
Botanical Drug: When the mixture works
Or works better than “the magic bullet single compound”

• Sinecatechins contains **8 tea catechins** and other components
  – “**United they work, divided they fail**” based on nonclinical data

• Crofelemer may contain 1000s+ of proanthocyanidins
  – A good candidate for a purified single molecule drug?
    • Polyphenols removed pre-screening for causing false-positive
  – Dragon’s blood in Peru for treating diarrhea
    • TCM herbs containing polyphenols also used as anti-diarrhea
Herbal / Traditional Medicines and Dietary Supplements

- Asian TMs
  - TCM, Ayurveda, Siddha, Unani
- European Traditional Medicines
- DS
- American Ethnomedicines
- African Ethnomedicines
Herbal / Traditional Medicines and Dietary Supplements

Asian TMs
TCM, Ayurveda, Siddha, Unani

European Traditional Medicines

American Ethnomedicines

African Ethnomedicines

DS
Herbal / Traditional Medicines and Dietary Supplements

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African Ethnomedicines

DS
Herbal / Traditional Medicines and Dietary Supplements

- Asian TMs: TCM, Ayurveda, Siddha, Unani
- European Traditional Medicines
- American Ethnomedicines
- African Ethnomedicines
Products from Natural Origin for Health Purposes: Transitioning from Dietary Supplements to Dietary Supplements and Traditional Medicines

Dietary Supplements Expert Committee, USP Staff

ABSTRACT The United States Pharmacopeial Convention (USP) publishes documentary standards (monographs) for dietary supplements legally marketed in the United States in a dedicated section of the United States Pharmacopeia (USP). These standards also are published in the USP Dietary Supplements Compendium (DSC), a separate compendium that contains both official and authorized text and serves as a resource for dietary supplement manufacturers and regulators. The standards area allied with reference materials that support the procedures provided in the documentary standards. The overall activity stems from a USP Convention resolution adopted in 1995 after the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA), which recognized the need for standards for dietary supplements marketed in the United States and regulated under DSHEA.
• Herbal Monographs currently in USP, NF, DSC, FCC
• Traditional Medicines do not have a home in USP
• New Compendium dedicated to Traditional/Herbal Medicines could fill the gap
• Modeled after Medicines Compendium
• Admission Criteria and Processes under development
Options for monograph placement

Status of ChP TCM Submissions

Received June 2008

September 2011

USP-NF (DS) 12
FCC 1
In development 3

Possibility of admission as DS, into USP-NF, or a food ingredient in FCC.

High 24
Medium 38
Low 21

Functional Claims

Approved Food

Traditional Medicines

USP NF

USP FCC

USP DSC

USP HMC
Herbal Medicines In the Global Marketplace

Registered/Compendial

Herbal Medicine Ingredients

Selected List of Herbal Medicine Ingredients

High Usage

High Value

Availability of information

PRIORITY SETTING CRITERIA

GLOBAL PHARMACOPEIAL WORKPLANS

GLOBAL PHARMACOPEIAL WORKPLANS

USP HERBAL MEDICINES COMPRENDIUM

Standards including USP RMs

USP DSC

USP-NF

PF

NATIONAL OR REGIONAL RS
A new addition to USP core compendial programs

Web-based, online only

Open access to public standards for herbal ingredients approved by national regulatory authorities and legally marketed in various regions of the world

_HMC_ standards are supported by validation data and reference materials
Herbal Medicines Compendium Process

1. Identify/Prioritize Candidates
2. Draft For Development Monograph
3. Reference Material Procurement
4. Post For Development Monograph
5. Reference Procedure Development
6. Draft For Comment Monograph
7. Post For Comment Monograph
8. Reference Material Testing
9. Expert Committee Approval
10. Post Final Authorized Monograph

Research
Development
Collaborative Testing
Expert Review Finalization
Standards for herbal ingredients (such as plant material, powder, extracts, fractions)

General chapters, reference tables, sections for reagents and glossary

Associated USP Reference Standards
HMC is intended for stakeholders seeking rigorous quality assurance measures where they otherwise might not exist.

Regulatory or compendial bodies may adopt or adapt HMC documentary standards without charge or USP’s permission.
Easy access to public standards

Support to stakeholders worldwide

A reliable reference for developing new products and standard operating procedures

Monographs for some herbals that had never before had public standards
<table>
<thead>
<tr>
<th>Monograph</th>
<th>Related Monographs</th>
<th>Version</th>
<th>Post date</th>
<th>Comments End</th>
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<tr>
<td>Alcohol</td>
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<td>August 18, 2013</td>
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<td>Dehydrated Alcohol</td>
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<td>May 20, 2013</td>
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Ganoderma lucidum FRuiting Body

Proposed For Comment Version 0.2

Ganoderma lucidum FRuiting Body

DEFINITION
The article consists of the dried fruiting bodies of Ganoderma lucidum (Curtis Fr.) P. Karst. (Family Ganodermataceae). It contains NLT 0.3% of triterpenoic acid, calculated on the dried basis as the sum of ganoderenic acid C, ganoderic acid C2, ganoderic acid G, ganoderenic acid B, ganoderic acid B, ganoderic acid A, ganoderic acid H, ganoderenic acid D, ganoderic acid D, and ganoderonic acid F.

SYNONYMS
Ganoderma lucidum (Leyss. Fr.) Karst.
Polyporus lucidum (Curtis Fr.) Fr.

POTENTIAL CONFOUNDING MATERIALS
Amauroderma rube
Amauroderma rugosum
Coriolus versicolor
Phellinus baumii
Related Ganoderma species including G. sinense (G. Japonicum), G. airm, G. isugae, G. applanatum, G. ungulatum, G. capense, and G. resinaceum

SELECTED COMMON NAMES
Chinese: 灵芝, 灵芝
English: Ganoderma, reishi, polypore luisant, ganoderma luisant
French: Polypore luisant, ganoderme luisant
German: Lackporling, glanzender lackporling
Japanese: 灵芝, 創生, レイシ
Korean: 영지
Pinyin: Ling zhi, ling zhi cao
Spanish: Ganoderma, hongo pipa, hongo michoacano (Mexico)

CONSTITUENTS OF INTEREST
Triterpenoic acids: Ganoderenic acid C, ganoderic acid C2, ganoderic acid G, ganoderenic acid

www.hmc.usp.org
• ARTICLES OF BOTANICAL ORIGIN, Alcohol-Soluble Extractives, Method 1 <561>: NMT 2.0%
• ARTICLES OF BOTANICAL ORIGIN, Water-Soluble Extractives, Method 1 <561>: NLT 3.0%
• ARTICLES OF BOTANICAL ORIGIN, Total Ash <561>
  Analysis: 3.0 g of Ganoderma lucidum Fruiting Body, finely powdered
  Acceptance criteria: NMT 4.0%

ADDITIONAL REQUIREMENTS
• PACKAGING AND STORAGE: Preserve in well-closed containers, protected from light and moisture, and store at room temperature.
• LABELING: The label states the Latin binomial and the part of the plant contained in the article.
• USP REFERENCE STANDARDS <11>
  USP Dextrose RS
  USP Ergosterol RS
  USP L-Fucose RS
  USP Galactose RS
  USP Ganoderic Acid A RS
  USP d-Gluconic Acid RS
  USP Mannose RS
  USP Ganoderma lucidum Fruiting Body Powdered Extract RS

This discussion has not yet started. Be the first to begin it!

Your name
Gabriel G.

Comment *

Attachment

Select any documents you want to attach to your comment.
Files must be less than 10 MB.
Allowed file types: doc docx xlsx xlx gif jpeg jpg pdf.

Post this comment anonymously
UHPLC (Triterpenoic Acids)

Representative chromatogram of Content of Triterpenoic acids in Ganoderma lucidum Fruiting Body

This chromatogram is supplied for information only

Solutions preparation: according to the monograph
Detector: UV, 257 nm
Phyllanthus amarus Aerial Parts — Identification

Thin-Layer Chromatography

Typical HPTLC Chromatograms

**Track assignment:** 1) USP Phyllanthin RS (0.1 mg/mL); 2) hypophyllanthin (0.1 mg/mL); 3) USP Phyllanthus amarus Powdered Extract RS (10 mg/mL); 4-10) Phyllanthus amarus Aerial Parts, commercial samples
General Notices/Resources

General Notices
General Notices describes many of the basic assumptions and definition of terms used in the Herbal Medicines Compendium. This document also provides information about the application of the standards presented on this website.

Guidelines
Monographs in the Herbal Medicines Compendium
This Guideline describes the information that the Herbal Medicines Compendium staff are seeking to aid in the development of monographs and reference materials.

Resources
Reagents, Indicators and Solutions
This resource includes reagents and solutions required in conducting compendial tests and assays in the Herbal Medicines Compendium.
Questions
Thank You