各國中醫藥發展與我方研發的銜接

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Outline

- Herbal Medicines in the U.S.
- Herbal Medicines in EU
- Herbal Medicines in Australia
- Herbal Medicines in Asia & Taiwan
- Regulatory Strategy in Taiwan

Intended uses in the U.S.

- Food
- Dietary supplements
  - Dietary supplement health &education act (DSHEA) 1994
  - FDA final rules, Jan 5, 2000
  - Proposed cGMP regulations for Dietary supplements, March 2003
- Drugs

The DSHEA of 1994

- Not drugs, No “disease claims”
- Health & structure/function claims
- No Pre-marketing Approval needed
- Substantiation of claims on file
- New ingredient not a subject of Investigational New Drug (IND)

Some Approved Structure/Function Claims

- mental sharpness, acuity
- well-being, mood elevation
- restful sleep
- normal prostate health
- vitality
- well-being during winter season
- maintenance of urinary tract health

The Structure/Function Claims must include:

"This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease."

(prominently displayed in bold face type)

FDA Final Rules of 2000

on Claims for Dietary Supplements

Distinguish disease & structure/ function claims

No “expressed” (prevent/treat/ cure/diagnose) c

“implied” disease claims.

Common, *non-serious* “life stages” symptoms a

not diseases.

Implied Disease Claims Not Allowed

- Prevent/Treat/Cure *conditions*
  ("bone fragility")
- Suggested in the *names* of products ("CircuCure")
- Through the *content* information
  ("contains aspirin")
- Medical packaging *vignettes/symbols*
  (ECG tracings)

Claims Allowed For Life Stage Symptoms

- Common, minor, non-serious conditions associated with:
  - Aging, Menopause, Adolescence (e.g., hot flushes, common PMS symptoms)
- Serious, life threatening excluded:
  - toxemia, osteoporosis
  - pregnancy (may affect fetus)

Proposed cGMP Rules For Dietary Supplements

- Proposed rules, March 13, 2003
- For public comments in 90 days
- Stakeholder meetings in April & May 2003

www.cfsan.fda.gov/~dms/supplmnt.html

The OTC Monographs

- Substantial OTC marketing history
- New clinical studies not necessary
- Approval of active ingredients only, Flexible labeling
- Data available to public, No sole marketing rights

Review of OTC Monographs

- General recognition of safety/efficacy (GRAS, GRASE)
- Quality standards publicly available
- Tests and specifications required
- cGMP compliance

Botanicals in OTC Monographs (ca. 1999-2000)

- Botanical ingredients mentioned
  20%(509/2484)
- Botanicals in final monograph
  74%(375/509)
- Botanicals under review:
  26%(134/509)

Regulatory Requirement: FDA Guidance

Guidance for Industry-

Botanical Drug Products

(June, 2004)

http:// www.fda.gov/cder/guidance

Regulatory Requirement: FDA Guidance

- A new drug under section 201(p) of the FD&C Act:
  - Evidence of effectiveness derived from adequate and well-controlled clinical studies
  - Evidence of safety
  - Adequate CMC (chemistry, manufacturing and controls) information

Regulatory Requirement: FDA Guidance

Approval of New Drug:

- IND process (Investigational New Drug)

  CMC , Pharm/Tox , Phase I-III Clinical Studies

- NDA (New Drug Application)

Regulatory Requirement: FDA Guidance

New Drug of Chemicals

- Purified materials
- Active ingredient identified
- Combination products: simple and well characterized

Regulatory Requirement: FDA Guidance

Botanical Drug Product: Definition

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, allergenic extracts and vaccines which contain botanical ingredients

Regulatory Requirement: FDA Guidance

Botanical Drugs: Regulatory Objectives

- Not to create an additional category different from dietary supplements and non-botanical drugs
- As drugs, to confer the same degree of confidence in quality and clinical usefulness as non-botanical drugs
- To bring the botanical drugs into the mainstream medical use

Regulatory Requirement: FDA Guidance

Botanicals:

- Further purification not required
- Identification of active constituents not essential
- Pre-clinical evaluations may be done concurrent with clinical development

Regulatory Requirement: FDA Guidance

Regulatory Requirements may be modified:

- In timing, sequence and/or extent of pre-clinical testing
- Either initiating an IND or for obtaining final NDA approval.

vs highly purified drugs

Regulatory Requirement: FDA Guidance

Regulatory requirements to initiate human studies will depend on:

- The past history
- The degree of modification (from the traditional use)
- The scales of clinical trials

Conclusion

Herbal Medicines in EU

- European Union (EU)
- Pharmaceuticals & Cosmetics (PC)
- European Commission (EC)
- European Agency for the Evaluation of Medicinal Products (EMEA)

Herbal Medicines in EU

- EMEA: Committee for Proprietary Medicinal Products (CPMP): new committee, new guidance
- EMEA: Herbal Medicinal Products Working Party (HMPWP, 1997)
  - Chairperson- Dr. Konstantin Keller
  - Federal Institute for Drugs and Medical Devices

Herbal Medicines in EU

- ESCOP: European Scientific Cooperative on Phytotherapy (1989)
- To uniform criteria for the assessment of safety and efficacy
- To support scientific research
- Contribution to the acceptance of phytotherapy on a European level

Herbal Medicines in EU

Marketing authorization application (MAA):

- National drug law
- ICH (International Conference on Harmonization) guidance
- EMEA
  - Notice to applicants
  - HMPWP guidance

Herbal Medicines in EU

Herbal Medicinal Product is Medicinal Product

- Quality
- Safety
- Efficacy

Herbal Medicines in EU

- Note for Guidance on Quality of Herbal Medicinal Products

  CPMP/QWP/2819/00 final July 2001

- New guidance on quality, safety and efficacy, e.g. Good Agricultural and Collection Practice (GACP)

Grading of Recommendation

- Grade A: New products, serious diseases
- Grade B: Major claims
- Grade C: Minor claims
- Grade T: Traditional medicinal products
- Grade X: Fraudulent or misleading claims

Grade A, B, C: well-established, herbal medicinal product for ….treatment, prevention….

Grading of Recommendation

- Grade A: Evidence Ia, Ib

  Requires at least one randomized controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendations

Grading of Recommendation

- Grade B: Evidence IIa, IIb, III

  Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommedation

- Grade C: Evidence IV

  Requires evidence from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable studies of good quality

Grade of Recommendation

- Grade T: Traditional medicinal product

  Traditionally used without supportive scientific evidence

Herbal Medicines in EU

Current status in EU

- Different tradition towards use of herbals
- Different legal situation
- Different medical education program

Herbal Medicines in EU

- The main thrust –to facilitate Mutual Recognition
- Regulatory & Marketing
- Safety and quality

Herbal Medicines in Australia

- Risk based approach
  - Licensing of manufacturers (GMP)
  - Pre-market controls
  - Post-market vigilance

Herbal Medicines in Australia

- Medicines assessed as having a higher level of risk must be registered not listed)
  - The degree of assessment and regulation is rigorous and detailed
  - Sponsor must provide comprehensive safety, quality and efficacy data

Herbal Medicines in Australia

- Listed medicines
  - Have a more streamlined approach at pre-market evaluation but this is counter balanced by rigorous and systemic post market vigilance

Herbal Medicines in Australia

Listed medicines

- Low risk
- Indicated for
  - Health maintenance or enhancement
  - Minor self-limiting conditions

Herbal Medicines in Australia

Pre-market assessment-Listed medicines

- Registered list of ingredients available for use in listed medicines
- Limited indications
- Good Manufacturing Practice

Herbal Medicines in Australia

- The features of regulatory system for complementary medicines in Australia
  - Risk based approach
  - Performance orientated outcomes
  - Consultative approach involving industry and consumers
  - Achieve appropriate balance between pre and post markets

Herbal Medicines in Asia

Regulatory Harmonization in Asia Region:

- Mainland China
- Japan
- Singapore
- Hong Kong & Macau
- Korea, Australia, etc.

Herbal Medicines in Asia

- Great potentiality
  - Taiwan
  - Hong Kong & Mainland China
  - Japan
  - Singapore
  - Korea

Herbal Medicines in Mainland Chi

- Regulatory requirement in Mainland China
  - GAP, GMP, GLP, GCP, GSP
  - New Drug Registration Regulation (2002/12)
  - Prescription Drug vs. OTC system
  - TCM Drug vs. Dietary Supplement

Regulations of new TCM R&D in Taiwan

- The registration regulation for new TCM drugs

  Published by CCMP in June 29, 1998; Revised in October 20, 1999

- Guidance for clinical trials of herbals extract products

  Published by BPA in March 21, 2000

Status & experience (1)

Current Status:

- 21 new TCM IND submission
- 10 cases were approved to conduct clinical trials (including conditional approval)
- 9 cases are under review process

Status & Experience (2)

21 IND Submission Analysis: Indication

DM, Stroke, Chronic Hep. B, Neutropenia, Hyperlipidemia, Impotency, Drug Addiction, AIDS, Chronic Pain, etc.

Status & Experience (3)

21 IND Submission Analysis : Different Categories:

- 2 traditional formulae
- 12 New combinations
- 3 marketed in other countries
- 2 secret (unpublished) formulae
- 1 new medicinal plant
- 1 Partial purify of traditional herbal

Status & Experience (4)

Clinical stage: 10 approved cases

- 1 Phase I/II
- 7 Phase II
- 2 Phase III
- All in medical center with CRC

Status & Experience (5)

21 IND Submission Analysis: Study Design

- 15 are Double-Blind, Randomized, Placebo Controlled Trials
- 3 are dose-response trials
- 1 is cross over design
- 17 with CRO involvement

Status & Experience (6)

Consideration of previous human use

- Marketing experiences
- Scientific journal
- Clinical observation report
- Classical literature
- Experience of physician

Status & Experience (7)

Consideration of CMC data:

- Species identification
- CMC related safety issues
  - Heavy metals
  - Pesticide residues
  - Bacteria count
- Batch amount

Status & Experience (8)

Consideration of Pre-clinical data:

- Toxicology data:
  - Base on previous human experience; Proposed clinical use vs. traditional use
  - Acute toxicity is required
  - GLP certificated lab
- Animal pharmacology data

Status & Experience (9)

Clinical consideration:

- Instruction for use
- Clinical trial design
  - Clinical trial is feasible and not too difficult (chronic conditions-----Tox data)
  - Endpoint, subgroup analysis
- GCP inspection

Efficacy driven approach: Pilot Study

- Exploratory
- Proof of Concept
- Clinical Observation
- Follow Good Clinical Practice (GCP)

Efficacy driven approach: Pilot Study

Flexibility of Study Design

- Open-label Design
- Small Sample Size (power)
- Dose Escalation (low starting dose)
- Pharmacological endpoints

Efficacy driven approach: Pilot Study

- Waive of CMC Data
  - Traditional usage
  - Specification
- Waive of Tox Data
  - Previous human experiences
  - Proposed use vs. traditional use (dosage, duration)

Efficacy driven approach: Pilot Study

- Without safety concern
- Not the only evidence of registration
- Maybe need to repeat the study after establishment of specification

Regulatory Strategy in Taiwan

- Registration Regulation for New TCM Drugs
  - Tradition & Public Health Concern
  - Regulatory Science: risk/benefit judgment
  - Experiences on INDs Review
  - Foreign Experiences

Regulatory Strategy in Taiwan

Registration Regulation for New TCM Drugs

- IND Process (Investigational New Drug)
  - Pilot study
- NDA (New Drug Application)
  - Grading of Labeling
- New Definition & New Classification

Regulatory Strategy in Taiwan

Registration Regulation for New TCM Drugs

- Previous Human Experiences
- Systemic, Complete & Feasible
- More Confidence
  - CMC data
  - Tox data
  - Pilot study
  - Grading of labeling

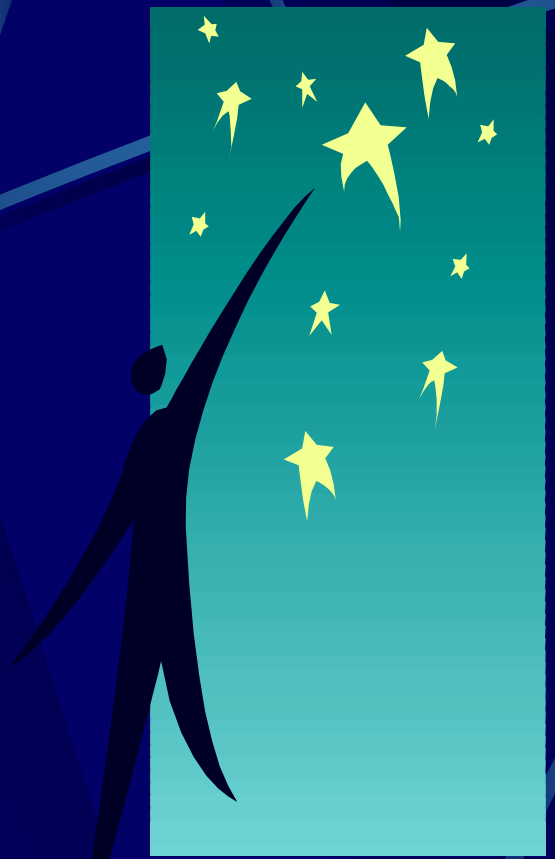
Regulatory Strategy in Taiwan

- Regulatory Consideration for TCM INDs
  - Previous Human Experiences
  - Pharm/Tox Data
  - CMC Data
  - Clinical Trial Design

Regulatory Strategy in Taiwan

Registration Regulation for New TCM Drugs

- International standard
- Two-way management on new TCM drugs
  - Importation (provide consumer protection)
  - Exportation (improve TCM industry)



Thanks For Your Attention