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Regulation of Traditional Chinese Medicine Drugs: Efficacy and Safety.

[Regulación de Medicinas Tradicionales Chinas: eficacia y seguridad]

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Abstract

Regulatory documents on requirements for TCM drug registration are officially issued, which are divided into 4 levels: Act, Rules, Regulation and Guidance. With the above-mentioned regulations, a two-phase (IND/NDA) and two-level evaluation (provincial and estate) for TCM drug registration for marketing is required. The requirements for R & D and production of TCM drugs are standardized based on internationally-acceptable standards, such as GLP, GCP, GMP and so on. In order to apply for the registration, 4 parts of dossiers should be submitted to SFDA (State Food & Drug Administration in China): Part I: Description and review on the TCM drug; Part II: CMC data; Part III: Pharmacology and toxicology data; and Part IV: Clinical study data. In Part III, there is a list of toxicological research works required for TCM drug registration for marketing. The requirements including toxicological works differ with different category's TCM drug in preclinical as well as clinical studies. In addition, considerations on TCM's safe use are described in details. Finally, progress in post-market surveillance of adverse reactions of TCM drugs in China is briefly discussed.

Keywords: Traditional Chinese Medicines, regulatory affairs, efficacy, standardisation, evaluation, safety.,

List of Abbreviations:
- ADR: Adverse Drug Reactions
- CDE: Committee for Drug Evaluation
- ChP: Chinese Pharmacopoeia.
- GAP: Good Agricultural Practices
- GCP: Good Clinical Practices
- GLP: Good Laboratory Practices
- GMP: Good Manufacturing Practices
- GSP: Good Storage Practices
- IND: Notice Of Claimed Investigational Exemption For A New Drug
- IND/ND: New Drug Application
- NDA: New Drug Application
- R&D: Research and Development
- SFDA: State Food and Drug Administration
- TCM: Traditional Chinese Medicine.

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INTRODUCTION: ADMINISTRATIVE LAW FOR TCM IN CHINA

The Drug Administration Law of the People’s Republic of China went into effect as of Dec. 1, 2001. There are regulations and explanations related with TCM.

In Article 102 There is definition of Drugs in China, i.e. Drugs refer to articles which are used in the prevention, treatment and diagnosis of human diseases and intended for the regulation of the physiological functions of human beings, for which indications, usage and dosage are established, including Chinese crude drugs, prepared slices of crude drugs, traditional Chinese medicine preparations, (chemical drug).

It is clear that TCM is administered strictly as drug, not as dietary supplements or health food in China. Some botanicals, especially with strong pharmacological action to the human, can not be used for dietary supplements or health food. The traditional Chinese medicines have therapeutic actions, the labelling of the crude drugs and their preparations shall include the Action and Indication, Usage & Dosage.

The following Regulations for TCM in China are enforceable or being made: (The practice for the source and production of Chinese Materia Medica), (Quality standard system in accordance with the characteristics of TCM}, (The practice for the manufacture of TCM), (The practice for the technical evaluation of the R&D and pre-marketing of TCM}, (The practice for its safety monitoring and re-evaluation of the post-marketing}, (The practice for registration and management of Drug).

THE PRACTICE FOR REGISTRATION OF TCM

The current practice for registration and management of Drug (TCM) divide it into two categories:

1. TCM refers to the material medica & its preparations using according to the theory of TCM.
2. Natural medicine refer to the material & its preparations using according to the theory of modern medicine

The main requirements of dossier for registration are as follows:

1. Pharmaceutical research materials (including origin and its identification of Chinese materia medica, cultivation, preparing method or processing of slices, production process, quality testing data, quality standard as well as stability test etc..
2. Pharmacological & toxicological research materials (including pharmacodynamics test, acute and long-term toxic studies, allergie, haemolytic test, cancer causing test etc.).
3. Clinical research materials (including clinical trial, ethical committee approval, testing report etc.).

QUALITY CONTROL AND STANDARDIZATION OF TCM

The development History of Quality Standards for TCM can be traced back to 200 AD, marked with Shennong's Classic of Materia Medica, which with description of 365 herbs, theories on pharmaceutical therapies, characteristics / toxicological characteristics / functions / indications of herbs, guidance on combination between herbs, guidance on administration, and preparation techniques and standards of different dosage forms are recorded. In 480 AD, the Collective Research on Shennong's Classic of Materia Medica was finished. It reinforced descriptions on characteristics, functions, and indications, while standards about source, collection time, and processing procedure were added. In 659 AD, the Tang Pharmacopeia was published. It was the first state pharmacopeia, in which 114 herbs were recorded. In 1078 AD, Formularies of the Bureau of People's Welfare Pharmacies was worked out. It contained explicated formulas, dosage forms, preparations, administrations, dosages, functions and indications of formulas. In 1505 AD, the Elite on TCM was finished. It recorded 1815 medicines, and described in 24 aspects, some of which are names, sources, plantation, collection, time, application, colors, odors, and tastes.

The current pharmacopoeia is 2005 versions of ChP, which was effective on July 1, 2005. It compiled a number of instruments, such as HPLC, have been extensively used for identification and assay of TCM, enhancing greatly the specificity and accuracy in the field.

The factors should be considered for TCM quality standardization (distinguished with Chemicals)are as follows:

1. Origin (Chinese crude drug), species, source, part of plant, collection, time, and processing procedure etc. As for example, the Root of Kudzu vine was divided into different species in ChP 2005, as ingredients varies (puerarin).
(2) Procedure (TCM preparations) all components of the preparation, processing procedure, quality control parameters etc.
(3) Description and Identification: shape, color, odor, taste as well as identifying with experiences, microscopic, physical and chemical identifications
(4) Test rancidity, swelling capacity, heavy metals, residual solvents, pesticides etc.
(5) Assay "king" component content as well as other indicator component.
Content range (not limit only) should be paid attention as TCM is a complex preparation usually
(6) Other method being studied TCM fingerprint analysis

CONSIDERATIONS FOR THE MANAGEMENT OF TCM

On the clinical evaluation of TCM
TCM being used according to the theory of TCM, which emphasize diagnosis and treatment based on an overall analysis of the illness and patient's condition. For the clinical evaluation of TCM, it may not suitable to take the short-term outward symptom cure as the unique criterion

On the analysis of ingredients of TCM
TCM come from nature. Some of them could be extracted to a single ingredient as modern drug (berberine, artemisinin, paclitaxel etc.), But some TCM proved by long term practice are effective with multi-components, multi-targets and their co-effection, better than any singles of it. We shall not take purify viewpoint to evaluate all TCM, practically impossible.

On the establishment of TCM Standard
In many cases, a single ingredient can not represent a TCM product composed with multi-components. It might not be necessary to isolate and measure all ingredients with great expenses (especially contents of some ingredients are very low, such as there are 48 ingredients with very low level in Heartleaf Houttuynia Herb). May take more macro-control method such as bioassay to fulfil safety even efficacy test. For example: breviscapine injection. Its improvement of mice brain blood circulation obstacle test and poisonous test to cell show obvious effect to distinguish the qualities of different manufacturer's products, although their major ingredients measurements show the same.

QUALITY CONTROL OF TCM
For the potential varies of source, climate, collection time etc. push GAP process be important; For the differences caused by processing procedure carry out GMP be necessary; For the complicated ingredients of TCM which be evidently effective using macro-analysis instead of each ingredient measurement may be an alternative.

REGULATORY SPECIFICATIONS
The requirement for NDA differs with the categories of TCM drug.
1) Less requirements for TCM drug consisting of commonly-used TCM drugs without any side effects reported
2) No pharmacological and toxicological data are needed for classic TCM prescription for IND submission if
   - no adverse reaction was found;
   - no toxic ingredient was contained;
   - And it has been extensively used clinically for a long time.

Box 1: Key regulatory documents on TCM
National People's Congress
   - (2001) "Act on the Drug Administration (ADA)",
State Council (2002)
   - "Rules on Implement of ADA"
State Food & Drug Administration
   - "Regulations for Approval of NDA"
   - "Requirements for R & D of TCM Drug"
   - "Guideline for a new TCM Drug"

Box 2: Categories for registration of TCM drugs
1. Pure compound isolated from natural material
2. Newly-discovered medicinal natural material
3. Substitute for raw material of TCM
4. Newly-discovered medicinal part of TCM herb
5. Effective fraction isolated from natural materia
6. Multi-ingredient TCM product
7. TCM injection
8. Changing administrative route
9. Changing dose form
10. Changing producing technology
11. Generic drug
Evaluating bodies and procedure for IND/NDA of TCM

A) Two-phase evaluation: IND evaluation:

- **IND evaluation**
  - Preclinical work
  - Problems or Deny

- **NDA evaluation**
  - Clinical studies
  - Problems or Deny

**Figure 1:** and procedure for Evaluating bodies IND/NDA of TCM

B) Evaluation procedure: 2 levels evaluation

**B1) Preliminary Evaluation at a Provincial Level**

- SFDU → Provincial office → Preliminary Evaluation (Verification, Spot-Inspection, Evaluation)
  - OK → Sponsor
  - ? or Deny → Sponsor

**B2) Final evaluation at state level:**

- SDA → Drug Registration Department → CDE → Outside Experts Committee
  - OK or deny → Evaluation → question → Sponsor

The Outside Experts Committee for Evaluation of TCM application is a consultant organization for technical evaluation under SFDA. The committee consists of outside experts with a variety of disciplines. The Committee for Drug Evaluation (CDE) and the experts work together to share the evaluation for a TCM new drug.

Standardization of pharmacological and toxicological studies

Administration of research, production and distribution of TCMs has adopted the international practice of modern drug administration. GLP, GCP, GMP and GSP are formulated and implemented on the basis of characteristic of TCMs.

3.1. GLP practice

"Good Laboratory Practice (GLP) for Non-Clinical Laboratory Studies (proposed)" was issued in 1994, and amended in 1998 by SFDA, which began to be tried out on January 1, 1994. Based on the requirement from "Regulations for Approval of New Drug Application" by SFDA, toxicological experiments for the safety evaluation of TCM drugs, especially TCM injections should be performed in accordance with GLP standards.

3.2. Establishment of GLP centers

Our government provides financial support to establish several GLP centers or labs as demonstrative examples, and among them, there are several TCM GLP centers or labs.

Right now, additional GLP centers are under construction by pharmaceutical companies and institutions.

Standardization of clinical study: GCP

The regulation for GCP is issued by SFDA, and many hospitals for the drug clinical trial have been established in accordance with GCP requirements, including several TCM hospitals. In addition, 36 TCM hospitals are approved for clinical investigation of TCM drugs. "Regulations for Approval of New Drug Application" requires that all the clinical trials of TCM new drugs should be performed in the approved hospitals above mentioned, and in accordance with GCP standards issued by SFDA.

Main purposes of any clinical study must be:
- Efficacy evaluation
- Safety evaluation
- Establish safe and effective dose range

The basic principle for clinical study random, double-blind, and control. Protection of the subjects in clinical trials is ensured by a consent form signed...
by the subject. The proposal for a clinical trial must be approved by ethical committee.

In order to ensure the efficacy of drugs, clinical trails for new drugs should be conducted. Class 1, 2 New drug should be conduct phase I to phase IV clinical trail. Class 3 new drugs should conduct phase II, III clinical trail. New drug below Class 4 should conduct phase II clinical trail. Clinical trails should adopt double blind tests and be in line with GCP.

GSP certification on drug distributors. GSP was promulgated in 2000 and is under trial implementation. Since then, 67 commercial enterprises have been certified.

Technical requirements for IND or NDA
The materials detailed in Box 3 must be submitted. However they take into account that TCM drugs present unique characteristics of:

- **Chemical composition:** Usually prepared as complex mixtures, in many cases, its active constituent(s) is/are not identified, and little is known about interaction among its constituents.
- **Therapeutics** TCM prescriptions consist of several medicinal plants or mineral or animals, used with direction of TCM theory (the treatment based on differentiation of symptoms and signs). TCM drugs have been extensively used in humans for a long time before IND application.
- **TCM R&D procedure different from chemical drugs**

Toxicological studies
Fewer requirements for TCM drug consisting of Commonly-used TCM drugs without any safety reports. No pharmacological and toxicological data might be needed for classic TCM prescriptions, which have a history of long term and extensive use in clinical practice. More toxicological data are needed for:

1) TCM drugs are reported to have safety concerns, such as *Aristolochia* plants, *Ephedra*, *antraquoinone*.
2) TCM consisting of Toxic materials such as arsenic,aconitum, *Tripterygium wilfordii* and so on.
3) Producing technology is significantly different from traditional technology (Traditional: water-extraction)
4) Highly-purified products (pure compound: e.g. artemisinin, ephedrine, berberine)
5) Semi-purified products (effective fraction: e.g. saponins from *Astragalus* or *ginseng*)
6) No experience or history of clinical use

**Box 3:** requirements for IND or NDA

- **Part I. General description and review**
  1. the drug name
  2. relevant documents (patent, GMP, and so on)
  3. the rationale of developing the TCM drug
  4. summary of the research work on the drug
  5. a proposed direction (draft) for clinical use
  6. a draft of package and label

- **Part II. CMC data**
  7. summary of CMC data
  8. source of TCM raw material and its identification
  9. habitat ecology, appearance, growing technique, preliminary processing, and
  10. processing method.
  11. Morphological and anatomical description, physico-chemical identification
  12. (method, data, photograph, conclusion)
  13. specimen of raw material (plant, mineral)
  14. manufacturing process and its research data
  15. chemical identification of a compound or a fraction
  16. quality control tests and their results
  17. quality standard proposal of drug substances and its final product for clinical investigation
  18. sample of a final product and a test report on its quality standards
  19. stability tests
  20. rationale of selecting package material and container that contact directly the drug

- **Part III. Pharmacol. & Toxicol. Data**
  21. summary of pharmacol & Toxicol
  22. Pharmacodynamics
  23. safety pharmacology (general phar)
  24. acute toxicity
  25. chronic (repeated dose) toxicity
  26. allergy, haemolysis, and local irritating tests
  27. mutagenic tests
  28. reproduction toxicity
  29. carcogenic tests
  30. pharmacokinetics

- **Part IV. Clinical data**
  31. summary of the clinical work on the drug
  32. protocol of clinical study design
  33. direction for clinical investigators
  34. a draft of the consent form and the certificate approved by a ethical committee
  35. a report on the clinical studies
Table 1 IND submission of pharmacological studies

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<th>Acute Toxicity</th>
<th>Chronic Toxicity</th>
<th>General Toxicity</th>
<th>Mutagenic tests</th>
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<th>Reproductive</th>
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Table 2 IND/ NDA submission of clinical studies

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<th>Phase</th>
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Considerations on TCM's Safe Use

**Establishment of medicinal herb's identity**
- Under the same name, there are different plant species, genera, or even families.
- Careful about the confusing fact that different herbs with the same name are easily misused, leading to severe adverse reaction.
  - *S. tetrandra* and *Aristolochia fangchi* sharing the same name in TCM, "fang-
- *Mutong* (*Aristolochia manshuriensis* and *Clematis armandii*) are another example.

**Use of TCM drugs under direction of TCM theory and a qualified physician.**
- The composition of a TCM formula varies with patients' conditions, although they suffer from the same disease, which is one of characteristic features in TCM clinical practice.
- It is much better to use TCM under direction of a well qualified TCM physician.
- The problem: TCM is treated as OTC or self-medication.

**Misunderstanding of TCM drugs**
Generally speaking, TCM drugs are relatively safe with low toxicity, but it doesn't mean that TCM drugs have no toxicity at all. Hence, it is incorrect to consider TCM drugs as the safest drug without any toxicity, which is more likely to result in abuse and misuse of TCM drugs such as overdose or over-duration of TCM therapy.

**Species and their growing location.**
For example, there are 2 species of Senecio plants: one is *Senecio scandens* grown in China; and the other *Senecio vulgaris* grown in European countries. Whilst *S. scandens* used in TCM contains pyrrolizidine alkaloids (PAs) 8 times less than *S. vulgaris*; and *S. scandens* has little toxicity to the liver, while *S. vulgaris* exhibits significant toxicity. A TCM preparation containing *S. scandens* is going to be prohibited, because *S. vulgaris* grown in European countries contains Pas that can causes liver toxicity. However they have never done research work on *S. scandens*.

In addition to the above factors, there are some more factors such as
- Combination of several Chinese herbs,
- Combination between Chinese herbs and Western medicines,
- Processing method of Chinese medicinal plants,
- Their growing area and so on.

**Progress in Post-market surveillance of adverse reaction in China**

**A. Regulations of drug post-market surveillance**
   - The Act provides:
     1) Surveillance and investigation of the approved drug for its quality, safety, and efficacy
     2) Reporting system of adverse reaction of the drug shall be enforced. Whenever the adverse reaction event occurs, the manufacturer, the medical institutions, and the sale-related company must report it to superior office.
   2. ADR requirement from GMP Regulation (SFDA, 1998)
      - "In pharmaceutical company, reporting system of the drug adverse reaction must be established."
      - "The side effects of its product must be reported to drug administration office."
   3. "Regulation of post-market surveillance of the drug adverse reaction" (SFDA)
      - Its contents the following chapters:
        1). General principles
        2). Organization structure and responsibility
        3). Report procedure and its requirements
        4). Rewards and punishments
        5). Supplementary articles
**B. State Center for post-market surveillance of the drug adverse reaction**

B. State Center for post-market surveillance of the drug adverse reaction” Its Functions:

1. To collect, analyze, manage ADR data, and report ADR to the authorities;
2. Establishment and operation of ADR database and network
3. Investigate the adverse reaction events sponsor and publish "Bulletin of ADR" and a journal, "Pharmacovigilance".

**Figure:** Post-market surveillance of adverse reaction in China

**REFERENCES**
