Regulatory Requirements for New TB Drug Approval in China

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1. Current TB Situation in China
2. The Plan for TB Disease Control in China (2001-2010)
3. The Policy of TB Treatment and Related Drug Management in China
4. The Procedure of Drug Registration and Technical Requirements in China
5. The R&D Status of TB Drug and Unmet Needs
6. Summary
Current TB Situation in China

As well known, TB is a chronic and transmitted disease. For a long period of time in mankind history, this disease has been harming human health. In recent years, due to the economic development, the migration of population leads to TB/HIV combined infection, and the resistance of human body to drug therapies has been making negative impact for general increase of TB cases.
• China is one of the major TB disease countries, accounting for 15% of cases worldwide.

• The comprehensive survey of epidemic diseases by Chinese CDC in 2000 indicated: the infection rate for TB is 44.5%, active TB rate is 367/100K, positive TB rate is 122/100K, the death rate is 9.8/100K, drug resistant rate is 27.8%, multiple-drugs resistant rate is 7.7%.

• Estimated the number of positive TB patients is 4.5 million, new patients are 130K per year in China.

• TB is the No.1 disease led to death among infectious diseases without other complication.
• Geographically, the TB cases in middle west region is 1.7 time of ones in eastern region in China, and 2 times in rural area compared to urban area
• Most seriously, the number of patients with TB/HIV combined infection is increasing
The Plan for TB Disease Control in China (2001-2010)

Major Objectives:

1. Based on county as an unit, the coverage of DOTS should be 100%
2. The rate for early detection of new positive TB patients should be over 70%
3. The rate for cured patients should be over 80%
4. Until 2010, 100% of medical institutes should participate in TB prevention activities
5. Until 2010, 90% of patients with multiple drugs resistance should be treated
6. Until 2010, 80% of patients with TB/HIV combined infection should be treated
7. Until 2010, 90% of migration TB patients should be treated
8. Until 2010, 90% of medical doctors in rural areas should be trained for professional Tuberculosis prophylaxis and treatment
9. Until 2010, 80% of all population should be trained for TB knowledge
The Policy of TB Treatment and Related Drug Management in China

• Free Medical Treatment for all patients
• Out-patient treatment as the major method
• In-patient treatment for acute patients, and patients with drug allergic reaction and other complications, etc.
• Government sponsored monitoring program for all patients after hospitalization, until fully cured
• All programs comply with WHO principle
• In order to better treat TB patients, there is an established system to maintain the consistency of supply and provide the high quality drugs.
• In order to assure the quality of drugs, keep continuous supply, avoid waste, lower the cost, a comprehensive management system has been completed for free TB drug supply.
The Procedure of Drug Registration and Technical Requirements in China

- Drug Registration Legislation
- Drug Registration Procedure
- Technical Evaluation Procedure
Drug Registration Legislation

1. *Drug Administration Law of P.R. China*  
   (Amended, 2001.12.01)

2. *Regulations for Implementation of the Drug Administration Law of P.R. China*  
   (Amended, 2002.09.15)

3. *Provisions for Drug Registration*  
   (Amended, 2002.12.01)

   ※ Consolidated several previous Provisions into one

4. *Provisions for Drug Registration*  
   (Amended, 2007.10.01)
Law Requirements for Drug Registration

1. The manufacturing of new drug or generics must be approved by SFDA, and a drug approval number shall be issued (all drugs have to be approved)

2. Drug importation must be approved by SFDA, while its quality, safety, and efficacy having been confirmed, and the Import Drug License shall be issued. The import drug shall be approved by the manufacturing country originally.

3. SFDA shall evaluate new drug application by evaluators and experts in the field.
Legislation History Briefing

1. Provisions for New Drug Approval  
   (1985.07.01, Chemical Drug, TCM)
2. Provisions for New Bio-Product Approval  
   (1985.07.01)
3. Provisions for Import Drug Administration  
   (1990.11.02, Chemical Drug, TCM, Bio-Product)
4. Directives for New Drug Protection and Technology Transfer  
   (1987.03.24)
5. Directives for the Approval of Foreign Sponsored Clinical Trials Tending to be Conducted in China  
   (1988.02.02)
Legislation History Briefing

1. Provisions for New Drug Approval
   (1999.05.01, Chemical Drug, TCM)
2. Provisions for New Bio-Product Approval
   (1999.05.01)
3. Provisions for Import Drug Administration
   (1999.05.01, Chemical Drug, TCM, Bio-Product)
4. Provisions for Generics Approval
   (1999.05.01)
5. Directives for New Drug Protection and Technology Transfer
   (1999.05.01)
Legislation History Briefing

1. *Provisions for Drug Approval*  
   (2002.12.01, Chemical Drug, TCM, Bio-Product)

2. *Provisions for Drug Approval*  
   (2007.10.01, Chemical Drug, TCM, Bio-Product)

3. *Directives for New Drug Technology Transfer*  
   (Have been discussing)
Drug Registration Procedure

Responsible Organizations:
1. Department for Drug Registration of SFDA (DDR)
2. The Center for Drug Evaluation (CDE)
3. The National Institute for the Control of Pharmaceutical and Biological Products (NICPBP)
4. Provincial authorities (Provincial DA) and quality control labs
Responsibilities Related to Registration

1. DDR
   - Policy maker regarding drug registration
   - Overall controlling drug registration functions around the country
   - Making decisions of final approval
2. CDE
   - Technical evaluation for all drugs
3. NICPBP
   - New drug specifications validation and verification
   - Reference substance preparation
4. Provincial DA
   - Site inspection
   - Primary review for the local applications
5. Provincial QC lab
   - Drug specifications validation and verification for the local applications
Relationship of the organizations

Director-General

DDR

CDE

NICPBP

Provincial DA

Provincial QC lab
General Approval Procedure

Applicant → Dossier Required

Reception office

CDE
Technical Evaluation

IMCT Report
IMCT Approved

DDR

Director General

MA Approved

- Approval No.
- Specification
- SPC

Refused

Rejected

Assessment Report
Core Procedure

Acceptance → Evaluation → Approval

Testing
Categories of Registration Application

- New Drug Application
- Generic Application
- Import Drug Application
- Supplementary Application
➢ Application for Clinical Trial
➢ Application for Marketing Authorization
Application Receiving

- Local Manufacturing Application: by PDA
- Import Application: by SFDA directly (including IMCT)
Technical Evaluation Procedure
Functions of CDE

- CDE is the technical evaluation unit under SFDA drug registration function, and provides technical supports for drug registration decision
- Responsible for technical evaluation of drug registration applications
- Others
Establishment of Technical Evaluation Procedure

- Basic Rules of Drug Evaluation
- Experiences learning
- Specific Chinese situation
Basic Organization Unit
- Project Team

Personnel
- Major Principal
- Specialty Evaluator (3)

Objectives
- Evaluation Plan
- Specialty Evaluation
- Integrate Evaluation
Evaluation Procedure

- Pharmaceutical Evaluator
- Pre-clinical Evaluator
- Clinical Evaluator
- Specialty Opinion
- Major Principal
- Integrate Opinion
- Approve

Task

Major Principal
Internal Procedure of Function Division

Major Principal

Specialty Evaluator

Specialty Evaluation Report

Delegate Tasks

Major Principal

Specialty Evaluation Meeting

Submit Plan

室主任

Consolidated Evaluation Report

室主任

Consolidated Evaluation Meeting

Expanded CEM Consulting Meeting

专题会

Division Director

Management of Evaluation Plan

Division Director

审评计划备案或协调
Consolidated Evaluation Solution

- Dossier
- Supplementation
- Consultation

- Approve
- Un-approve
- Reject
Application Dossiers

Part I: General data and Administrative Documents
Part II: Chemical, Pharmaceutical and Biological Data
Part III: Pharmacological and Toxicological data
Part IV: Clinical Data
Application Dossiers (1)

Part I
1. Name of the drug
2. Document for attestation
3. Aim and justification of the selected project
4. Summary and review of the study results
5. Sample of package inserts, drafting description and reference materials
6. Sample of package and label
Application Dossiers(2)

Part II

7. Review of the pharmaceutical study.
8. Manufacturing process and literatures for API; the formulation, manufacturing process and literatures for pharmaceutical preparation.
9. Identification data and literatures for chemical structure or components,
10. Quality study data and literatures
13. The origin and specifications of the excipients.
14. Stability data and literatures
15. Immediate packaging materials selection, and its specifications
Application Dossiers(3)

Part III

16. Review of the pharmacological and toxicological study data.
17. The main pharmacodynamics data and literatures
18. General pharmacology data and literatures
19. Acute toxicity data and literatures.
20. Long term toxicity data and literatures
21. Special toxicity data and literatures related to topical and systematic administration, such as hypersensitivity (topical, systematic and photosensitive toxicity), hemolysis and topical (blood vessel, skin, membrane muscle, etc.) irritation, etc.
22. Interaction data and literatures of efficacy, toxicity and pharmacodynamics for multiple components.
23. Mutagenicity data and literatures.
24. Reproductive toxicity data and literatures
25. Carcinogenicity data and literatures
26. Drug dependence data and literatures
27. Animal pharmacokinetics data and literatures
Application Dossiers(4)

Part IV

28. Overview of related clinical study literatures.
29. Clinical study protocol and plan.
31. The copy of Informed Consent and ethics committee approval.
Other Key Requirements

1. The manufacturer must obtain GMP Certificate
2. The samples for CT must be produced according to GMP requirements
3. Production samples have to be produced by a manufacturer already obtained GMP Certificate
4. APIs used for formulating a drug has to be approved
5. Pre-clinical study should conforms to GLP requirements
6. Import drug and domestic approval apply to the same criterion
Technical Evaluation Concern

1. Quality/Safety/Efficacy Aspects, based on self-produced dossier
2. Risk/Benefits Analysis
3. Literatures
4. Other Authorities approval information
5. Public health needs
Evaluation and Approval Timelines

1. Provincial DA Primary Evaluation: 30 days
2. Provincial QC lab’s tests: 60 days; Bio-product: 60 or 90 days
3. SFDA Dossier Reception Office: 5 days
4. CDE technical Evaluation for CTA: 90 days
   (fast-track: 80 days)
5. CDE technical Evaluation for new drug production application:
   150 days (fast-track: 120 days)
6. CDE technical Evaluation for generics: 160 days
7. CDE technical Evaluation for variations: 40 days
8. SFDA marketing approval: 20 days
Requirements for Clinical Trial

1. All CT have to be approved by SFDA in advance
2. All CT have to be carried out according to China GCP requirements
3. CT is divided into Phase I, Phase II, Phase III and Phase IV accordingly.
4. The number of subjects for a CT has to conform to the requirements of both the minimum limit and statistic meaning
5. All CT have to be conducted by designated hospitals
Patient Number Requirements

For NCE

1. Statistically meaningful
2. The minimum patient number requirements:
   - Phase I: 20-30 patients
   - Phase II: 100 patients
   - Phase III: 300 patients
   - Phase IV: 2000 patients

For first import drug application:

1. PK study
2. 100 pairs of patients, controlled, randomized, study
3. At least 60 patients for each indication
Ethics Committee

- 5 persons at least
- Composed of professional, laypeople, lawyer, other related persons
- Different gender
- Independent decision
- Decision made after CT approval
Chinese GCP

- Published in 1998, amended in 1999, latest reversion Aug. 6, 2003
- Protecting subjects is the utmost purpose (such as Informed Consent)
- Helsinki Declaration as fundamental
- ICH, WHO guidelines as bases
Fast Track

1. TCM derived from Herbal, animal, and mineral that have never been previously used as therapeutics
2. New chemical entity (NCE)
3. Anti-HIV/AIDS products (treatment, prevention, Diagnosis)
4. Products for malignant tumor
5. Products for rare diseases (orphan drug)
6. Products for the diseases that efficacious treatment are not available yet
Registration Decisions

1. Approval
2. Approval with conditions
3. Rejection
Technical Guideline

- Delegated by SFDA
- Drafted by CDE
- Approved and Issued by SFDA
- 49 Guideline have been published

website: www.cde.org.cn
The R&D Status of TB Drug and Unmet Needs

- In recent several decades, there is no new drugs for TB entering the market
- There are only few drugs which can be prescribed for TB
- There is an urgency for drug therapy to administrate drug-resistant TB patients
Summary

Challenges:

- The number of patients of migration population is showing an increase
- The patients with drug resistance have been increasing

Measures:

- Prevention drug resistant TB: early detection, canonical treatment.
- Encouragement for new drug discovery for prevention and drug therapy of TB (supports from Government, international foundations and organizations, etc.)
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