Review Policies for Global Drug Development: Korea’s Perspective

April 15, 2008

In-Beom Kim
**Review Process in KFDA**

1. **Application**
   - Applicants
   - Civil Support Div or KiFDA system

2. **Technical Documents**
   - Pharmac. Safety Policy Div
   - Clinical Management Div
   - CMC, Pharm/Tox and Clinical data

3. **Administrative Documents**
   - Review Report

4. **Review Report**
   - Approve (Reject)
   - Demand

5. **Approve (Reject)**
   - Drug Evalu. Dep.

6. **Approve (Reject)**
   - Pharmaceutical safety Bureau

All application documents could submit by **KiFDA online system** with electronical documents from Oct. 2\textsuperscript{nd}, 2006
## Major Regulatory Changes

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
</table>
| Dec. 12, 1999 (enforced Jul. 1, ‘00) | **Adoption of the Bridging Concept**  
- Harmonized to ICH guideline E5  
- Diverse bridging strategies were required |
| Jan. 4, 2000 (enforced Jan. 1, ‘01) | **KGCP Amendment for Harmonizing with ICH GCP**  
- Harmonized with ICH guideline E6  
- Protect the rights and safety of subjects  
- Responsibility of investigator |
| Dec. 3, 2002 | **Introduction of IND System**  
- Separation between developmental clinical stage and commercial product approval, such as IND and NDA  
- Participation in international study enabled |
| Jun. 30, 2006 | **Organization of Clinical management Division** |
| Jan. 4, 2007 | **Introduction of Joint-IRB** |
Change of Clinical Trial Status

- Introduction of Bridging Concept and IND System
- Increase in the Number of Domestic Clinical Trials Approved
  - Increase of Participation in Multinational Clinical Trials
- Change in Type of Clinical Trials
  - Increase in Initial Clinical Trials
- Demand the Necessity of Amending Guidelines of Bridging Data Evaluation
Clinical Trials approved by KFDA

- Local
- Multinational

Year: '99, '00, '01, '02, '03, '04, '05, '06, '07

- 1999: Local 31, Multinational 18
- 2000: Local 5, Multinational 28
- 2001: Local 17, Multinational 27
- 2002: Local 46, Multinational 38
- 2003: Local 61, Multinational 97
- 2004: Local 75, Multinational 90
- 2005: Local 90, Multinational 95
- 2006: Local 110, Multinational 108
- 2007: Local 134, Multinational 147

EAPRS 2008(2008.4.15)
Clinical Trial Status
Bridging Concept

New Product

Ethnic Factors (Ethnic difference)
- Intrinsic factor (genetic)
- Extrinsic factor (culture, environment)

Approval in Korea

“Bridging Data” = “Korean Data”
“Bridging Study” = “A trial conducted in Korean”

Evaluation

- Ethnic Sensitivity
- Foreign clinical data
- Bridging Data
**New Product Approval**

- **New Product Candidate**
- **Clinical Data in Koreans (Global or Local)**
  - **Bridging Study in KOREAN**
  - **Bridging Data**
- **Foreign Clinical Data**
  - **Bridging Study Exemption**
- **Bridging Data Waiver**
  - 7 waiver categories
Bridging Waiver Categories

- Orphan drugs (or used to be orphan drugs)
- Drugs for life-threatening disease or AIDS
- Anticancer therapy for the following
  - No standard therapy
  - Therapy after failure of a standard therapy
- New drugs for which clinical trials conducted on Koreans
- Diagnostic or Radioactive drugs
- Topical drugs with no systemic effect
- Drugs that have No ethnic differences
Case of Bridging Waiver

- Renagel (Sevelamer, Tab., Che-il, renal dysfunction)
  - Polymer, Excretion with binding of Phosphorous in renal dysfunction Patient
- Travatan (Travaprost, Ophthalmic sol., Alcon, Glaucoma)
  - Drug Conc. & receptor: Less in systemic body
- Elidel (Pimecrolimus, Cream, Novartis,)
  - No systemic effect Local effect etc.
- Arixtra (Fondaparinux, Inj., Sanofi-Synthelabo, Antithrombotic)
  - Low MW Heparins, enough experiences in Korea
- Invanz (Ertapenem, MSD, Antibiotics)
  - Susceptibility test in Korean and western population: similar
- Cancidas (Caspofungin, Inj., MSD)
  - Life-threatening disease
New Drug based on Bridging Strategy (1)

- Based on the New chemical entity approved by KFDA from 2002 to Sep. 2007
New Drug based on Bridging Strategy(2)

Based on the New chemical entity approved by KFDA from 2002 to Sep. 2007
Type of Bridging Study

- Pharmacokinetics
- Pharmacodynamics with pharmacological endpoints
- Dose-response
- Phase III confirmatory study
- Phase III with surrogate marker
Reasons for the failure of bridging study

- Phase III study
  - Active controlled study, Single arm study
  - Power Deficiency
  - No sufficient in the statistical theory
  - No evidence on the no ethnic difference between ethnics

- PK study
  - No consistency between single and multiple dose result
  - No ethnic similarity
Overall Evaluation of Bridging Data

- Application of foreign clinical data to Korean population without changes in dosage
- Application of foreign clinical data to Korean population (;PMS recommended)
- Application of foreign clinical data to Korean population with modification of the dosage (;PMS recommended)
- Additional clinical trials are required.
**Evaluation on Foreign Clinical Data and Bridging Data (1)**

- Comparative analysis between the Korean data and non-Korean data with proper statistics methods, if possible
- Data of PK and PD correlate well,
- Safety and efficacy end points are predictable from PD end points
- There is sufficient experience with application of confirmatory studies conducted in the given country to Korea, and
- Medical practice, design and conduct of clinical trials are similar between two ethnic groups
Evaluation on Foreign Clinical Data and Bridging Data (2)

- Well-established PK-PD and dose-response relationships are necessary for PK study for bridging
- GCP Compliance
- In case Korean population participate in the multi-national clinical trials: Comparative analysis of the whole study result with the Korean subgroup included

(; Sufficient sample size is needed)
Case of Dose Adjustment

- Actos (Pioglitazone, Tab, Lilly, Diabetics)
  - Pharmacokinetics study with healthy Korean volunteers (n=24)
  - Adjusted Dosage in Korean
    - Mono-therapy : 15 mg, 30 mg
    - Combination therapy : 15mg

- Morniflu (Morniflumate, Tab, Kolon, Analgesics & Antipyretics)
  - Phase III study with Korean patients
  - Dose Adjustment to ½ with Safety issued of NSAID

- Crestor (Rosuvastatin, Tab, Astrazeneca, Hypercholesterolemia)
  - Phase III study with primary hypercholesterolemia
  - Dose Adjustment by Asian PK data different from Caucasian
New Drug based on Bridging Strategy (3-1)
New Drug based on Bridging Strategy (3-2)

- Numbers of approved New Drug
- % of applications based on "Bridging Strategy"

- New Chemical Entity
- Bridging Study
- Multinational Study

**Past Experience**

- Western Data
  - Bridging study 1
    - New Region 1
  - Bridging study 2
    - New Region 2
  - Bridging study 3
    - New Region 3

1. No clear scientific evidence regarding racial difference
2. No clear statistical approach—similarity, sample size
3. No unified regulatory authority requirements

*Presented by Masahiro Takeuchi in 2nd Kitasato University-Havard School*
Present & Future Application

Western Data

Similar regions

Region 1 ↔ Region 2 ↔ Region 3

Similar Region:
- Intrinsic Factors
- Extrinsic Factors (medical practice, etc)
- GCP

One Global Protocol

- Presented by Masahiro Takeuchi in 2nd Kitasato University-Havard School -
When to jump into Global Clinical Development with what Data on own Population?

Phase I

Phase II

Phase III

PK?

PK?

Dose-Finding?

Clarifying Ethnic Factors to enlarge Ethnic Basis should HELP!

- Presented by Toshiyoshi Tominaga (MHLW) in Japan-Korea joint workshop, July, 18th, 2007 -
Challenges for implementation

- Qualification of Investigator
- Importance of IRB review
- Importance of SOP
- Need for Clinical Research Resources
- Need for Regulatory Service from Authorities
- Need for communication and harmonization with Foreign Authorities
Strong Supporting Plan

- Supported plan for Clinical Centers by MOHW
  - 9 Regional centers designated in 2004-2006
  - Support for Facilities, Operation systems, R&D etc.
  - $0.5 ~ 1 million/center/yr for 5 years

- Ko-NECT
  (Korea National Enterprise of Clinical Trials)
  - Clinical Hub of North-East Asia
  - Regional centers will be increased by 15 centers until 2010
  - Regional centers will be network
  - Training center and Development center to support clinical trials

- MOHW: Ministry of Health and welfare
Korean Investigator’s Contribution to Global Trials

- Prof. Byung-Hee Oh: Cardiology, SNUH
  Global PI of Aliskiren, Norvatis

- Prof. Yoon-Ku Kang: Oncology, AMC
  Global PI of Xeloda Phase III study in GC, Roche

- Prof. Young-Joo Bang: Oncology, SNUH
  Global PI of Sunitinib Phase II study in GC, Pfizer

- Prof. Sun-Young Ra: Oncology, YUMC
  AP PI of Sunitinib Phase II study in RCC, Pfizer

- Prof. Sun-Woo Kim: Endocrinology, SMC
  Global PI of Vildagliptin, Phase III study in T2DM, Norvatis

- Dr. Jin Soo Lee: Oncology, NCC
  Global PI of ZD6474 Phase III study for LC, AZ

- Prof. Joon Soo Kwon: Psychiatry, SNUH
  Global PI of 11286 Sertindole, Phase III study for schizophrenia, Lundbeck

More than these.....
Tripartite Cooperation to study Ethnic Factors

If Ethnic Factors are small, Data from 3 Countries can be combined and analyzed for quicker Delivery of Drugs in the Countries.

- Presented by Toshiyoshi Tominaga (MHLW) in IFPMA, March, 12th, 2008 -
Cooperation among Korea, China and Japan

- Based on the currently available data, it is difficult to examine closely whether there is a difference in drug sensitivity caused by ethnic factors.

- Make a comparison of clinical data from Korea, China and Japan on the same products for the purpose of a more explicit comparison.

- Establishment of action plan designed to collect sufficient data:
  - Working group with tripartite reviewer and experts.
Harmonization of East Asia

- Harmonization of International Standard
  - Korea isn’t ICH member, but accepted ICH Guideline
  - Implementation of GLP, GCP, GMP, DMF

- Adoption of ICH CTD
  - step by step from New drugs (2009.3)

- Harmonization of Japan, US, EU
  - Harmonization of Japan, China, Korea
  - Compare the regulation, system, process etc
Evaluation of Multinational Clinical Trial Data

- Acceleration of participation in multinational clinical trials at the early stage

- Numerous participation simultaneously in multinational clinical trials with the same protocol
  - Acquisition of statistically significant figures

- Bridging study < Bridging data

- Change in evaluation policy based on accumulation of experience
Thank you!

KFDA
Pharmaceutical Safety Policy Division

Tel. 82-2-3156-8006 / Fax. 82-2-3156-8029
E-mail. Kib2502@kfda.go.kr