Asia Town Hall:
Asia as a Drug R&D Center in the World
Updates of MRCT in Japan

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Outline

- Recent trend of MRCT in Japan
- Guidance documents “Basic principles”
- Future activities
- Summary
Trend of new drug application approvals in Japan

Approved new drugs based on GCT in Japan

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<tr>
<td>2006-2009</td>
<td>Tolterodine</td>
<td>Denosumab</td>
<td>Lamotrigine</td>
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<td>2010</td>
<td>Losartan</td>
<td>Aripiprazole</td>
<td>Aflibercept (PM)</td>
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<td>2011</td>
<td>Trastuzumab</td>
<td>Pertuzumab</td>
<td>Aflibercept (DME)</td>
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<td>Tadalafil</td>
<td>Trastuzumab</td>
<td>Regorafenib</td>
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<td>Everolimus</td>
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<td>Tofogliflozin</td>
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<td>2014</td>
<td>Panitumumab</td>
<td>Panitumumab</td>
<td>Nonacog Gamma</td>
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<td>2015</td>
<td>Laninamivir</td>
<td>Denosumab</td>
<td>Eftrenonacog alfa</td>
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**Red : Asian GCTs**

- **Guidance 2007**
  - “Basic Principles on Global Clinical Trials”

- **Guidance 2012**
  - “Basic Principles on Global Clinical Trials – Reference Cases”

- **Guidance 2014**
  - “Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials”

100 applications were approved as of March 31, 2015
Trend of clinical trial notifications of GCTs

Preliminary results

Year


N of Notifications of GCT

N/A  Global  Asia  East Asia
Guidelines in Japan -Basic Principles-

2007 Guideline

September 28, 2007
Notification No.0928010

Attention to:
Commissioners of Prefectural Health Supervising Department

From Director of Evaluation and I
Pharmaceutical and Medical Devices Agency
Ministry of Health, Labour and Welfare

Basic Principles on Global Clinical Trials*5

Up to the present according to “Ethnic Factors in the Acceptability of Foreign based on ICH-E5 guideline (Notification No. 672), Director of Evaluation and I, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, cited utilizing foreign clinical trial data in a new drug application what is called “B accepted in Japan, and post-marketing data in USA and EU have been taken into review for regulatory approval when necessary.

2012 Guideline

Basic Principles on Global Clinical Trials (Reference Cases)

September 5, 2012
Pharmaceutical and Medical Devices Agency

Introduction
Since the issuance of “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007), Japan’s position on global clinical trials has been steadily increasing. In recent years, global clinical trials in East Asia (e.g., Japan, China and South Korea) have been increasing. The roles of cooperation between Japan and foreign countries has also been diversified. Specifically, Japan has been actively taking the lead in drug development and participating in global trials in thousands of subjects. The regulatory cooperation is also being maintained so that moving Japan, US and EU. In the current trend of global drug development, research and development especially in East Asia is of critical importance not only for Japan but also for regulatory authorities that conduct real world studies.

In order to respond to these progress and changes, the Basic Principles on Global Clinical Trials (Reference Cases) has been re-organized in order to further promote better understanding of the former notifications and the current situation in Japan’s research participation in global trials as well as research and appropriate conduct of global clinical trials in East Asia when necessary in such trials in order to promote cooperation with regulatory authorities. The following recommendations are based on the current scientific knowledge. It should be noted that they may be revised in the light of the current scientific knowledge.

1. Points to consider for global clinical trials in East Asia

As one of the key factors toward timely patient access to new drugs, the “Basic principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) and the “Basic Principles on Global Clinical Trials (Reference Cases)” (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 5, 2012) have been issued from the perspective of promoting Japan’s active participation in global clinical trials.

2014 Guideline

Administrative Notice
October 27, 2014

To: Prefectural Health Department (Bureau)
Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles for Conducting Phase I Trials in the Japanese Population
Prior to Global Clinical Trials


“Basic Principles on Global Clinical Trials”

Issued in 2007

First guideline for GCT

Outlined to promote GCT in order to resolve “Drug lag”

Based on the experience in Clinical Trial Consultations

September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Basic principles on Global Clinical Trials

Up to the present according to “Ethnic Factors in the Acceptability of Foreign Clinical Data” based on ICH-E5 guideline (Notification No. 762, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign clinical trial data in a new drug application what is called “Bridging” has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.

On the other hand, in the report entitled “Institutional reform for promoting science and technology and passing on the benefits of the scientific and technological advance” (Council for Science and Technology Policy, dated December 2006), it is mentioned to encourage global clinical trials in terms of efficient and rapid developments of new drugs. Moreover, in the final report of the special committee for “Effective & Safe Drugs Quick to Patients” (dated July, 2007), it is pointed out to promote global clinical trials in order to resolve “Drug lag (Circumstances where drug approved in EU and US are not approved in Japan and can not be provided to nations)” and to clear points to consider for conducting global clinical trials from the perspective of a review for regulatory approval.
“Basic Principles on Global Clinical Trials”

Contents of the notification

– Basic requirements to conduct a GCT
– Appropriate timing to participate in global drug development
– Importance of Phase I study prior to a GCT
– Importance of dose-finding study
– Basic points to consider in designing a GCT
– Sample size and proportion of Japanese subjects.

etc.
“Basic Principles on Global Clinical Trials (Reference Cases)”

- Issued in 2012
- New scientific knowledge and regulatory experiences accumulated after the publication of the 2007 guideline
- Includes 4 points to consider for East Asian GCT and 13 general points to consider
- Encourage to conduct GCTs in East Asia as part of drug development plan
What are the special points to consider when conducting a global clinical trial in East Asia?

- Data from well-designed and conducted GCTs in East Asia can be acceptable in support of marketing applications in Japan.
- The difference in ethnic factors may affect the efficacy and safety of drugs even within East Asia.
- Need to be designed based on prior sufficient evaluation of the effect of ethnic difference on the efficacy and safety of drugs.
- Separate clinical pharmacology studies may provide useful data.
What therapeutic areas are recommended for global clinical trials to be conducted in East Asia?

- A global clinical trial in East Asia can be performed for any target disease area.
- For diseases with high morbidity in East Asia of which conduct of confirmatory studies in Japan alone is difficult, GCT in East Asia may contribute to the clinical development of a drug. (e.g., gastric cancer and hepatitis)
What type of global drug development strategy can generally be planned based on data of interethnic comparison of pharmacokinetic profiles?

- When there is no remarkable PK difference between Japanese and other East Asian populations, an East Asian exploratory clinical trial including Japanese and other East Asian population can be considered.
- Whether to conduct a confirmatory trial as a GCT should be determined based on the result of prior exploratory studies.
- In addition to the difference in PK profiles, effects of ethnic factors affecting the efficacy and safety of a drug should be evaluated.
Is it acceptable to conduct a bridging study as a GCT in East Asia and extrapolate the data from US/European studies to the Japanese population?

- In Japan, a bridging study generally intends to extrapolate foreign data to the Japanese population and is conducted in Japanese subjects.

- Sufficient data and information should be collected in advance to scientifically demonstrate that the ethnic difference between Japanese and other East Asian populations will not affect the data evaluation of the study.

- For individual cases, it is recommended to consult with PMDA in advance.
Administrative Notice  
October 27, 2014

To: Prefectural Health Department (Bureau)  
Evaluation and Licensing Division,  
Pharmaceutical and Food Safety Bureau,  
Ministry of Health, Labour and Welfare

Basic Principles for Conducting Phase I Trials in the Japanese Population  
Prior to Global Clinical Trials

As one of the key factors toward timely patient access to new drugs, the “Basic principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) and the “Basic Principles on Global Clinical Trials (Reference Cases)” (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 5, 2012) have been issued from the perspective of promoting Japan’s active participation in global clinical trials.

Based on the accumulated knowledge up to now, the “Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials” has been compiled as attached. We ask you to inform manufacturers and sellers placed under your administration to utilize this for their business operations.
Background of the new guideline

- Basically, tolerability data of the test drug in the Japanese population should be ensured before participating in the global clinical trial.

- When considering whether or not Japan should participate in a GCT, there are many cases in which human data in a foreign population has already been obtained to some extent.
Principles

If at the point of initiating global clinical trial tolerability in human has not been sufficiently confirmed or the safety risk is thought to be high in the Japanese population, a phase I trial should be conducted in the Japanese before participating in GCT.

If safety in the Japanese population is ensured by foreign data (= if tolerability of the test drug has been confirmed in human and ethnic factors are thought to have little effect on the safety of the test drug), there may be cases where Japanese phase I trials are not necessarily required prior to GCT.
Main points to be considered

1. Characteristic of the drug
   – Method of administration is highly invasive?

2. PK properties
   – Linear?
   – Metabolic pathways is multiple?
   – Any ethnic differences in the associated metabolizing enzymes?

3. PD properties
   – Linear?
   – Any ethnic differences in genetic polymorphism of the target molecule?

4. Safety
   – Safety evaluation in the Japanese population is possible from preceding clinical trials overseas?
Two reference cases

Case 1
- Serious safety concerns in early clinical trials conducted overseas.
- No reliable data indicating that those risks in the Japanese population are equal to or less than those in foreign populations.

Case 2
- Immediate participation in a large-scale comparative study or a comparative study for an orphan disease should be considered
- Safety of the test drug has been confirmed based on sufficient dosing experience in a foreign clinical trial
- No remarkable differences in ethnic factors
ICH Guideline: E17 for MRCTs

The ICH Steering Committee Approved the establishment of the new expert working group, E17 EWG, focusing on “General principles on planning/designing Multi-Regional Clinical Trials” with MHLW/PMDA as the Rapporteur.

This guideline will provide common points to consider in planning/designing MRCTs and minimize conflicting opinions from regulatory bodies.

Advanced Review with Electronic Data in PMDA

**NDA submission**
- e-Submission of data
  - Submission of electronic data from clinical and nonclinical studies

**Regulatory Review**
- Use of electronic data
  - Accessible, visualized electronic data for each reviewer
  - Easy to identify individual clinical case data, drilling down of data
  - Operation of various analyses - simple, subgroup analysis for the present

**Utilization of Accumulated Data**
- Integration of cross-products information
  - Utilization of exhaustive information by therapeutic category for review/consultation
  - Internal review on particular theme – e.g.) active utilization of M&S
    - Review on pediatric dosage
    - Preparation of disease model
    - Development of evaluation indicator
  - Utilization in preparation of guideline

Storage of electronic data in the dedicated server and registration in the database

Visualization and analysis of data, supported by browsing software

Scientific discussion and decision making on the basis of internal analysis result

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab
Medium- and long-term Prospect

Tentative assumption and expectation

- e-data can be received and managed appropriately
- e-data can be utilized in the review
- without extension of review period, industries’ workload would decrease gradually

Present FY2015

FY2016
Setup e-data management and utilization

FY2018
Ordinary utilization of e-data in the product review

FY2019 - 2021
Starting earnest cross-product analysis

FY2019 - 2021
More predictable efficacy/safety
Consideration of expanding scope to toxicological study and post-approval clinical study

FY2022 - 2023
Establishment of disease model
Publication of disease-specific guidance
Publication of guidance to contribute to drug development

- e.g. guidance and disease models based on data on Asian population

First-class review authority

FY in Japan is from Apr to Mar in the next year
Summary

- The number of GCT including Japan is still increasing, and the type of GCT may be selected to optimize the development.
- Consideration of impacts of ethnic factors on drug efficacy/safety is the key to select efficient strategy for global drug development.
  - GCT
  - Asian GCT
  - Regional PI trial
- Further accumulation of review experiences and study data will lead to more efficient drug development.
Thank you very much for your attention!

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