Asia Town Hall:
Asia as a Drug R&D Center in the World

Updates of MRCT in Japan

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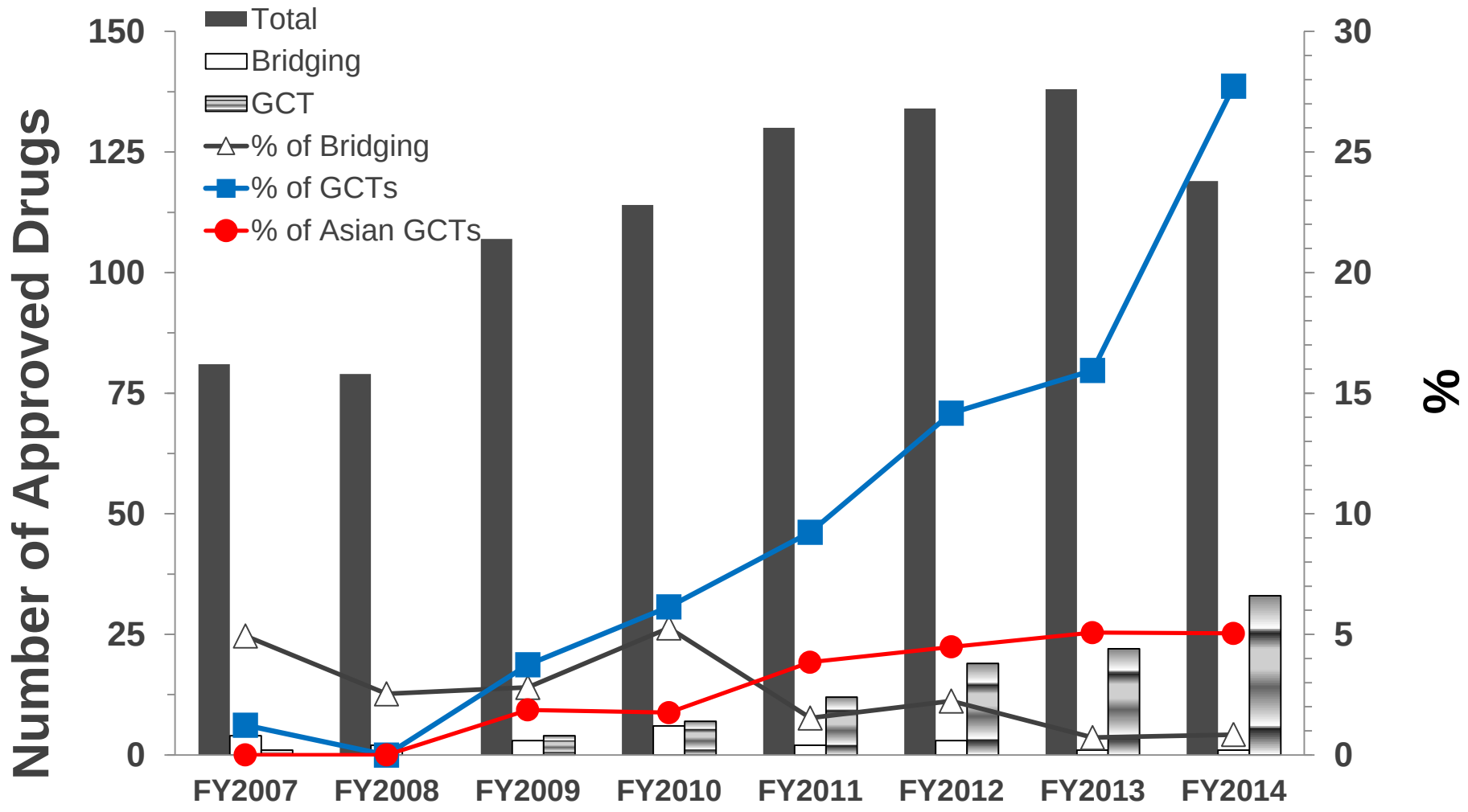
Disclaimer

- The views expressed in this presentation are those of the presenter and do not necessarily reflected the official views of the PMDA.

Outline

- Recent trend of MRCT in Japan
- Guidance documents “Basic principles”
- Future activities
- Summary

Trend of new drug application approvals in Japan



Preliminary results for FY2014

FY2007～FY2012：Asano,K *et al.*,*Clinical Pharmacology & Therapeutics,* 2013；94（2）：195–198.

DIA DEVELOP INNOVATE ADVANCE

Approved new drugs based on GCT in Japan

Guidance 2007 | Guidance 2012 | Guidance 2014

2006～2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015

2006～2009
- Tolterodine
- Losartan
- Trastuzumab
- Insulin-Glulisine
- Tadalafil

2010
- Peramivir
- Everolimus
- Panitumumab
- Travoprost/ Timolol
- Temsirolimus
- Laninamivir
- Nilotinib

2011
- Dabigatran
- Trastuzumab
- Pramipexole
- Edoxaban
- Dasatinib
- Indacaterol
- Linagliptin
- Gefitinib
- Everolimus

2012
- Denosumab
- Aripiprazole
- Olanzapine
- Exenatide
- Crizotinib
- Budesonide/ Formoterol
- Esomeprazole
- Formoterol
- Axitinib
- Budesonide/ Formoterol
- Atomoxetine
- Aflibercept
- Insulin-Degludec
- Glycopyrronium
- Pazopanib
- Everolimus
- Fesoterodine
- Apixaban
- Insulin-Degludec +Aspart

2013
- Paclitaxel
- Pregabalin
- Tofacitinib
- Regorafenib
- Ofatumumab
- Bevacizumab
- Pertuzumab
- Lixisenatide
- Ranibizumab
- Regorafenib
- Indacaterol/ Glycopyrronium
- Paliperidone
- Vilanterol/ Fluticasone
- Bevacizumab
- Aflibercept

2014
- Riociguat
- Tadalafil
- Afatinib
- Turoctocog alfa
- Ranibizumab
- Pazopanib
- Goserelin
- Everolimus
- Tolvaptan
- Favipiravir
- Tapentadol
- Tofogliflozin
- Alogliptin
- Sorafenib
- Anti-Inhibitor Coagulant Complex
- Efinaconazole
- Delamanid
- Umeclidinium/ Vilanterol
- Sirolimus
- Ruxolitinib
- Eftrenonacog alfa

2015
- Lamotrigine
- Aflibercept (PM)
- Edoxaban (AF)
- Edoxaban (VTE)
- Bosutinib
- Suvorexant
- Aflibercept (DME)
- Tiotropium
- Darbepoetin alfa
- Empagliflozin
- Elosulfase alfa
- Secukinumab
- Insulin glargine (BS1)
- Nonacog Gamma
- Efraloctocog alfa

- Riociguat
- Lenvatinib
- Eliglustat
- Gadobutrol
- Aripiprazole
- Umeclidinium
- Trifluridine/ Tipiracil
- Ramucirumab
- Catridecacog

Red : Asian GCTs

Guidance 2007
"Basic Principles on Global Clinical Trials"

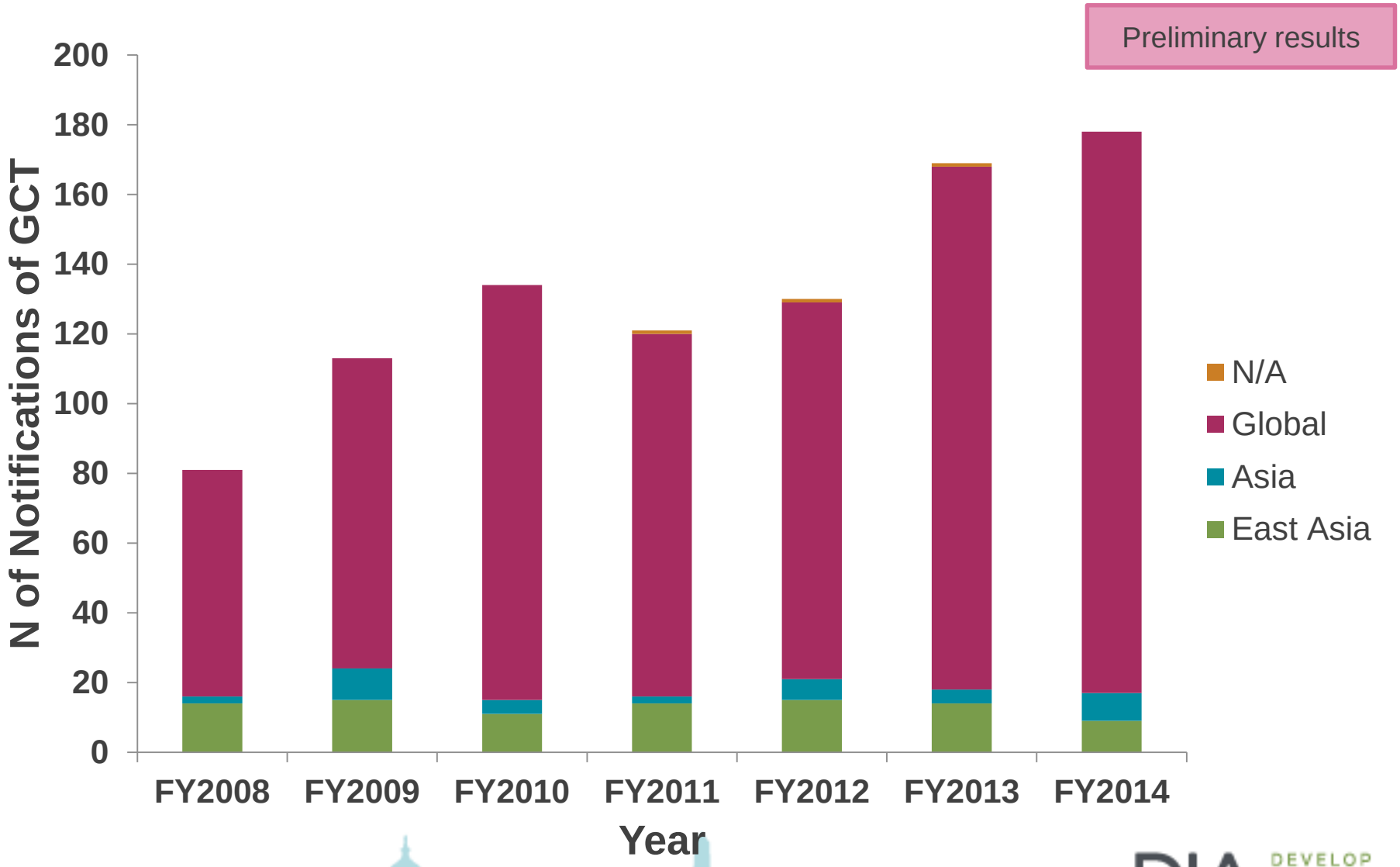
Guidance 2012
"Basic Principles on Global Clinical Trials –Reference Cases"

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

DIA DEVELOP INNOVATE ADVANCE

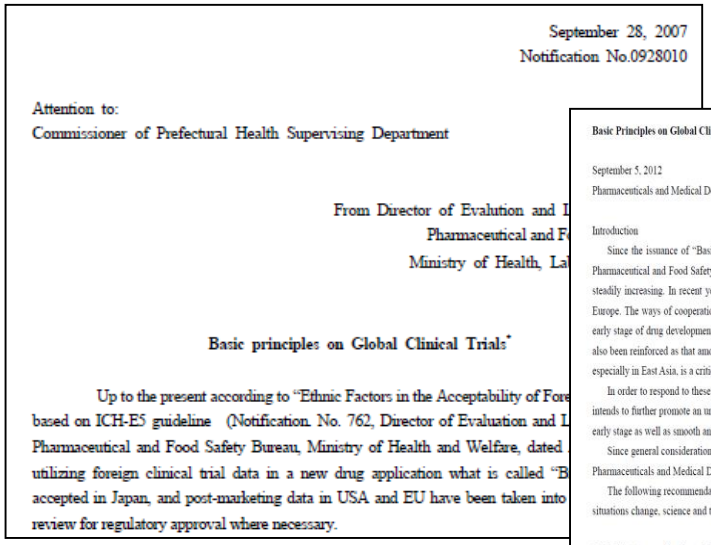
Trend of clinical trial notifications of GCTs



DIA DEVELOP INNOVATE ADVANCE

Guidelines in Japan -Basic Principles-

2007 Guideline



September 28, 2007
Notification No.0928010

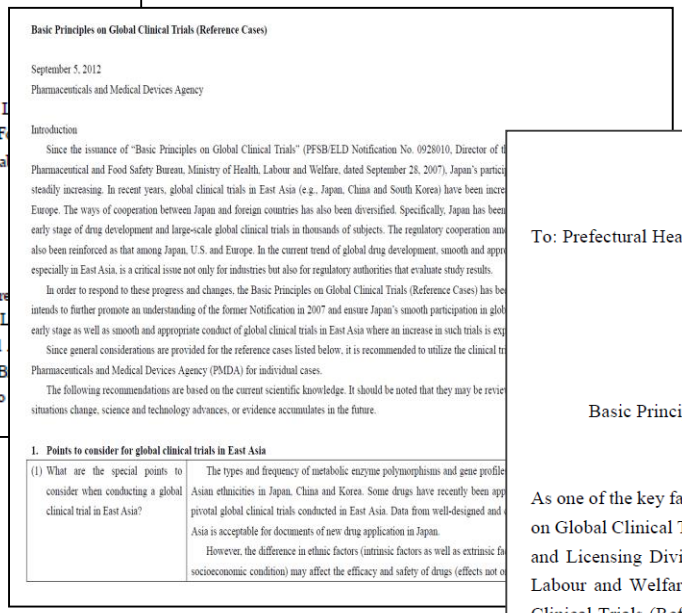
Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evalution and I
Pharmaceutical and F
Ministry of Health, La

Basic principles on Global Clinical Trials*

Up to the present according to "Ethnic Factors in the Acceptability of Fore
based on ICH-E5 guideline (Notification No. 762, Director of Evaluation and I
Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated
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 where necessary.

2012 Guideline



Basic Principles on Global Clinical Trials (Reference Cases)

September 5, 2012
Pharmaceuticals and Medical Devices Agency

Introduction

Since the issuance of "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, Director of t
Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007), Japan's partici
steadily increasing. In recent years, global clinical trials in East Asia (e.g., Japan, China and South Korea) have been incre
Europe. The ways of cooperation between Japan and foreign countries has also been diversified. Specifically, Japan has been
early stage of drug development and large-scale global clinical trials in thousands of subjects. The regulatory cooperation an
also been reinforced as that among Japan, U.S. and Europe. In the current trend of global drug development, smooth and appr
especially in East Asia, is a critical issue not only for industries but also for regulatory authorities that evaluate study results.

In order to respond to these progress and changes, the Basic Principles on Global Clinical Trials (Reference Cases) has be
intends to further promote an understanding of the former Notification in 2007 and ensure Japan's smooth participation in glob
early stage as well as smooth and appropriate conduct of global clinical trials in East Asia where an increase in such trials is ex

Since general considerations are provided for the reference cases listed below, it is recommended to utilize the clinical tr
Pharmaceuticals and Medical Devices Agency (PMDA) for individual cases.

The following recommendations are based on the current scientific knowledge. It should be noted that they may be revie
situations change, science and technology advances, or evidence accumulates in the future.

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

(1) What are the special points to consider when conducting a global clinical trial in East Asia?	The types and frequency of metabolic enzyme polymorphisms and gene profile Asian ethnicities in Japan, China and Korea. Some drugs have recently been app pivotal global clinical trials conducted in East Asia. Data from well-designed and Asia is acceptable for documents of new drug application in Japan. However, the difference in ethnic factors (intrinsic factors as well as extrinsic fa socioeconomic condition) may affect the efficacy and safety of drugs (effects not o

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

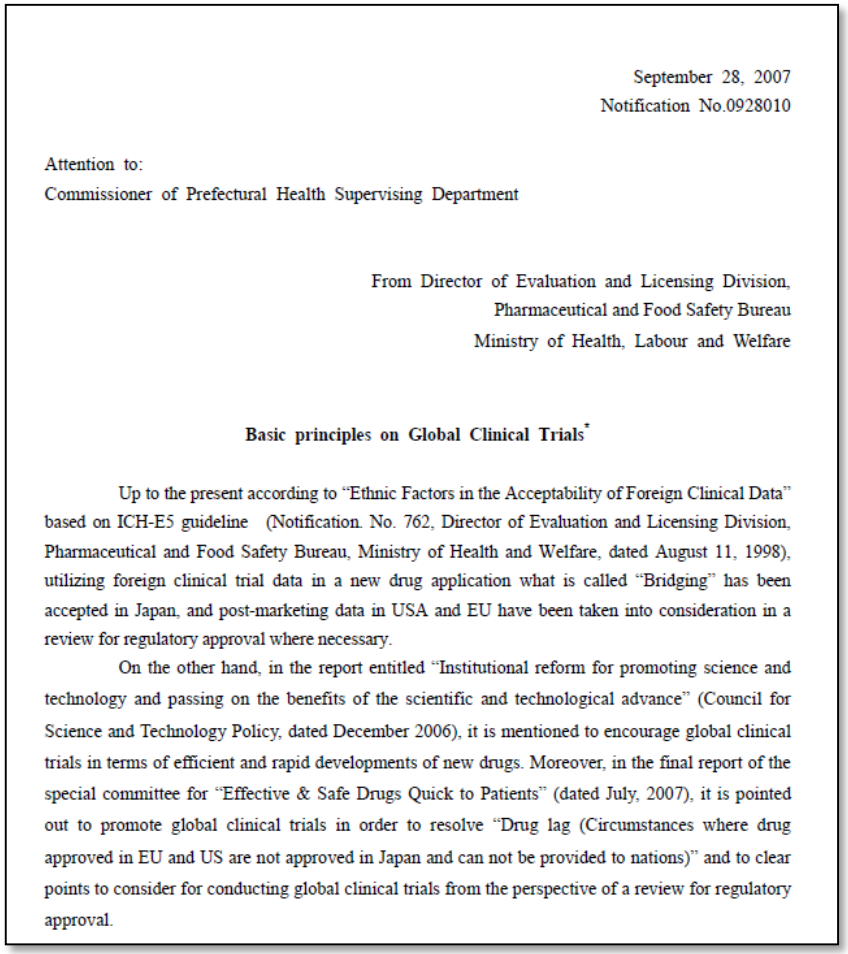
As one of the key factors toward timely patient access to new drugs, the "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) 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.

Japanese : http://www.pmda.go.jp/files/000157000.pdf
English : http://www.pmda.go.jp/files/000157900.pdf

Japanese : http://www.pmda.go.jp/files/000157901.pdf
English : http://www.pmda.go.jp/files/000157451.pdf

Japanese : http://www.pmda.go.jp/files/000157480.pdf
English : http://www.pmda.go.jp/files/000157777.pdf

“Basic Principles on Global Clinical Trials”



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.

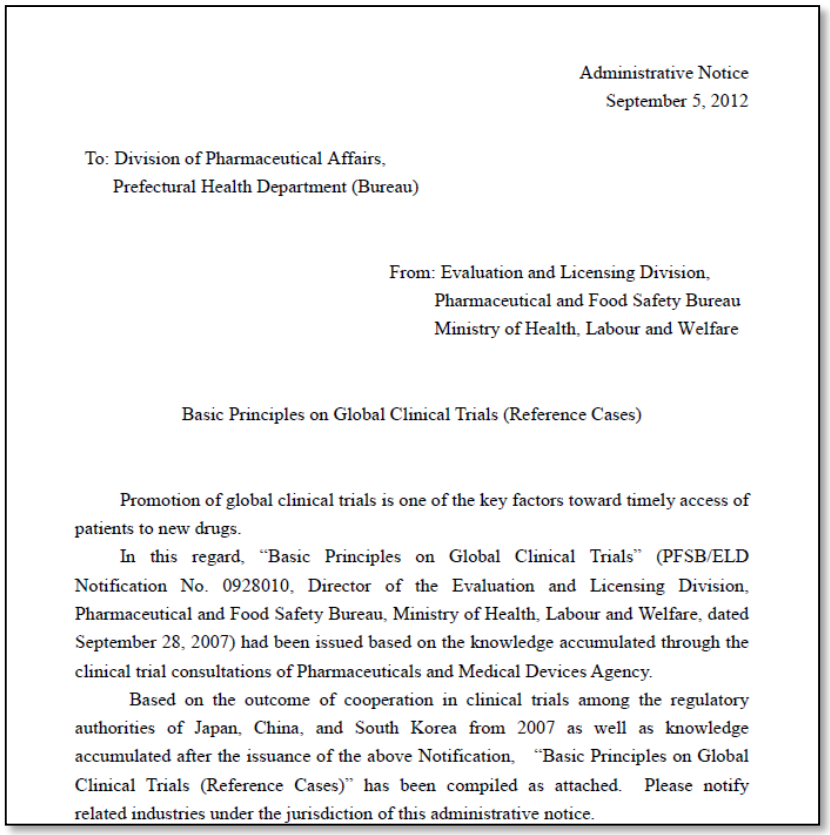
- Issued in 2007
- First guideline for GCT
- Outlined to promote GCT in order to resolve “Drug lag”
- Based on the experience in Clinical Trial Consultations

“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)”



Administrative Notice
September 5, 2012

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

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

Basic Principles on Global Clinical Trials (Reference Cases)

Promotion of global clinical trials is one of the key factors toward timely access of patients to new drugs.

In this regard, “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) had been issued based on the knowledge accumulated through the clinical trial consultations of Pharmaceuticals and Medical Devices Agency.

Based on the outcome of cooperation in clinical trials among the regulatory authorities of Japan, China, and South Korea from 2007 as well as knowledge accumulated after the issuance of the above Notification, “Basic Principles on Global Clinical Trials (Reference Cases)” has been compiled as attached. Please notify related industries under the jurisdiction of this administrative notice.

- 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

Special points to consider in East-Asian GCTs -1

- 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.

Special points to consider in East-Asian GCTs -2

- 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)

Special points to consider in East-Asian GCTs -3

- 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.

Special points to consider in East-Asian GCTs -4

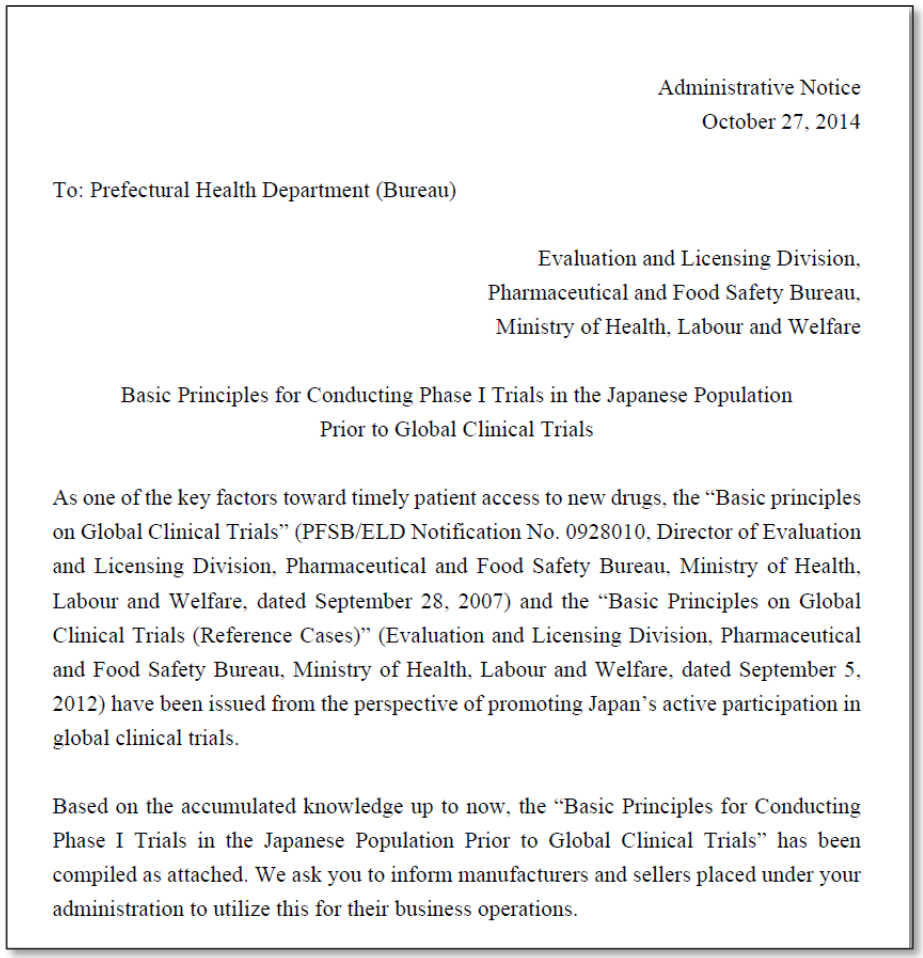
- Is it acceptable to conduct a bridging study as a GCT in East Asia and extrapolate the data from US/European studies to the Japanese population?

✓ 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.

Basic Principles for Conducting Phase I Trials in the Japanese Population



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.

- "Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials"
- Issued in 2014

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

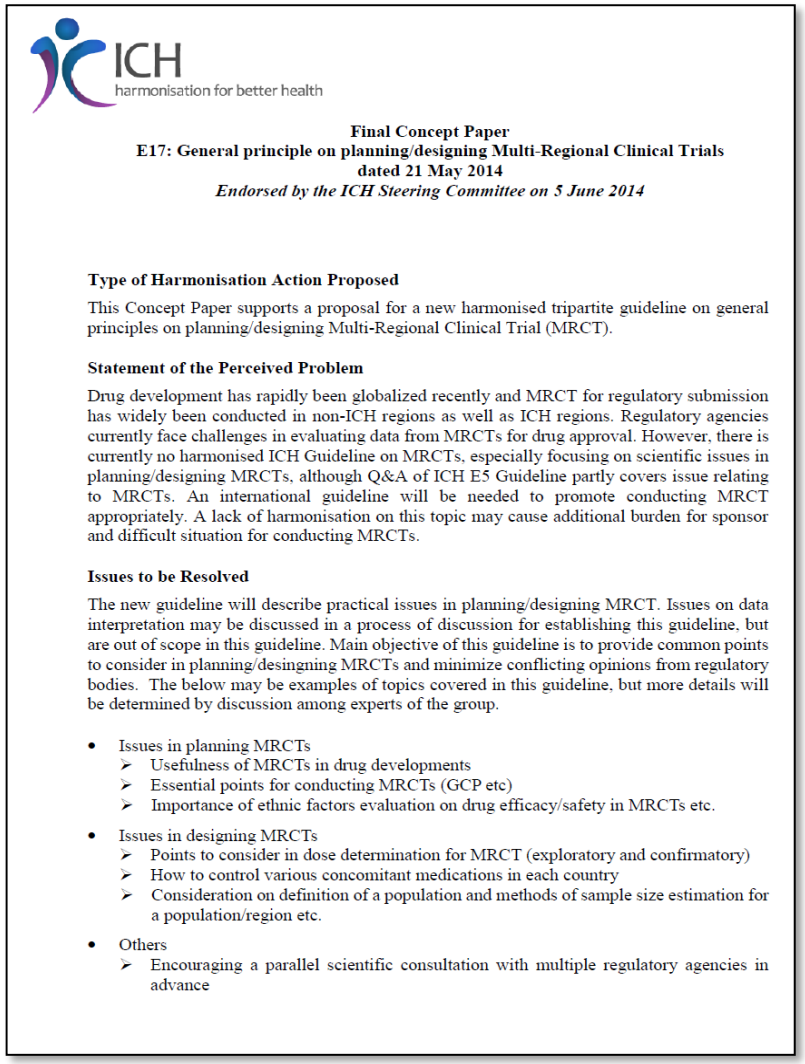
- Case 1
  - Serious safety concerns in early clinical trials conducted overseas.
  - No reliable data indicating that those risks in the Japanese population are equal to or less than those in foreign populations.

PI trials are required prior to GCT

- 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

PI trials may not be necessarily required prior to GCT .

ICH Guideline: E17 for MRCTs



ICH
harmonisation for better health

Final Concept Paper
E17: General principle on planning/designing Multi-Regional Clinical Trials
dated 21 May 2014
Endorsed by the ICH Steering Committee on 5 June 2014

Type of Harmonisation Action Proposed

This Concept Paper supports a proposal for a new harmonised tripartite guideline on general principles on planning/designing Multi-Regional Clinical Trial (MRCT).

Statement of the Perceived Problem

Drug development has rapidly been globalized recently and MRCT for regulatory submission has widely been conducted in non-ICH regions as well as ICH regions. Regulatory agencies currently face challenges in evaluating data from MRCTs for drug approval. However, there is currently no harmonised ICH Guideline on MRCTs, especially focusing on scientific issues in planning/designing MRCTs, although Q&A of ICH E5 Guideline partly covers issue relating to MRCTs. An international guideline will be needed to promote conducting MRCT appropriately. A lack of harmonisation on this topic may cause additional burden for sponsor and difficult situation for conducting MRCTs.

Issues to be Resolved

The new guideline will describe practical issues in planning/designing MRCT. Issues on data interpretation may be discussed in a process of discussion for establishing this guideline, but are out of scope in this guideline. Main objective of this guideline is to provide common points to consider in planning/desingning MRCTs and minimize conflicting opinions from regulatory bodies. The below may be examples of topics covered in this guideline, but more details will be determined by discussion among experts of the group.

- Issues in planning MRCTs
  - Usefulness of MRCTs in drug developments
  - Essential points for conducting MRCTs (GCP etc)
  - Importance of ethnic factors evaluation on drug efficacy/safety in MRCTs etc.
- Issues in designing MRCTs
  - Points to consider in dose determination for MRCT (exploratory and confirmatory)
  - How to control various concomitant medications in each country
  - Consideration on definition of a population and methods of sample size estimation for a population/region etc.
- Others
  - Encouraging a parallel scientific consultation with multiple regulatory agencies in advance

- 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.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E17/E17_Final_Concept_Paper_July_2014.pdf

Advanced Review with Electronic Data in PMDA

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

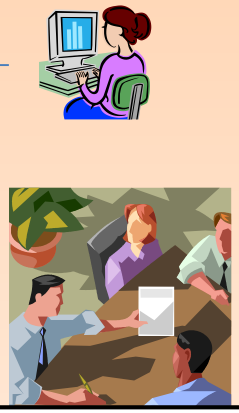
Storage of electronic data in the dedicated server and registration in the database

Visualization and analysis of data, supported by browsing software

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



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

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

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

Present
FY2015

- 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

FY2016

Setup e-data management and utilization

FY2018

Ordinary utilization of e-data in the product review

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

FY2019 - 2021

Starting earnest cross-product analysis

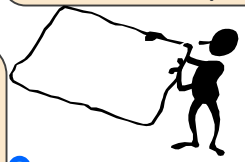
- Develop guidance and related documents
- Earnest cross-product analysis, development of disease models

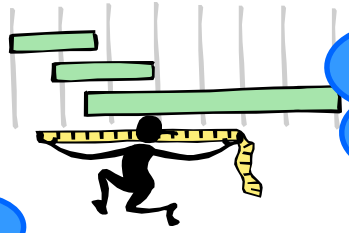
FY2022 - 2023

Publication of guidance to contribute to drug development

- Establishment of disease model
- Publication of disease-specific guidance

First-class review authority





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

Promotion of paperless offices

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

DIA DEVELOP INNOVATE ADVANCE

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!

Yuki Ando

Senior Scientist for Biostatistics

Pharmaceuticals and Medical Devices Agency (PMDA)

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