Japan’s Activities and Challenges to promote Multi Regional Clinical Trials

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Contents

- Action plan to promote clinical trials
- Activities to promote MRCT in consideration of ethnic factors
Regulatory Authorities in JAPAN

PMDA

Pharmaceuticals & Medical Devices Agency
- Scientific Review for Drugs & Medical Devices
- GCP, GMP Inspection
- Consultation on Clinical Trials etc.

MHLW

Pharmaceuticals and Food Safety Bureau, MHLW
- Final Authorization of applications
- Publishing Guidelines
- Advisory committee
- Supervising PMDA Activities
Number of IND Notifications

New GCP publication
ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

New GCP enforcement

3-Years Clinical Trial Activation Plan (prolonged 1 year)

First IND IND
IND

First IND

IND

800

500

400

300

250

200

150

100

50

0


(by MHLW)
New 5-Years Clinical Trial Activation Plan

Targets:

- Build nationwide infrastructure to perform innovative and valuable clinical research in a smooth manner
- Network core clinical research sites where research skills and resources are highly integrated

(1) Clinical Study Infrastructure Building
(2) Human Resource Development for Clinical Research
(3) Public Promotion of Clinical Trial and Encouraging Participation
(4) Efficient Clinical Research Management
Network of clinical research centers

Institutional reinforcement of staff and IT environment to support trials
Build site networking to accumulate subjects → cost down and speed-up

10 Core clinical research centers
Total 1,000M\$/year (approx. 10M$ / year)
- Train human resources in-house and in the institutions in the net work
- Strengthen IRB capacity
- Consolidate data management system
- Plan, Do, Assess clinical research

30 Major clinical trial institutions
Total 750M\$/year (approx. 7.5M$ / year)
- Secure Recruiting CRCs and other trial supporting staff
- Support promotion of common IT plat home

Expedite trial performance

Ensure timely access to new drug from clinical trial stage (satisfy unmet needs)
Promote innovation of new drug

Alliance with related trial sites and accumulate trial subjects

Infrastructure improvement
MCRC is a center to smoothly perform trials (MHLW)

CCRC is able to plan and manage multi-center trials (MHLW)

- Core Clinical Research Centre
- Major Clinical Research Centre
- TR Centers
- Local Trial Network (based on clinical trial promotion program)

TR center is to translate basic medical research to clinical trial (MEXT)
(2) Human Resource Development for Clinical Research

1. Training Programs (FY 2009)
   - CRC (basic, Advanced)
   - Local Data Manager
   - IRB member

2. e-Learning Systems for Clinical Researchers, CRC etc.

http://icrweb.jp/icr/  https://etrain.jmacct.med.or.jp/
(3) Public Promotion of Clinical Trial and Encouraging Participation - Japan Primary Registries Network (JPRN) -

Since Oct. 2007

Public

WHO-ICTRP

MHLW

- Promotion
- Regulation and guidance

National Institute of Public Health Search Portal Site

- Portal site management
- Promotion
- Coordination with 3 sites of clinical trial registry
- Coordination with WHO-ICTRP

UMIN Clinical Trial Registry

- System management
- Investigator initiated trials
- Promotion

http://www.umin.ac.jp/ctr/index-j.htm

JMA Centre for Clinical Trials

- Sponsor-investigator trials
- Promotion

https://dbcentre2.jmaacct.med.or.jp/ctrials/

JAPIC Trial Information System

- System management
- Company initiated trials
- Promotion

http://www.clinicaltrials.jp/user/cte_main.jsp

Investigator or company
(4) Efficient clinical research management

- Harmonize administrative document formats
- Streamline administrative work share between hospitals and sponsors
Contents

- Action plan to promote clinical trials
- Activities to promote MRCT in consideration of ethnic factors
Trends of MRCTs including Japan

- % of MRCTs in Clinical Trial Notifications -

![Graph showing trends of MRCTs in Japan](chart.png)
Increasing trend toward multi-centered trials

PMDA’s trial consultation basis

Number of consultations

Ratio of multi-centered trials (%)

Source: PMDA
Operational Regions of Global Clinical trials in FY2009

- **World-Wide**: 55.8%
- **Japan+ US/EU**: 15.0%
- **East-Asia Only**: 12.4%
- **Unknown**: 16.8%
Global Core Research Center for Clinical Trial

Goal: Reinforcement of clinical trial institution in Japan and promotion of simultaneous global development of innovative drugs

Started in 2009 with budget of ¥400 million

Functions to be provided:
- System for smoothly working out English contract and accounting based on international standards
- Central ethical review function
- International research planning/data analysis (Senior data managers and computer technicians can be secured)
- Setup as a domestic exploratory clinical research center (securing doctors, test technicians, radiologic technicians, etc.)
- Fostering of doctors to become international research support personnel and supply the personnel to the sites and bases
- To secure human resources for constructing systems and strategies for the management of intellectual property.
- Accumulation and organizational coordination of case information.

Network of core/basic medical facilities for activating clinical research/trials
How to extrapolate Foreign Data
- Suitable Doses can be different among regions -

For 32% of drugs, US/EU dose was \( \geq 2 \) times higher than Japanese dose

The purpose of ICH E5 Guideline

Ethnic Factors in the Acceptability of Foreign Clinical data

- To describe the characteristics of foreign clinical data that will facilitate their extrapolation to different populations and support their acceptance as a basis for registration of a medicine in a new region*.
- To describe regulatory strategies that minimize duplication of clinical data and facilitate acceptance of foreign clinical data in the new region.
- To describe the use of bridging studies*, when necessary, to allow extrapolation of foreign clinical data to a new region.
- To describe development strategies capable of characterizing ethnic factor influences on safety, efficacy, dosage and dose regimen.
Usual Bridging Strategy
- Shorten Drug Lag but still -

JAPAN

Phase I

II

III

Foreign Data

Phase I

II

III

Review

NDA Approval

Bridging Study

Compare PK/PD, Dose finding

Extrapolate

NDA Approval

“Drug Lag”

Shorten

1 2 3 4 5 6 7 8 9 year
Simultaneous Global Clinical Trial

If MRCT doesn’t consider ethnic factors such as intrinsic & extrinsic, -----

Applications will be submitted in Each Country at the same time and early

Not approved in some Countries without additional clinical data
Q.1 I am planning to develop my new drug globally. Does E5 provide guidance for this approach?

A. (extract)

The bridging study would allow extrapolation of an adequate data base to the new region. It would seem possible, and efficient, to assess potential regional differences as part of a global development program, i.e. for development of data to occur simultaneously in various regions, rather than sequentially. For example, if multi-regional trials had a sufficient number of trial subjects from the new region, it might be possible to analyze the impact of ethnic differences in those studied, to determine whether the entire data base is pertinent to the new region.
Concept of simultaneous drug development

Foreign

Phase I

Phase II
MRCT (Dose finding)

Japan

Phase I

Accessing whether Ethnic factors are significant/critical or not

Phase III

Phase III

Yes

No

Phase III

MRCT

Phase III

NDA

Yes
Guidance: Basic Principles On Global Clinical Trials: MHLW’s notification


- Providing basic principle for the design & conduct global clinical trials in 12 Q&As
  - Dose finding study in Japan is necessary?
  - How to determine a sample size & proportion of Japanese subjects
  - In case foreign evaluation index is not established in Japan
  - In case active control drugs are not approved in Japan
  - In case concomitant medications/therapies are not identical manner among regions

PMDA consultation for individual case
Collaboration in East-Asia

Background:
- In the era of globalization of Drug Development
- The necessity of evaluation on ethnic factors
- East Asian Situation
  - Ethnic Similarities in China/Korea/Japan East-Asia
    - Genetic similarities
    - Cultural similarities (e.g.; chopsticks countries)
  - Improvement of clinical trial environment in East-Asia
  - Emerging drug market in East-Asia

To develop better drugs through collecting clinical data efficiently in East-Asia, Regulatory collaboration is important
1 Activities of Japan
   - FY2008 Collecting available PK data of Chinese, Korean and Japan and review the data
   - FY2009–2010 Conducting **Prospective PK study Including Chinese, Korean and Japanese in order to compare ethnic difference more precisely**

2 Activities of Korea, China & Japan Tripartite Cooperation
   Collecting available data and discussing ethnic factors

3 Japanese Perspective
   To develop consideration for collecting East Asian clinical data in MRCT
Symposiums related to MRCT

1. Korea, China and Japan Tripartite Cooperation
   - East Asian Pharmaceutical Regulatory Symposium 2008
   - Japan-Korea-China Drug Clinical Trial Symposium 2009
   - Multi-Regional Clinical Trials Seoul Workshop, highlighting Korea, China and Japan Tripartite Symposium 2010

2. China-Japan Symposium; May 2010
   China-Japan Symposium on Global Clinical Trials and Ethnic Factors 2010

3. APEC-LSIF; 2009 & 2010
   Multi-Regional Clinical Trials Seoul Workshop

Continuous activities are necessary

Strategic Approach is helpful
APEC LSIF
(Life Science Innovation Forum)

Leaders Meeting

Ministerial Meeting

Senior Officials Meeting

Committee on Trade and Investment

LSIF

Regulatory Harmonization Steering Committee (RHSC)

Regulatory Member: Canada, China, Japan, Korea, Peru, Chinese Taipei, Thailand, USA
Goal:
Implementation of ICH E5 guideline and Promoting harmonization on Regulatory Procedures on MRCT in order to facilitate MRCT and acceptance of foreign clinical data for drug review.

Activities:
Economy Step-by-Step Implementation

Step 1: Assessment
Step 2: Training/workshop
Step 3: Assessment for training /workshop
Step 4: Training/workshop to reach the goal
Conclusions

It is important -

- To improve circumstances to conduct Clinical trial
- To design MRCT whose data can be utilized by regulatory authorities
- To promote international cooperation
Thank you

Homepages,

MHLW Homepage: http://www.mhlw.go.jp/english/index.html

PMDA Homepage: http://www.pmda.go.jp/english/index.html
ICH (International Conference of Harmonization)

JAPAN
MHLW/PMDA・JPMA

EU
EC/EMEA・EFPIA

USA
FDA・PhRMA

Observer: WHO, Health Canada, EFTA
Secretariat: IFPMA

Beyond ICH
1. Global Cooperation Group (GCG: 1999-)
2. Regulators Forum (2008. 6 - )
GCP activities under Regulators Forum

- **Background**
  - ICH-E6 (GCP) was identified as primary area of interest in the Regulators Forum
  - Discussion Group was established

- **Objectives**
  - Identify critical factors for a proper implementation of ICH-GCP
  - Propose a practical way to improve a proper implementation of ICH-GCP