Progress and Challenges to approve a drug based on data from global clinical trials: PMDA’s experience

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Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide. Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007.
APEC MRCT Road Map
-Gap Analysis-

• Target Economies:
  – Canada, Chinese Taipei, Indonesia, Japan, Malaysia, Mexico, Peru, Singapore, Korea, Thailand, and the United States
• Period : October 2013 ~ April 2014
• Methodology : Questionnaire by e-mail
• Responses received : 8 regions
• Collection rate : 72.7 % (8/11 regions)
Q: Please propose the number of CTs conducted in your country from 2010 to 2012 by phases and starting years. Please list the number by starting years. Among those CTs, how many MRCTs were included in each figure?
Q: Please propose the number of CTs conducted in your country from 2010 to 2012 by phases and starting years. Please list the number by starting years. Among those CTs, how many MRCTs were included in each figure?
Q: Please describe the annual number of new drugs approved in your country from 2010 to 2012.
Basic principles on Global Clinical Trials

Japanese version

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.

English version

Trend of new drug application approvals in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>MRCT</th>
<th>Bridging</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2007</td>
<td>81</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>FY2008</td>
<td>79</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>FY2009</td>
<td>107</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>FY2010</td>
<td>114</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>FY2011</td>
<td>130</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>FY2012</td>
<td>134</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>FY2013</td>
<td>133</td>
<td>21</td>
<td>1</td>
</tr>
</tbody>
</table>
Approved new drugs based on GCT in Japan

- Tolterodine
- Losartan
- Trastuzumab
- Insulin - Glulisine
- Tadalafil
- Peramivir
- Dabigatran
- Denosumab
- Insulin - Degludec
- Paclitaxel
- Nilotinib
- Pramipexole
- Olanzapine
- Aripiprazole
- Pregabalin
- Apixaban
- Everolimus
- Exenatide
- Everolimus
- Everolimus
- Gefitinib
- Crizotinib
- Gefitinib
- Formoterol
- Esomeprazole
- Insulin-Degludec+Aspart
- Gefitinib
- Formoterol
- Gefitinib
- Atomoxetine
- Afibercept
- Gefitinib
- Formoterol
- Gefitinib
- Atomoxetine
- Afibercept
- Gefitinib
- Formoterol
- Gefitinib
- Atomoxetine
- Afibercept

Red: Asian Clinical Trial
Guidance: “Basic Principles on Global Clinical Trials”
Guidance RC: “Basic Principles on Global Clinical Trials – Reference Cases”

- 59 applications were approved as of March 1, 2014
Riociguat: Example of GCT (1)

- New active ingredient indicated for the treatment of persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
- Soluble guanylate cyclase (sGC) stimulator
- Orphan drug
- Application date: Feb 2013 (US/EU)
  May 2013 (JP)

http://www.info.pmda.go.jp/shinyaku/P201300173/630004000_22600AMX00013000_A100_2.pdf
http://www.info.pmda.go.jp/shinyaku/P201300173/index.html
### PIII: Efficacy

#### Primary endpoint: 6MWD (m)

<table>
<thead>
<tr>
<th>Region</th>
<th>Drug</th>
<th>N</th>
<th>Change from baseline to last visit</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>All region</td>
<td>Riociguat</td>
<td>173</td>
<td>42.0 (-376, 335)</td>
<td>45.69 [24.74, 66.63]</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>88</td>
<td>5.0 (-389, 226)</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Riociguat</td>
<td>11</td>
<td>64.0 (-376, 217)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>5</td>
<td>14.0 (6, 85)</td>
<td></td>
</tr>
</tbody>
</table>

#### Secondary endpoint: PVR (dyn·sec·cm⁻⁵)

<table>
<thead>
<tr>
<th>Region</th>
<th>Drug</th>
<th>N</th>
<th>Change from baseline to last visit</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>All region</td>
<td>Riociguat</td>
<td>151</td>
<td>-175.94 (-1753.2, 511.0)</td>
<td>-246.43 [-303.33, -189.53]</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>82</td>
<td>14.89 (-679.6, 969.2)</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Riociguat</td>
<td>9</td>
<td>-159.16 (-291.5, 146.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>5</td>
<td>-14.18 (-125.6, 205.1)</td>
<td></td>
</tr>
</tbody>
</table>

Change from baseline: Median (Min, Max), Difference between groups: LS mean [95 CI]

a: Last observed value (not including follow-up) for subjects who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit or a measurement at that termination visit.

b: ANCOVA model with baseline value, treatment group, and region as fixed effects.
Tofacitinib: Example of GCT (2)

**Japan**

Ph2 (3921039 study)
- Placebo, 1mg, 3mg, 5mg, 10mg BID with MTX
- Duration: 12 weeks
- Endpoint: ACR20%
- N=317

Ph3 (3921044 study)
- Placebo, 5mg, 10mg BID with MTX
- Duration: DB 6 months, Open 18 months
- Endpoint: ACR20, structural damage, physical function
- N=797 (Japanese 118)

**US/EU**

Ph2 (3921025 study)
- Placebo, 1mg, 3mg, 5mg, 10mg, 15mg, 20mg BID with MTX
- Duration: 24 weeks
- Endpoint: ACR20%
- N=507

Tofacitinib: Example of GCT (2)
Dose response of tofacitinib

Modified Total Sharp Score (vs placebo)

FAS

Japanese

5mg N=277
10mg N=290
5mg N=44
10mg N=44

Average & 95%CI
Review experiences of GCT data

• **Ethnic factor consideration** is important even in Asian GCTs
• **Extrinsic** ethnic factors such as concomitant therapies sometimes have impacts on data evaluation
• **PPK** data are useful for ethnic factor consideration
• Confirming efficacy in overall population and **consistency evaluation** in Japanese sub-population
  – limitation in evaluating data when sample size of Japanese was so small
• Differences in **adverse event rate** are not uncommon; partly due to difference on categorization or data collection process of adverse events in GCTs
New Guidance (Sep 5th 2012):
Basic principles on Global Clinical Trials
(Reference Cases)

Future Drug Development
Regulatory and Scientific Issues Regarding Use of Foreign Data in Support of New Drug Applications in the United States: An FDA Perspective

NA Khin¹, P Yang², HMJ Hung³, K Maung-U³, Y-F Chen², A Meeker-O’Connell³, P Okwesili³, SU Yasuda¹, LK Ball⁴, S-M Huang⁵, RT O’Neill⁶ and R Temple⁴,⁷

Globalization of clinical research has led to an increase in clinical trials conducted outside of the United States that are submitted to the US Food and Drug Administration (FDA) in new drug applications. This article discusses the experience with these submissions in specific therapeutic areas, including the extent of this practice, differences between the effectiveness and safety outcomes of studies conducted inside and outside the United States, and the approach to acceptance of these trials.


Regulatory Challenges in the Review of Data from Global Clinical Trials: The PMDA Perspective

K Asano¹, A Tanaka¹, T Sato¹ and Y Uyama¹

Regulatory agencies face challenges in reviewing data from global clinical trials (GCTs) in the era of globalization of drug development. One major challenge is consideration of ethnic factors in evaluating GCT data so as to extrapolate foreign population data to one’s own national population. Here, we present the Pharmaceuticals and Medical Devices Agency (PMDA) perspective in reviewing GCT data in new drug applications (NDAs) and discuss future challenges for new drug approval.

Recent Trends and Success Factors in Reducing the Lag Time to Approval of New Drugs in Japan

PK Honig¹

For many years, approvals of new drugs in Japan have lagged behind those in the United States and Europe. As a result of simultaneous global development strategies, more widespread inclusion of Japan in multiregional clinical trials, and significant reforms and investment in Japan’s Pharmaceuticals and Medical Devices Agency reviewer capacity and capability, the drug lag appears to be diminishing. This is allowing new medicines to be approved sooner in Japan, improving the efficiency of drug development and benefiting patients.
GCTs can contribute to reducing the lag in drug development

• Simultaneous **global drug development** is a useful strategy to **provide a drug earlier** to Japanese patients

• But, we are facing **some challenges** in the future drug development
Challenges for better GCTs

• Effects of *ethnic factors* on drug efficacy/safety should be *more characterized*

• *Methods for planning/evaluation* should be established
  – Sample size calculation, consistency evaluation etc.

• *Regulatory harmonization*

Advancing regulatory science
PMDA GCT Project Team

- 12 members as a representative from various offices (New drug, Biologics, Conformity audit)
- Discuss various regulatory issues relating to GCTs
- Responsible for a guideline relating to GCTs
- Periodically hold meetings with industries for discussion

Promoting conduct of GCTs more appropriately for drug approval
PMDA’s New Initiative:
Advanced workflow of review/consultation

Analysis by PMDA
Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

Practical use of Innovative Medical Products
More rational & effective evaluation process for regulatory decision

NDA etc.
e-Submission of study data

Sophisticated review
- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis
- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - Disease model
  - Objective B/R assessment
  - Identifying AE-related factors etc.

Sophisticated Consultation
- More evidence-based consultation

More effective and high quality Review
- More predictable efficacy/safety after approval
- Reduction of applicant’s work load
- More scientific regulatory decision

More efficient and Successful Development
- Epoch-making proposal leading the world
- Proactive publication of guideline

Data Accumulation
Database
Possible Development Strategy

PK, Safety → POC → Exploratory, Dose-Finding → Confirmatory

US/EU → J/W GCT → J/W GCT → J/W GCT

Japan → Asian GCT → Asian GCT → Asian GCT

Other Asia → Asian GCT → Asian GCT → Asian GCT

West only → Early Japan/West Japan/West Asia Leading

Real West/Japan/Asia Asia

DIA 2014 50TH ANNUAL MEETING
PMDA’s proposal: New ICH guideline on MRCTs

Draft Concept Paper
General principle on planning/designing multi-regional clinical trials
Dated: May 21st 2014
Endorsed by the ICH SC on [day/Month/Year]

Type of Harmonization Action Proposed
This concept paper supports a proposal for a new harmonized tripartite guideline on general principles on planning/designing multi-regional clinical trial.

Statement of the Perceived Problem
Drug development has rapidly been globalized recently and multi-regional clinical trial (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 harmonized 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 harmonization 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/designing 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.

Business Plan
General principle on planning/designing multi-regional clinical trials
May 21, 2014

The proposal expected to tackle?
Drug development has rapidly been globalized recently and MRCTs for regulatory submission are widely being conducted in non-ICH regions as well as ICH regions. Regulatory agencies are currently facing challenges in evaluating data from MRCTs for drug approval. However, there is currently no harmonized 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 harmonization on this topic may cause additional burden for sponsor and difficult situation for conducting MRCTs.

Social/health and financial) to our stakeholders associated with the
requirements on data from MRCT are leading to duplication of
unnecessary clinical trials and delaying drug development, which result in inefficiency of drug development and a delay of drug approval.
Drugs from Asia to the world

Cooperation for better drug development
Information

• HOMEPAGE (English)

• Regulatory Science Page
  http://www.pmda.go.jp/regulatory/index.html

• E-mail:
  uyama-yoshiaki@pmda.go.jp

Thank you for your attention