Acceptance of Clinical Data - The Challenge of Generalizability -

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• Introduction
• Efficient process for simultaneous drug development
• Japan’s experience in the evaluation of multi-regional clinical trials
• Statistical consideration
• Ongoing and future tasks
• Summary
• Objectives
  – To avoid drug lag and enable rapid access to new drugs in many regions
  – To minimize duplication of clinical data in the development program
Simultaneous drug development

• Challenges
  – To plan the new drug development program so that the data package acceptable to all regions
  – To collect sufficient data for efficacy and safety for each region
  – To meet regulatory requirements in each region
Implementation of efficient development

• Importance of step-by-step development and building-up of evidence
  – Prior information, collected data, interpretation, and decision making for next step
  – Investigation of factors which affect the efficacy and safety of the drug from the beginning stage of its development
  – Collection of information on possible intrinsic and extrinsic ethnic factors
• Planning of data collection in major population at every stage based on the prior information
  – Possibility of the ethnic factors
  – Quantitative relationship among PK, PD and clinical efficacy and safety
Regional data in global development

- In Japanese new drug review, the information on efficacy and safety in Japanese subjects is considered important.
- Why are we interested in regional results in Japan?
  - There were many cases approved with different recommended dose compared to other regions.
  - In some cases, dose-response relationship shown in the bridging study was different from that in the corresponding study.
- These experiences and ideas are also useful in other East Asian regions.
Regional data in global development

• How should we handle the possibility of regional difference in global simultaneous drug development?
A model of global drug development

Investigate PK/PD and intrinsic ethnic factors among several regions
A model of global drug development

Investigate PK/PD, dose-response relationship, and possibility of conducting/participating multi-regional confirmatory trial(s) with same dose (range).
A model of global drug development

**Trial Phase**

<table>
<thead>
<tr>
<th>P1: PK(PD)</th>
<th>EU</th>
<th>US</th>
<th>Japan/Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="Circles" /></td>
<td><img src="image2" alt="Circles" /></td>
<td><img src="image3" alt="Circles" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P2: Dose-Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4" alt="Bar chart" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>P3: Efficacy confirmation</th>
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<tr>
<td><img src="image5" alt="Bar chart" /></td>
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Conduct confirmatory clinical trial(s) among regions where ethnic difference may not be a problem and the same dose (range) can be used.
A model of global drug development

- It is also important:
  - to develop meaningful endpoints/biomarkers for early phase investigation of consistency/differences
  - to check extrinsic ethnic factors in each stage
• Step-by-step consideration is important
  – To select the best way to have sufficient data for all regions under the possibility of regional differences
  – To avoid eventual duplication of clinical data based on the evidence

• Investigating East Asian data may be the key in confirming appropriate doses for Asian population and to establishing good foundation of global study including Asian regions.
Japan’s experience

- In Japan, we use foreign data based on the ICH E5 guidance document, its supplemental Q&A, and “Basic Principles on Global Clinical Trials” by MHLW
  - Conducting bridging study in Japan
  - Participating in multi-regional clinical trials (MRCTs)
- We have more than ten cases of approved new drug applications with multi-regional clinical trials as confirmatory trials
## Approved cases with MRCTs

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Indication</th>
<th>Approval</th>
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<tbody>
<tr>
<td>Tolterodine</td>
<td>Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency</td>
<td>Apr. 2006</td>
</tr>
<tr>
<td>Losartan</td>
<td>Diabetic nephropathy with proteinuria and hypertension in patients with type 2 diabetes</td>
<td>Apr. 2006</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Adjuvant therapy for HER2-positive breast cancer</td>
<td>Feb. 2008</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>Diabetes mellitus</td>
<td>Apr. 2009</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Pulmonary arterial hypertension</td>
<td>Oct. 2009</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Type A and Type B Influenza virus infection</td>
<td>Jan. 2010</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Metastatic renal cell carcinoma</td>
<td>Jan. 2010</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Metastatic colorectal carcinoma with wild-type KRAS tumors</td>
<td>Apr. 2010</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Advanced renal cell carcinoma</td>
<td>Jul. 2010</td>
</tr>
<tr>
<td>Laninamivir</td>
<td>Type A and Type B Influenza virus infection</td>
<td>Sep. 2010</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Newly diagnosed chronic myeloid leukemia in chronic phase</td>
<td>Nov. 2010</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Stroke and systemic embolism in patients with non-valvular atrial fibrillation</td>
<td>Jan. 2011</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER-2 positive metastatic gastric cancer</td>
<td>Feb. 2011</td>
</tr>
</tbody>
</table>
Evaluation of MRCTs

- Results of late stage MRCTs are evaluated basically according to the standard procedure.
  - Checking prior information
  - Checking subject characteristics
  - Evaluation of the results
    - Results of primary analysis
    - Results of secondary analyses
- However, the regional results and the factor “region” are focused on.
• Checking prior information
  – Information on the possibility of ethnic difference
    • Disease characteristics
    • Mechanism of the drug and information on similar drugs
  – Information from the early-phase clinical trials
    • PK/PD, dose-response
  – Relationship between the endpoints in each phase
• Checking subject characteristics
  – Distribution of factors
• Evaluation of the results for all subjects
  – Whether the primary objective was achieved
• Evaluation of subgroup analyses
  – By region = Evaluation of the results for Japanese subjects (in Japan) and the consistency of the results among regions
  – By other factors
• Comparison of results for Japanese subjects against results for all subjects
  – Sample size and variability of the results for the subgroup
  – Differences in patient characteristics
  – Possibility of regional differences
  – Implications of differences

Whether the results of the MRCT can be regarded as the evidence for Japanese population?
We need a statistical aspect to the evaluation of the study plan and the results of late-stage multi-regional clinical trials.

- Sample size estimation for one region
- Statistical analysis of the results of one region

Two methods for sample size estimation are mentioned in Japanese guidance as examples.

- However, there is no generally recommended statistical methods.
• Basically, late stage MRCTs are planned on the assumption that there are no major ethnic difference among the participating regions.

• The selection of the statistical methods may possibly depend on the plausibility of regional differences and sufficiency of the early clinical data.
Selection of analysis methods

- Analysis methods
  - A certain level of statistical test for the results of one region
  - (Comparison of point estimates of the results among regions)
  - Evaluation of the impact of the results of one region in the trial
  - Checking possible variability of the results of one region

- The methods for sample size estimation basically correspond to the analysis methods
• Model-based drug development
  – MBDD may be useful for planning efficient development program that takes the possibility of ethnic differences into consideration

• Interim analysis and adaptive design
  – Patient recruitment speed by regions and timing of interim analysis should be considered
Ongoing and future tasks

• China-Japan-Korea tripartite project
  – To investigate ethnic difference/similarity within East Asia
  – To make a solid foundation for the possibility of extrapolating data from one region to others in East Asia

• Recommendation of efficient global drug development in PMDA consultation meetings
  – To select efficient combination of regional and multi-regional data from early stage of the development
• For efficient global drug development,
  – It is important to collect sufficient data about ethnic sensitivity and evidence of the efficacy and safety of the drug.
  – There are many options for development strategy, such as multi-regional clinical trials, and it is important to choose one of them based on the accumulated data.
  – Step-by-step generalization of the data is reasonable.
  – East Asian collaboration may accelerate generalization of clinical data and lead to more efficient development.
Thank you for your attention!

• Acknowledgement
  – Dr. Yoshiaki Uyama

• Information
  – Email: ando-yuki@pmda.go.jp
  – PMDA Homepage (English)
    • http://www.pmda.go.jp/english/index.html
  – PMDA Drug Information (Japanese)
    • http://www.info.pmda.go.jp/