International cooperation and consideration on Multi Regional Clinical Trial among Asia

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• Trend of MRCT including in Japan
• Recent PMDA activities among Asia
  - China, Japan, Korea Tripartite cooperation
  - APEC Life Science Innovation Forum
  - PMDA seminar
• Guidance & Reference Cases for MRCT
Trend of MRCT including in Japan

![Graph showing the trend of MRCT in Japan from FY2007 to FY2011. The graph compares the numbers of all CTN and the percentage of MRCTs.](attachment:image.png)
Approved cases based on GCTs

- Tolterodine
- Losartan
- Trastuzumab
- Insulin - glulisine
- Tadalafil
- Peramivir
- Everolimus
- Panitumumab
- Travoprost/ Timolol
- Temsirolimus
- Laninamivir
- Nilotinib
- Dabigatran
- Trastuzumab
- Pramipexole
- Edoxaban
- Dasatinib
- Indacaterol
- Linagliptin
- Gefitinib
- Everolimus
- Denosumab
- Aripiprazole
- Olanzapine
- Exenatide
- Crizotinib
- Budesonide
- Formoterol
- Esomeprazole
- Formoterol
- Axitinib
- Budesonide
- Formoterol
- Atomoxetine
- Aflibercept
- Insulin - degludec
- Glycopyruronium
- Pazopanib

36 applications were approved as of Nov 1, 2012

Red: Asian GCT
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Collaboration in East-Asia

Background:
- In the era of globalization of Drug Development
- The necessity of evaluation on ethnic factors
- East Asian Advantage

- 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 among China/Korea/Japan is important
China/Korea/Japan Tripartite Cooperation

Health Ministers’ Joint Statement among China, Korea & Japan (April 8, 2007)

April 2008 Tokyo
Dec. 2009 Beijing
Sep. 2010 Seoul
Nov. 2011 Tokyo
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 Members: Canada, China, Japan, Korea, Peru, Chinese Taipei, Thailand, US

Aims for regulatory convergence involving the 21 member economies
## Priority Work Areas

<table>
<thead>
<tr>
<th>Project</th>
<th>Champion</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-regional Clinical Trials</td>
<td>Japan</td>
<td>Roadmap approved. Workshop held in Seoul and Tokyo</td>
</tr>
<tr>
<td>Supply chain integrity</td>
<td>US</td>
<td>Established the expert working group</td>
</tr>
<tr>
<td>Good Review Practices</td>
<td>Chinese Taipei</td>
<td>Roadmap approved. Workshop will be held in November</td>
</tr>
<tr>
<td>Good Clinical Practices</td>
<td>Thailand</td>
<td>Preparing questionnaire to compare the member economies’ status of implementation</td>
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<tr>
<td>Combination Products</td>
<td>Chinese Taipei</td>
<td>Roadmap approved. Workshop will be held in November</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>Korea</td>
<td>Workshop held in April. Discuss definition of terms</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>Korea</td>
<td>Roadmap approved. Discussion focused on pharmaceuticals</td>
</tr>
<tr>
<td>Advanced Therapies</td>
<td>Singapore</td>
<td>Roadmap approved</td>
</tr>
</tbody>
</table>
Roadmap to promote MRCT

Goal: To facilitate MRCTs and acceptance of MRCT results for drug review by regulatory authorities in APEC region

Overview:
- Evaluate current practices relative to international best practices
- Establish common understanding regarding the following key issues and other issues within APEC region under the auspices of LSIF.
  [Key Issues]
  - Implementation of ICH E5 guideline
  - Study design of MRCT
  - Operational/Regulatory procedure to facilitate MRCT efficiently
  - Cooperative regulatory approach to facilitate MRCTs on diseases prevalent in sub-regions of APEC.
- Implement training for those involved in MRCT
- Develop necessary items for Training/Workshop to promote MRCT
  - APEC economies share best practices
  - MRCTWS as well as each economy considers developing training curricula
- Issue recommendation on regulatory harmonization regarding MRCT
- RHSC will support the activities and development of recommendation for next step.
PMDA Training Seminar

2010 November – December
PMDA’s role in regulation, and Scientific review process on new drug applications biological applications

35 trainees participated from Indonesia, Singapore, China, Taiwan, Korea and Nigeria

2011 December
Pharmaceutical GMP inspection

27 trainees participated from Indonesia, Korea, India, ....
3rd PMDA Training Seminar

2013 January 21-25
Post-Marketing Safety & Relief Services

18 trainees:
Korea
Taiwan
Indonesia
Singapore
Brazil
Ukraine

http://www.pmda.go.jp/english/events/3rd_pmda_training_seminar.html
Release of information regarding approval review of new drugs

- “Review Reports” that describe the details and results of reviews are released on PMDA’s website.
- as well as “Summaries of Product Application” that summarize submitted data by pharmaceutical companies.

Some review reports are translated into English.

on the Medical Product Information page of PMDA website
- Information Related to Drugs
  http://www.info.pmda.go.jp/info/syounin_index.html
- Information regarding the application review of new drugs (listed deliberation products basis)
  http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html
- Information regarding the application review of new drugs (listed in the order of the Brand Name (Applicant Company)
  http://www.info.pmda.go.jp/shinyaku/shinyaku_hanbaimei_index.html
- the release of re-examination reports of new drugs
  http://www.info.pmda.go.jp/saishinsa/saishinsa_hanbaimei_list.htm
The following English translations of review reports are intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese originals and the translations, the former shall prevail. PMDA shall not be responsible for any consequence resulting from use of the English versions.

The review reports were selected for translation among those of drugs with a new active ingredient that recently received marketing approval, in consideration of relevant factors including the novelty and priority.

<table>
<thead>
<tr>
<th>Name</th>
<th>Active Ingredient</th>
<th>Approved In</th>
<th>PDF EN</th>
<th>PDF JP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actemra</td>
<td>tocilizumab (genetical recombination)</td>
<td>Apr. 2008</td>
<td><img src="https://www.pmda.go.jp/english/service/drugs.html" alt="PDF" /></td>
<td><img src="https://www.pmda.go.jp/english/service/drugs.html" alt="PDF" /></td>
</tr>
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<td>Adsorbed Influenza Vaccine (H5N1) &quot;HOKKEN&quot;</td>
<td>adsorbed influenza vaccine (H5N1)</td>
<td>Oct. 2007</td>
<td><img src="https://www.pmda.go.jp/english/service/drugs.html" alt="PDF" /></td>
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<tr>
<td>Adsorbed Influenza Vaccine (H5N1) &quot;BIKEN&quot;</td>
<td>adsorbed influenza vaccine (H5N1)</td>
<td>Oct. 2007</td>
<td><img src="https://www.pmda.go.jp/english/service/drugs.html" alt="PDF" /></td>
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<tr>
<td>Avastin</td>
<td>bevacizumab (genetical recombination)</td>
<td>Apr. 2007</td>
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<tr>
<td>Clozaril</td>
<td>clozapine</td>
<td>Apr. 2009</td>
<td><img src="https://www.pmda.go.jp/english/service/drugs.html" alt="PDF" /></td>
<td><img src="https://www.pmda.go.jp/english/service/drugs.html" alt="PDF" /></td>
</tr>
<tr>
<td>Diquas</td>
<td>diquafosol sodium</td>
<td>Apr. 2010</td>
<td><img src="https://www.pmda.go.jp/english/service/drugs.html" alt="PDF" /></td>
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“Basic Principles on Global Clinical Trials” issued on Sep 28, 2007.

- To encourage Japan’s participation to GCTs from an early stage of drug development
- To provide points to be considered in GCTs
- To promote conducting GCTs more appropriately in consideration of ethnic factors
- Based on accumulated experiences mainly in PMDA consultation meetings
• There were few approved cases when previous guidance document was issued.
  – General cases were assumed.
    • Ex. Example of a few hundred subjects of study in the explanation of sample size of Japanese population
  – Points to be considered for evaluating the results of GCT were not provided.

• Number of conduct of Asian trials have been increased and East Asian contribution has been recognized.
“Basic Principles on Global Clinical Trials (Reference Cases)” was issued on Sep 5, 2012.

- Based on recently accumulated scientific data and our experiences in consultation meetings and new drug review.
- Reflect the outcome of cooperation in clinical trials among the regulatory authorities of Japan, China, and Korea

• Purpose of “Reference cases”
  – To promote further understanding of the former “Basic Principles” issued in 2007
  – To ensure Japan’s smooth participation in global drug development activities from an early stage
  – To ensure smooth and appropriate conduct of global clinical trials in East Asia

• 17 Q&As
  – 4 points to consider for global clinical trials in East Asia
  – 13 general points to consider on global clinical trials
1. Special points to consider for global clinical trial in East Asia
2. Recommended therapeutic areas
3. Global drug development strategy plan based on data of interethnic comparison of pharmacokinetic profiles
4. Points to consider for East Asian clinical trial as a bridging study
Special points to consider for global clinical trial in East Asia

• Data from well-designed and conducted global clinical trials in East Asia is acceptable for documents of new drug application in Japan.

• Global clinical trials conducted in East Asia need to be designed and conducted based on prior sufficient evaluation of the effect of ethnic difference on the efficacy and safety of drugs.

• Further accumulation and review of scientific data and information on East Asian populations will deepen our understanding of ethnic differences and ensure a smooth and appropriate conduct of global clinical trials in this region.

• It is encouraged to consider to include global clinical trials to be conducted in East Asia as part of drug development plan and accumulate information.
A global clinical trial in East Asia can be performed for any target disease area.

For diseases with high morbidity in East Asia (e.g., gastric cancer and hepatitis) of which conduct of confirmatory studies in Japan alone are difficult, proactive planning of a global clinical trial in East Asia may contribute to the improvement of the efficiency and quality of clinical development of a drug.

When planning global clinical development including East Asia and other regions such as the U.S. and Europe, the role of a clinical trial to be conducted in East Asia in the entire development plan should be defined in advance, and the activities in East Asia should be carried out in cooperation with those in the U.S. and Europe.
Global drug development strategy plan based on data of interethnic comparison of pharmacokinetic profiles

- There is no general rule for a drug development strategy since it should be determined based on a variety of factors.
- If a drug development strategy aimed at regulatory approval in Japan is discussed based on pharmacokinetic (PK) differences of a drug among populations, comparison of the PK profile between Japanese and Caucasian or between Japanese and other East Asian populations will provide useful information.
- Whether to conduct a confirmatory trial as a global clinical trial 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 thoroughly evaluated by data from stratified analyses, etc. Prior to the confirmatory study, the appropriateness of setting and evaluating the treatment outcome in the overall study population as the primary endpoint needs to be explained.
Points to consider for East Asian clinical trial as a bridging study

- A bridging study generally intends to extrapolate foreign data to the Japanese population and is conducted in Japanese subjects.
- To extrapolate US/European study data by conducting a global clinical trial in East Asia as a bridging study, 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.
- Furthermore, the consistency of the results between the Japanese and non-Japanese populations should be confirmed in such bridging study before the evaluation based on the bridging concept. For individual cases, it is recommended to consult with PMDA in advance.
Thank you!

- **Review Report**
  [http://www.pmda.go.jp/english/service/review.html](http://www.pmda.go.jp/english/service/review.html)
- **Japanese Pharmacopoeia**
  [http://www.std.pmda.go.jp/jpPUB/index_e.html](http://www.std.pmda.go.jp/jpPUB/index_e.html)