Model informed drug development: Japanese regulatory perspectives

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Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.
Outline

• Reviews and consultations in Japan
• Review experiences of clinical pharmacology (CP) data in global drug development
  • Guidance to promote global drug development
  • Recent trends of global clinical trials (GCTs) and CP data (PPK approach, PKPD/E-R): survey on approved NMEs in Japan
  • Recent review experiences of CP data in GCTs (Asian trials)
• Future perspectives
  • Advanced review with electronic data
• Summary
Outline

• Reviews and consultations in Japan
• Review experiences of clinical pharmacology (CP) data in global drug development
  • Guidance to promote global drug development
  • Recent trends of global clinical trials (GCTs) and CP data (PPK approach, PKPD/E-R): survey on approved NMEs in Japan
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• Future perspectives
• Advanced review with electronic data
• Summary
Guidance to promote global drug development in Japan

ICH guideline
• E5: Ethnic Factors in the Acceptability of Foreign Clinical Data.

Japanese guidance document
• Basic principles on Global Clinical Trials (2007 Sept)
  • Basic requirements to conduct a Global Clinical Trial (GCT)
  • Importance of PK study prior to a GCT
  • Importance of global dose-finding study
  • Basic points to consider in designing a GCT
  • Sample size and proportion of Japanese subjects

• Basic principles on Global Clinical Trials – Reference Cases (2012)
• Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials (2014)
Impacts of global drug development on regulatory approval in Japan: literatures published by PMDA


Basic scheme on global clinical trials including Japanese population

Correlation in PK-efficacy?
- Yes

Global PK study

Adjustable differences (including a case to show PK similarity, and correlation of PD and clinically relevant PD)

PK comparisons: Japanese vs non-Japanese

D-E-R comparison

Unadjustable differences

Global Dose-Finding study

Adjustable differences (including a case of parallel shift of dose-response relationship)

Global confirmatory study
Dose finding/selecion/adjustments
Clinical pharmacology review points

• Study design for identifying the dose
  MRCTs/Asian regional clinical trials/Bridging strategy

• Specific Populations and medical practices in Japan
  Elderly population/Pediatric population/Asian population/Patients
  with impaired liver or renal function/Concomitant drugs etc.

• Dose-Exposure-Response (D-E-R) information
  utilization of D-E-R analysis and discussion on effectiveness and
  safety issues, labeling decisions, PMS and/or further development

• Utilization of analytical approaches and tools
  Population PK approach, PKPD/E-R analysis, PBPK analysis
  Modeling and Simulation
Recent trends of global clinical trials in Japan

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</thead>
<tbody>
<tr>
<td>Number of Notifications of GCTs</td>
<td>82</td>
<td>113</td>
<td>134</td>
<td>121</td>
<td>130 (556)</td>
<td>169 (601)</td>
<td>178 (601)</td>
</tr>
<tr>
<td>Number of consultations on GCTs for NMEs</td>
<td>51</td>
<td>56</td>
<td>66</td>
<td>73</td>
<td>64</td>
<td>59</td>
<td>67</td>
</tr>
</tbody>
</table>

J-FY: the financial year in Japan, NMEs: new molecular entities
In J-FY 2014, of 601 clinical trial notifications submitted, 178 were for GCTs, and 67 consultations were GCTs for NMEs.
https://www.pmda.go.jp/english/about-pmda/annual-reports/0001.html
Trends of GCTs on approval reviews in Japan: NMEs approved between 2012 and 2014

Number of approved drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Total NDAs</th>
<th>NMEs</th>
<th>GCT</th>
<th>GCT/NME (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>150</td>
<td>50</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>2013</td>
<td>140</td>
<td>40</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>2014</td>
<td>130</td>
<td>30</td>
<td>15</td>
<td>50</td>
</tr>
</tbody>
</table>

Therapeutic Area (Category):

- Oncology
- Respiratory/anti-allergy/inflammatory
- Hormone/Metabolic disorders

NMEs (J-FY2012-2014) from top to bottom,
Others, Oncology, Respiratory/anti-allergy/inflammatory, urogenital system, Anti-bacterial/viral/fungal, Hormone/metabolic disorders, Central & peripheral nervous/anesthetic drugs, Cardio-renal,
Trends of PPK approach
NMEs approved between 2001 and 2011

Number of approved drugs

- PPK (JPN)
- PPK
- NME
- PPK/NME

10~15%
20~30%
40~60%

Trends of PPK approach
NMEs approved between 2001 and 2011

Number of approved drugs
percentage

J-FY


ACoP 6 Oct.6,2015
Trends of PPK approach and PKPD/E-R analysis
NMEs approved between 2012 and 2014

Number of approved drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>NMEs</th>
<th>PPK</th>
<th>PKPD</th>
<th>PPK/NME</th>
<th>PPK(JP)</th>
<th>PPK(JP)/NME</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>2013</td>
<td>55</td>
<td>45</td>
<td>35</td>
<td>25</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>2014</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

percentage

<table>
<thead>
<tr>
<th>Year</th>
<th>NMEs</th>
<th>PPK</th>
<th>PKPD</th>
<th>PPK/NME</th>
<th>PPK(JP)</th>
<th>PPK(JP)/NME</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
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<td>2013</td>
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<tr>
<td>2014</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Therapeutic Area (category)
from top to bottom,
Others, Oncology, Respiratory/anti-allergy/inflammatory, urogenital system, anti-HIV, Anti-bacterial/viral/fungal, Hormone/metabolic disorders, Central & peripheral nervous/anesthetic drugs, Cardio-renal, Gastrointestinal
Summary: recent trends of GCTs and CP data in Japanese NDAs

• Number of notifications/consultations on GCTs including Japanese patients has been increasing.

• Number of NDAs (NMEs) with GCTs has been increasing
  • Of total NMEs: about 25% → 30% → 35% (from J-FY 2012 to 2014)
  • Development strategy: MRCTs/Asian regional trials/bridging studies
  • Development phase: not only phase 3 but also early clinical phase
  • Therapeutic Area: variety, top3 category (oncology > respiratory/allergy/inflammatory > hormone/metabolic disorders)

• Number of NDAs (NMEs) with PPK approach, PKPD/E-R analysis and M&S has been increasing.
  • Of total NMEs: PPK approach, more than 50% (after J-FY 2010) PKPD/E-R analysis, about 40% (J-FY 2012-2014)
  • Therapeutic Area: variety, top3 category for both PPK and PKPD/E-R (oncology > hormone/metabolic disorders > antibacterial/antiviral/antifungal)
  • In J-FY2014, almost all NDAs for approved NMEs with PPK approach provided PPK information in Japanese population

ACoP 6 Oct.6, 2015
Evaluation of Asian regional clinical trial/clinical pharmacology data in NMEs approval in Japan-1/3

<table>
<thead>
<tr>
<th>NMEs (approval year)</th>
<th>Indication</th>
<th>Development strategy</th>
<th>CP data (PPK, PKPD/E-R, M&amp;S) on approval review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine tartrate (2006)</td>
<td>urinary urgency, urinary frequency and urge urinary incontinence associated with overactive bladder</td>
<td>Bridging Japan &amp; Korea (III) Japan, Korea &amp; US/EU(I)</td>
<td>1 and 3 (evaluated by STS approach)</td>
</tr>
<tr>
<td>Insulin glulisine * (2009)</td>
<td>diabetes mellitus where insulin therapy is indicated.</td>
<td>Type 1: Bridging Type 2: Global(Asian) Japan &amp; Korea (III) Japan &amp; Korea, Japan &amp; US/EU(I)</td>
<td>1 and 3 (evaluated by STS approach)</td>
</tr>
<tr>
<td>Peramivir hydrate (2010)</td>
<td>Influenza A or B virus infections</td>
<td>Global(Asian) Japan, Korea &amp; Taiwan (III)</td>
<td>1,2 (patients with renal impairment), 3 (within east Asia) and 4(PK Section)</td>
</tr>
</tbody>
</table>

* genetical recombination

STS: standard two stage

http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html
https://www.pmda.go.jp/english/search_index.html

1: Supporting dosing regimen for labeling, 2: Supporting dose adjustment for special population, 3: Consideration of PK and PD variabilities, including ethnic difference/similarity, 4: providing information in drug label
Evaluation of Asian regional clinical trial/clinical pharmacology data in NMEs approval in Japan-2/3

<table>
<thead>
<tr>
<th>NMEs (approval year)</th>
<th>Indication</th>
<th>Development strategy Asian trial (phase)</th>
<th>CP data (PPK, PKPD/E-R, M&amp;S) on approval review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laninamivir octanoatehydrate (2010)</td>
<td>Influenza A or B virus infections</td>
<td>Global(Asian) Japan, Korea, Taiwan &amp; Hong Kong (III)</td>
<td>1,2(patients with renal impairment, pediatrics) and 3 (within east Asia)</td>
</tr>
<tr>
<td>Edoxaban tosilate hydrate (2011)</td>
<td>prevention of venous thromboembolism in patients undergoing orthopedic surgery of lower limbs including total knee arthroplasty, total hip arthroplasty and hip fracture surgery.</td>
<td>Global(Asian) Japan &amp; Taiwan (IIb) Japan &amp; Taiwan (III)</td>
<td>1,2 (patients with renal impairment) and 3 (Japanese vs Chinese)</td>
</tr>
<tr>
<td>Indacaterol maleate (2011)</td>
<td>alleviation of various symptoms due to airway obstructive impairment in chronic obstructive pulmonary diseases (chronic bronchitis and emphysema).</td>
<td>Global(Asian) Japan, Korea, Taiwan, India, Hong Kong &amp; Singapore (III)</td>
<td>1,2 (elderly patients) and 3 (US/EU vs Asia, Japanese vs non-Japanese )</td>
</tr>
<tr>
<td>Fesoterodine fumarate (2012)</td>
<td>urinary urgency, urinary frequency and urge urinary incontinence associated with overactive bladder</td>
<td>Bridging Japan, Korea, Taiwan &amp; Hong Kong (II)</td>
<td>1,2 (patients with renal/liver impairment) and 3 (Japanese vs non-Japanese, within east Asia)</td>
</tr>
</tbody>
</table>

http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html
https://www.pmda.go.jp/english/search_index.html

1: Supporting dosing regimen for labeling, 2: Supporting dose adjustment for special population, 3: Consideration of PK and PD variabilities, including ethnic difference/similarity, 4: Providing information in drug label
Evalulation of Asian regional clinical trial/clinical pharmacology data in NMEs approval in Japan-3/3

<table>
<thead>
<tr>
<th>NMEs (approval year)</th>
<th>Indication</th>
<th>Development strategy</th>
<th>CP data (PPK, PKPD/E-R, M&amp;S) on approval review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin degludec * (2012)</td>
<td>diabetes mellitus in cases where insulin therapy is indicated</td>
<td>Type 1: Global (MRCT) Type 2: Global(Asian) Japan, Korea, Taiwan, Thailand, Hong Kong &amp; Malaysia (III)</td>
<td>1 and 3 (Japanese vs non-Japanese, within east Asia)</td>
</tr>
<tr>
<td>Ofatumumab* (2012)</td>
<td>relapsed or refractory CD20-positive chronic lymphocytic leukemia.[Orphan drug]</td>
<td>Global Japan &amp; Korea (I/II)</td>
<td>1 and 3 (Japanese vs non-Japanese)</td>
</tr>
<tr>
<td>Tapentadol hydrochloride (2013)</td>
<td>moderate to severe pain in various types of cancer</td>
<td>Global (Asian) Japan &amp; Korea (I and III)</td>
<td>3 (mainly evaluated by STS approach)</td>
</tr>
<tr>
<td>Paliperidone palmitate (2013)</td>
<td>schizophrenia</td>
<td>Global (Asian) Japan, Korea &amp; Taiwan (MD-PK study and III)</td>
<td>1(dosing regimen), 2(patients with renal impairment), 3(within east Asia) and 4(PK Section)</td>
</tr>
</tbody>
</table>

* genetical recombination

http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html
https://www.pmda.go.jp/english/search_index.html

1: Supporting dosing regimen for labeling, 2: Supporting dose adjustment for special population, 3: Consideration of PK and PD variabilities, including ethnic difference/similarity, 4: Providing information in drug label
Summary: recent review experiences
Asian regional clinical trials/Clinical Pharmacology Data

• Review experiences of GCTs including Asian regional clinical trials have rapidly been increasing since 2009.

• Oncology is the therapeutic area where GCTs is most actively conducted for new drug development.

• Asian regional clinical trials tended to be planned and conducted in the specific therapeutic areas/indications,
  • Influenza A or B virus infections
  • Diabetes mellitus (Type 2)
  • Some anti-neoplastic drugs, nervous system drugs

• CP data obtained in Asian regional clinical trials, especially PPK, PKPD/E-R and M&S has also been increasing and actively discussed in recent approval reviews in Japan.
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  • Guidance to promote global drug development
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• Summary
Health and Medical Care Strategy
(Agreement of Chief Cabinet Secretary, Minister of Health, Labour and Welfare and other concerned Ministers; June 14, 2013)

Three Basic Principles

- Achievement of a healthy, long-lived society
- Contribution to economic growth
- Global contribution

Enhancing the PMDA

- Enhancement of the Pharmaceutical Affairs Consultation on R&D Strategy
- Organizing and enhancing the consultation service in close coordination with the Drug Discovery Support Network
- **PMDA-initiated promotion of research and analysis based on clinical study data**
- Increase of the quantity and quality of the large-scale medical information database for early achievement of the 10-million data set
- Identification of an appropriate financial base for the PMDA’s tasks and necessary measures
  * Including more proactive proposals than those made for the Japan Reconstruction Strategy and matters not discussed therein.
Accumulation and utilization of data

**NDA submission**

- Submission of electronic data from clinical and nonclinical studies

**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

**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

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

Visualization and analysis of data, supported by browsing software

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

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab.

What the review authority can do with the information of all products.
## Timeline for implementation of electronic study data submission

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Guidance and related documents</td>
<td></td>
<td></td>
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<tr>
<td>Release of related information</td>
<td></td>
<td>![△] Issuance of “Notification on the consultation for the clinical e-data submission”</td>
<td>![△] 3.5 years of Transitional period</td>
</tr>
<tr>
<td>Review</td>
<td>2014 1&lt;sup&gt;st&lt;/sup&gt; Pilot</td>
<td>![△] 2014 2&lt;sup&gt;nd&lt;/sup&gt; Pilot</td>
<td>![△] 2015 Pilot</td>
</tr>
<tr>
<td>Consultation for e-study data submission</td>
<td>![△] Pilot</td>
<td>![△] New Consultation framework</td>
<td>![△] Initiation of e-study data submission</td>
</tr>
<tr>
<td>System Development</td>
<td>![△] System Development</td>
<td>![△] Pilot for data submission</td>
<td>![△] Today</td>
</tr>
</tbody>
</table>

**Notes:**
- ACoP 6 Oct.6,2015
- The timeline includes key milestones such as issuance of documents, pilot implementations, and system development phases.
- The 3.5 years transitional period is indicated for the final phase of implementation.
Notifications and guide released for industry

- **The most recent notification and guide provide practical procedures and technical information** regarding submissions of e-study data for new drug applications.

<table>
<thead>
<tr>
<th>Notifications/Guide</th>
<th>Release Date</th>
<th>Issuer</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Principles on Electronic Submission of Study Data for New Drug Applications</td>
<td>June 20, 2014</td>
<td>Ministry of Health, Labour and Welfare</td>
<td>• The first official announcement that MHLW/PMDA will require electronic study data in NDA.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Both of Japanese and English versions are available on PMDA website</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• States the start date of e-study data submission for NDA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Subject to updates based on the accumulated experience and/or the revisions of the data standards</td>
</tr>
</tbody>
</table>

* An English version is under preparation.
“Technical Notification”: major contents

“Technical Notification on the e-study data submission” mainly covers the following contents;

1. Handling of clinical study data subject to e-study data submission
2. Format and method of e-study data submission
3. Electronic datasets to be submitted
4. Process of consultations concerning e-study data
5. Initiation timing of submissions of e-study data and transitional period
“Technical Notification”: handling of clinical study data subject to e-study data submission -1/3

The scope of documents subject to e-study data submission:

• Evaluation data that provide the major basis for the efficacy, safety, dose and administration (i.e. results of phase II and III studies in most cases, including long-term studies)

• The following studies in phase I studies and clinical pharmacology studies
  • Phase I studies of oncology drugs
  • Phase I studies that have been conducted on both Japanese and non-Japanese subjects
  • QT/QTc studies based on ICH E14 guideline
“Technical Notification”: handling of clinical study data subject to e-study data submission -2/3

Documents from the following studies or analyses are also subject to e-study data submission if PMDA deems necessary.

<table>
<thead>
<tr>
<th>Study or Analysis</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard two stage analysis</strong></td>
<td>• Phase I and phase II studies of antibacterial drugs, where the results of pharmacokinetics or pharmacokinetics/pharmacodynamics provide a major evidence for the dosage and administration</td>
</tr>
<tr>
<td></td>
<td>• Clinical pharmacology studies that provide a major evidence for dosage and administration or dose adjustment in pediatric, elderly, and hepatic/renal disorder patients</td>
</tr>
<tr>
<td><strong>Population analysis (including simulations)</strong></td>
<td>• Population analysis that investigated the similarity in pharmacokinetics or pharmacokinetics/pharmacodynamics between Japanese and non-Japanese subjects in a development using global and bridging studies</td>
</tr>
<tr>
<td></td>
<td>• Population analysis that provides a major evidence for dosage and administration</td>
</tr>
<tr>
<td><strong>Physiologically-based pharmacokinetic model analysis</strong></td>
<td>• Physiologically-based pharmacokinetic model analysis that provides a major evidence for dose adjustment because of drug interaction and basis for dosage and administration or dose adjustment in pediatric, elderly, and hepatic/renal disorder patients</td>
</tr>
</tbody>
</table>
### Types and Submission Formats of Documents Subject to Electronic Submission

<table>
<thead>
<tr>
<th>Section in notification of the Basic Principles</th>
<th>Content</th>
<th>Individual clinical study data</th>
<th>Analysis dataset Concerning efficacy and safety analysis</th>
<th>Analysis dataset Concerning PK or PK/PD analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. (2) a</td>
<td>Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dosage and administration</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>For study results from phase I studies and clinical pharmacology studies, results from studies listed right are required to be electronically submitted.</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM (In principle, ADaM, but other formats may be acceptable in certain cases)</td>
</tr>
<tr>
<td></td>
<td>Phase I studies of oncology drugs</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
<tr>
<td></td>
<td>Phase I studies that have been conducted in both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies)</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
<tr>
<td></td>
<td>QT/QTc studies based on ICH E14 guideline</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) Note</td>
<td>Phase I and clinical pharmacology studies other than a and b, which were deemed necessary by PMDA</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM is preferable, but other formats are acceptable</td>
</tr>
<tr>
<td></td>
<td>Clinical studies where standard pharmacokinetic analysis was performed</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
<tr>
<td></td>
<td>Population analysis</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Physiologically-based pharmacokinetic model analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. (2)</td>
<td>References other than a and b, which were deemed necessary by PMDA</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM (If necessary, consult beforehand)</td>
</tr>
<tr>
<td>2. (2)</td>
<td>Integrated summary of safety and efficacy (ISS/ISE)</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM (In principle, submission of the analysis dataset by ADaM is required, but if the SDTM dataset had been used for analysis, submission of SDTM study data is acceptable)</td>
</tr>
</tbody>
</table>
Development of related guidelines in Japan

The Working Group has been discussing on M&S related issues since October, 2014

• Population Pharmacokinetics
  • Updating existing document and establishing best practices/guidance in population analysis
  • Guidance publication in J-FY2015 (tentative schedule)

• D-E-R Relationships and Modeling
  • New guidance development
  • Drug development strategy and clinical study plan for pediatric patients

• Cross-Product Analysis
  • Discussion on the therapeutic areas
  • General considerations
Pilot projects for utilization of electronic data

- Step-by-step implementation of pilot projects
  - Confirmation of feasibility
  - Consideration of data utilization in the review process
  - Pilot intended for actual new drug review

<table>
<thead>
<tr>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>11</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>FY2013 Pilot</td>
<td>FY2014 1st Pilot</td>
<td>FY2014 2nd Pilot</td>
<td>FY2015 Pilot</td>
</tr>
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</table>

Pilot projects of Pharmacometrics (PPK, PPK-PD and E-R analysis etc.)
**Overview of the pilot projects**

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<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Feasibility</td>
<td>Feasibility &amp; utilization</td>
<td>Utilization of study data</td>
<td>Utilization of study data for actual</td>
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<td></td>
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<td>of study data in review</td>
<td>in review process</td>
<td>review</td>
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<td>process</td>
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<tr>
<td><strong>Target studies</strong></td>
<td>5 drugs</td>
<td>CDISC: 4 drugs</td>
<td>CDISC: 3 drugs</td>
<td>CDISC: 13 drugs</td>
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<td></td>
<td></td>
<td>CP: 3 PPK datasets</td>
<td>CP: 3 PPK/PD datasets</td>
<td>CP: Standard Two-Stage</td>
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<td>Approach: 4 datasets</td>
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<td>Population Approach: 7 datasets</td>
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<td>(As of May 29, 2015)</td>
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<tr>
<td><strong>Persons in charge</strong></td>
<td>Around 80 reviewers</td>
<td>Around 180 reviewers</td>
<td>Around 190 reviewers</td>
<td>Around 190 reviewers + 20 from</td>
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<td></td>
<td>+ 20 from promotion group</td>
<td>+ 20 from promotion group</td>
<td>+ 20 from promotion group</td>
<td>promotion group (tentative)</td>
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<tr>
<td><strong>Details</strong></td>
<td>- All the reviewers try</td>
<td>- All the reviewers try</td>
<td>- Some reviewers</td>
<td>- Pilot project which is almost</td>
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<td></td>
<td>to reproduce the several</td>
<td>to replicate the main</td>
<td>including biostatisticians</td>
<td>parallel with actual new drug</td>
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<td>analysis results in CTD</td>
<td>analysis results in CTD</td>
<td>in each review team are</td>
<td>review</td>
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<td>assigned mainly handle</td>
<td>- The pilot project will NOT affect</td>
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<td>the data analysis</td>
<td>the actual regulatory review of the</td>
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<td>Team meetings for the</td>
<td>drug</td>
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<td>discussion on the review</td>
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<td>process with data analysis</td>
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<td>- Team meetings for the</td>
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<td>discussion on the</td>
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<td>necessary analyses for</td>
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<td>the review and the</td>
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<td>review process with data</td>
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<td>analysis</td>
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Now in Progress
Prospect of e-study data utilization in Japan

Prospect As of Oct, 2015 (Subject to Change)

**J-FY2015**
Setup e-data management and utilization

**Present**
Promotion of paperless operation

**J-FY2016**
Ordinary utilization of e-data in the product review

**J-FY2018**
• More predictable efficacy/safety
• Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study

**J-FY2019 - 2021**
• Preparations of guidelines and related documents
• Earnest on cross-product analysis and development of disease models

**J-FY2022**
• Establishment of disease models
• Publication of disease-specific guidelines

First-class review authority

**Transitional period are taken until March 31st, 2020**

• e-study data can be received and managed appropriately
• e-study data can be utilized in the review
• Industries’ workload is reduced gradually while keeping the same review period

Prospect As of Oct, 2015 (Subject to Change)

Start e-study data submission for NDA* from Oct 1st, 2016

*NDA=New Drug Application

ACoP 6 Oct.6,2015

**e.g. guidelines and disease models based on data on Asian population**

ACoP 6 Oct.6,2015

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Summary

• Regulatory experiences and current status on GCTs including Asian trials and CP data (PPK, PKPD/E-R) are presented.

• PMDA/MHLW have continuously been updating regulatory guideline, “Basic principles on Global Clinical Trials” to promote efficient drug development in Japan.

• Advanced Review/consultation with Electronic Data Project is being executed successfully so far.
  • Publication of the Basic Principles, Technical Notification, and Technical Guide
  • Experiences of the step by step pilot projects
  • Active discussion with industry and academia

• We will proceed our project to promptly reach future goal, such as high quality reviews/consultations as well as implementation of cross product analysis to develop disease models/new guidelines based on data on Asian population.

• We believe effective utilizations of submitted electronic data and PMx approach lead to efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.
Thank you for your attention!

PMDA Homepage

PMDA Advanced Review with Electronic Data Promotion Group
E-mail: jisedaiPT@pmda.go.jp
http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html