Role of Pharmacometrics in Drug Development and Regulatory Review: PMDA 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

- Introduction
- Guidelines and review experiences
- Future perspectives
- Summary
Introduction

• Model informed approaches and global clinical trials are expected to improve drug development.

• Various approaches are utilized.
  • Multi-regional clinical trials/Asian clinical trials
  • Population analysis
  • Physiologically based pharmacokinetic model analysis
  • Modeling and simulation
  • Adaptive design etc.

• Global utilization/sharing of clinical data based on understanding of ethnic difference/similarity and appropriate application of new methodology will contribute to more efficient drug development and more scientific decision-making.
Outline

• Introduction
• Guidelines and review experiences
• Future perspectives
• Summary
Relevant guidelines and documents

MHLW (Ministry of Health, Labour and Welfare)

ICH guidelines
- E4 (Dose – Response), E5 (Ethnic factors), E7 (Geriatrics), E11 (Pediatrics), M4 (CTD)
- E15 and 16 (Pharmacogenomics, Biomarkers)
6.2.2 Population Pharmacokinetic Approach

- This approach is considered suitable for special population such as the elderly and children.
- Representative values of pharmacokinetic parameters of population, factors that affect pharmacokinetics, the degree of the effects and inter- and intra-individual variability can be obtained from a population analysis that is appropriately planned and implemented.
Guideline on Population Pharmacokinetics and Pharmacodynamics (Draft)

Table of Contents

1. Introduction
2. Study procedures
3. Model application
4. Reporting and providing information
5. Related guidelines and regulatory documents
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)
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)
  - Global confirmatory study
    - 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)
Dose finding/selection/adjustment
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
Trends of Population PK analysis
NMEs approved between 2001 and 2011

Number of approved drugs

percentage

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

J-FY

PMDA-Keio joint symposium  Dec.8,2015
Trends of Population PK 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>PKPD</th>
<th>PPK</th>
<th>PPK(JP)</th>
<th>PPK(JP)/NME</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>50</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2013</td>
<td>45</td>
<td>35</td>
<td>25</td>
<td>15</td>
<td>7.5</td>
</tr>
<tr>
<td>2014</td>
<td>60</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

Percentage

PPK

- Oncology
- Metabolic disorders
- Hormone
- Respiratory

PKPD

- Anti-bacterial/viral/fungal
- Metabolic disorders
- Respiratory
- Others

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

J-FY PMDA-Keio joint symposium Dec.8,2015
Trends of GCTs on approval reviews in Japan: NMEs approved between 2012 and 2014

Number of approved drugs

![Bar chart showing the number of approved drugs by therapeutic area from 2012 to 2014.]

Therapeutic Area (Category)

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,
# Review experiences in PMDA

<table>
<thead>
<tr>
<th>NDAs (approval year)</th>
<th>Indication</th>
<th>Development program (phase, region)</th>
<th>Pop PK, PKPD/E-R, PBPK and M&amp;S evaluation on approval reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peramivir hydrate (2010)</td>
<td>Influenza A or B virus infections</td>
<td>MRCTs (phase 3: Japan, Korea and Taiwan) Pediatrics</td>
<td>1,2 (patients with renal impairment, pediatrics) 3 (within east Asia) and 4 (Precaution, PK Section)</td>
</tr>
<tr>
<td>Voriconazole (2014)</td>
<td>Fungal infections (serious, intolerant or refractory)</td>
<td>Local (phase 2: Japan) pediatrics, additional dosage form (oral suspension)</td>
<td>1,2 (pediatrics, patients with renal impairment) 3 (CYP2D6 phenotype, non-linear PK) and 4 (PK Section)</td>
</tr>
<tr>
<td>Paliperidone palmitate (2013)</td>
<td>Schizophrenia</td>
<td>MRCTs (phase 3, MD-PK study: Japan, Korea and Taiwan)</td>
<td>1 (dosing regimen), 2 (patients with renal impairment), 3 (within east Asia) and 4 (PK Section)</td>
</tr>
<tr>
<td>Panobinostat Lactate (2015)</td>
<td>Multiple myeloma</td>
<td>MRCTs (phase 3: 34 countries/regions including Japan)</td>
<td>1,2 (drug interactions), 3 and 4 (PK Section)</td>
</tr>
</tbody>
</table>

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

1: Supporting dose and administration in approval labels, 2: Supporting dose adjustment for special population, 3: Consideration of PK or PD variability, including ethnic difference/similarity, 4: Providing information in drug labels
Peramivir hydrate: Plasma concentrations in Asian trial
Measured and population mean values by Population PK and M&S


PMDA-Keio joint symposium Dec.8,2015
Dose for pediatric phase 3 study was determined by M&S, based on adult PK data.
AUC or Cmax in pediatric patients after IV administration of 10mg/kg are within the ranges of adult patients, by bayesian estimation(open circle) and predicted values(solid line) based on population mean and body weight.

Peramivir hydrate: Special population (patients with renal impairment)

Dosage recommendation for adult patients with renal impairment was determined, based on the results of
• Clinical pharmacology study with renal impaired patients
• PPK analysis of pooled data of phase 1 and 2 trials, and M&S

Drug Label: Dosage and Administration Precaution Section

Renal function and recommended dose

<table>
<thead>
<tr>
<th>Ccr (mL/min)</th>
<th>Single Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For adult patients</td>
</tr>
<tr>
<td>50 ≤ Ccr</td>
<td>300mg</td>
</tr>
<tr>
<td>30 ≤ Ccr &lt; 50</td>
<td>100mg</td>
</tr>
<tr>
<td>10 ≤ Ccr &lt; 30</td>
<td>50mg</td>
</tr>
</tbody>
</table>

Drug Label: PK Section

Plasma concentration in patients with severe/moderate/mild/normal renal function

Discussion on dose selection/adjustment based on evaluation of clinical pharmacology data

1. Dose selection (Clinical development and approval dose in Japan)

2. Ethnic differences (PK comparison between Japanese and non-Japanese)

3. Scaling PK/PD from adults to children
# Voriconazole: Dose selection
(Clinical development and approval dose in Japan)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>IV loading dose</th>
<th>IV maintenance dose</th>
<th>PO maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 2 yr ≤ Age &lt; 12 yr</td>
<td>9 mg/kg</td>
<td>8 mg/kg</td>
<td>9 mg/kg</td>
</tr>
<tr>
<td>Adolescents 12 yr ≤ Age &lt; 15 yr</td>
<td>6 mg/kg</td>
<td>4 mg/kg</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Adolescents 12 yr ≤ Age &lt; 15 yr</td>
<td></td>
<td></td>
<td>200 mg</td>
</tr>
<tr>
<td>Adults 15 yr ≤</td>
<td>6 mg/kg</td>
<td>4 mg/kg</td>
<td>3 mg/kg</td>
</tr>
</tbody>
</table>

http://www.info.pmda.go.jp/shinyaku/P201400130/671450000_21700AMY00171_A100_1.pdf
Voriconazole: PK comparisons
(Japanese and European, adults and children, CYP2C19 phenotype)
Paliperidone palmitate plasma concentrations predicted by Pop PK analysis and simulation

**Dosage and Administration**

150mg im of Week 0, 100mg im of Week 1 and 75mg im of each 4 Week.

**Dosage and Administration Precaution Section**

Dosing interval/timing and precaution

**PK Section**

Predicted plasma concentrations after 150mg im of Week 0, 100mg im of Week 3, 75mg im of Week 5 and 75mg im of each 4 Week.

**Week 0**

- **Plasma concentration (ng/mL)**
  - Upper limit of 90% prediction interval for steady state Cmax
  - Median
  - Lower limit of 90% prediction interval for steady state Cmin

**Week 1**

- 150mg im of Week 0, 100mg im of Week 1 and 75mg im of each 4 Week.

**Week 5**

- 100mg im of Week 3, 75mg im of Week 5 and 75mg im of each 4 Week.
### Drug Label: Drug Interaction Section

**Precaution**

| 藥剤名等   | 臨床症状 | 本剤の血中濃度が低下するおそれがあるため、併用を避けることが望ましい。
|------------|---------|-------------------------------------------------------------|
| 強いCYP3A阻害剤 | 本剤の薬効が著しく低下するおそれがあるため、併用を避けることがある。
| リファンビシン | これらの薬剤のCYP3A阻害作用により、本剤の代謝が促進される。【薬物動態】の項参照 |
| カルバマゼピン | 本剤の血中濃度が上昇するおそれがあるので、併用する場合には、患者の状態を注意深く観察すること。
| フェニトイン | 本剤によるCYP2D6阻害作用により、これらの薬剤の代謝が阻害される。【薬物動態】の項参照 |

### PK Section: drug interactions

**Strong CYP3A Inhibitors**

| 藥剤名等       | 臨床症例 | 本剤の血中濃度が低下するおそれがあるため、併用を避けることが望ましい。
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>アゾール系抗真菌剤（イトラコナゾール、ポリコナゾール、ケトコナゾール※等）</td>
<td>これらの薬剤のCYP3A阻害作用により、本剤の代謝が促進される。【薬物動態】の項参照</td>
<td></td>
</tr>
</tbody>
</table>

**Strong CYP3A inducers**

| 藥剤名等       | 臨床症例 | 本剤の血中濃度が上昇するおそれがあるので、併用する場合には、患者の状態を注意深く観察すること。
<table>
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<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>カルバマゼピン</td>
<td>本剤によるCYP2D6阻害作用により、これらの薬剤の代謝が阻害される。【薬物動態】の項参照</td>
<td></td>
</tr>
</tbody>
</table>

**CYP2D6 substrates**

| 藥剤名等       | 臨床症例 | 本剤の血中濃度が上昇するおそれがあるので、併用する場合には、患者の状態を注意深く観察すること。
<table>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ダモキシフェン</td>
<td>本剤によるCYP2D6阻害作用により、これらの薬剤の代謝が阻害される。【薬物動態】の項参照</td>
<td></td>
</tr>
</tbody>
</table>

**Precaution**

- 強いCYP3A阻害剤
- リファンビシン
- カルバマゼピン
- フェニトイン
- セイヨウトギリソウ（StJohn'sWort（セント・ジョーンズ・ワート））含有食品等

**PK Section: drug interactions**

- 強いCYP3A阻害剤
  - アゾール系抗真菌剤（イトラコナゾール、ポリコナゾール、ケトコナゾール※等）
  - リファンビシン
  - カルバマゼピン
  - フェニトイン
  - セイヨウトギリソウ（StJohn'sWort（セント・ジョーンズ・ワート））含有食品等

- 強いCYP3A誘導剤
  - リファンビシン

- CYP2D6 substrates
  - ダモキシフェン
  - プロパフェノン
  - リスペリドン等

**Drug Label: Drug Interaction Section**

- 強いCYP3A阻害剤
  - アゾール系抗真菌剤（イトラコナゾール、ポリコナゾール、ケトコナゾール※等）

**PK Section: drug interactions**

- 強いCYP3A阻害剤
  - アゾール系抗真菌剤（イトラコナゾール、ポリコナゾール、ケトコナゾール※等）

In vitroにおいて、パノビノスタットはP-糖タンパク（P-gp）の基質であることが示されている。
Role of Regulatory Science
Importance of providing various tools (MRCTs, M&S etc)

Balancing Societal Needs and Regulatory Certainty: The Case Study of Peramivir in Japan

T Tominaga¹, Y Ando¹, N Nagai², J Sato¹ and T Kondo³

Regulators must balance societal and medical requirements against the need for certainty about benefit and risk for new medicines. This is described in a case study of the expedited review and approval of peramivir, a novel neuraminidase inhibitor, in Japan in the context of the emergence of new strain of influenza in 2009. The case illustrates the importance of regulatory science and transparency in supporting such decision making.

¹Office of International Programs, Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan; ²Center for Product Evaluation, Office of New Drug IV, Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan; ³Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan. Correspondence: Y Ando (ando-yuki02@pmda.go.jp)

Received 23 July 2012; accepted 17 December 2012; advance online publication 20 February 2013. doi:10.1038/cptd.2012.268

Role of regulatory science

Regulatory science provides various tools used for development, review, and postmarketing assessment of drugs as stressed in the US Food and Drug Administration’s Critical Path Initiatives. The development and review of peramivir were informed by regulatory science in several ways.

Conclusion

Drug regulators are often faced with a challenge of balancing the public’s need for access to new medicines with the need for certainty. This can result in situations in which a previously uncharacterized adverse event can significantly change the benefit:risk profile of an approved medicine. Consideration of societal and medical needs, regulatory science, and transparency in regulatory decision making are crucial for building a regulatory framework that encourages innovation, enables balanced decisions, and maintains public confidence.
Outline

• Introduction
• Guidelines and review experiences
• Future perspectives
• 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**
- e-Submission of data
  - 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.

PMDA-Keio joint symposium Dec.8, 2015
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>
</table>
| **Basic Principles** on Electronic Submission of Study Data for New Drug Applications (“Basic Principles”) | June 20, 2014 | Ministry of Health, Labour and Welfare | • The first official announcement that MHLW/PMDA will require electronic study data in NDA.  
• Both of Japanese and English versions are available on PMDA website |
• States the start date of e-study data submission for NDA |
• Subject to updates based on the accumulated experience and/or the revisions of the data standards |
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**
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>
</table>
| **Standard two stage analysis**                        | • 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  
  • Clinical pharmacology studies that provide a major evidence for dosage and administration or dose adjustment in pediatric, elderly, and hepatic/renal disorder patients |
| **Population analysis (including simulations)**         | • 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  
  • Population analysis that provides a major evidence for dosage and administration |
| **Physiologically-based pharmacokinetic model analysis** | • 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 |
M&S in regulatory decision making

Framework for M&S evaluation will be established in J-FY2016.

Objectives

• Scientific discussion on M&S issues
  • Clinical trial consultation
  • NDA review

• Sharing of knowledge and experiences across multi-offices/professionals

• International regulatory collaboration on M&S issues

Experts

• Clinical Pharmacology
• Biostatistics
• Clinical
• Others

Co-operation with other projects in PMDA

• Advanced review with Electronic Data Promotion Group
• Pediatric WG
• Orphan WG
Guideline development

“Research on utilization of modeling and simulation in clinical development including pediatric drugs and unmet medical needs” by Japan Medical Research and Development Agency (AMED)

• Population Pharmacokinetics:
  • Updating existing document and establishing best practices/guidance in population analysis
  • Guidance publication in FY2016 (tentative schedule)

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

• Cross-Product Analysis:
  • Discussion on the therapeutic areas
  • General considerations
Prospect of e-study data utilization in Japan

Prospect As of Oct, 2015 (Subject to Change)

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

Present J-FY2015

J-FY2016
- Setup e-data management and utilization

J-FY2018
- Ordinary utilization of e-data in the product review
- Promotion of paperless operation

J-FY2019 - 2021
- Starting earnest cross-product analysis

J-FY2022
- Establishment of disease models
- Publication of disease-specific guidelines
- Publication of guidelines to contribute to drug development

First-class review authority

Transitional period are taken until March 31st, 2020

- Preparations of guidelines and related documents
- Earnest on cross-product analysis and development of disease models

* NDA=New Drug Application

Prospect of e-study data utilization in Japan

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

J-FY2022 -

First-class review authority

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

PMDA-Keio joint symposium Dec.8, 2015
Summary

- Regulatory experiences and current status on pharmacometrics in Japan are presented.
- Advanced Review/consultation with Electronic Data Project is being executed successfully so far.
  - Publication of regulatory documents
  - Experiences of the step by step pilot projects
  - Active discussion with industry
- PMDA will proceed e-study data utilization to reach future goal, such as high quality reviews/consultations and implementation of cross product analysis to develop disease models/new guidelines.
- PMDA believe effective utilizations of submitted electronic data and PMx approach lead to more efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.
Thank you for your attention!

Acknowledgements

• Dr. Takao Yamori
• Advanced Review with Electronic Data Promotion Group
• Office of New Drug III, IV and V
• Clinical Pharmacology/ADME reviewers

PMDA Homepage: http://www.pmda.go.jp/english/index.html

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