Model Building Drug Development (MBDD) and Bridging in Asia – Japanese Regulatory Perspective

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Outline

- Introduction
  MBDD and bridging in drug development and drug review
- Current status of PPK approach and examples in Japan
- Project team across multiple offices in PMDA
- Conclusion

WCoP 2012, Sep.6 2012
Role of PPK, PK-PD, M&S, Bridging and Global Clinical Trials (GCTs) in Drug Development/Review

- **Scientific rationale for dosage and dose regimen**
  
  For examples,
  
  - Determining dose and regimen for phase 3 trials using PPK and M&S
  - Confirming dose-response relationship using PPK-PD analysis in phase 2 and/or 3 trials

- **Additional Information on dose adjustment for special population**
  
  impaired renal/liver function, pediatric and elderly patients etc.

- **PK data in the target disease Japanese patients for PIs**

- **Evaluation of various factors such as ethnic differences on PK, efficacy and safety, based on the results from global clinical development program**
Regulatory Support for MBDD and Bridging
- Guidelines and Regulatory Documents -

MHLW (Ministry of Health, Labour and Welfare)
- Clinical PK studies of Pharmaceutics (2001) and referential document including PPK (2003)
- Basic principles on Global Clinical Trials (2007)

ICH
- E4 (Dose – Response), E5 (Ethnic factors), E7 (Geriatrics), E11 (Pediatrics), M4 (CTD)
- E15 & 16 (Pharmacogenomics, Biomarkers)
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- Current status of PPK approach and examples in Japan

  PPK approach:
  Collection of sparse PK and/or PD data obtained from any phase of drug development for the purpose of estimating covariate effects, designing dosing regimens and/or exploring C (or E) - R relationships

- Project team across multiple offices in PMDA

- Conclusion
Trends of PPK Approach in Approved NDAs
NDAs Approved between 2001 and 2011

Numbers of approved NDAs

% of NDAs with PPK

Approved year

<10%  10~20%  30~40%


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Trends of PPK Approach in NDAs
NMEs approved between 2001 and 2011

- Numbers of approved NMEs
- % of NMEs with PPK

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

Approved year: 2001 to 2011

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Target Disease Areas for PPK Approach
NMEs approved between 2009 and 2011

Disease areas were classified according to the review terms in PMDA.

- Standard PK
- PPK approach

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Current Status of PPK in Pediatric Development
Approved NDAs with pediatric development between 2009 and 2011

Numbers of approved NDAs for pediatrics

- Approved NDAs
- PPK approach

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Current Status of PPK Approach in NDAs in Japan

Summary

- Approved NDAs (All, NMEs) with PPK approach have been increasing from 2001 to 2011.
- 50% of recent NMEs development have utilized PPK approach, suggesting change of drug development strategy in Japan.
- Major target disease for NMEs development with PPK:
  - Primary: infectious, cardiorenal,
  - 2nd: cancer, neurologic/psychiatric, allegic/immunologic
- Pediatrics: almost all drug development for infectious and allegic diseases have incorporated PPK approach.

WCoP 2012, Sep. 6, 2012
### Example : Peramivir

<table>
<thead>
<tr>
<th><strong>Brand name</strong></th>
<th>Rapiacta 300mg bag/150mg vial for intravenous drip infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-proprietary name</strong></td>
<td>Peramivir Hydrate</td>
</tr>
<tr>
<td><strong>Applicant</strong></td>
<td>Shionogi &amp; Co., Ltd</td>
</tr>
<tr>
<td><strong>Date of approval</strong></td>
<td>January 2010</td>
</tr>
<tr>
<td><strong>Application classification</strong></td>
<td>Prescription drug (1) with a new API</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Influenza A or B virus infection</td>
</tr>
</tbody>
</table>
| **Dosage and administration** | For adults: 300mg IV  
For high risk patients: 600mg IV | For pediatrics: 10mg/kg IV  
Maximum: 600mg IV |
|  | According to the patient’s symptoms, 600mg IV once-daily multiple dose |
| **Clinical trials** | Multinational clinical trial in Asia  
(Japan, Korea, Taiwan) | Phase 3 trial (Japan) |
| **Special mention** | Priority Review/Prior assessment consultation |
Peramivir: Plasma Concentrations in Asian Trial
Measured and Population Mean Values by PPK and Simulation

300mg infusion

600mg infusion

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Peramivir: Additional Information on Dose Adjustment for Patients with Renal Impairment

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

<table>
<thead>
<tr>
<th>renal function, Ccr (mL/min)</th>
<th>recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild renal impairment</td>
<td></td>
</tr>
<tr>
<td>50≦Ccr</td>
<td>300mg for adults patients</td>
</tr>
<tr>
<td></td>
<td>600mg for patients at high risk</td>
</tr>
<tr>
<td>Moderate renal impairment</td>
<td></td>
</tr>
<tr>
<td>30≦Ccr &lt; 50</td>
<td>100mg for adults patients</td>
</tr>
<tr>
<td></td>
<td>200mg for patients at high risk</td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td></td>
</tr>
<tr>
<td>10≦Ccr &lt; 30</td>
<td>50mg for adults patients</td>
</tr>
<tr>
<td></td>
<td>100mg for patients at high risk</td>
</tr>
</tbody>
</table>


WOcP 2012, Sep.6 2012
Dose for pediatric phase 3 trial was determined by M&S, based on the data from adults. AUC or $C_{\text{max}}$ in pediatric patients by baysian estimation(open circle) and predicted values (solid line) after administration of 10 mg/kg IV, based on both population mean and body weight are within the ranges of adult patients after administration of 300 and 600 mg.
Peramivir Development : Summary

- PPK and M&S were efficiently utilized for
  - Evaluation of PK similarity in the pivotal phase 3 trial conducted in Japan, Korea and Taiwan
  - Providing additional information on dose adjustment for adult patients with renal impairment
  - Determining pediatric dose for phase 3 trial, based on the data from adult patients

- Asian CT, PPK and M&S contributed rapid access of a new influenza drug to patients in Japan (1st approval in the world).
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Project Team (PT) across Multi-offices in PMDA

- In vitro companion Diagnostic Devices Project
- Pediatric and Orphan Drug Project
- QbD assessment Project
- Innovative Statistical Strategies for New Drug Development
- Nanomedicine Initiative Project
- Global Clinical Study Project
- Cardiovascular Risk Evaluation Project
- Omics Project
Innovative Statistical Strategies for New Drug Development

Organized in August 2011

- Professionals: Clinical Pharmacologist, Clinicians, Biostatistition,
- Current topics:
  - Application of PK-PD and M&S for pediatric dose
  - Effect of ethnic factors on efficacy/safety in global drug development programs
  - Natural disease course/placebo effect on neurological/psychiatric

- Global Clinical Study Project
- Pediatric and Orphan Drug Project

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Conclusion

- New concept/methodology such as M&S as well as new development strategy such as GCTs have large potentials for efficiently planning clinical development program and application data package.

- Intensive discussion and positive communication among experts with different fields are expected for appropriate use of innovative methodology and development strategy.

- PMDA’s PT will contribute to collaborate and share successful experiences with industry and academia.
Information on package Insert and review report for approved new drugs is provided through Website

nagai-naomi@pmda.go.jp

PMDA Drug Information (Japanese)
http://www.info.pmda.go.jp/

PMDA Homepage (English)
http://www.pmda.go.jp/english/Index.html

Thank you for your attention.