Regulatory Evaluation and Perspectives on Dose-Exposure-Response Information in New Drug Applications

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Disclaimer

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

• Introduction:
  • Finding the dose for Japanese subjects
  • Guidance to promote efficient drug development

• Example and current status
  • NDA review: suvorexant
  • PK-PD(D-E-R) information in the NDAs

• Future perspectives:
  • About advanced review/consultation
  • Pilot projects for advanced review
  • Guideline development

• Summary
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Finding the Appropriate Dose for Japanese Subjects

• Generally...
  • Definitive dose-response is not established in Ph2 studies
  • Sometimes the Ph2 endpoint differs from Ph3.

• In addition, to select a adequate dose range for licensing in Japan....
  • Understand the D-E-R data and ADME.
  • Consider the possibility that D-E-R or ADME may differ between Japanese and non-Japanese.
Guidance to promote efficient drug development in Japan

- Japanese guidance document “Basic principles on Global Clinical Trials” (2007 Sept)
  - Basic requirements to conduct a 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 GCT including Japan

Correlation in PK-efficacy?
- Yes

Global PK study

PK comparisons: Japanese vs non-Japanese

Unadjustable differences

Global Dose-Finding study

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

Global confirmatory study

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

• D-E-R may differ across differing populations and regions.

• Where differences in D-E-R are known and understood, doses may be adjusted by population and regions to provide equivalent dose in GCT.

• To understand the differences in D-E-R between Japanese and non-Japanese, global dose finding study is important.
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Example: Suvorexant (1)

• Sleep drug of new MOA (antagonist for orexin receptors)
• In Ph2 study (P006) the D-E-R of Suvorexant 10-80 mg was examined and 40 mg was considered to be appropriate for further evaluation in the subsequent Phase 3 trials.
• 30 mg and 15 mg doses in elderly subjects were considered to be equivalent to 40 mg and 20 mg in non-elderly subjects respectively.
• Ph3 studies (P028, P029) were designed to evaluate the efficacy of Suvorexant high dose (HD: 40 mg/30 mg) compared with placebo. Low dose (LD: 20 mg/15 mg) was also examined to evaluate for secondary objectives.
• 34 and 247 Japanese patients (approx. 13% and 24% of the total) were enrolled in P006 and P028 respectively.
Example: Suvorexant (2)

- Japanese exposure similar to western population in clinical trials.
- D-E-R differences were not found between Japanese and western population

<table>
<thead>
<tr>
<th></th>
<th>1month</th>
<th>3month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese sTSO</td>
<td>-4.8[-17.2, 7.7]</td>
<td>-3.4[-12.9, 6.1]</td>
</tr>
<tr>
<td>Japanesewestern</td>
<td>-6.3[-12.4, -0.3]</td>
<td>-6.5[-12.2, -0.8]</td>
</tr>
<tr>
<td>HD</td>
<td>-9.2[-20.3, 1.9]</td>
<td>-4.9[-13.4, 3.5]</td>
</tr>
<tr>
<td>HDwestern</td>
<td>-7.9[-13.3, -2.5]</td>
<td>-10.3[-15.5, -5.2]</td>
</tr>
</tbody>
</table>

LS Means versus placebo in minutes[95%CI]
Example: Suvorexant (3)

- D-E-R in Ph3 trials appears different between the subjective and the objective endpoints.
Example: Suvorexant (4)

- Suvorexant was approved in August 2014 in US and September 2014 in Japan.
- Approved recommended dosage in Japan is higher than in US.

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>US</th>
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<tbody>
<tr>
<td>Recommended dose</td>
<td>Recommended dose is 20 mg once daily in non-elderly adults, 15 mg once daily in elderly adults.</td>
<td>Recommended dose is 10 mg once daily in non-elderly and elderly adults. If the 10 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 20 mg once daily</td>
</tr>
</tbody>
</table>
Example: Suvorexant (5)

• In US, the 10 mg dose was concluded as effective for many patients, though there were only limited number of subjects in P006 study.

• Since a study showed impairment of 20 mg Suvorexant in driving skills and there is overlap in exposure from 15 mg and 20 mg, 10 mg was judged as a starting and recommended dose.

• In Japan, PMDA concluded it is difficult to recommend the Suvorexant 10 mg, since there were only limited number of subjects of 10 mg dose in clinical trials and efficacy and safety were not fully evaluated.
Finding the Appropriate Dose

- Study design for identifying the dose
- Considerations for Specific Populations
  - Elderly subjects
  - Asian subjects
- Is the D-E-R information sufficient to judge the approved dose?

...We are still in the regulatory situation of differing decisions on dosing from single global clinical trial package.
About half of the recent NDAs for NMEs include D-E-R information.

**Chart Description:**
- **Count**:
  - All NDAs: Decreasing trend from 2011/4 to 2012/12.
  - NMEs: Increasing trend from 2011/4 to 2012/12.
  - NMEs with PK-PD information: Steady increase from 2011/4 to 2012/12.
- **Year**:
- **Therapeutic Area**:
  - Infectious Disease: 12
  - Endocrinology: 10
  - Oncology: 13
  - CNS: 8
  - Immunology: 3
  - Cardiorenal: 7
  - Others: 2
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Advanced workflow of review/consultation

Analysis by PMDA
- Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

Practical use of Innovative Medical Products
- More rational & effective evaluation process for regulatory decision

NDA etc.
- e-Submission of study data

Data Accumulation

Database

Sophisticated review
- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis
- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - Disease model
  - Objective B/R assessment
  - Identifying AE-related factors etc.

Sophisticated Consultation
- More evidence-based consultation

More effective and high quality Review
- More predictable efficacy/safety after approval
- Reduction of applicant’s work load
- More scientific regulatory decision

More efficient and Successful Development
- Epoch-making proposal leading the world
- Proactive publication of guideline
## 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

### Chart

<table>
<thead>
<tr>
<th>Year</th>
<th>FY2013 Pilot</th>
<th>FY2014 1st Pilot</th>
<th>FY2014 2nd Pilot</th>
<th>FY2015 Pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td></td>
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<tr>
<td>2014</td>
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<td>2015</td>
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</tr>
<tr>
<td>2016</td>
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### Notes

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

EMA EFPIA Workshop  Dec.4-5,2014
FY2014 1\textsuperscript{st} pilot project (outline)  
(Apr. 2014 - Sep. 2014)

• Purpose
  • To confirm that the data for population pharmacokinetic (PPK) analysis can be stored and managed appropriately with in-house system, and that persons in charge* are able to analyze the stored data by utilizing introduced software.

*more than 10 reviewers, in the areas of clinical pharmacology from each review office.

• Target studies
  • Datasets for PPK analysis of blood concentration data that include those of Japanese subjects obtained from one or more clinical studies on new drugs.
  • PPK datasets for three drug products, one from each of three companies, were provided.

• Implementation details
  • Confirm that the provided clinical study data can be stored and managed appropriately with in-house system, and analyzed by utilizing introduced software (NONMEM, R, Xpose, PDx-POP).
FY2014 2nd pilot and future projects (outline)

• Period
  • Data collection: September – October 2014
  • Analysis: November 2014 – January 2015

• Purpose
  • To confirm that the data for PPK-PD analysis and exposure-response (E-R) analysis can be stored and managed appropriately with in-house system, and that persons in charge are able to analyze the stored data by utilizing introduced softwares.
  • To consider the utilization of the analysis results in the new drug review process.

• Target studies
  • Datasets for analysis of blood concentration, clinical endpoints and AE data that include those of Japanese subjects obtained from one or more clinical studies on new drugs (3 NMEs, from three companies).

• We already announced the pilot project in FY2015.
  • The pilot will be conducted under the actual situation of regulatory review using the electronic study data of new drug application submitted during the data receiving period (from Jan 1 to Sep 30, 2015).
Discussion with the industry

Periodic new drug opinion exchange meetings to achieve the review/consultation goals (Jul and Dec)

Proposal of items to be discussed

Outcome reporting

Working-level meeting

WG for technical matters concerning regulatory review (Review WG)

(Add new discussion items Systematic issues will be primarily discussed to develop an electronic NDA data system)

SWG for electronic NDA data system development

(Technological issues (ex. Data handling) will be primarily discussed)

CDISC Technical Team

In order to avoid misunderstanding or misuse of the CDISC standards, provide explanation for particular issues Also consider the measure to submit the data which is not compliant to the CDISC

Clinical Pharmacology Team

Consider standardized format of the electronic data for clinical pharmacology review
Guideline development

The new MHLW Working Group started discussion on D-E-R Relationships related issues in October, 2014

- Population Pharmacokinetics:
  - Updating existing document and establishing best practices/guidance in population analysis
  - Guidance publication in 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
Medium- and long-term prospect

Tentative assumption and expectation

FY2014*: April 2014 – March 2015

• e-data can be received and managed appropriately
• e-data can be utilized in the review
• without extension of review period, industries’ workload would decrease gradually

FY2016
Set up e-data management and utilization

FY2018
Ordinary utilization of e-data in the product review

FY2019 - 2021
Starting earnest cross-product analysis

• More predictable efficacy/safety
• Consideration of expanding scope to toxicological study and post-approval clinical study

• Develop guidance and related documents
• Earnest cross-product analysis, development of disease models

FY2022 - 2023

• Establishment of disease model
• Publication of disease-specific guidance

Publication of guidance to contribute to drug development

EMA EFPIA Workshop Dec.4-5,2014
Summary

• Regulatory experiences and current status on D-E-R information in the new drug review are presented.

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

• New review/consultation process with submitted electronic data will be thoroughly considered based on the experiences of the pilot projects and active discussion with industry and academia.

• Effective utilization of submitted electronic data lead to efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.

• We will proceed our project and guidance development to promptly reach future goal, such as the implementation of cross product analysis and high quality review.

• We appreciate your understanding and cooperation.
Thank you for your attention!

- PMDA Homepage
- “Task force for advanced review and consultation with electronic data” Homepage