PMDA’s experiences to review data of bridging study based on ICH E5 guideline.

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E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

- Describes factors when extrapolating foreign clinical data to a new region.
- Facilitates acceptance of foreign clinical data in the new region.
- Describes development strategies for ethnic factor-sensitive drug.
### Classification of intrinsic and extrinsic ethnic factors

<table>
<thead>
<tr>
<th>INTRINSIC</th>
<th>EXTRINSIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Environmental</td>
</tr>
<tr>
<td>Physiological and pathological condition</td>
<td>Climate</td>
</tr>
<tr>
<td>Gender</td>
<td>Sunlight</td>
</tr>
<tr>
<td>Height</td>
<td>Pollution</td>
</tr>
<tr>
<td>Body weight</td>
<td>Culture</td>
</tr>
<tr>
<td>Liver</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>Kidney</td>
<td>Educational status</td>
</tr>
<tr>
<td>Cardiovascular functions</td>
<td>Language</td>
</tr>
<tr>
<td>ADME</td>
<td>Medical practice</td>
</tr>
<tr>
<td>Receptor sensitivity</td>
<td>Disease definition/Diagnostic</td>
</tr>
<tr>
<td>Race</td>
<td>Therapeutic approach</td>
</tr>
<tr>
<td>Genetic polymorphism of the drug metabolism</td>
<td>Drug compliance</td>
</tr>
<tr>
<td>Genetic diseases</td>
<td>Smoking</td>
</tr>
<tr>
<td>Diseases</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Regulatory practice/GCP</td>
<td>Food habit</td>
</tr>
<tr>
<td>Methodology/Endpoints</td>
<td>Stress</td>
</tr>
<tr>
<td>ICH E5 guideline</td>
<td>Regulatory practice/GCP</td>
</tr>
<tr>
<td>Pharmaceuticals &amp; Medical Devices Agency</td>
<td>Methodology/Endpoints</td>
</tr>
</tbody>
</table>

**Intrinsic Factors:**
- Genetic
- Physiological and pathological condition
- Gender
- Height
- Body weight
- Liver
- Kidney
- Cardiovascular functions
- ADME
- Receptor sensitivity
- Race
- Genetic polymorphism of the drug metabolism
- Genetic diseases
- Diseases

**Extrinsic Factors:**
- Environmental
  - Climate
  - Sunlight
  - Pollution
  - Culture
  - Socioeconomic status
  - Educational status
  - Language
  - Medical practice
    - Disease definition/Diagnostic
    - Therapeutic approach
    - Drug compliance
- Smoking
- Alcohol
- Food habit
- Stress
- Regulatory practice/GCP
- Methodology/Endpoints
No need to repeat later phase clinical trials in a new region, if bridging was successful.
Criteria for Successful Bridging Strategy

- No major impacts of ethnic factors in drug responses (Efficacy & Safety)
  - Extrinsic ethnic factors
    - Medical Practices, Culture, etc.
  - Intrinsic ethnic factors
    - Genetic profiles, Disease, etc.

Effects of ethnic factors in drug responses can be confirmed in the bridging study
Approved Drugs based on the bridging strategy in Japan
In Japan, drug approval based on the bridging strategy has rapidly increased in early 2000, since ICH E5 guideline was established in 1998.
Target Disease Area for Bridging Study

Cancer: 5 (PC, BC, CC, LC)
Allergy & Immunological diseases: 5 (Rh, Ur, RT, RA)
Endocrinological diseases: 4 (OP, DM, ED)
Neurological diseases: 7 (AD, MI, PD)
Gastrointestinal disease: 1 (Hp)
Ophthalmologic diseases: 2 (GC, AMD)
Viral diseases: 3 (Flu, RSV)

AD: Alzheimer’s disease
MI: Migraine
PD: Parkinson’s Disease
PC: Prostate Cancer
BC: Breast Cancer
CC: Colon Cancer
LC: Lung Cancer
Rh: Rhinitis
Ur: Urticaria
RT: Renal transplantation
RA: Rheumatoid Arthritis
OP: Osteoporosis
DM: Diabetes Mellitus
ED: Erectile Dysfunction
Flu: Influenza Infection,
RSV: Respiratory Syncytial Virus Infection
GC: Glaucoma and Ocular Hypertension
AMD: Age-related Macular Degeneration
Hp: H pylori eradication

Combination Patterns of PK study and Bridging study

Patient Numbers enrolled in a Bridging Study

A Bridging Strategy shorten a period of clinical development in Japan

<table>
<thead>
<tr>
<th>Development based on Bridging Strategy in Japan</th>
<th>Median: 32 M</th>
<th>NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Development in Japan</td>
<td>Median: 56 M</td>
<td>NDA</td>
</tr>
</tbody>
</table>

Time from starting Phase II to NDA submission

Actual review cases of the bridging data
SPIRIVA® (tiotropium bromide)

- An anticholinergic with specificity for muscarinic receptors
- Chronic obstructive pulmonary disease (COPD)

**Japan**

**Phase II**
- DB, Placebo+3 doses, Single, FEV1.0, PK
  - N=27

**Phase II**
- DB, 2 doses + Active control, 4W, FEV1.0
  - N=201

**Phase III**
- Long-term safety study
  - N=161

**Foreign**

**Phase I**
- Phase II (Dose Response)
  - DB, Placebo+4 doses, Single FEV1.0, PK
  - N=35

**Phase II**
- DB, Placebo + 4 doses, 4W FEV1.0
  - N=169

**Phase III**
- Long-term safety study
  - N=161

**Phase III**
- DB, Placebo + 1 dose, 1 Year, FEV1.0
  - N=471 and N=451 (2 studies)

**Phase III**
- DB, 1 dose + Active control, 1 Year, FEV1.0
  - N=288 and N=247 (2 studies)

**Phase III**
- DB, Placebo + 1 dose + Active control, 6M
  - N=623 and n=584 (2 studies) FEV1.0

**Other studies**
<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>Foreign</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I</strong> (PK)</td>
<td>Single Dose</td>
<td>PK study</td>
</tr>
<tr>
<td></td>
<td>Repeated Dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dietary Effect</td>
<td>Dietary Effect</td>
</tr>
<tr>
<td></td>
<td>Other studies</td>
<td>Other studies</td>
</tr>
<tr>
<td><strong>Bridging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase II</strong></td>
<td>Early Phase II</td>
<td></td>
</tr>
<tr>
<td><strong>Dose Finding</strong></td>
<td>Late Phase II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long term trial</td>
<td></td>
</tr>
<tr>
<td><strong>Bridging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase III</strong> BMD</td>
<td>BMD trial</td>
<td>BMD trial 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMD trial 2</td>
</tr>
<tr>
<td><strong>Bridging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bone Fracture</strong></td>
<td></td>
<td>Bone Fracture trial 1 &amp; 2</td>
</tr>
</tbody>
</table>
PK comparison on Risedronate

2.5mg for Japanese is comparable to 5.0mg for foreign clinical data.
For BMD change rate, 2.5mg for Japanese is similar to 5.0mg for Foreign data.
BMD Change rate for Risedronate

<table>
<thead>
<tr>
<th>(Month)</th>
<th>BMD change rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>

Japanese 2.5mg Data

Foreign 5mg Data

平均±SD
## Examples of Different Approved Dose in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Indication</th>
<th>Reason</th>
<th>Difference in Japanese dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Sildenafil</td>
<td>Erectile dysfunction</td>
<td>Safety</td>
<td>A half of Caucasian dose (25-50 mg)</td>
</tr>
<tr>
<td>2002</td>
<td>Risedronate</td>
<td>Osteoporosis</td>
<td>PK/Efficacy</td>
<td>A half of Caucasian dose (2.5 mg OD)</td>
</tr>
<tr>
<td>2002</td>
<td>Eletriptan</td>
<td>Migraine</td>
<td>Safety</td>
<td>A half of Caucasian dose (20 mg, Max: 40 mg)</td>
</tr>
</tbody>
</table>
| 2005 | Etanercept   | Rheumatoid Arthritis   | Efficacy   | Japan: 10-25 mg/day  
Caucasian: 25 mg/day                                               |
| 2005 | Rosuvastatin | Hypercholesterolemia   | PK         | A half of Caucasian dose (Initial: 2.5-5 mg OD、 
Maintenance: 2.5-10 mg OD、Max: 20mg/day)                         |
Arava®
(Leflunomide)

- Dihydroorotate dehydrogenase inhibitor
- Target Disease:
  - Rheumatoid Arthritis (RA)
# Ethnic Factor Considerations on effects of leflunomide in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>US/EU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>ACR criteria</td>
<td></td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>Similar Symptom</td>
<td>No major differences in Epidemiological data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard Drug Therapy</strong></td>
<td>DMARDs(MTX), Steroid, NSAIDs or Surgery</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Endpoint</strong></td>
<td>ACR20, 50, 70</td>
<td></td>
</tr>
<tr>
<td><strong>Patient Background</strong> (age, gender, body weight etc.)</td>
<td>• More serious and longer length of disease patients were enrolled in Japanese study, and BW is lighter in Japanese, but no major impacts in drug responses</td>
<td>• the other factors were no major difference</td>
</tr>
<tr>
<td><strong>Clinical Trial</strong></td>
<td>ICH-GCP</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Data Package for Leflunomide in Rheumatoid Arthritis

- PK Study
- Dose-Response Study
  - Placebo-controlled Dose-Response Study (YU203) n=419
  - Placebo-controlled Confirmatory Study (US301) n=485
- 1Y Long-term Safety Study n=110
- Placebo and Active controlled Confirmatory Study (MN301) n=359
- Active-controlled Confirmatory Study n=1000
- Active-controlled Long-term Study
- Special Population etc.

Extrapolation
PK Comparison in Single Administration

- No Major Differences on PK in leflunomide administration
- Similar PK have been also confirmed in multiple administration

Blood concentration of A771726 in single administration of Leflunomide 20mg in Japanese and Caucasian populations
Efficacy Comparison at 28 weeks

- Logistic analysis indicates similar dose-response relationship between populations
Risks in hepatotoxicity, bone marrow suppression were major concerns in the foreign study and these points were also carefully reviewed in Japan.

Risks of infectious diseases have been also discussed.

- In the submitted data, no major differences in seriousness and event rates
- But, sample size of Japanese populations was smaller
The foreign data can be extrapolated into Japanese populations in terms of dose-response effects of leflunomide.

However, risks in hepatotoxicity, bone marrow suppression as well as infectious diseases were identified.

In terms of safety, because of small sample size in Japanese, it is difficult to conclude that safety profiles of leflunomide in Japanese are similar to foreign population.

Leflunomide was approved with the condition (mandatory post-market surveillance).
In post-marketing stage of leflunomide

- All leflunomide-administered patients must be registered into the survey before starting leflunomide therapy.

- Serious cases of interstitial lung diseases (ILD) have been reported
  - 5 death cases in 3 month after launch.
  - 16 ILD cases in 3412 patients enrolled in the survey

“Box Warning” in the label were revised to increase the precaution level about ILD
Examples of Different Risks

- Japanese have higher risks of drug-induced Interstitial lung disease (ILD) than foreign population

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence Rate in Japan</th>
<th>Incidence Rate Overseas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>3.98% (4,473 cases)</td>
<td>0.3% (23,000 US cases)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1.81% (3,867 cases)</td>
<td>0.017% (861,860 cases)</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>0.66% (3,772 cases)</td>
<td>0.01% (295,800 cases)</td>
</tr>
</tbody>
</table>

The incidence rate is markedly higher in Japan than abroad for any of the causative agents.

Factors affecting to safety measure on post-approval in Japan

<table>
<thead>
<tr>
<th>Factors</th>
<th>Safety-Related Regulatory Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population Estimate in million patients</td>
<td>1.18 ± 0.07 (p&lt;0.01)</td>
</tr>
<tr>
<td>Launch Lag</td>
<td>0.28 ±0.18 (p&lt;0.05)</td>
</tr>
<tr>
<td>Similar Mode of Action</td>
<td>0.23 ±0.10 (p&lt;0.01)</td>
</tr>
<tr>
<td>Bridging Study</td>
<td>2.50 ±1.24 (p&lt;0.1)</td>
</tr>
</tbody>
</table>

Lessons learned (Bridging data review)

- More than 45 NDAs have been approved based on ICH E5 strategy to extrapolate foreign clinical data to Japanese population.

- Comparison of PK profiles among populations is useful to expect similarities/differences in safety and to enable to set appropriate dose range in dose-finding study.

- Data regarding dose response relationships in Japanese population is critical and important information to determine an optimal dose.
Lessons learned (Bridging data review)

- A drug behaves *sometimes differently* in Japanese from foreign population
  - Number of Japanese patients in “Bridging NDA” is *smaller* than that in full NDA (full development in Japan)
  - Possibility to have *unexpected serious adverse event* after drug approval is higher in “Bridging NDA” than that in full NDA
  - An approved drug based on Bridging Strategy should be *closely monitored* at post-market stage
Information

• HOMEPAGE (English)

• Regulatory Science Page
http://www.pmda.go.jp/regulatory/index.html

• E-mail:
uyama-yoshiaki@pmda.go.jp

Thank you for your attention