Future Directions of Global Drug Developments on the basis of Japanese Regulatory Experience to Accept Foreign Clinical Data

Pharmaceuticals & Medical Devices Agency (PMDA)
Yoshiaki Uyama, Ph.D.
31.2% (13/41 products) of the approved dosage in Japan was different from US/EU (FY2003-FY2005)

Maximal daily dose in Japanese is usually lower than that in Caucasian

Nakajima K, Yakugaku Zasshi, 129: 223-229, 2009
Review Experiences of Bridging Study
Approval Cases based on ICH E5 in Japan

[Graph showing approval cases from 1999 to 2006]

Pharmaceuticals & Medical Devices Agency
More than 40 NDAs have been approved based on ICH E5 strategy to extrapolate foreign clinical data to Japanese population.

% of Bridging Cases in total NDAs has been recently decreased because of a diversity of the strategy.

A bridging strategy has been already established as one of drug development strategy.
Lesson Learn

- Lesson learn from review experiences of “Bridging NDAs”
  - Comparison of PK profiles among populations is useful to expect an optimal dose in Japanese population
    - Recognize similarity and difference in PK
    - Expectation of clinical outcome (efficacy and safety)
  - Data regarding dose response relationships in Japanese population is critical and important information to determine an optimal dose
    - Recognize similarity and difference in clinical outcome (efficacy and safety)
### Lesson Learn (Continue)

Examples of Approved drugs based on “Bridging Strategy”, but final approved dose is different from Caucasian dose

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Indication</th>
<th>Safety</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 foreign dose (25-50 mg)</td>
</tr>
<tr>
<td>2002</td>
<td>Risedronate</td>
<td>Osteoporosis</td>
<td>PK/Efficacy</td>
<td>A half of foreign dose (2.5 mg OD)</td>
</tr>
<tr>
<td>2002</td>
<td>Eletriptan</td>
<td>Migraine</td>
<td>Safety</td>
<td>A half of foreign dose (20 mg, Max: 40 mg)</td>
</tr>
<tr>
<td>2005</td>
<td>Etanercept</td>
<td>Rheumatoid Arthritis</td>
<td>Efficacy</td>
<td>Japan: 10-25 mg/day Foreign: 25 mg/day</td>
</tr>
<tr>
<td>2005</td>
<td>Rosuvastatin</td>
<td>Hypercholesterolemia</td>
<td>PK</td>
<td>A half of foreign dose (Initial: 2.5-5 mg OD, Maintenance: 2.5-10 mg OD, Max: 20mg/日)</td>
</tr>
</tbody>
</table>
Lesson Learn (Continue)

- Lesson learn from review experiences of “Bridging NDAs”
  - 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
Japanese have higher risks of drug-induced Interstitial lung disease (ILD) than foreign population

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>Overseas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>3.98%</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>(4,473 Japanese cases, AstraZeneca’s cohort study)</td>
<td>(23,000 US cases, FDA Approval Letter)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1.81%</td>
<td>0.017%</td>
</tr>
<tr>
<td></td>
<td>(9,067 Japanese cases)</td>
<td>(801,860 overseas cases)</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>0.66%</td>
<td>0.01%</td>
</tr>
<tr>
<td></td>
<td>(3,772 Japanese cases)</td>
<td>(295,800 global cases)</td>
</tr>
</tbody>
</table>

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

Review Experiences of Global Clinical Trials
Losartan: Phase III trials

- Superior to placebo in overall population
- Supportive results in Japan and other Asian country
  But,
- no effects in US
- Inconsistent results among countries/regions
**Tolterodine: Global PK study**

Different PK profile between Japanese and Korean

Japanese = Caucasian < Korean

- **Cmax (tolterodine+active metabolite)**

<table>
<thead>
<tr>
<th></th>
<th>2mg</th>
<th>4mg</th>
<th>6mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese</td>
<td>1.07 ± 0.40</td>
<td>2.07 ± 0.83</td>
<td>4.00 ± 1.15</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.31 ± 0.74</td>
<td>2.70 ± 0.90</td>
<td>3.92 ± 1.82</td>
</tr>
<tr>
<td>Korean</td>
<td>1.61 ± 0.79</td>
<td>2.65 ± 1.18</td>
<td>5.15 ± 1.75</td>
</tr>
</tbody>
</table>

- **AUC (tolterodine+active metabolite)**

<table>
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<th></th>
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<th>6mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese</td>
<td>12.5 ± 3.59</td>
<td>23.9 ± 9.61</td>
<td>42.8 ± 7.67</td>
</tr>
<tr>
<td>Caucasian</td>
<td>15.2 ± 5.27</td>
<td>30.3 ± 12.4</td>
<td>40.1 ± 15.2</td>
</tr>
<tr>
<td>Korean</td>
<td>20.5 ± 10.7</td>
<td>33.9 ± 13.1</td>
<td>55.7 ± 16.9</td>
</tr>
</tbody>
</table>
More examples of Global Clinical Trials

- **Trastuzumab**: Phase III for HER2-positive breast cancer after adjuvant chemotherapy
  - Japan/Asia, North America, EU, Australia etc 39 countries
  - Total: 3389 patients
- **Insulin glulisine**: Phase III for type II diabetes
  - Japan + Korea
  - Total: 387 patients

*No major differences among populations*
Future Drug Development Strategy for successful regulatory approval in Japan
Basic Principles on Global Clinical Trials

Japanese version

English version


Important points in planning drug development Strategy

In the era of globalization of Drug Development

- Japanese population should be included from early stage of drug development
  - POC, Dose-finding stage

- A clinical trial should be designed to obtain consistent results among populations
  - Enough numbers of Japanese population

- A drug development strategy should be flexible and modified accordingly based on results in previous stage
Flexible Global Drug Development Strategy

- Global communication including regulatory agency from an initial stage is a key to establish a best strategy

Simultaneous NDA in Japan and other countries
PMDA HOMEPAGE
http://www.pmda.go.jp/index-e.html/

PMDA DRUG Information
http://www.info.pmda.go.jp/

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