Review Policies for Global Drug Development: Japan’s Perspective

East Asian Pharmaceutical Regulatory Symposium 2008
April 15, 2008

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Pharmaceuticals and Medical Devices Agency (PMDA)
Why Global Drug Development?

• Objective of ICH
  – to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost-effective manner.
  – These activities have been undertaken to promote public health, prevent unnecessary duplication of clinical trials in humans, and minimize the use of animal testing without compromising safety and effectiveness.

• Drug-Lag Problem
  – Simultaneous multi-national drug development, NDA review, and approval etc...
Why Global Drug Development?

• Participation of Asian countries in global drug development
  – Contribution to the global study
  – Planning and conduct of Asian study
  – More useful safety & efficacy data collection of Asian population
  – Innovative New drugs from Asian area
Health Risk in Asian Region/Population

- Economic growth make people become health conscious
- Specific Health Risk in .....  
  - Asian Region
  - Asian Population
- Aging population $\rightarrow$ lifestyle disease
- Emerging (rapid and/or steady) diseases
Asia as a Hot spots of Avian Flu (H5N1 influenza)

Cervical Cancer and HPV vaccine
Big impact in Asian public health

Asian participation in global drug development

• From the beginning of 21st century, East Asian countries took part in the multi-national clinical trials (MCTs)
• Korea, Taiwan, Hong-Kong, Singapore, etc. have much experience in planning and conducting the multi-national clinical trials
• Japan is running after….. But!
Current status of Japan

- ICH-E5 guideline (bridging study)
- ICH-E5 Q&A (Q11 for multi-national trials)
- Drug lag problem
- **Basic principles on global clinical trials**
  (Sep. 28th 2007)
- Rapid increase in planning MCTs (including Asian study)
- NDA approval by MCTs including Asian area
Japanese version

東京中央平安北教の研究開発

Attention to:
Commissioner of Prefectural Health Supervising Department

Basic principle: on Global Clinical Trials

Up to the present according to “Ethnic Factor in the Acceptability of Foreign Clinical Data” based on ICH-E5 guidelines (Notification No. 76), Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1996, utilizing foreign clinical trial data in a new drug application what is called “Bridging” has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.


English version

September 28, 2007
Notification No.0928010

From Director of Evaluation and Licencing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Message of the document

• Both regulatory authority and industry would like to participate global drug development in a timely manner
• Recommends to participate earliest possible timing in clinical development
• Pro-Active, Constructive, Scientific, flexible discussion with PMDA is encouraged
Global clinical trials consultations

Fiscal Year

Numbers of Consultation

% Global Trial Consultation

East Asian Pharmaceutical Regulatory Symposium 2008
Global clinical trial consultations
(by therapeutic area)

- Cancer
- Cardiovascular
- Hormonal
- Neurological
- Psychiatry
- Antibacterial
- Immunological
- Pulmonary
- Ophthalmology
- Others
IND notification of MCTs

- FY2007: 508 IND notice (total)
- 18 company notified to conduct 38 MCTs
  - Japan based: 5 company, 8 protocol
  - Global pharma: 13 company, 30 protocol
- Development Phase
  - P-I: 1, P-II: 5, P-III: 32
- Therapeutic area
  - **Oncology:** 17, CV: 5, CNS: 4, Respiratory 3
Example from approved NDA

Approved on **Apr. 20th 2006**

- **Detrusitol (Tolterodine tartrate)** (Pfizer)
  - Korea-Japan study for bridging (n≒600)
  - OAB

- **NU-LOTAN (Losartan potassium)** (BANYU)
  - RENAAL study as global study (n≒1500)
  - Nephropathy in Type 2 Diabetic Patients

Approved on **Feb. 29th 2008**

- **Herceptin (Trastuzumab)** (Chugai)
  - HERA study as global study (n≒3400 asian≒400)
  - Adjuvant therapy for HER2-positive breast cancer

**Review report**
http://www.info.pmda.go.jp/shinyaku/r07/0104/45004500_21300AMY00128_A100_1.pdf
Scientific/Practical discussions

• Ethnic similarities
• Ethnic differences
  – Caucasian vs. Asian
  – Within Asian populations
• Various cultures, languages, religions, medical practices
• Standardized practice between trial sites (hospitals, medical institutes, etc...)
Japanese genome look alike Chinese

Ethnic difference in CYP2C19

- Asian $\equiv$ Japanese
- Asian $\neq$ Caucasian

Myrand SP et al, Clin Pharmacol Ther, Jan 30th, 2008
Relationship between SJS/TEN and HLA alleles

Table 1  Frequency of HLA alleles in patients with Stevens–Johnson syndrome

<table>
<thead>
<tr>
<th>HLA allele</th>
<th>CBZ–SJS</th>
<th>CBZ-tolerant</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*1502</td>
<td>44 (100%)</td>
<td>3 (3%)*</td>
<td>8 (6.6%)†</td>
</tr>
<tr>
<td>Cw*0801</td>
<td>41 (63.2%)</td>
<td>17 (18.8%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>A*1101</td>
<td>36 (61.8%)</td>
<td>51 (69.5%)</td>
<td>53 (57%)</td>
</tr>
<tr>
<td>DRB1*1202</td>
<td>33 (75%)</td>
<td>12 (11.9%)</td>
<td>18 (19.4%)</td>
</tr>
<tr>
<td>B<em>1502, Cw</em>0801</td>
<td>41 (63.2%)</td>
<td>3 (3%)</td>
<td>7 (7.3%)</td>
</tr>
<tr>
<td>B<em>1502, A</em>1101</td>
<td>36 (61.8%)</td>
<td>2 (2%)</td>
<td>5 (6.5%)</td>
</tr>
<tr>
<td>B<em>1502, DRB1</em>1202</td>
<td>33 (75%)</td>
<td>11 (11%)</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>B<em>1502, Cw</em>0801, A<em>1101, DRB1</em>1202</td>
<td>29 (66%)</td>
<td>0 (0%)</td>
<td>3 (3.2%)</td>
</tr>
</tbody>
</table>

Frequencies (by number and percentage) of individual or combined haplotypes of the B*1502 ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS; n = 44), and in carbamazepine-tolerant (n = 101) and normal subjects (n = 92). For methods, see supplementary information.

*Odds ratio (CBZ–SJS/CBZ-tolerant): 2.504 (95% CI, 1.26–49.522); corrected P value: $P = 3.13 \times 10^{-5}$.
†Odds ratio (CBZ–SJS/normal): 8.95 (95% CI, 5.0–15.869); $P = 1.38 \times 10^{-21}$.

WH Chung, SI Hung, HS Hong, MS Hsih, LC Yang, HC Ho, JY Wu, and YT Chen

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**TABLE.** Frequency of HLA Class I Alleles In Patients with Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

<table>
<thead>
<tr>
<th>HLA Allele</th>
<th>SJS/TEN with Ocular Complications</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Carrier frequency</th>
<th>(n = 40)</th>
<th>(n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A*0206</td>
<td>19/40</td>
<td>17/113</td>
</tr>
<tr>
<td>A*1101</td>
<td>1/40</td>
<td>25/113</td>
</tr>
<tr>
<td>Gene frequency</td>
<td>(n = 80)</td>
<td>(n = 226)</td>
</tr>
<tr>
<td>A*0206</td>
<td>21/80</td>
<td>22/192</td>
</tr>
<tr>
<td>A*1101</td>
<td>1/80</td>
<td>1/226</td>
</tr>
</tbody>
</table>

*: Corrected P is P after correction for multiple (9) comparisons.

M Ueta, C Sotozono, K Tokunaga, T Yabe, and S Kinoshita
## Ethnic difference in HLA-B*1502

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>1.9-7.1 %</td>
</tr>
<tr>
<td>Japanese</td>
<td>&lt;0.3 %</td>
</tr>
<tr>
<td>Thailand</td>
<td>8.5 %</td>
</tr>
<tr>
<td>Singapore</td>
<td>5.7 %</td>
</tr>
<tr>
<td>Korean</td>
<td>0.2 %</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0-1 %</td>
</tr>
</tbody>
</table>

- Difference exists within Asian populations
Asian drug development as global player

- More experience & scientific research
- Net-working & collaboration in Asian region
- Develop best fit drugs for Asian populations
Very near future style of Global Development (Asia + US + EU)

• Asian drug development as a part of global development is very important
• Positive dialog about Asian Clinical Trial Network for information/experience exchange
• Challenge to conduct Asia+EU+US Study
• Let's try for a win-win situation
Key message to industry

• Join and contribute Global Drug Development
  – Encourage to participate, plan, conduct MCTs

• Patient Safety Ensuring (Vigilance system)
  – Clinical Developing Phase (up to thousands, limited)
  – Post-marketing Phase (up to millions, unlimited)

• Patient Benefit Ensuring
  – Ensure patient’s accesses to innovative products

• Quality & Reliability of Data/Products
  was not built in one day! (GLP, GCP, GMP)
All the players in good harmony

“for the welfare of patient!”