Review Policies for Global Drug Development: Japan’s Perspective

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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 → 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 21\textsuperscript{st} 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

Attention to:
Commissioners 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 guideline (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


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 trial consultations
(by therapeutic area)

- Cancer
- Cardiovascular
- Hormonal
- Neurological
- Psychiatry
- Antibacterial
- Immunological
- Ophthalmology
- Others (by therapeutic area)
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 ≈ Japanese
- Asian ≠ 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 (8.6%)†</td>
</tr>
<tr>
<td>Cw*0801</td>
<td>41 (83.2%)</td>
<td>17 (18.8%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>A*1101</td>
<td>36 (61.8%)</td>
<td>51 (50.5%)</td>
<td>53 (57%)</td>
</tr>
<tr>
<td>DRB1*1202</td>
<td>33 (57.5%)</td>
<td>12 (11.9%)</td>
<td>18 (19.4%)</td>
</tr>
<tr>
<td>B<em>1502, Cw</em>0801</td>
<td>41 (83.2%)</td>
<td>3 (3%)</td>
<td>7 (7.5%)</td>
</tr>
<tr>
<td>B<em>1502, A</em>1101</td>
<td>36 (61.8%)</td>
<td>2 (2%)</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>B<em>1502, DRB1</em>1202</td>
<td>33 (57.5%)</td>
<td>1 (1%)</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 = 93). For methods, see supplementary information.

*Odds ratio (CBZ–SJS/CBZ-tolerant): 2.504 (95% CI: 1.26–49.522); corrected P value: P<sub>c</sub> = 3.13 × 10<sup>−77</sup>.
†Odds ratio (CBZ–SJS/normal): 8.95 (95% CI: 50–15,869); P<sub>c</sub> = 1.38 × 10<sup>−71</sup>.

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