New Approach
Japanese clinical trial with the sites of Asian countries

Hironobu Saito
Vice Director
Clinical Development Department
Sankyo Co., LTD
Issues on Clinical Trial

- A few subjects are enrolled at each site
- Only large-scale Hospitals participate in Trials (Lack of Central IRB, Deal with SAE etc)
- Investigators conduct trials between their jobs
- CRCs are not well-established
- A lot of Documentation

Trials proceed more slowly than we desire
The status of IRB

1) In Japan
   - Site 73: IRB 71 (280 patients)
   - The document for Each IRB: Preparation (20 sets)

2) In USA: 10 years ago
   - Investigator meeting
     - Investigator / CRC attended for 2 days
   - Site 44: IRB 3 (42 sites have central IRB)

3) In UK and Hong Kong
   - Cluster system (Each site attend the IRB of each Block(Cluster)).
   - Hong Kong (7 million) has 7 clusters. If the IRB of one cluster approves it, those of other clusters will review based on the approval documents. (Mutual Recognition Procedure)
One approach of Clinical Trials

1) Infra-structure for Clinical Trials in Japan
   In Japan, we need pivotal Japanese original data for approval. Therefore, we need the site which can conduct the global standard clinical trials.

   Infra-Structure of the System which Manages the Clinical Trials

2) Using the abroad data.
   Multinational study with EU/USA or Asian countries
Central-IRB (Not-Commercial IRB)

1) By decreasing the numbers of IRB's in a study, we can decrease the number of monitors. (cost-conscious)

2) If CRC manages to site-documentation (investigator's task), monitor can focus on handling for ADR or SDV.
Clinical Trials in abroad

Trials for other countries

1) Singapore (comments in ICH6): HSA (Health Sciences Authority) the lists of Patients is prepared in the Public-Public Hospitals or Private-Private Hospitals.

2) Hong Kong: Hospital Authority Clinical Management System Electric Patients Records: In each cluster, one site can check all records in the hospitals which are in the cluster. If patients go to other hospital, other doctors recognize this patient is in the clinical trial.
## Safety data - Gaps between Japan and West -

### Laboratory AEs

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related laboratory AEs</td>
<td>18.3</td>
<td>1.8</td>
</tr>
<tr>
<td>BUN increased</td>
<td>1.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Uric acid increased</td>
<td>2.9</td>
<td>0.0</td>
</tr>
<tr>
<td>K increased</td>
<td>1.9</td>
<td>0.0</td>
</tr>
<tr>
<td>AST increased</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>ALT increased</td>
<td>4.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

% of patients

--> Really more AEs in Japan?
**Safety data - Gaps between Japan and West -**

Difference in the ways of assessment of laboratory AEs by investigators - Concept of clinically relevant changes -

- **Japan:** More conservative decision resulted in more AEs
- **US:** Less conservative decision resulted in less AEs
### Table of Death Causes in Japan and Hong Kong

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Japan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>(31.0%)</td>
<td>Heart Disease</td>
<td>Stroke</td>
<td>Pneumonia</td>
<td>Accident</td>
</tr>
<tr>
<td></td>
<td>(31.0%)</td>
<td>(15.3%)</td>
<td>(13.6%)</td>
<td>(8.8%)</td>
<td>(4.1%)</td>
</tr>
<tr>
<td><strong>Hong Kong</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>(33.0%)</td>
<td>Heart Disease</td>
<td>Stroke</td>
<td>Pneumonia</td>
<td>Accident</td>
</tr>
<tr>
<td></td>
<td>(33.0%)</td>
<td>(16.3%)</td>
<td>(10.5%)</td>
<td>(8.9%)</td>
<td>(5.6%)</td>
</tr>
</tbody>
</table>

### Male Age and Female Age

<table>
<thead>
<tr>
<th></th>
<th>Male Age</th>
<th>Female Age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Japan</strong></td>
<td>77.6</td>
<td>84.6</td>
</tr>
<tr>
<td><strong>Hong Kong</strong></td>
<td>78.0</td>
<td>83.9</td>
</tr>
</tbody>
</table>
Summary

1) According to E5 guideline, a lot of USA/EU data have been tried to use as the reviewed data for approval. Most of all cases were failed because of the differences of PK, efficacy and safety data.

2) Chinese and Japanese are Asian, therefore, these differences may be smaller than the differences between Japanese and Caucasian. This is the time we try to conduct the clinical trial with Asian countries.

3) Because of medical records in English, we can check the quality and the AE detection method of all data by ourselves. These situation is very important. In addition, we can understand the Hong Kong / Singapore way like the US/EU style.

4) Regulatory issue and Ethical issue should be discussed.