Expectations of Asian Collaboration and Contribution to New Medicines

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Kazuhiko Nakajima
Chairperson, Drug Evaluation Committee
JPMA
Key Words for JPMA

The pharmaceutical industry contributes to improve the health and wealth of people all over the world, through the effort to develop innovative and useful pharmaceuticals, and deliver them to patients.

(http://www.jpma.or.jp)
### Japan-Originated Drugs Sold Overseas

**Sales over $500m**

#### CY1997

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Product</th>
<th>Company (Developed by)</th>
<th>Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Mevalotin</td>
<td>Sankyo</td>
<td>2,748</td>
</tr>
<tr>
<td>8</td>
<td>Gaster</td>
<td>Yamanouchi</td>
<td>1,708</td>
</tr>
<tr>
<td>15</td>
<td>Leuplin</td>
<td>Takeda</td>
<td>1,181</td>
</tr>
<tr>
<td>29</td>
<td>Takepron</td>
<td>Takeda</td>
<td>857</td>
</tr>
<tr>
<td>30</td>
<td>Herbesser</td>
<td>Tanabe</td>
<td>848</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Japan-originated Drugs</strong></td>
<td><strong>5</strong></td>
<td><strong>7,342</strong></td>
</tr>
</tbody>
</table>

#### CY2003

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Product</th>
<th>Company (Developed by)</th>
<th>Sales</th>
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<tbody>
<tr>
<td>3</td>
<td>Takepron</td>
<td>Takeda</td>
<td>5,142</td>
</tr>
<tr>
<td>6</td>
<td>Mevalotin</td>
<td>Sankyo</td>
<td>4,746</td>
</tr>
<tr>
<td>26</td>
<td>Harnal</td>
<td>Yamanouchi</td>
<td>2,247</td>
</tr>
<tr>
<td>32</td>
<td>Leuplin</td>
<td>Takeda</td>
<td>1,989</td>
</tr>
<tr>
<td>33</td>
<td>Cravit</td>
<td>Daiichi</td>
<td>1,954</td>
</tr>
<tr>
<td>43</td>
<td>Actos</td>
<td>Takeda</td>
<td>1,660</td>
</tr>
<tr>
<td>44</td>
<td>Clarith</td>
<td>Taisho</td>
<td>1,656</td>
</tr>
<tr>
<td>47</td>
<td>Blopress</td>
<td>Takeda</td>
<td>1,616</td>
</tr>
<tr>
<td>54</td>
<td>Pariet</td>
<td>Eisai</td>
<td>1,406</td>
</tr>
<tr>
<td>58</td>
<td>Aricept</td>
<td>Eisai</td>
<td>1,323</td>
</tr>
<tr>
<td>82</td>
<td>Prograf</td>
<td>Fujisawa</td>
<td>975</td>
</tr>
<tr>
<td>86</td>
<td>Campto</td>
<td>Yakult</td>
<td>938</td>
</tr>
<tr>
<td>99</td>
<td>Gaster</td>
<td>Yamanouchi</td>
<td>827</td>
</tr>
<tr>
<td>117</td>
<td>Sevofrane</td>
<td>Maruishi</td>
<td>712</td>
</tr>
<tr>
<td>145</td>
<td>Basen</td>
<td>Takeda</td>
<td>532</td>
</tr>
<tr>
<td>149</td>
<td>Meropen</td>
<td>Sumitomo</td>
<td>511</td>
</tr>
<tr>
<td>150</td>
<td>Cefzon</td>
<td>Fujisawa</td>
<td>507</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Japan-Originated Drugs</strong></td>
<td><strong>17</strong></td>
<td><strong>28,741</strong></td>
</tr>
</tbody>
</table>

**Source:** Pharma Future No.163, Utobrain 2006

**Reference:** OPIR research paper No.23 2004.10
Clinical trials in Japan are declining.

New drug price calculation review

New GCP issued

Complete implementation of new GCP
Expanded acceptance of foreign clinical data

Source: Yakumu Koho
Development status of Japanese pharmaceutical companies

Actual status of overseas advanced development

Source: Office of pharmaceutical Industry Research, JPMA
## Problems and current status of clinical trials in Japan

<table>
<thead>
<tr>
<th>Category</th>
<th>Status</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Markedly improved</td>
<td>Over-quality</td>
</tr>
<tr>
<td>Speed</td>
<td>Partially improved</td>
<td>Ads for recruiting subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contribution of CRC, SMO, CRO</td>
</tr>
<tr>
<td>Cost</td>
<td>Markedly increased</td>
<td>Abovementioned costs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequent visits by CRAs</td>
</tr>
<tr>
<td>J-GCP</td>
<td>Improved very little</td>
<td></td>
</tr>
</tbody>
</table>
Current status of clinical trials in Asia (1)

Patient Recruitment

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recruitment Rate (pts/site/mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asia*</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2.4</td>
</tr>
<tr>
<td>Acute MI</td>
<td>4</td>
</tr>
<tr>
<td>Acute MI</td>
<td>2.5</td>
</tr>
<tr>
<td>Pain relief</td>
<td>5</td>
</tr>
</tbody>
</table>

* Except for Japan and China

Source: Quintiles Translational (partially modified)
# Current status of clinical trials in Asia (2)

## Development Costs

Hypothetical protocol for treatment of patients with mild to moderate essential hypertension

<table>
<thead>
<tr>
<th>Costs of facilities and investigators*</th>
<th>China Mainland</th>
<th>Korea</th>
<th>Chinese Taipei</th>
<th>Hong Kong</th>
<th>Singapore</th>
<th>Thailand</th>
<th>Malaysia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs incurred before starting trial</td>
<td>0.18</td>
<td>0.29</td>
<td>0.26</td>
<td>0.27</td>
<td>0.27</td>
<td>0.19</td>
<td>0.21</td>
<td>1</td>
</tr>
<tr>
<td>Costs of CRO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulation-related costs</td>
<td>0.24</td>
<td>0.27</td>
<td>0.27</td>
<td>0.23</td>
<td>0.23</td>
<td>0.24</td>
<td>0.27</td>
<td>1</td>
</tr>
<tr>
<td>Monitoring cost</td>
<td>0.48</td>
<td>0.27</td>
<td>0.16</td>
<td>0.16</td>
<td>0.14</td>
<td>0.17</td>
<td>0.18</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>0.22</td>
<td>0.28</td>
<td>0.26</td>
<td>0.25</td>
<td>0.25</td>
<td>0.21</td>
<td>0.23</td>
<td>1</td>
</tr>
</tbody>
</table>

Comparison estimated by a large size CRO

*In Japan, these costs correspond to clinical trial/research costs and investigator drug management cost at participating institutions.

Current status of clinical trials in Asia (3)

Trend in Korean Clinical Trial Notification & Taiwanese Clinical Trial Approval

Rapid increase of clinical trials in Korea since 2003
Many multinational trials are Phase III and Phase IV

Korea

Source: KFDA Data

Chinese Taipei

Source: CDE Data, Taiwan
Clear awareness of the pharmaceutical industry as a customer

Key infrastructure such as Clinical facilities and Clinical Trial Centers have been established

Multi-national CROs have expanded their business all around Asia

Many Asian clinical sites can conduct clinical trials of good quality (inspected several times by sponsors or the FDA)

Clinical studies characterized by fast patient recruitment with less cost

Multi-national clinical studies have increased since introduction of ICH-GCP or domestic GCP in conformity with ICH-GCP in Asian countries following the ICH-GCP agreement in 1996

### Situations of key medical institutions involved with clinical researches and trials in the U.S., South Korea and Chinese Taipei

<table>
<thead>
<tr>
<th>Country</th>
<th>Core Center</th>
<th>Clinical Research/Trial Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U.S.</strong></td>
<td>NIH clinical center</td>
<td>GCRC/ CRC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approx. 80 facilities</td>
</tr>
<tr>
<td><strong>South Korea</strong></td>
<td>Clinical research centers</td>
<td>Accredited clinical trial</td>
</tr>
<tr>
<td></td>
<td>9→15 facilities</td>
<td>centers</td>
</tr>
<tr>
<td></td>
<td>(up to ‘14)</td>
<td>109 facilities</td>
</tr>
<tr>
<td><strong>Chinese Taipei</strong></td>
<td>General clinical research centers</td>
<td>Qualified hospitals</td>
</tr>
<tr>
<td></td>
<td>15 facilities</td>
<td>134 facilities</td>
</tr>
</tbody>
</table>
Current situation in Japan:
Due to the lack of an appropriate infrastructure for clinical research, clinical research of high quality aimed to develop new diagnoses and treatments for clinical applications has hardly been implemented in Japan.
Administrative initiatives to improve the clinical trial environment in Japan:
- Major initiatives -

- 3 Year Plan for Clinical Trial Activation:
  FY2003~2005
  MHLW, MECSST

- Planning for Next Clinical Trial Activation:
  Including Clinical Research Infrastructure Improvement
  FY2006
  MHLW, MECSST

- Clinical Research Infrastructure Improvement Plan:
  FY2006~2008
  MHLW
**Ethnic Similarity in Asia (1)**

Distribution of HBV genotype

**Ethnic Similarity in Asia (2)**

Comparison in terms of human genomes

![Graphs showing ethnic similarity](image)

Source: Nature 437, 1300-1320 (2005)
Ethnic Similarity in Asia (3)

Height & Weight

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Height</td>
<td>Weight</td>
</tr>
<tr>
<td>Chinese</td>
<td>Adult</td>
<td>169.7cm</td>
</tr>
<tr>
<td>Japanese</td>
<td>40’s</td>
<td>169.3cm</td>
</tr>
<tr>
<td></td>
<td>50’s</td>
<td>165.7cm</td>
</tr>
</tbody>
</table>

Life expectancy

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

Cause of death

<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>Hong Kong</td>
<td>Cancer (33.0%)</td>
<td>Heart disease (16.3%)</td>
<td>Brain disease (10.5%)</td>
<td>Pneumonia (8.9%)</td>
<td>Sudden accident/Poisoning (5.6%)</td>
</tr>
<tr>
<td>Japan</td>
<td>Cancer (31.0%)</td>
<td>Heart disease (15.3%)</td>
<td>Brain disease (13.6%)</td>
<td>Pneumonia (8.8%)</td>
<td>Sudden accident (4.1%)</td>
</tr>
</tbody>
</table>

Comparison of Max. Daily Doses in Japan and US/EU

Cardiovascular

- Pravastatin
- Simvastatin
- Captopril
- Enalapril
- Nifedipine
- Amlodipine

Statin

- Pravastatin
- Simvastatin

ACE-I

- Enalapril
- Captopril

Ca-B

- Nifedipine
- Amlodipine

PPI

- Omeprazole
- Lansoprazole
- Rabeprazole

H2-RB

- Famotidine
- Ranitidine
- Cimetidine
Differences in views on optimal doses between Japan and Europe/US

Using Captopril as an example

1971 Separated teprotide (nonapeptide) from snake toxin and synthesized it

\[ \text{Pyr-Trp-Prp-Arg-Pro-Gln-Ile-Pro-Pro} \]

1973 Administered teprotide intravenously to healthy people and hypertension patients
1973 Launched R&D of oral ACE-I
1974 Discovered lead compounds
1975 Synthesized captopril. Succeeded in optimizing lead compounds.

1977 Clinical trial of captopril
1981 Squibb: Obtained approval as a hypotensive agent (with usage restrictions)
1982 Sankyo: Obtained approval as a hypotensive agent (no usage restrictions)
1985 Squibb: Usage restrictions are lifted

\[ \sim 150 \text{ mg} \sim 75 \text{ mg} \sim 37.5 \text{ mg} \sim \]

High incidence of adverse drug reactions
Usage restrictions

Views on optimal dosage: Image

Other countries in Asia  South Korea Chinese Taipei  Japan

Accept doses used in Europe and the US
Seek doses suited to own country
Rigorous process to determine optimal dosage

It’s about time we begin considering doses suited for us
The Purpose of ICH

- Ensure a more timely introduction of new medicinal products to patients
- Contribute to the protection of public health
- Lead to a greater mutual acceptance of research and development to reduce and obviate the need for duplicate testing
- Maintain safeguards on quality, safety and efficacy

Source: ICH website (modified)

The Situation of Clinical Trials in Asia

- Quality: ICH-GCP
- Speed
- Cost
- Ethnic Similarity

It is natural for Asian countries to collaborate.
Role of Early Clinical Trials

• Comprehensive clinical assessment for establishment of a late clinical trial plan
  ➢ Tolerability, safety and pharmacokinetics
  ➢ Effects of meals and drug interactions
  ➢ Evaluation of the efficacy and therapeutic doses

• Determinants for a global development strategy
  ➢ Evaluation of the similarity between Japanese and non-Japanese in terms of tolerability, safety and pharmacokinetics
  ➢ global cooperative trials or regional trials

• Selection of projects with a high probability of success

→ Important stage for development strategy and investment decisions

The aim is to enable implementation of early clinical trials in Asia under the same strategy.
Problems for Japan’s in collaborating with Asia

Clinical trial
- J-GCP different from ICH-GCP: Essential documents, contracts, safety information, reliability survey, management
- Small number of patients enrolled for each site
- Distinct safety assessment method
- Rigorous views on optimal dosage

Scientific advice
- Not implemented in a timely manner

- There are numerous problems that must be actively resolved in order for Japan to participate
- Actively promote country-country dialogues in Asia
Promote approach to collaboration and mutual acceptance in Asia

- Clinical data for NDA: acceptance
- GCP inspection: acceptance, recognition (MOU)
- P-IV study: usage, acceptance

Aim at attaining even more comprehensive mutual acceptance in the future

So as to efficiently provide new therapeutic means to citizens of various countries
Existence of Unmet Medical Needs

- Parkinson's Disease
- Atopic dermatitis
- Chronic rheumatoid arthritis
- AIDS
- Chronic hepatitis C
- Diabetic neuropathy
- Osteoarthritis
- Diabetic nephropathy
- Neuromuscular disorder / myopathy
- Multiple sclerosis
- Alzheimer Disease
- Senile dementia
- MRSA infection
- SLE
- Pressure gangrene
- Cerebral apoplexy (including subarachnoid bleeding)
- Chronic glomerulonephritis
- Chronic renal failure
- Urinary incontinence / frequency
- Endometriosis
- Breast cancer
- Uterus cancer
- Prostatic cancer
- Gastric cancer
- Colon cancer
- Glaucoma
- Parkinson's Disease
- Alzheimer Disease
- Senile dementia
- Multiple sclerosis
- Neuromuscular disorder / myopathy
- Atopic dermatitis
- Chronic rheumatoid arthritis
- AIDS
- Chronic hepatitis C
- Diabetic neuropathy
- Osteoarthritis
- Diabetic nephropathy
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- Colon cancer
- Glaucoma