Overview of Drug Registration in China

- Focus on Current Status of Global Clinical Trials in China

Hong-Hao Zhou, MD
Why the need to globalize R&D?

- Expansion to regions with attractive R&D resources
  - Excellent human resources, high-level research/skills, government programs/support

- R&D that addresses regional illnesses
  - Tropical diseases, viral diseases, malignant tumors, etc.

- Selection of ideal companies
  - Incorporation of new compounds and technology
Asia, Pharma Market Growth

- A market with a huge population
- Vigorous momentum of economic development
- Rich resources of clinical cases
- Potentially huge Pharma market

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Global population</td>
<td>6.38 billion</td>
</tr>
<tr>
<td>Asian population</td>
<td>3.06 billion (48%)</td>
</tr>
<tr>
<td>China</td>
<td>1.31 billion</td>
</tr>
<tr>
<td>India</td>
<td>1.06 billion</td>
</tr>
<tr>
<td>Japan</td>
<td>0.13 billion</td>
</tr>
<tr>
<td>ASEAN</td>
<td>0.56 billion</td>
</tr>
</tbody>
</table>
Number of studies according to year of registration on Clinical Trials

Phase 3 Global Studies from 2005 to 2008

Number of studies according to year of registration on Clinical Trials

Japan
Korea
China
Singapore
Taiwan

- 2005
- 2006
- 2007
- 2008

Japan: 10, 24, 46, 103
Korea: 13, 24, 46, 80
China: 21, 46, 48, 103
Singapore: 48, 48, 41, 48
Taiwan: 69, 69, 69, 81
In 2011, China will become the third biggest market for pharmaceuticals in the World

<table>
<thead>
<tr>
<th>2009</th>
<th>2011</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>USA</td>
<td>USA</td>
</tr>
<tr>
<td>Japan</td>
<td>China</td>
<td>China</td>
</tr>
<tr>
<td>France</td>
<td>Germany</td>
<td>Germany</td>
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<tr>
<td>Germany</td>
<td>France</td>
<td>France</td>
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<tr>
<td>China</td>
<td>Spain</td>
<td>Spain</td>
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<tr>
<td>Italy</td>
<td>Italy</td>
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<tr>
<td>Spain</td>
<td>Brazil</td>
<td>Brazil</td>
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<tr>
<td>UK</td>
<td>UK</td>
<td>UK</td>
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<tr>
<td>Brazil</td>
<td>Australia</td>
<td>Australia</td>
</tr>
<tr>
<td>Canada</td>
<td>Russia</td>
<td>Russia</td>
</tr>
<tr>
<td>Russia</td>
<td>Turkey</td>
<td>Turkey</td>
</tr>
<tr>
<td>Turkey</td>
<td>India</td>
<td>India</td>
</tr>
<tr>
<td>India</td>
<td>Korea</td>
<td>Korea</td>
</tr>
<tr>
<td>Korea</td>
<td>Mexico</td>
<td>Mexico</td>
</tr>
<tr>
<td>Mexico</td>
<td>Venezuela</td>
<td>Venezuela</td>
</tr>
<tr>
<td>Venezuela</td>
<td>Greece</td>
<td>Greece</td>
</tr>
<tr>
<td>Greece</td>
<td>Poland</td>
<td>Poland</td>
</tr>
<tr>
<td>Poland</td>
<td>Dutch</td>
<td>Belgium</td>
</tr>
</tbody>
</table>

- 2009-2013:
  - 17 countries’ total sale of medicines: 90 billion USD
  - accounts for 48% of the total increase throughout the world. (2009: 37%)
China has been in the Global Expansion of Japanese Drug Company R&D

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>2002</td>
<td>Eisai establishes clin. research company</td>
</tr>
<tr>
<td>China</td>
<td>2003</td>
<td>Otsuka establishes clin. R&amp;D center in Beijing</td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>Otsuka establishes new-drug R&amp;D center in Shanghai</td>
</tr>
<tr>
<td>Singapore</td>
<td>2004</td>
<td>Takeda establishes clin. research company</td>
</tr>
<tr>
<td>Europe</td>
<td>2005</td>
<td>Astellas reorganizes research center in EU</td>
</tr>
<tr>
<td>India</td>
<td>2007</td>
<td>Eisai opens manufacturing and research center</td>
</tr>
<tr>
<td>Germany</td>
<td>2008</td>
<td>Daiichi-Sankyo acquires a bio-drug company as a subsidiary</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>2008</td>
<td>Otsuka buys bulk drug substance manufacturing company</td>
</tr>
<tr>
<td>UK</td>
<td>2007</td>
<td>Takeda buys bio venture company Paradigm Therapeutics</td>
</tr>
</tbody>
</table>
The shift from Japan to China

Relocation of research centers from Japan to China

<table>
<thead>
<tr>
<th>Company</th>
<th>Home Country</th>
<th>Location in Japan</th>
<th>Year of Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer</td>
<td>Germany</td>
<td>Kyoto</td>
<td>2004</td>
</tr>
<tr>
<td>Merck</td>
<td>US</td>
<td>Okazaki, Aichi Prefecture, Kumagaya, Saitama Prefecture</td>
<td>2006</td>
</tr>
<tr>
<td>Bayer</td>
<td>Germany</td>
<td>Kobe</td>
<td>2007</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>UK</td>
<td>Tsukuba</td>
<td>2007</td>
</tr>
<tr>
<td>Pfizer</td>
<td>US</td>
<td>Taketoyo, Aichi Prefecture</td>
<td>2008</td>
</tr>
<tr>
<td>Novartis</td>
<td>Switzerland</td>
<td>Tsukuba</td>
<td>2008</td>
</tr>
</tbody>
</table>
China is a very important area for Conducting MCTs in Asian region

Chinese and Japanese are very similar in genes

## Acceptance of Clinical Research Application in China

<table>
<thead>
<tr>
<th>Acceptance (BE excluded)</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic enterprise</td>
<td>2599</td>
<td>1447</td>
<td>646</td>
<td>757</td>
<td>697</td>
</tr>
<tr>
<td>Foreign enterprise</td>
<td>294</td>
<td>282</td>
<td>437</td>
<td>460</td>
<td>517</td>
</tr>
<tr>
<td>Intl. multi-center</td>
<td>72</td>
<td>74</td>
<td>70</td>
<td>131</td>
<td>205</td>
</tr>
</tbody>
</table>
Status of approval for entry into clinical trials in China in 2009

- 13 (category 1.1) new compounds of chemical drugs
- 1 (category 1) new compounds of TCM
- 48 new prescription formula of TCM (category 6)
- 28 clinical trial applications

Approved for manufacturing
Special review and approval
Status of international multicenter clinical trials in China

Fig. 1 Volume of international multicenter clinical trials approved from 2005 to 2009

Volume approved (number)

Time (Year)
<table>
<thead>
<tr>
<th>Benefits of Conducting International Multicenter Trials in China</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Country:</strong> Saving clinical research source</td>
</tr>
<tr>
<td>2. <strong>Doctor:</strong> Improving physician’s professional competence</td>
</tr>
<tr>
<td>3. <strong>Patients:</strong> Obtaining new therapies</td>
</tr>
<tr>
<td>4. <strong>Industry:</strong> Promoting new drug development</td>
</tr>
</tbody>
</table>
Evaluation of Foreign Trial Data

Core of Evaluation:

- Does the drug’s safety and efficacy profile provide adequate risk/benefit to the treated patient population?
Evaluation of Foreign Trial Data

- **Discovery**
  - Early development clinical trials
  - Clinical pharmacology assessment
  - PK/PD
  - Dosing regimen

- **Exploratory Development**
  - LEARN

- **Full Development**
  - COMFIRM
  - Pivotal Trials
  - Global study data
  - Asian data
  - Design: eligibility criteria, primary endpoints, comeds, safety endpoints, Medical practice difference
  - Label
Evaluation of Foreign Trial Data

- Global trial data
- Asian data
- Clinical pharmacology difference
- Medical practice difference, when compared to China
Evaluation of Data from Japan & Korea

Global trial data

Asian data

✓ Clinical pharmacology difference

✓ Medical practice difference, when compared to China
Impact of medical practice diff. among China, Japan, and Korea on drug safety & efficacy

- **Disease definition**: differences in epidemiology of the same disease in China vs. foreign countries
- **Patient population**: influence of food, lifestyle, and culture on the drug treatment
- **Disease diagnosis/treatment**: diagnostic method, SOC, cosmeds, compliance, experience with the drug of individual doctors
- ............
Difference in medical practice

Impact of medical practice diff. among China, Japan, and Korea on drug safety & efficacy

- **Impact on efficacy**
  - Epidemiology, diagnostic methods, comeds, ......

- **Impact on safety**
  - Food, culture, comeds, ......
Evaluation Considerations

- Global study data
- Asian data
- Clinical pharmacology
- Medical practice differences, when compared to China

Does ADME involve receptors, enzymes, and transporters that show ethnic differences?
Evaluation of Ethnic Pharmacokinetic (PK) Data

- Global data contain Chinese PK data
  - Doses (two dose arms)
  - Methodology

- Comparison of ethnic PK data
  - Chinese
  - Caucasian
  - Japanese
  - Black
Evaluation of Ethnic Pharmacokinetic Data (Cont’d)

(1) Linear PK in the studied dose range
(2) Comparable PK in different ethnic groups
(3) Comparable PK variability in different ethnic groups
**Evaluation of Ethnic Pharmacokinetic Data (Cont’d)**

Evaluate PK exposures: Chinese vs. Caucasian

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ratio</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0~24</td>
<td>0.90</td>
<td>0.81-1.11</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.92</td>
<td>0.83-1.01</td>
</tr>
</tbody>
</table>

- No statistically significant difference in PK exposures between Chinese and Caucasian
- In general, comparable PK in different ethnic groups
Key Considerations When Extrapolating Data Among China, Japan, and Korea

- Differences in drug safety and efficacy among three countries
  - Reflect combined differences in races, regions, and countries
  - Can not be solely explained by ethnic differences in genes and drug disposition
Considerations of CDE:
Acceptability of Foreign Data

- Global study data
- Asian data
- ADME
- Medical practice differences, when compared to China
# Japan Application by Using Foreign Clinical Trial Data

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### Centered in Asian Data

<table>
<thead>
<tr>
<th>Product</th>
<th>DETRUSITOL (Tolterodine)</th>
<th>NULOTAN (Losartan)</th>
<th>HERCEPTIN (Trastuzumab)</th>
<th>CRAVIT (Levofloxacin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Company</strong></td>
<td>Pfizer</td>
<td>Banyu</td>
<td>Chugai</td>
<td>Daiichisankyo</td>
</tr>
<tr>
<td><strong>Approval</strong></td>
<td>April, 2006</td>
<td>April, 2006</td>
<td>Feb, 2008</td>
<td>April, 2009</td>
</tr>
<tr>
<td><strong>Study Type</strong></td>
<td>Asian Study</td>
<td>Global Study</td>
<td>Global Study</td>
<td>(Domestic Study)</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>New active element</td>
<td>New indication</td>
<td>New indication/ New dosage</td>
<td>New dosage/New formulation</td>
</tr>
</tbody>
</table>
Key Factors to the Success of CT in China

<table>
<thead>
<tr>
<th>Investigator’s Cooperation</th>
<th>Patient Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>The IMP and the therapeutic area</td>
<td># of the potential subjects</td>
</tr>
<tr>
<td>Safety and effectiveness as proved via overseas CT</td>
<td>Coastal cities with Beijing &amp; Shanghai as the central point</td>
</tr>
<tr>
<td>Budget</td>
<td>PI’ s reputation and impact</td>
</tr>
<tr>
<td>Relationship with the investigator</td>
<td>Appropriate inclusion</td>
</tr>
<tr>
<td>Academic support</td>
<td>Attractive compensations</td>
</tr>
<tr>
<td>MNC’s advantage in terms of opportunities in academic exchange</td>
<td>Appropriate inclusion and exclusion criteria</td>
</tr>
<tr>
<td>Proactive approach to issues</td>
<td>Proactive approach to issues</td>
</tr>
</tbody>
</table>
Time for Examination and Approval of Clinical Trials (IND)

IND

review
Communication

China  6M+2M (review meeting)
Japan  1M
Korea  2M
Singapore  2M
Hong Kong  2M

Longer Period
1. w.e.f Oct 1, 2007

2. on-site inspections for Manufacturing Application on NDA application was added

3. allows “Special Examination”
In order to encourage research and development of new drugs and strengthen risk control and management, the SFDA formulated Requirements on Special View and Approval of New Drug Registration, which was formally issued and implemented as of January 7, 2009.

The Requirements follow the general principles for special approval of new drug registration:
- early intervention
- priority review
- multi-channel communication
- dynamic data supplement
Special Examination and Approval

Following requirements should be met:

1. New active ingredients and its preparation extracted from natural drugs, or preparation made of material from plant, animal and minerals, which have not been marketed in China;

2. Drug raw material and its preparations, and biological product that have not been marketed domestically or outside China;

3. New antiviral drug for AIDS and drug used for diagnosis and prevention of AIDS, cancer and orphan drug;

4. New drugs which treat diseases for which there is no effective therapy.

Drugs satisfied requirements 1 and 2 will be applied in IND phase. Drugs satisfied requirements 3 and 4 will be applied in NDA phase.
Advantages to Obtain Special Examination and Approval

- Pre-consultation is available.

- Shorter technical evaluation:
  - IND: 90 Days → 80 Days
  - NDA: 150 Days → 120 Days

- Supplemental information can be submitted.
Article 44

1. The drug used for an international multi-center clinical study shall be one already registered in a foreign country or in phase II or phase III clinical trials.

2. SFDA may request the applicant to firstly conduct the Phase I clinical trials in China;

3. During a study conducted in China, the Applicant shall report to SFDA any serious adverse events or unexpected adverse events which occur in any countries

4. Upon the completion of the study, the Applicant shall submit the complete clinical study report to SFDA

5. Data generated from an international multi-center clinical trial used for drug registration in China, shall be in accordance with the relevant provision of this Regulation, and the applicant shall submit the complete research information of the study
CT in China: Today and Tomorrow

**Opportunities**
- Lower cost
- Larger patient pool
- Rapid patient recruitment

**Challenges**
- Slow regulatory process
- Less experience in conducting CT according to ICH GCP
- Blood/tissue export permit
Outlook for Drug Development in Asia

- Accelerated interaction/information exchange between regulatory authorities
- Progression of specific clinical development projects within the drug industry

If the industry and the regulatory authorities unite their efforts in tackling issues, we will be able to achieve things that we couldn’t in the past.
Chinese Govt. Actively Encourages MNCs to Establish R&D Centers in China

Zhongguancun Science and Technology Park, Beijing, China
China Medical City, Taizhou, China

Zhangjiang High-Tech Park, Shanghai, China (Red frame: bio Valley [Medicine Valley])
Chinese Govt. Actively Encourages MNCs to Establish R&D Centers in China
Regulatory Trends in CHN, JPN and KOR

April 2007: Joint Communiqué of Health Ministers

April 2008: Agreement at Director-General Level Meeting

August 2009: First meeting of Working Group
CHN, JPN and KOR Working Group Meeting

1st
Aug 18, 2009
Tokyo

2nd
Dec 18, 2009
Beijing

3rd
Sep 14, 2010
Seoul
2010年9月13日在韩国召开了第三次中日韩三国药品监管部门司局长级会议，会议同意了会议工作小组规程，并同意了有关在工作小组中进行药品临床试验种族差异研究项目的设想草案中的主要内容。

**Concept Paper (概念文件)**

Research Project on ethnic factors in clinical data from three countries
China-Japan-Korea Working Group on Drug Clinical Trials
In 2007 three Health Ministers from China, Japan and Korea agreed to cooperate to enhance Clinical Trials in the Countries.

In their meeting on Dec.17, 2009, the responsible Director-Generals (DGs) from the three countries’ drug regulatory authorities, i.e. SFDA, KFDA and MHLW/PMDA agreed to establish Working Group on Drug Clinical Trials (WG) to further advance the cooperation.

The DG meeting tasked the WG to implement two projects:
- Research on ethnic factors in clinical data from three countries
- Information on drug clinical trials.

The establishment of the research project reflects the fact that the ethnic factors in clinical data are one of the crucial issues in today’s global drug development.
Research Group

- **Research Group**
  In order to pursue the research project on ethnic factors, Research Group on Ethnic Factors (RG) is established as a subsidiary body of WG.

- **RG members**
  Each county nominates up to 6 experts. One of them is designated as the country’s Principal Researcher (PR). One member from the regulatory authority is designated as a contact point for each country.

- **RG objectives**
  RG itself does not conduct any co-operative experiment. The mission of the RG is to make scientific discussion to achieve the objective of research on ethnic factors in Drug Clinical Trial data from three countries, described in WG Terms of Reference.
Methods of RG

f. RG members can conduct research (wet and/or dry study) on their own or in cooperation with other RG members and submit the outcome to RG.

g. RG discussion can include the following items, but is not limited to them;

- Evaluation of data/material for discussion
- Existence and magnitude of ethnic factors in clinical data
- Implication of ethnic factors in clinical development and drug review.
Acknowledgement

Many thanks to

Dr. Tatsuya Kondo from Pharmaceuticals and Medical Devices Agency and

Dr. Zhi-Min Yang from Center for Drug Evaluation, State Food & Drug Administration of China

for their kindly providing important data and slide materials.