Drug Development / Regulatory Issues in Asia

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Acknowledgements & Affiliations

• Contributors to ideas presented today
  – Faculty of ACDRS, CCDRS
  – **Toshi Tominaga**, Food and Drug Evaluation Center, Osaka City Univ. Hospital
  – **Peter Honig**, AstraZeneca
  – **Zili Li**, Gates Foundation
  – **Theo Jang**, Seoul National University, Seoul, South Korea

• Disclosures
  – [CDDS](http://cdds.ucsf.edu)
  – NDA Partners LLC ([www.ndapartners.com](http://www.ndapartners.com))
Summary

- Drug development & regulatory capacities are rapidly evolving in several Asian countries
  - Most aggressive in Japan, Korea and China
  - Key influencing factors vary
  - Clinical trial infrastructure development is needed in most Asian countries
  - Drug regulatory agencies are evolving, mostly limited in resources, and conservative -- presenting barriers to innovation and development
DD / R Issues in Asia

• Why this topic?

  – 55% of all (170 million) HepC patients worldwide are Asian *

  – HepC prevalence 2-3 X that of USA (1.3%) *

  – Asians are among the fastest growing groups of new Americans
    • Risk to non-Asian Americans
    • Opportunities for R&D ?

Population: 4 Billion (2011)

Countries: China, Japan, India, Singapore, Thailand, Hong Kong, North Korea, Malaysia, Philippines, Indonesia, South Korea, Vietnam, Turkey, Myanmar, Israel, Pakistan, Cambodia, Iran, Maldives, Sri Lanka, Bangladesh, Taiwan, Kazakhstan, Syria, Saudi Arabia, United Arab Emirates, Qatar, Laos, Afghanistan, Nepal, Mongolia, Macau, Kyrgyzstan, Bhutan, Bahrain, Uzbekistan, Kuwait, Azerbaijan, Brunei, Jordan, Oman, Lebanon, Yemen, Iraq, Tajikistan, Turkmenistan, Timor-Leste, Christmas Island, Cocos (Keeling) Islands, Palestinian National Authority, ...
DD/R Issues in Asia

• Drug Development
  – Capacity for
    • Innovation / Discovery
    • Non-clinical studies
    • Learning Trials
    • Confirming Trials

• Regulation
  – Agencies
    • Rules / barriers
    • Opportunities
    • Harmonization
Drug Development Capacities

• Innovation –
  – Maturing in Japan, Korea
  – Infrastructure evolving in China, India
  – Important factors
    • Government funding and private investment
    • Entrepreneurial culture
    • University supply of researchers and research
    • Collaboration & translation resources
    • Patent protection
    • Reward
we identified 376 medicinal or vaccine candidates within the pipelines of 66 indigenous companies in China, India and Brazil (Unpublished Results). An estimated 60% of the 376 candidates involve new chemical or molecular entities.
### Innovation

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>China</td>
<td>1.5 (2008)</td>
<td>102</td>
<td>12%, [23.4%]</td>
<td>26.5%</td>
<td>25.7 (48.8)</td>
</tr>
<tr>
<td>India</td>
<td>0.80</td>
<td>24.8</td>
<td>2.3%, [4.7%]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>42%*</td>
<td>14.1 (30.4)</td>
</tr>
<tr>
<td>Brazil</td>
<td>1.10</td>
<td>20.3</td>
<td>1.6%, [12.2%]&lt;sup&gt;***&lt;/sup&gt;</td>
<td>N/A</td>
<td>15.3 (34.4)</td>
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<tr>
<td>Canada</td>
<td>1.84 (2008)</td>
<td>24.0</td>
<td>2.7%</td>
<td>3.9%</td>
<td>26.6 (30.2)</td>
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<tr>
<td>Germany</td>
<td>2.54</td>
<td>72.2</td>
<td>4%08</td>
<td>5.7%</td>
<td>37.9 (41.5)</td>
</tr>
<tr>
<td>Japan</td>
<td>3.44</td>
<td>148</td>
<td>4.8%</td>
<td>4.5%</td>
<td>72.4 (102.7)</td>
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<tr>
<td>United States</td>
<td>2.82 (2008)</td>
<td>398</td>
<td>16%</td>
<td>2.6%</td>
<td>292.8 (344.7)</td>
</tr>
</tbody>
</table>

China

- 1992-12: 54 high-tech parks, 20 w/ life sciences component

- Publication & citation rates increasing 16.5%/yr, now 5th globally

Japanese pharmaceutical R&D ability

Origins of the world top 100 medicines


Source: Office of Pharmaceutical Industry Research (OPIR), based on the data from IMS LifeCycle (IMS Health) and Pharmaprojects

Adapted from Toshi Tominaga presentation “The Role of Japan in Global Drug Development”. ACDRS 2012
Drug Development Capacities

• **Discovery & Non-clinical services – China, India**
  – High throughput chemistry, target screening, biology, lead optimization
  – DMPK
  – Toxicology
  – Biopharmaceutics & formulation

• **India** - strong in biopharmaceutics university education and generics industry
  – Some generics companies now developing new drugs

• **China** – WuXi et al, emerging generics industry
  – Growing concentration of global pharma & biotech companies in Shanghai, Tianjin
Drug Development Capacities

• Phase 1/2 “Learning” Trials
  – As far as I know, with the exception of South Korea, few if any first-in-human trials of NME’s are permitted in Asian countries
  – University and CRO based phase 1 learning studies units are active in China, Japan and South Korea
SOUTH KOREA
Phase I trials
Seoul National University Hospital (SNUH)
### SOUTH KOREA
Multi-Ethnic PK Studies
SNUH

<table>
<thead>
<tr>
<th>Duration/Subject No.</th>
<th>Design</th>
<th>Purpose of Study</th>
<th>Etc.</th>
</tr>
</thead>
</table>
| **2012**  
Japanese 36 + Chinese 36 | Dose block-randomized, double-blind, placebo-controlled | Tolerability, PK | Recruit Japanese in Japan, Chinese in Korea |
| **2011**  
| **2011**  
Japanese 24 + Chinese 24 + Caucasian 8 | Dose block-randomized, double-blind, placebo-controlled | Tolerability, PK | Recruit Japanese in Japan, Chinese & Caucasian in Korea |
| **2012**  
Chinese 5 + Caucasian 11 | Randomized, double-blind, placebo-controlled | Tolerability, PK | Recruit Chinese and Caucasian in Korea |
| **2012**  
Japanese 50 + Chinese 50 | Dose block-randomized, double-blind, placebo-controlled | Tolerability, PK, PD | Recruit Japanese in Japan and Korea, Chinese in Korea |
Drug Development Capacities

• Confirming Trials
  – Japan, China, India participate in multinational clinical trials
  • Quality issues include
    – Investigator and trial staff training and competence
    – Protocol execution
Global trends in Participation in Clinical Trials

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Number of sites</th>
<th>Share (%)</th>
<th>ARAGR (%)</th>
<th>Trial capacity</th>
<th>Trial density</th>
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<tr>
<td>1</td>
<td>United States</td>
<td>36,281</td>
<td>48.7</td>
<td>-6.5↓</td>
<td>43.7</td>
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<td>2</td>
<td>Germany</td>
<td>4,214</td>
<td>5.7</td>
<td>11.7↑</td>
<td>10.9</td>
<td>51.2</td>
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<td>3</td>
<td>France</td>
<td>3,226</td>
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<td>-4.0 ↓</td>
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<td>3,032</td>
<td>4.1</td>
<td>-12.0↓</td>
<td>8.6</td>
<td>92.2</td>
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<td>5</td>
<td>Spain</td>
<td>2,076</td>
<td>2.8</td>
<td>14.9↑</td>
<td>6.8</td>
<td>46.4</td>
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<td>8.1↑</td>
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<td>10.3↑</td>
<td>33.4</td>
<td>15.7</td>
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<td>1,753</td>
<td>2.4</td>
<td>-9.9↓</td>
<td>7.6</td>
<td>29.1</td>
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<td>Netherlands</td>
<td>1,394</td>
<td>1.9</td>
<td>2.1↑</td>
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<td>1.6</td>
<td>17.2↑</td>
<td>5.3</td>
<td>30.9</td>
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<td>11</td>
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<td>1,131</td>
<td>1.5</td>
<td>8.1↑</td>
<td>5.4</td>
<td>54.4</td>
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<td>Russia*</td>
<td>1,084</td>
<td>1.5</td>
<td>33.0↑</td>
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<td>757</td>
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<td>5.1</td>
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<td>Sweden</td>
<td>739</td>
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<td>Mexico*</td>
<td>683</td>
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<td>22.1↑</td>
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<td>20</td>
<td>Hungary*</td>
<td>622</td>
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<td>22.2↑</td>
<td>4.1</td>
<td>62.5</td>
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<tr>
<td>21</td>
<td>South Africa*</td>
<td>553</td>
<td>0.7</td>
<td>5.5↑</td>
<td>4.3</td>
<td>11.0</td>
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<td>22</td>
<td>Austria</td>
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<td>65.1</td>
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<tr>
<td>23</td>
<td>China*</td>
<td>533</td>
<td>0.7</td>
<td>47.0↑</td>
<td>5.3</td>
<td>0.4</td>
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<tr>
<td>24</td>
<td>Denmark</td>
<td>492</td>
<td>0.7</td>
<td>9.2↑</td>
<td>4.4</td>
<td>90.3</td>
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<tr>
<td>25</td>
<td>South Korea*</td>
<td>466</td>
<td>0.6</td>
<td>17.9↑</td>
<td>3.4</td>
<td>9.5</td>
</tr>
</tbody>
</table>

*Countries in emerging regions; ARAGR, average relative annual growth rate. Trial capacity is the number of sites in the country involved in large trials (20 or more sites) divided by the number of large trials in the country. Trial density is the number of recruiting sites on April 17th 2007 divided by the country population in millions.

Significant Growth in Asia and other Emerging Economies

Drug Development Capacities

• Regulation
  – Agencies
    • Rules / barriers
    • Opportunities
    • Harmonization
**US FDA and Chinese State FDA (SFDA)**

**Innovative Drug**
- CDER: 3712*
  - Medical Reviewers: 350-450
  - CMC Reviewers: 250-300

**Generic Drug**
- SFDA/CDE: 120
  - Medical Reviewers: 22
  - CMC Reviewers: 31

*Based on Proposed FTE for 2012, excluding field activities, CDE website

Adapted from Zili Li presentation “The Role of China and Emerging Market in Global Drug Development – A Regulatory Perspective”. ACDRS 2012
SFDA
IND and NDA Review Times

Domestic Clinical Trials

IND Review Times (months)

<table>
<thead>
<tr>
<th>Year</th>
<th>Data Source</th>
<th>N</th>
</tr>
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<td>12.1</td>
<td>16</td>
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<tr>
<td>2007</td>
<td>13.6</td>
<td>18</td>
</tr>
<tr>
<td>2008</td>
<td>17.5</td>
<td>23</td>
</tr>
<tr>
<td>2009</td>
<td>15.7</td>
<td>34</td>
</tr>
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<td>2010</td>
<td>17.6</td>
<td>35</td>
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<tr>
<td>2011</td>
<td>21.5</td>
<td>14</td>
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</table>

NDA Review Times (months)

<table>
<thead>
<tr>
<th>Year</th>
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<th>N</th>
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</thead>
<tbody>
<tr>
<td>2006</td>
<td>11.5</td>
<td>5</td>
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<tr>
<td>2007</td>
<td>15.1</td>
<td>6</td>
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<tr>
<td>2008</td>
<td>18.2</td>
<td>17</td>
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<td>2009</td>
<td>17.2</td>
<td>8</td>
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<td>2010</td>
<td>18</td>
<td>17</td>
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<tr>
<td>2011</td>
<td>21.4</td>
<td>5</td>
</tr>
</tbody>
</table>

Data Source: RDPAC regulatory taskforce report, August 2012

Adapted from Zili Li presentation “The Role of China and Emerging Market in Global Drug Development – A Regulatory Perspective”. ACDRS 2012
SFDA
IND and NDA Review Times

Multinational Clinical Trial Applications

Data Source: RDPAC regulatory taskforce report, August 2012

Adapted from Zili Li presentation “The Role of China and Emerging Market in Global Drug Development – A Regulatory Perspective”. ACDRS 2012
Japanese Drug Regulatory Authority

1. Ministry of Health, Labour and Welfare (MHLW)
   - takes ultimate responsibility

2. Pharmaceuticals and Medical Devices Agency (PMDA)

PMDA Staff Size

Adapted from Toshi Tominaga presentation “The Role of Japan in Global Drug Development”. ACDRS 2012
# PMDA

## NDA Review Times

### Priority Review Products

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</thead>
<tbody>
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<td>Total Review Time (Month)</td>
<td>12.3</td>
<td>15.4</td>
<td>11.9</td>
<td>9.2</td>
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<td>9</td>
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<td>Regulatory Review Time</td>
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<td>4.2</td>
<td>6</td>
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<tr>
<td>Applicant's time</td>
<td>6.5</td>
<td>6.8</td>
<td>6.4</td>
<td>3.4</td>
<td>2.0</td>
<td>3</td>
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### Standard Review Products

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<td>Total Review Time (Month)</td>
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<td>7.6</td>
<td>6.3</td>
<td>9</td>
</tr>
<tr>
<td>Applicant's time</td>
<td>7.9</td>
<td>7.4</td>
<td>6.7</td>
<td>6.4</td>
<td>5.1</td>
<td>3</td>
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</tbody>
</table>
Regional Harmonisation Initiatives:

ICH - Global Cooperation Group (GCG)
- Regional Harmonisation Initiative representatives and individual DRAs participate in ICH technical discussions

Asia Pacific Economic Cooperation (APEC) and Association of Southeast Asian Nations (ASEAN)
- Asian Economic Community (AEC) - harmonization of technical standards and regulatory requirements under the Pharmaceutical Product Working Group (PPWG)
Assisting SFDA/CDE in Building Regulatory Capacity and Capability – US FDA

Adapted from Zili Li presentation “The Role of China and Emerging Market in Global Drug Development – A Regulatory Perspective”. ACDRS 2012
Summary

• Drug development & regulatory capacities are rapidly evolving in several Asian countries
  – Most aggressive in Japan, Korea and China
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