Industry Perspectives on the Adoption of ICH Guidelines in Asia

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Comments in this presentation reflect the views of the presenter and not necessarily those of PhRMA nor of Pfizer Inc.
Outline of Topics

• Why Is This Discussion Important?

• Regional Harmonization Initiatives

• Progress in Implementing ICH - One Industry Person’s perspective

• Success and The Future
A reminder.....

Why is this discussion even important?
Asian Unmet Medical Need

Cardiovascular
• Stroke is much more prevalent than coronary artery disease (CAD) in Asia.
• In China alone: 800,000 to 1 Million deaths per year from Stroke
  Six Million Stroke Survivors

Infectious Disease
• Hepatitis B affects 2 billion people worldwide
• 360 Million chronically infected
• 25% of chronically affected will die of complications
• No effective treatments: Lamuvidine-resistance; Adenovir- nephrotoxicity

Oncology
• More than half of all cancer deaths worldwide occur in Asia
• Second and Third most common causes of cancer death worldwide are Stomach and Liver Cancer (rare in the West)
• Most Asia Specific Cancers are unmet medical needs with few options
Unprecedented Asian Oncology Unmet Medical Need

**Unmet medical need**

**Annual deaths from cancer (Millions)**

- **US**: 0.7
- **Asia**: 3.4

- **Prevalent Cancers in Asia**: 57%
- **Head and neck**:
- **Oesophagus**:
- **Liver**
- **Stomach**
- **All other**
Gross Domestic Product (GDP) Per Capita Vs Health Expenditures Per Capita

Direct correlation between GDP per capita & healthcare spending

Healthcare Spenditure Per Capita

R = 0.9116

GDP Per Capita
Status of Countries Participating in Global Clinical Trials

Number of Phase III trials sponsored by industry

2003-2006 Cumulative Average Growth Rate of Phase III trials by region*

- North America: 34%
- Australia/New Zealand: 41%
- Western Europe: 48%
- Africa/Middle East: 48%
- Eastern Europe: 52%
- Latin America: 53%
- Asia: 59%

* Trials may contribute to growth in multiple regions
Source: Clinicaltrials.gov; team analysis
# CAGR of Phase III Clinical Trials By Country

Phase III trials sponsored by industry

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>58</td>
<td>4</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>India</td>
<td>106</td>
<td>9</td>
<td>11</td>
<td>54</td>
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<tr>
<td>Czech</td>
<td>100</td>
<td>963</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td>Poland</td>
<td>144</td>
<td>378</td>
<td>23</td>
<td>26</td>
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<tr>
<td>Russia</td>
<td>128</td>
<td>90</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Argentina</td>
<td>99</td>
<td>250</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Brazil</td>
<td>92</td>
<td>48</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Mexico</td>
<td>89</td>
<td>85</td>
<td>8</td>
<td>25</td>
</tr>
</tbody>
</table>

Source: Clinicaltrials.gov; Global Insight; IMS; team analysis
*CAGR Cumulative Annual Growth Rate
### Participation In Clinical Trials 2005 Versus 2008

<table>
<thead>
<tr>
<th>COUNTRY / REGION</th>
<th>Year 2005</th>
<th>%</th>
<th>Year 2008</th>
<th>%</th>
<th>Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>WORLDWIDE *</td>
<td>13007</td>
<td>100.0%</td>
<td>16972</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>6469</td>
<td>49.7%</td>
<td>8348</td>
<td>49.2%</td>
<td>-1.1%</td>
</tr>
<tr>
<td>CANADA</td>
<td>1299</td>
<td>10.0%</td>
<td>1146</td>
<td>6.8%</td>
<td>-32.4%</td>
</tr>
<tr>
<td>GERMANY</td>
<td>1024</td>
<td>7.9%</td>
<td>1082</td>
<td>6.4%</td>
<td>-19.0%</td>
</tr>
<tr>
<td>UK</td>
<td>669</td>
<td>5.1%</td>
<td>774</td>
<td>4.6%</td>
<td>-11.3%</td>
</tr>
<tr>
<td>EUROPE</td>
<td>3348</td>
<td>25.7%</td>
<td>4274</td>
<td>25.2%</td>
<td>-2.2%</td>
</tr>
<tr>
<td>SOUTH AMERICA</td>
<td>312</td>
<td>2.4%</td>
<td>532</td>
<td>3.1%</td>
<td>30.7%</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>182</td>
<td>1.4%</td>
<td>363</td>
<td>2.1%</td>
<td>52.9%</td>
</tr>
<tr>
<td>CHINA</td>
<td>141</td>
<td>1.1%</td>
<td>321</td>
<td>1.9%</td>
<td>74.5%</td>
</tr>
<tr>
<td>INDIA</td>
<td>139</td>
<td>1.1%</td>
<td>231</td>
<td>1.4%</td>
<td>27.4%</td>
</tr>
</tbody>
</table>

Source: DIA 21st EuroMeeting; Challenges, Risks and Benefits of Conducting Clinical Trials in Developing Regions
ICH and Regional Harmonization Initiatives

• Why This Matters

• Regional Harmonization Initiatives

• Progress in Implementing ICH - One Industry Person’s perspective

• Success and The Future
INTERNATIONAL CONFERENCE ON HARMONIZATION of Technical Requirements for the Registration of Pharmaceuticals for Human Use

http://www.ich.org
Hosted by ICH Secretariat
IFPMA-Geneva, Switzerland

Source: APEC/LSIF meeting in Peru in July, 2008
Historical Perspective

• 1990: ICH was created (Regulators and Industry from Europe, Japan, and the US)
  – Canada, EFTA, and WHO as Observers
  – Goal to make regulatory environment for drug development more efficient and to avoid duplication
• 1999: Global Cooperation Group (GCG) formed by ICH
  – Goal to make ICH information available to any requestor
  – Regional Harmonization Initiatives (RHIs) added in 2003
  – Individual Drug Regulatory Authorities invited: Australia, Brazil, China, Chinese Taipei, India, Russia, Singapore, and South Korea
• 2008: Regulators Forum established by ICH
Regional Harmonization Initiatives

Pan American Network on Drug Regulatory Harmonization (PANDRH)
Southern African Development Community (SADC)
Association of Southeast Asian Nations (ASEAN)
Asia-Pacific Economic Cooperation (APEC)
Gulf Cooperation Countries (GCC)
Regional Harmonization Initiatives (RHIs) Brought in New Opportunities

- Establishes two-way dialogue, collaboration

- Provides opportunity to better understand ICH guidelines and process

- Provides opportunity to better understand the needs of other regions

- Provides opportunity for sharing of best practices

*Shifted from information-sharing to implementation/training*
ICH Harmonized Guidelines

- **Serve as standard** - with regulators in ICH and many non-ICH regions.

- **Define fundamentals of GCP** – e.g., US FDA uses ICH as benchmark on which to base compliance actions (ICH E6)

- **Provide framework** around which to develop good review practices

- **Implementation is the key next step**
  - Current focus of ICH activity
Progress in the Region

- Quality
- Good Clinical Practice
- Common Technical Document
- Success and The Future
## Identified Challenges in Non-ICH Regions

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Relevant ICH Topics</th>
<th>Industry perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability testing in special</td>
<td>ICH Q1A(R2), Q1B, Q1C, Q1D, &amp; Q1E</td>
<td>Good Progress</td>
</tr>
<tr>
<td>climate zones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality by Design</td>
<td>Newer ICH “Q” topics (Q8/Q8R, Q9, Q10)</td>
<td>Under consideration</td>
</tr>
<tr>
<td>When to conduct bridging studies</td>
<td>ICH E5</td>
<td>Some Progress</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>ICH E6 (GCP), other “E” topics</td>
<td>Good Progress</td>
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<tr>
<td>Registration dossier and</td>
<td>ICH M4 (CTD) &amp; M2 (eCTD)</td>
<td>Concept being embraced, electronic tools limited</td>
</tr>
<tr>
<td>variations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety reporting</td>
<td>ICH E2A, E2B(R2) &amp; MedDRA</td>
<td>Being embraced</td>
</tr>
<tr>
<td>Inspections (GMP/GCP/PV)</td>
<td>Not direct ICH topic, but being addressed in ICH Regulators Forum</td>
<td>ICH guidelines provide framework; Regulators to share good practices</td>
</tr>
</tbody>
</table>
## Impact of ICH Quality

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>ICH Q1A guideline: <em>Stability Testing of New Drug Substances and Products</em></td>
</tr>
<tr>
<td>2000</td>
<td>ICH Q1A(R): Revision to expand practical application</td>
</tr>
<tr>
<td>2003</td>
<td>ICH Q1A(R2): Revision as a consequence of Q1F</td>
</tr>
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**Before ICH Q1A:** Acceptable storage conditions included uncontrolled room temperature and uncontrolled humidity. **After ICH Q1A was implemented:** Carefully controlled storage conditions (e.g., $25 \pm 2 \, ^\circ\text{C}$ temperature and $60 \pm 5\%$ relative humidity) were instituted to preserve product quality.

**NB:** Regulatory authorities in the ICH regions have agreed that the use of more stringent humidity conditions, such as $30\, ^\circ\text{C}/75\%$ RH, are acceptable should the applicant decide to use them.
Good Clinical Practice

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- Investigators, Regulators, and Sponsors have increased dialogue directed at supporting global clinical trials and understanding when bridging studies/local studies needed

- More global studies are being placed in Asia
  - Increasing capability of investigators and staff
  - Increasing quality of data
  - Increasing drug development capability in country/region

- AND ….there is more to do
Indicators of Success in the clinical area

Indicators of Success:

• The number and sites for clinical trials increase
• Faster approvals to start clinical trials
• Types of trials reflect the innovation a country wants to attract, e.g., multi-national vs local trials or both
• Increased numbers of patients recruited into studies
• Level of quality of data increases
• Level of compliance to regulatory requirements and international best practices increases
• Increased number of applications and approvals for clinical trials
• The review timeline for marketing applications shortens
Singapore Health Sciences Authority

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</tr>
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<tbody>
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<td>ICH M4 (CTD) and M2 (eCTD)</td>
<td>Concept being embraced, electronic tools limited</td>
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- All new and generic drug applications must conform to either the ICH CTD format or the ASEAN CTD format
- As of December 2008, more than 50% of applications are in ICH CTD format

**ICH M4 CTD**
- Module 1: Local Administrative
- Module 2: Overview & overall summaries
- Module 3: Quality
- Module 4: Non-clinical
- Module 5: Clinical

**ASEAN CTD**
- Part I: Local Administrative
- Part II: Quality
- Part III: Non-clinical
- Part IV: Clinical
• Adoption of the ICH Common Technical Document (M4) in APEC is also important in structuring information, particularly Quality information, according to global standards.
• Korea has accepted CTDs to date only requiring the local information (Module 1) in Korean.
• New guidance on CTDs for Korea available
• Local promotion of Good Review Practices in Korea are consistent with FDA review practices.
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- Adoption of the ICH regulatory definitions of seriousness of adverse reactions (ICH E2A) extends far beyond the ICH regions in the interest of protecting patient safety.
- Use of the MedDRA terminology to classify adverse reaction terms and other medical concepts is important for best use of medicines.
- National pharmacovigilance centers may use either MedDRA or WHO-ART to report ADRs to the WHO Uppsala Monitoring Centre.
- Electronic reporting (E2B) of individual case safety reports will improve efficiency as local capacity evolves.
Conclusion and The Future

• The geographical face of international drug development and trade is rapidly changing

• ICH guidelines support science and risk-based regulatory decision-making in all regions including non-ICH regions

• Unnecessary duplication of effort in ICH and non-ICH regions is not in the interest of patients

• Sharing of perspectives and experience between ICH and non-ICH regions must continue
Closing thoughts.....
### Top ten countries of origin of non-US citizens earning doctorates in US universities in 2006

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>China</td>
<td>4774</td>
</tr>
<tr>
<td>2</td>
<td>India</td>
<td>1742</td>
</tr>
<tr>
<td>3</td>
<td>Korea</td>
<td>1648</td>
</tr>
<tr>
<td>4</td>
<td>Taiwan</td>
<td>718</td>
</tr>
<tr>
<td>5</td>
<td>Canada</td>
<td>561</td>
</tr>
<tr>
<td>6</td>
<td>Turkey</td>
<td>454</td>
</tr>
<tr>
<td>7</td>
<td>Japan</td>
<td>322</td>
</tr>
<tr>
<td>8</td>
<td>Thailand</td>
<td>268</td>
</tr>
<tr>
<td>9</td>
<td>Germany</td>
<td>257</td>
</tr>
<tr>
<td>10</td>
<td>Russia</td>
<td>253</td>
</tr>
</tbody>
</table>

The Road To Enlightenment...Follow The Lights
What Success Looks Like

- Partnership
- Commitment
- Meeting Patients
- Medical Needs
- Communication
- Regulatory Partnership
- Increase GDP
- Make Medicines Affordable

100 global agencies
Thank you