Paradox Of Conducting Clinical Trials In China

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Perfect Storm or Perfect Wave
Agenda

• China Clinical landscape
• Brief on regulatory
• CRO landscape
• Clinical trails in China
• Cultural considerations
• Proposed Clinical Trial Solutions
• Risks Rewards
The pharmaceutical industry has historically lagged other industries in off-shoring.

### Offshore Industry Lifecycle Curve – *Pharmaceutical vs. Other Industries*

<table>
<thead>
<tr>
<th>Stage 1 Capacity Augmentation</th>
<th>Stage 2 Proof of Concept</th>
<th>Stage 3 Value Realization</th>
<th>Stage 4 Strategic Supplier Management</th>
<th>Stage 5 Global Operating Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Utilities</td>
<td>Pharmaceuticals</td>
<td>Automotive</td>
<td>Financial Institutions</td>
</tr>
<tr>
<td></td>
<td>Southern Company</td>
<td></td>
<td>Ford</td>
<td>GE, Citi, Amex, HSBC</td>
</tr>
<tr>
<td></td>
<td>AEP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consumer Products &amp; Retail</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P&amp;G, Nestlé</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmaceuticals</td>
<td></td>
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</tr>
</tbody>
</table>

However, the pace of off-shoring within the pharmaceutical industry has intensified over the last 5 years.

Source: A.T. Kearney analysis
Speed to market and reduced costs have been cited as primary reasons for offshoring clinical trials.

### Selection of Offshoring Location

<table>
<thead>
<tr>
<th>Short Term Offshoring Goals – Supplement U.S. and Western European Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Offshore trials can “rescue” a U.S. trial that is lagging due to slow patient recruitment</td>
</tr>
<tr>
<td>- Companies have used offshore trials for parallel development tracks when FDA concerns caused delays in the U.S.</td>
</tr>
</tbody>
</table>
  - Full disclosure with the offshore country’s regulatory authorities is needed to avert ethical concerns |
| - Introduction of vaccines in developing countries prior to introduction in U.S. has been shown to be successful |

<table>
<thead>
<tr>
<th>Long Term Offshoring Goals – Reduce Costs, Gain In-Country Experience, Develop New Markets</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Many low-cost countries are improving their regulatory conditions and level of clinical trials expertise</td>
</tr>
<tr>
<td>- Pharma companies are positioning themselves to gain operating experience in these countries, where per patient costs can be as low as one third of the U.S. costs</td>
</tr>
<tr>
<td>- Several low-cost countries, including India and China are attractive as potential new markets for innovative drugs</td>
</tr>
</tbody>
</table>

A structured and fact-based approach to identifying country attractive for clinical trials is an important component of any offshoring strategy.

Source: Global clinical trial conference discussions and A.T. Kearney analysis
A.T. Kearney developed an index to assess the attractiveness of countries for conducting clinical trials.

**Patient Pool (30%)**
- Size and availability of suitable patient pool

**Cost Efficiency (20%)**
- Cost efficiency of labor
- Cost efficiency of facilities and travel

**Regulatory Conditions (20%)**
- Food and Drug Administration visibility
- Country’s regulatory laws
- Strength of intellectual protection

**Relevant Expertise (15%)**
- Number of clinical research organizations
- Number of clinical trials
- Size and availability of labor force with relevant skills

**Infrastructure and Environment (15%)**
- Protection of intellectual property
- Health-care infrastructure
- Country infrastructure
- Country risk factors
Our research indicates that China and India are the most attractive offshore locations to perform clinical trials outside the US.

### Overall Country Attractiveness Index

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>6.10</td>
</tr>
<tr>
<td>India</td>
<td>5.58</td>
</tr>
<tr>
<td>Russia</td>
<td>5.55</td>
</tr>
<tr>
<td>Brazil</td>
<td>5.26</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>5.00</td>
</tr>
<tr>
<td>UK</td>
<td>5.00</td>
</tr>
<tr>
<td>Argentina</td>
<td>4.90</td>
</tr>
<tr>
<td>Poland</td>
<td>4.84</td>
</tr>
<tr>
<td>Hungary</td>
<td>4.81</td>
</tr>
<tr>
<td>Germany</td>
<td>4.69</td>
</tr>
<tr>
<td>South Africa</td>
<td>4.56</td>
</tr>
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<td>Taiwan</td>
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<td>Singapore</td>
<td>4.27</td>
</tr>
<tr>
<td>Ireland</td>
<td>3.86</td>
</tr>
<tr>
<td>USA</td>
<td>6.88</td>
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Note: (1) Higher scores indicate higher level of attractiveness
(2) The set of 15 countries analyzed has been selected based on size, diversity, and geographical distribution, and is not meant to be comprehensive across all potential locations for offshoring.
Large patient pools, availability of relevant expertise, and lower costs make China and India attractive.

Country Attractiveness Components – Patient Pool, Relative Expertise and Cost Efficiency

Increasing bubble size indicates greater cost efficiencies

Sources: World Bank 2003, World Development Indicators database 2003 and A.T. Kearney analysis
Improvements in regulatory conditions and the infrastructure of emerging markets will drive the pace of change of offshoring.

Country Attractiveness Components – Regulatory Conditions, Infrastructure/Environment and Patient Pool

Source: A.T. Kearney analysis
Massive, Reagent Grade Tx Naïve, Patient Population

- 67,800 Hospitals and clinics
- 104,400 independent outpatient clinics
- Estimate of 2.2 billion hospital visits and 50 million in-patient visits every year
- Growing disparity between leading hospital and rural clinics
So how does one cross this “Valley of Death”

Bench

Bedside

Phase I Units in China

• Peking Union (SNBL)
  – http://www.pumch.cn/Category_1200/Index.aspx

• Shanghai Clinical Research Center (SCRC)
  – http://www.scrcnet.org/eindex.asp

• Huaxi West China Hospital, Chengdu
  – http://eng.cd120.com/

• South Texas Accelerated Research Therapeutics’ (START) Fudan
  – http://www.startthecure.com/about_start_shanghai.php
Phase I

- DMPK
- First in Human (FIH)
  - PRC born and bred
- Clinical Pharmacology
- Safety Pharmacology
- Drug/Drug Interactions
  - TCM
Phase II A B

Early Safety and Efficacy

• Clinical Pharmacology
• Dosage selection
  – TCM, Genetics
• Early Safety
  – TCM
Larger Multi-national Trials

• Catch Up
  – Big mistake unless you start early

• Multicenter international trials (MCCT)

• Phase IV
  – Some generics if have novel delivery system
  – Medtech
    • Stent, devices, etc. (Huge PRC gov. pull through now)
Center Watch

- http://www.centerwatch.com/clinical-trials/listings/location/international/China

- http://www.centerwatch.com/clinical-trials/listings/location/international/China/Chengdu/
Chinese Clinical Trial Registry

- Chinese Clinical Trial Register (ChiCTR) is supported by
  - Chinese Evidence-Based Medicine Center, Ministry of Health (MOH)
  - of the People’s Republic of China (PRC),
- West China Hospital, Sichuan University, and is a member of Ottawa Statement Group
  - Chinese Evidence-Based Medicine Center, MOH of the PRC
- Chinese Cochrane Center,
- Ministry of Education Virtual Research Center of Evidence-Based Medicine,
- and United Kingdom Cochrane Centre are technique supporters.

Chinese Clinical Trial Registry

2012  2014

- Complete registration 3049  Complete registration 4462
- Prospective registration 2273  Prospective registration 3377
- Retrospective registration 776  Retrospective registration 1085
- Interventional 2030  Interventional 2883
- Prevention 76  Prevention 103
- Diagnostic test 96  Diagnostic test 148
- Cause 44  Cause 69
- Prognoses study 29  Prognoses study 43
- Epidemiological research 44  Epidemiological research 77
- Relative factors research 84  Relative factors research 134
- Observational 642  Observational 1002

Chinese Clinical Trial Registry

- **Anhui**
  - Code of Disease: Primary sponsor(s) Secondary sponsor(s) Funding source
  - 17 (3.61%)
  - Anhui province Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 1 (0.21%)

- **Beijing**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 81 (17.20%)

- **Changchun**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 1 (0.21%)

- **Chengdu**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 2 (0.42%)

- **Chongqing**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 1 (0.21%)

- **Fujian**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 41 (8.70%)

- **Guangdong**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 164 (15.24%)

- **Hong Kong**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 49 (4.55%)

- **Hunan**
  - Code of Disease Primary sponsor(s) Secondary sponsor(s) Funding source
  - 85 (7.90%)

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China Clinical Trials by Disease

Number of Clinical Trials

Study Start Date

Source: Clinicaltrials.gov as of 17-Oct-09. Excludes Hong Kong and Taiwan studies without sites in mainland China
Status of Clinical Research in China

Yonghua Hu, Yueqin Huang, Jie Ding, Yulan Liu, Dongsheng Fan, Tiejun Li, Chengchao Shou, Jianjun Fan, Weimin Wang, Zhe Dong, Xueying Qin, Weigang Fang and Yang Ke

The Lancet
Volume 377, Issue 9760, Pages 124-125
(January 2011)
Overall country attractiveness index

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Scale: 1–10

Source: A.T. Kearney
Notes: Higher scores indicate higher levels of attractiveness. The 15 countries analyzed were selected based on size, diversity and geographical distribution. The Index is not meant to be comprehensive across all potential offshore locations.
CFDA Clinical Trials Code of Conduct

- Guideline on strategies to identify and mitigate risks for first-inhuman clinical Trials with investigational medicinal products.
- Association of British Pharmaceutical Industry Guidelines for Phase I Trials
- EMA’s Guidelines for GCP
- Question Where are all of the Clinical Pharmacologist?
- Who really understands safety pharmacology?
- How Reliable is the Pre-clinical data?

http://www.abpi.org.uk/media-centre/newsreleases/2012/Pages/140812.aspx
Despite significant growth in number of trial sites used in China in recent years - the number is still comparatively small (source: ClinicalTrial Magnifier)
Limited experienced clinical research sites

Accredited sites VS Experienced site for global clinical trials

<table>
<thead>
<tr>
<th>Therapy Area</th>
<th>Accredited sites by sFDA</th>
<th>Experienced Quality sites*</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinology</td>
<td>89</td>
<td>30-40</td>
<td>Coastal cities/Eastern China</td>
</tr>
<tr>
<td>Respiratory</td>
<td>161</td>
<td>30-40</td>
<td>Coastal cities/Central China</td>
</tr>
<tr>
<td>Oncology</td>
<td>139</td>
<td>30-40</td>
<td>Coastal cities</td>
</tr>
<tr>
<td>CV</td>
<td>145</td>
<td>40-50</td>
<td>Coastal cities/Eastern China</td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>56</td>
<td>15-20</td>
<td>Northern</td>
</tr>
</tbody>
</table>

Note:
- *Estimated based on top ten Pharmaceuticals company clinical Dept feedback
- Accredited sites number’s cut off date 1-Jul-2009
- China regulation: all clinical trials must be conducted in sFDA authorized centers and all certified center will

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A real life story on site selection

All SFDA approved study sites for Diabetes: 94

30%
Agreed: 28

70%
Denied: 66

35 (53%):
- Competitive Trials

31 (47%):
- Protocol issue
- Interesting

28 (100%)
- Competitive Trials

17 (61%)
- Similar design studies
11 (39%):
- Other diabetes studies

Final Study Site
Advantages and challenges of doing clinical research in China

**Advantages**
- Large patient pool
- Fast recruitment
- Experienced and motivated investigators
- High patient numbers per site
- Overall lower cost of clinical research
- High level of GCP compliance at Chinese sites and high quality data
- Patient compliance good

**Challenges**
- Regulatory approval timelines
- Talent war: shortage of well trained and experienced CRA, CPMs, CRC, MW, Stats,
- Technical/Trial Logistics
CFDA Laws and Regulations

1. 药品管理法
2. 药物临床试验质量管理规范
3. 药品注册管理办法
4. 药物临床试验机构资格认定办法
5. 关于开展药物临床试验机构资格认定复核检查工作的通知
6. 药品注册现场核查管理规定
7. 药物临床试验机构资格复核检查标准
8. 药物临床试验伦理审查工作指导原则
9. 医疗器械监督管理条例
10. 医疗器械临床试验规定
11. 体外诊断试剂临床研究技术指导原则
12. 药品临床研究的若干规定
13. 药品研究和申报注册违规处理办法
14. 关于印发药物 I 期临床试验管理指导原则（试行）的通知
15. 药物临床试验生物样本分析实验室管理指南（试行）

Remember you are working in China, documents with some exceptions will need to be in Chinese.
Regulatory Environment

- 200 Reviewers at SFDA, 2034 at USFDA
- Enforcement/Graft  SFDA vice chairman jailed in March
  - Zheng Xiaoyu, 62, who was head of the State Food and Drug Administration (SFDA) from its founding in 1998 until mid-2005, was given the death sentence
- Generic- & TCM-traditions Vs. NCE & NBE
- CRO/CMO; Mindset and level of understanding
Sichuan University
Huaxi Medical Center
Chengdu

- Huaxi Medical Center -- West China Center of Medical Sciences, Sichuan University 4300 beds
  Located in Sichuan Province City of Chengdu Wuhou
- Certified by SFDA earliest in mid 1990’s
- New Clinical Pharmacology Unit
- Multiple Western Clients CROs and Pharma
- 460 GCP MDs
- Great contracting terms
Peking Union Medical College

- The Clinical Pharmacological Research Centre (CPRC) is attached to the PUMCH as the department of clinical pharmacology.
- The center is well-known for its extensive experience in a variety of clinical trials on drugs of different developmental phases.
- PROMASYS® is an integrated clinical data management and EDC system for clinical data capture and data management processes.
Keys to Success Factors

成功因素的关键

• Talent – “Hai Gui”
  – Leadership – recruitment and retention
  – Technical expertise – industrial R&D, regulatory and manufacturing experience
  – Communication with international sponsors

• Regulatory and compliance
  – GCP training and practice enforcement
  – IND, NDA, ANDA experience

• Communication and client interface
  – Working language – English and Chinese, notebook, verbal and written communication
  – Recognizing culture differences on both sides ("fee for service" and "guaranteed results")

• Supporting mechanism – logistics, infrastructure and funding
  – Need greater support – Ease of procuring patients, sample shipping MOH and MOST issues, etc.

• Training – start with a clean slate
  – Technical training (PRC and USA)
  – Compliance training needs time
Risks

• Dynamic / fluid Environment
  - Economics, work force training & retention
    • (high cost of living & poaching in 1st Tier Cities)
  - CFDA regulatory uncertainties
    • leading to reluctant clients
    • Delayed programs
  - Governmental oversight / monitoring (Internet)
    • Repatriating monies out of country
    • Internet privacy; data corruption; investigator/ hospital corruption
Threat: Competition for talent

- Increasing preference to work for domestic companies
- Relatively slow pay raise compared to emerging domestic companies
- Booming economy entrepreneurship
- Aggressive advancement expectations
Conclusions

• Dynamic landscape in China
• 2000 yrs. of culture hits Western CGP
• Unintended consequences
• 2^{nd} tier cities
• SEC FCPA never want these two in same sentence
  – stay clean from day one
• Use intermediaries with long-standing experience
• Use more technology remove human factors as much as possible
Action Items

• Inculcate technology faster
• Training, training and more training
• Build vs buy cGCP capabilities
• 不要用斧头从你的朋友的额头上取下一只苍蝇。Do not use a hatchet to remove a fly from your friend's forehead.
China: the sleeping giant has awoken.

“Young man/woman, go East!”
Contact

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