How To Conduct Clinical Trials in China when You Are Not Big Pharma

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Hong Kong, SAR
Xemilofiban Summary

• Product has already been studied in both Phase II and Phase III clinical trials 12K patient experiences
• Proven safety and efficacy
• Advantages over existing products
• Growing total market flattening sales with expanded indications

Advantage of IV to oral conversion
Why China

Market:
China is expected to become the world's 2nd-largest prescription drug market in 2014, and the market in China may be doubled by 2013 (IMS data) CAGR 20-25% vs. USA 2-5%

Special SFDA Regulations:
• Clinical trials are required for all imported drugs before marketing. So, trials for marketing registration will be greatly increased
• Data generated from Chinese sites in a global trial can be used for an import drug registration, so that the clinical trial can be exempted if the data comply with SFDA’s requirements. This may save 2-4 years for a new drug to be marketed in China.
• More global trials are anticipated as more and more pharmaceutical companies become aware of this regulatory strategy.
Business environment - China

• Perceived market – true market
  – Pharma market grew 21% in 2010, becoming 2nd largest in 2014.
  – Resources needed to penetrate the many diverse markets
  – Pricing; Biologics 50 – 90% below west, so far all sub-standard drugs
  – Ability/Inability to pay for a treatment
  – Public health insurance, pricing practices and change!

• Hidden / “Unaccounted” costs
  – HR; poaching, high turn-over, training, efficiency, foreign staff as local employees (rent, schools, corporate credit cards, foreign currency exchange …)
  – Unpredictable and changing regulations SFDA changes in positive direction
  – Corruption
  – State sponsored industrial espionage
Business environment - China

- Tax incentives for new and high tech R&D
  - Exempt of import duty and VAT for equipment and reagents.
- Price pressure on pharmaceuticals.
  - New “Measures for the Administration of Drug prices” announced June 2010, off-patented originator pricing will go down continued price pressure
- Legal and Regulatory hurdles:
  - Product registration 6-9 months minimum for approvals to begin trials often 1 year of more
  - Clinical trial data acceptance, 1868 trials have been conducted in China by MNCs since 2008. Mostly Phase III-IV
  - Levies and import duties
  - Competition watchdog; M&A (In 2010 Pfizer forced to sell animal vaccine to local company)
  - Force foreign business to set-up manufacturing and operations in China.
East Asia  8808
China  2460
Hong Kong  641
Korea, Republic  2800
Mongolia  4
Taiwan  2341  2011 to date

http://clinicaltrials.gov/ct2/search/map/click?map.x=112&map.y=61&map=ES
China Clinical Trials by Disease

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

![Graph showing the status of clinical research in China from 2000 to 2009. The graph includes bars for the number of publications and a line graph for the ratio of basic science to clinical research. The years and the corresponding data points are indicated.]
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
Why China

Trends of Drug Development:

• Large number of R&D centers set up by major MN pharmaceutical companies in China in the last 5 years over $3B FDI. As a consequence, more global trials for new drugs will be led from China.

• Vice Finance Minister Wang Jun will inject 1,134. B CNY (rmb yuan) another 234B already announced into health care in China: hospitals, innovative product development, rural HC clinics.

• Even industrial policy like new GMP regulations can lead to social stability issues/opportunities; corruption; supply chain disruption, EDL pricing to control antibiotic use, and self preservation attempts.

• “Two Conference” (NPC, and Chinese people’s Political Consultative Conference) in March 2011 led to unprecedented new regs on drug pricing the only commodity still under government price control; many question the paradox; why are we in this business?
Acceptability by FDA — Ethnicity Issues

— “Ethnicity in Drug Development and Therapeutics” by E. Frackiewicz
  • Personalized medicine is “leading to the need for understanding genetic polymorphism and for promoting racial and ethnic diversity in clinical trials.”
  • “ICH, FDA and NIH guidelines and recommendations have been instituted to encourage participation in clinical trials.”
— Many drugs have ethnic differences in pharmacokinetics of drug metabolism
  • Anti-hypertensives, psychotropics, anti-diabetics, Cytochrome P 450 enzymes
— Additionally, there are often differences in the pharmacokinetics of drugs in absorption, distribution, elimination
## Languages Spoken in China

<table>
<thead>
<tr>
<th>Region in China</th>
<th>Languages</th>
<th># of Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beijing &amp; throughout China</td>
<td>Mandarin (130 Dialects)</td>
<td>850 million</td>
</tr>
<tr>
<td>Guangdong &amp; Guangxi Provinces</td>
<td>Yue (Cantonese)</td>
<td>70 million</td>
</tr>
<tr>
<td>Southern, Northern, &amp; East Central Fujian Province, Guangdong Province</td>
<td>Min (Taiwanese, Hokkien, S., N., &amp; E. Min)</td>
<td>70 million</td>
</tr>
<tr>
<td>Shanghai</td>
<td>Wu (Shanghainese)</td>
<td>90 million</td>
</tr>
<tr>
<td>South Eastern China</td>
<td>Hakka</td>
<td>30 - 40 million</td>
</tr>
<tr>
<td>Hunan, Sichuan, Guangxi &amp; Guangdong Provinces</td>
<td>Xiāng (Hunanese)</td>
<td>25 million</td>
</tr>
</tbody>
</table>

http://www.omniglot.com/writing/chinese_spoken.htm
Complex language

“mother”

• 母亲
• 妈妈
• 的母亲
• 母
• MA
Complex language

• In Mandarin Chinese the words for ‘assess’, ‘assessing’, and ‘assessment’ all use the same character, as do ‘treat’, ‘treating’, and ‘treatment’ thus the original English title, “Assessing and Treating Symptoms of Critically Ill ICU Patients” most closely translated into Chinese as “ICU Critically Ill Patients' Symptom Assessment and Treatment”.

• The English term ‘short of breath’ was problematic because in Mandarin Chinese ‘short’ means ‘not long’ and ‘breath’ is not described as short or long. Thus, ‘short of breath’ was changed to ‘hard to breathe’ for Chinese patients.
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
# Market Attractiveness Matrix for Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Patient Access</th>
<th>Cost</th>
<th>Market Opportunity</th>
<th>Regulatory Approval timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>2 - 3 months</td>
</tr>
<tr>
<td>India</td>
<td>+++++</td>
<td>+++++</td>
<td>++</td>
<td>3 - 4 months</td>
</tr>
<tr>
<td>China</td>
<td>+++++</td>
<td>+++</td>
<td>+++++</td>
<td>10 - 12 months</td>
</tr>
<tr>
<td>Korea</td>
<td>+++</td>
<td>++</td>
<td>+++++</td>
<td>3 - 4 months</td>
</tr>
<tr>
<td>Taiwan</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>3 – 4 months</td>
</tr>
<tr>
<td>Singapore</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>1- 2 months</td>
</tr>
<tr>
<td>Indonesia</td>
<td>+++</td>
<td>+++++</td>
<td>+</td>
<td>3 – 4 months</td>
</tr>
<tr>
<td>Malaysia</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>3 – 4 months</td>
</tr>
<tr>
<td>Thailand</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>3 – 4 months</td>
</tr>
<tr>
<td>Philippines</td>
<td>+++</td>
<td>+++++</td>
<td>+</td>
<td>3 - 4 months</td>
</tr>
<tr>
<td>Vietnam</td>
<td>+++</td>
<td>+++++</td>
<td>+</td>
<td>4 – 5 months</td>
</tr>
</tbody>
</table>
Perfect Storm or Perfect Wave
Drug development model in China

US/EU

IND App. → Phase 1 → Phase 2, 3 → NDA

China, Yesterday

Sequential Development Model Following International Approval ≥4 years drug lag

CTA App. (category 7) → PK, Phase 3 → NDA

China, Today

Parallel Development Model ≥2 years drug lag

IMCT CTA (category 1) → PK, Phase 3 → CTA+NDA (category 7)

China, Future

Simultaneous Development Model <1 year

IMCT CTA (category 1) → Phase 1, 2, 3 → CTA+NDA (category 1)

<1 years
## Cost savings: Blood Draw

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Country</th>
<th>Flag</th>
<th>Low (USD)</th>
<th>Medium (USD)</th>
<th>High (USD)</th>
</tr>
</thead>
<tbody>
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<td>Blood Draw</td>
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<td>🇺🇸</td>
<td>22</td>
<td>26</td>
<td>33</td>
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<tr>
<td></td>
<td>China</td>
<td>🇨🇳</td>
<td>5</td>
<td>6</td>
<td>7</td>
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<tr>
<td></td>
<td>Hong Kong</td>
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<td>7</td>
<td>10</td>
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<tr>
<td></td>
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<td>🇰🇷</td>
<td>5</td>
<td>6</td>
<td>7</td>
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<tr>
<td></td>
<td>Thailand</td>
<td>🇹🇭</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td></td>
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<td>10</td>
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Source: GrantPlan® ([www.ttc-llc.com](http://www.ttc-llc.com))
Cost Savings: ECG

<table>
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<th>Procedure</th>
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<th>High (USD)</th>
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<td>103</td>
<td>128</td>
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<td></td>
<td>China</td>
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<td>42</td>
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<tr>
<td></td>
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<tr>
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<td>49</td>
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Source: GrantPlan® (www.ttc-llc.com)
## Initial Physical Exam (~60 min.)

<table>
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<th>Procedure</th>
<th>Country</th>
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<th>Medium (USD)</th>
<th>High (USD)</th>
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<td>101</td>
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Source: GrantPlan® ([www.ttc-llc.com](http://www.ttc-llc.com))
Physical Exam (~15 min.)

<table>
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<th>Procedure</th>
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<th>High (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
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<td>🇺🇸</td>
<td>130</td>
<td>151</td>
<td>152</td>
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<tr>
<td></td>
<td>China</td>
<td>🇨🇳</td>
<td>36</td>
<td>50</td>
<td>60</td>
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<tr>
<td></td>
<td>Hong Kong</td>
<td>🇭🇰</td>
<td>63</td>
<td>88</td>
<td>105</td>
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<tr>
<td></td>
<td>Korea</td>
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<td>40</td>
<td>48</td>
<td>55</td>
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<tr>
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<td>89</td>
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<tr>
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<td>Taiwan</td>
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<td>51</td>
<td>73</td>
<td>94</td>
</tr>
</tbody>
</table>

Source: GrantPlan® (www.ttc-llc.com)
Darwinian Evolutitional Pressures on Big Pharma
# Research Spending Per New Drug

<table>
<thead>
<tr>
<th>Company</th>
<th>Ticker</th>
<th>Number of drugs approved</th>
<th>R&amp;D Spending Per Drug ($Mil)</th>
<th>Total R&amp;D Spending 1997-2011 ($Mil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>AZN</td>
<td>5</td>
<td>11,790.93</td>
<td>58,955</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>GSK</td>
<td>10</td>
<td>8,170.81</td>
<td>81,708</td>
</tr>
<tr>
<td>Sanofi</td>
<td>SNY</td>
<td>8</td>
<td>7,909.26</td>
<td>63,274</td>
</tr>
<tr>
<td>Roche Holding</td>
<td>AG RHHBY</td>
<td>11</td>
<td>7,803.77</td>
<td>85,841</td>
</tr>
<tr>
<td>Pfizer</td>
<td>PFE</td>
<td>14</td>
<td>7,727.03</td>
<td>108,178</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>JNJ</td>
<td>15</td>
<td>5,885.65</td>
<td>88,285</td>
</tr>
<tr>
<td>Eli Lilly &amp; Co.</td>
<td>LLY</td>
<td>11</td>
<td>4,577.04</td>
<td>50,347</td>
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<tr>
<td>Abbott Laboratories</td>
<td>ABT</td>
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<td>4,496.21</td>
<td>35,970</td>
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<tr>
<td>Merck &amp; Co Inc</td>
<td>MRK</td>
<td>16</td>
<td>4,209.99</td>
<td>67,360</td>
</tr>
<tr>
<td>Bristol-Myers Squibb Co</td>
<td>BMY</td>
<td>11</td>
<td>4,152.26</td>
<td>45,675</td>
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<tr>
<td>Novartis AG</td>
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<td>21</td>
<td>3,983.13</td>
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</tr>
<tr>
<td>Amgen Inc.</td>
<td>AMGN</td>
<td>9</td>
<td>3,692.14</td>
<td>33,229</td>
</tr>
</tbody>
</table>

Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems
Harbin Pharmaceuticals

• Louis XV, a resident of the original Versailles: “après nous, le déluge” — or to paraphrase, “when this is over, all hell’s gonna break loose.”
Harbin Pharmaceutical Group Co., Ltd.
Shijiazhuang Pharmaceutical Group Co., Ltd.
Shanghai Pharmaceutical Group Co., Ltd.
Jilin Xiuzheng Pharmaceutical Group Co., Ltd.
Yangtze River Pharmaceutical Group Co., Ltd.
Guangzhou Pharmaceutical Group Co., Ltd.
Tianjin Pharmaceutical Group Co., Ltd.
North China Pharmaceutical Group Co., Ltd.
Buchang Group
Tianjin Kingyork Group Co., Ltd
China Beijing Tong Ren Tang (Group) Co., Ltd.
Tasly Group Co., Ltd.
China National Biotec Group
Beijing Pharmaceutical Group Co., Ltd.
Hangzhou Huadong Medicine Group Co., Ltd.
Zhejiang Medicine Co., Ltd.
China Resources Sanjiu medical and Pharmaceutical Co., Ltd.
Qilu Pharmaceutical Co., Ltd.
The United Laboratories International Holdings
Jiangxi Jimin Kexin Group Co, Ltd
Taiji Group Co., Ltd.
Shangdong Ruiyang Pharmaceutical Co., Ltd.
Northeast Pharmaceutical Group Co., Ltd.
Strategy

• Three largest problems with clinical trials in China
  • Hospital infrastructure
  • Physician (Red Envelop)
  • Under reporting of AE’s

• Unmet Need
  – Domestic and MNC need to conduct cGCP trials to gain market approval in China and maintain a Global portfolio

• Mitigate Risk
  – Similar risk just different geography different culture
  – Second third tier cities
Long-term Strategy: Hospital Partner

• Use only 3 A hospitals only
• SFDA approved to conduct research: over 300 to choose from
• Western Systems, equipment, staffing and accounting
• Services

Strategy

• Hospital infrastructure
  • Work with CROs who have local presence and ties to #A hospitals Fountain, Frontage Laboratories, MicroConstants, and Heyuan Co-Source, Tigermed etc.
  • Watch the Evolving preclinical CRO’s to Clinical CRO WuXi, JOINN

• Mitigate Risk
  • Work in Second Tier Cities e.g., Chengdu, Xi’an, Kunming, Jinan, Tsingtao, Tianjin, etc.
Make the Hospital a Partner
Who is Affected by Corruption?
谁是由腐败的影响？

- Academia 学术界
- Industry 工业界
- 3rd parties 相关的第三方
  - Stakeholders 利益关联方
  - Patients 病人
  - Support organizations 支持性的组织
Western Big Pharma
大型制药公司

• Intense public scrutiny 严密的公众审查
• Drug safety concerns 药物的安全问题
• “money driven” image “金钱驱动”的形象
  — Intense regulatory scrutiny 严密的监管审查
• Ever increasing reliance on outsourcing 日益增加的对外包的依赖
Results to CRO
对合同研究组织的影响

• Being held to a higher standard
必须维持一个更高的标准

• Still expected to deliver fast and inexpensive research products
交付快速和低价研究结果的期望仍然存在
Ethical Considerations

• In accordance with professional standards for right conduct or practice
  符合专业标准的正确行为或实践

• Leadership in the field
  在该领域的领导地位
Public Disclosure

• Has helped assure responsible research
曾经在确保研究工作的责任性方面起过作用

• Can be an obstacle to scientific achievement
亦可以是科学进步的障碍

• A simple lie is easier to believe than a complicated truth
简单的谎言比复杂的真相容易让人相信

• Focused attention on contract facilities
注意力集中在合同机构
CORRUPTION

Controversial

备受争议

龍
Risks

• Dynamic / fluid Environment
  – Economics, work force training & retention
    • (high cost of living & poaching in 1st Tier Cities)
  – SFDA regulatory uncertainties
    • leading to reluctant clients
    • Delayed programs
  – Governmental oversight / monitoring (Internet)
    • Repatriating monies out of country
    • Internet privacy and data corruption

• Conflicts between different cultures, traditions, as well as value systems.
  – Goal mis-alignment between partners
  – Moral Hazard

• Ethical concerns & corruption is endemic
  – There are “no secrets” in China
  – Contract law
  – “Red Envelop mentality”
Risks

• Delays in obtaining regulatory and IRB approvals
• Delays in site initiation
• Delays in patient recruitment
• Inefficiency and quality issues from staff changeover or inexperience
• Difficulties with logistic management of clinical trial supplies
• Issues with local vendors
• Delays with the processing of CRFs
• Utilization of resources at a level that exceeds the budget
In the **Qin Dynasty**, 秦朝 the 5-clawed dragon was assigned to represent the Emperor while the 4-clawed and 3-clawed dragons were assigned to the commoners. The dragon in the **Qin Dynasty** appeared on **national flags**. 
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 MOST issues, etc.

• Training – start with a clean slate
  – Technical training [(PRC and USA (Cato, Beckloff Associates etc....)]
  – Compliance training needs time
Change the Expectations

• More consistent model 更具一致性的模型
  – Better client relations 更好的客户关系
  – Successful business 成功的生意
  – Leadership in the field 在该领域的领导地位

• Clean slate: training training training
China: the sleeping giant has awoken.

“Young man/woman, go East!”
Contact

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+86.15021242314 (Cell China)
+1(615)445-5761 (Cell USA)
http://www.dragonbio-consultants.com/
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