

# Clinical CROs in China

--- Prospective and Globalization

中国临床CROs, 现状及发展



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上海

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## New Drug Development Cost - Continues Going High

### Highly Risky

Successfully approved, 1/5000,  
Failure rate around 90% (Genomen Tech, 2009), vs.  
other industry products, at 23-30%,  
commercial products, at 30-40%

### Extremely Time Consuming

8-13 yrs or longer for a new drug reaching the market

### Hugely Expensive

500M to 1.3 Bn (Morgan Stanley 2008)  
1.2Bn to 1.3Bn, Nature Review (Drug discover, 2009)



## **R&D Productivity for the Global Biopharm Industry Has Been Declining Since the Later 1990s** 药物研发的成果今年来不断下降


- ◉ **Average clinical trials (I,II, III) exceed their timeline by 20%**
- ◉ **Life -saving treatment, delayed.**
- ◉ **Industry invests twice as much in R&D as in a decade ago, produces 25% of the new medicines it then produced (Financial Times, 2007)**



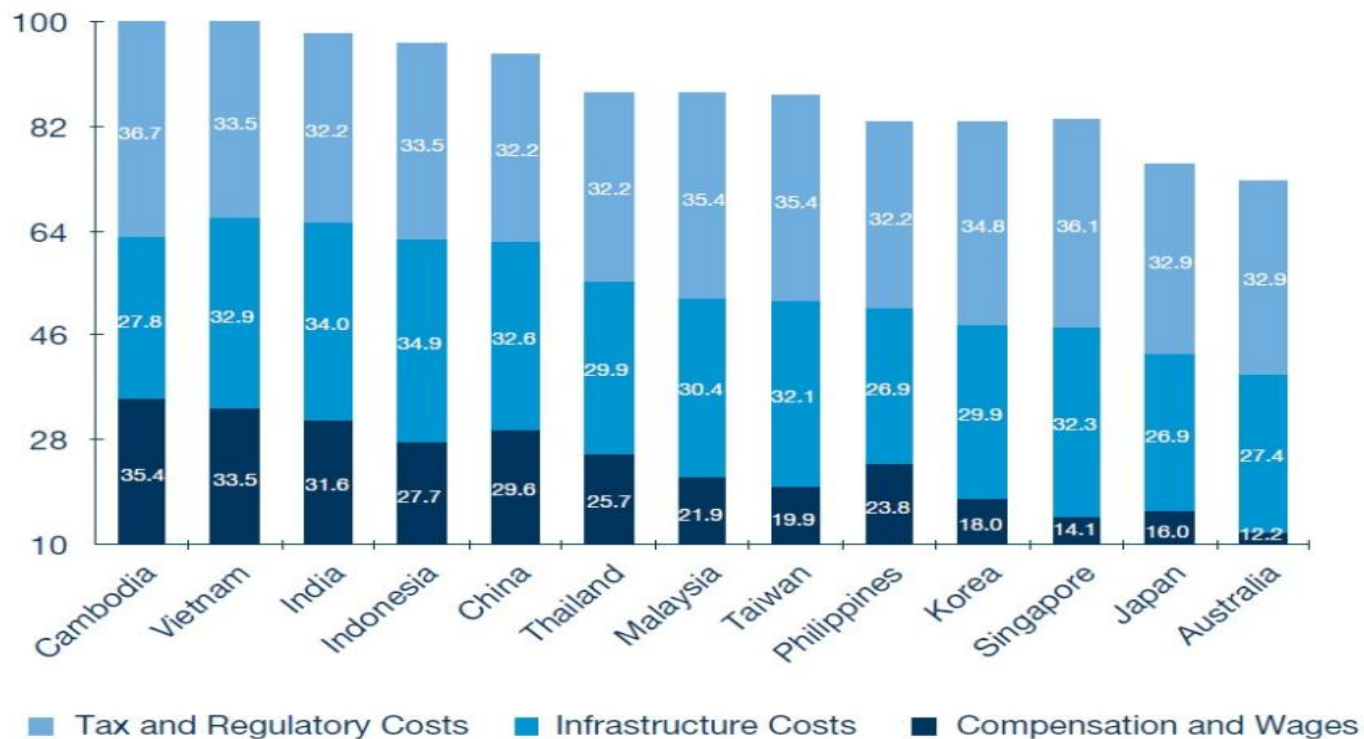
## Current Pharm Business Model is Unsustainable

### Outsourcing Drug R&D to Asia \_ Inevitable Choice

*-Price Waterhouse Coopers (2007)*

- Most pharma MNCs now have Asia in their global drug development strategy setting up their own brick and mortar facility, virtual labs or partnering with R&D/service providers in the region.
  - 72% Pharma MNCs having clinical trials to Asia
  - The two attracting highest demand are **China and India**.
- 

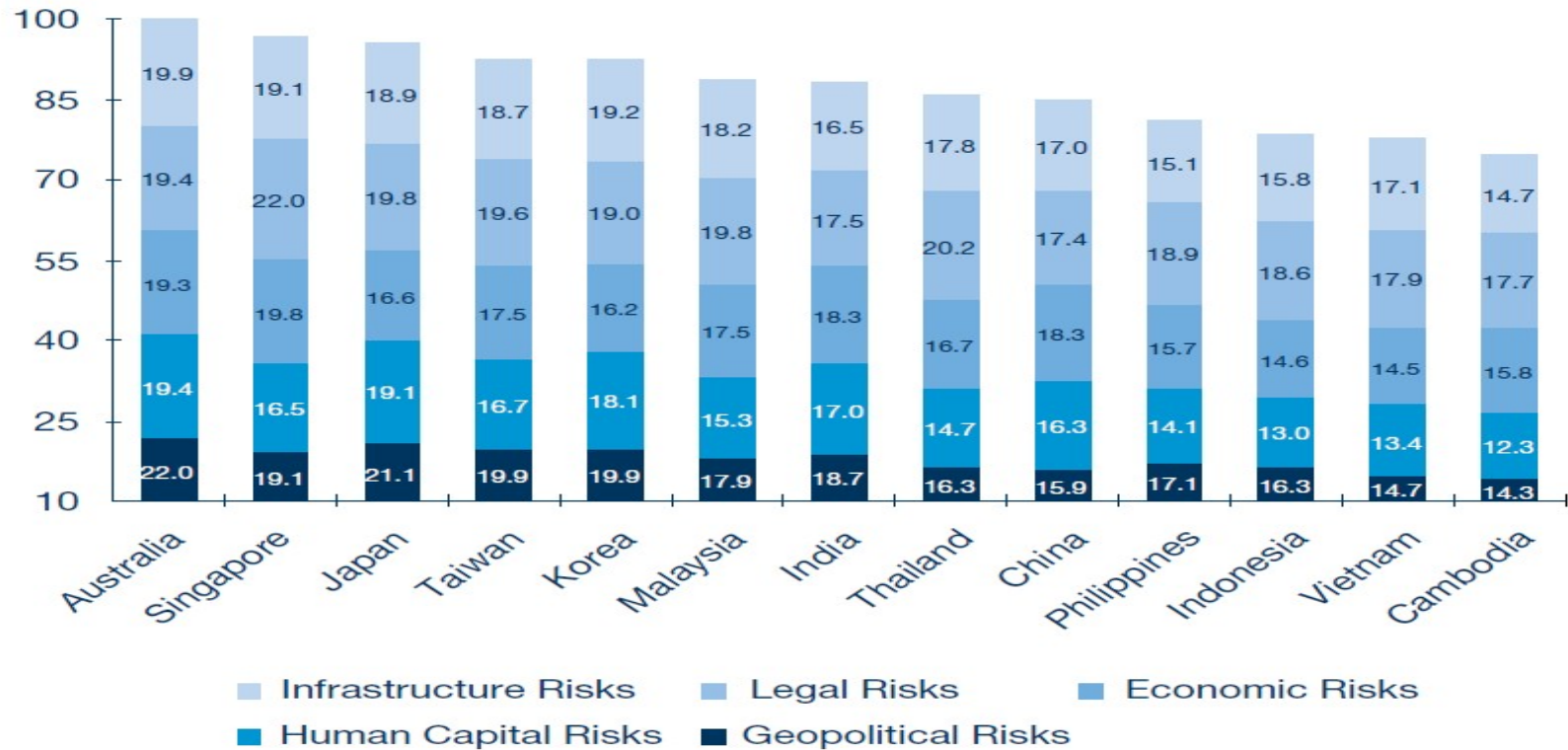
## Cost Ranking of Asian Territories



(Scores are 'normalised' with the best ranking territory = 100. Thus, higher scores indicate lower costs.)

Source, Industry pharmaceutical, PriceWaterhouseCoopers2008

## Wider Risk Ranking of Asian Countries



(Scores are 'normalised' with the best ranking territory = 100. Thus, higher scores indicate lower risks.)

Source, Industry pharmaceutical, PriceWaterhouseCoopers2008



## China Position in Global Drug Development

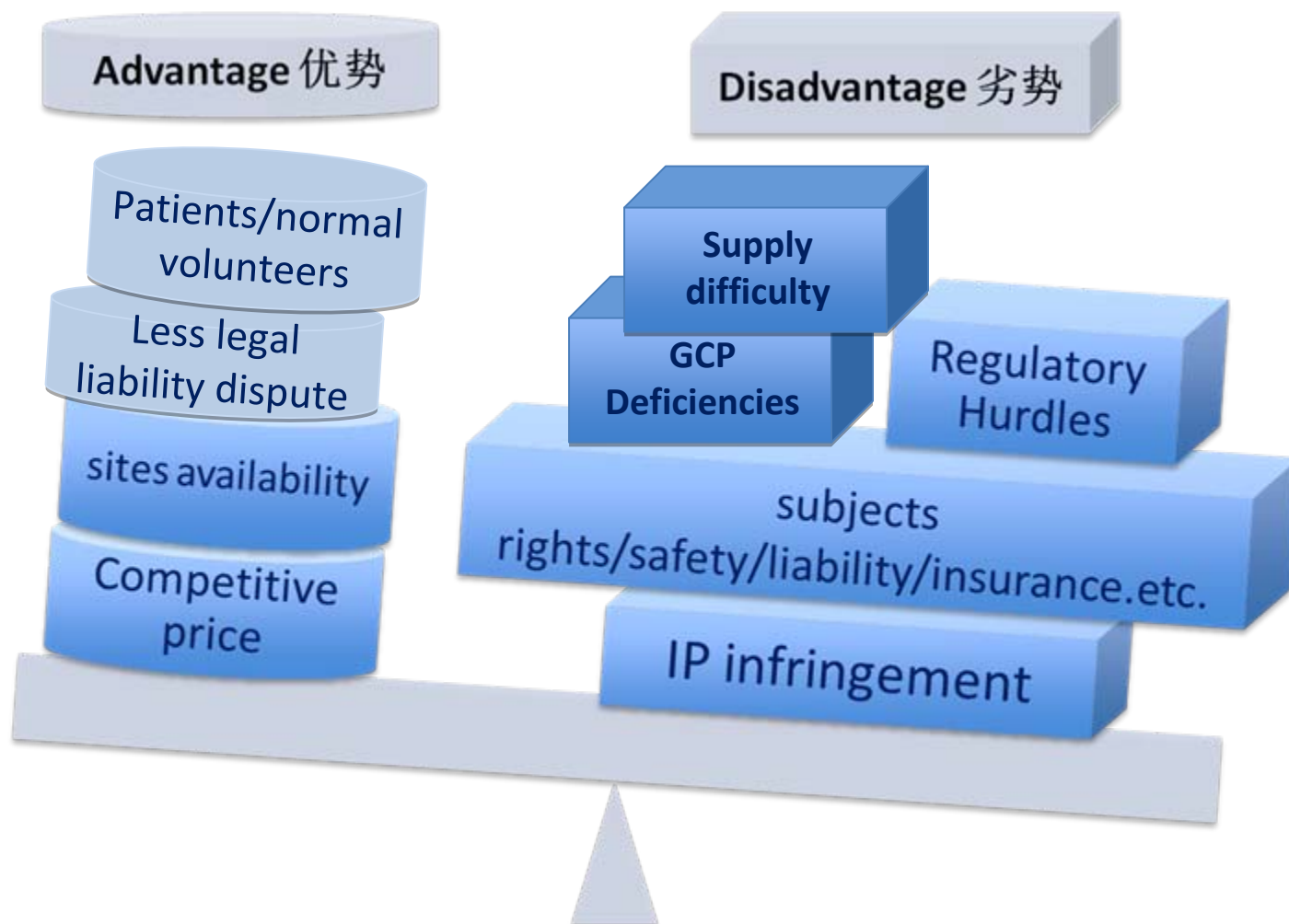
### 中国在全球药物研发的地位

- China “arguably ranks **as the best pharmaceutical outsourcing destination** among all Asian Territories” when looking at the multiple factors of cost, risks, and market opportunities
  - *PriceWaterhouseCooper, 2008*

(China, Japan, India, Singapore, Taiwan, Australia, Korea, Malaysia, Thailand, Indonesia, Philippines)

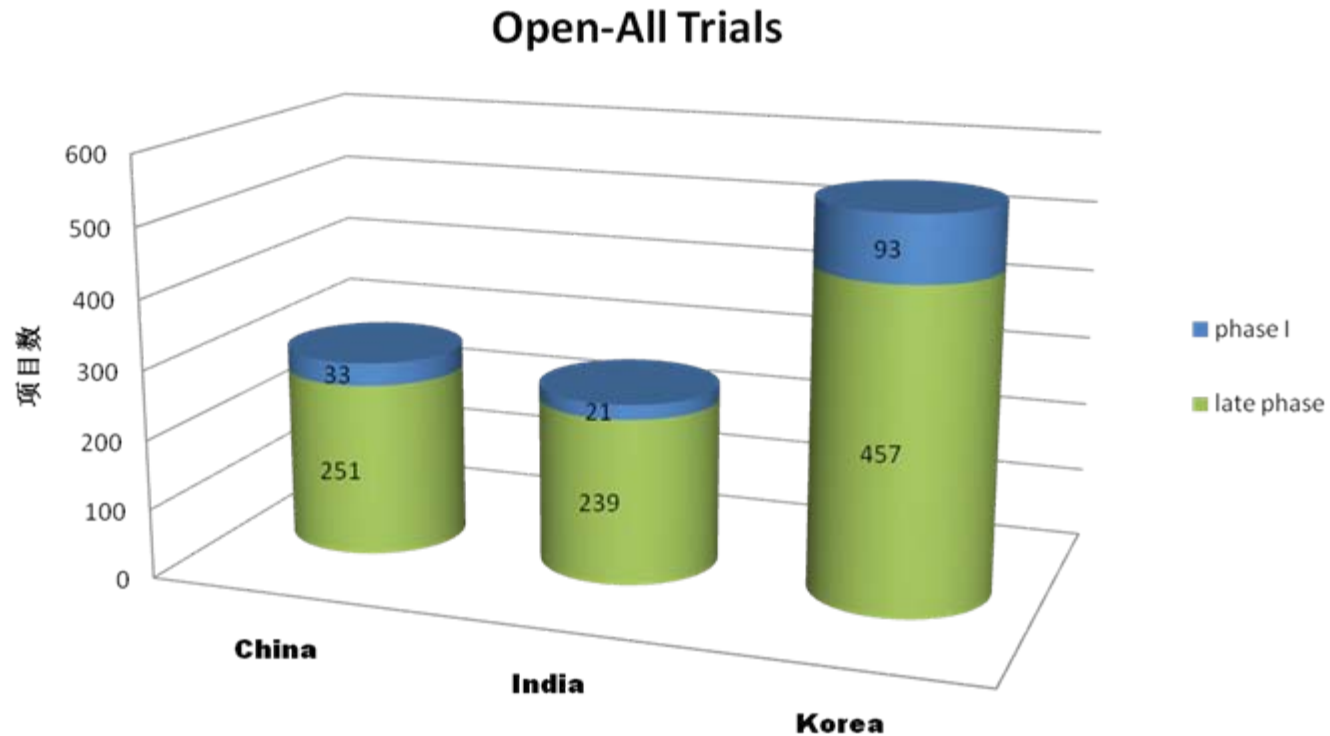


## Can China Become the Hub for Clinical Development ?





## 目前在招募的项目 2012-05

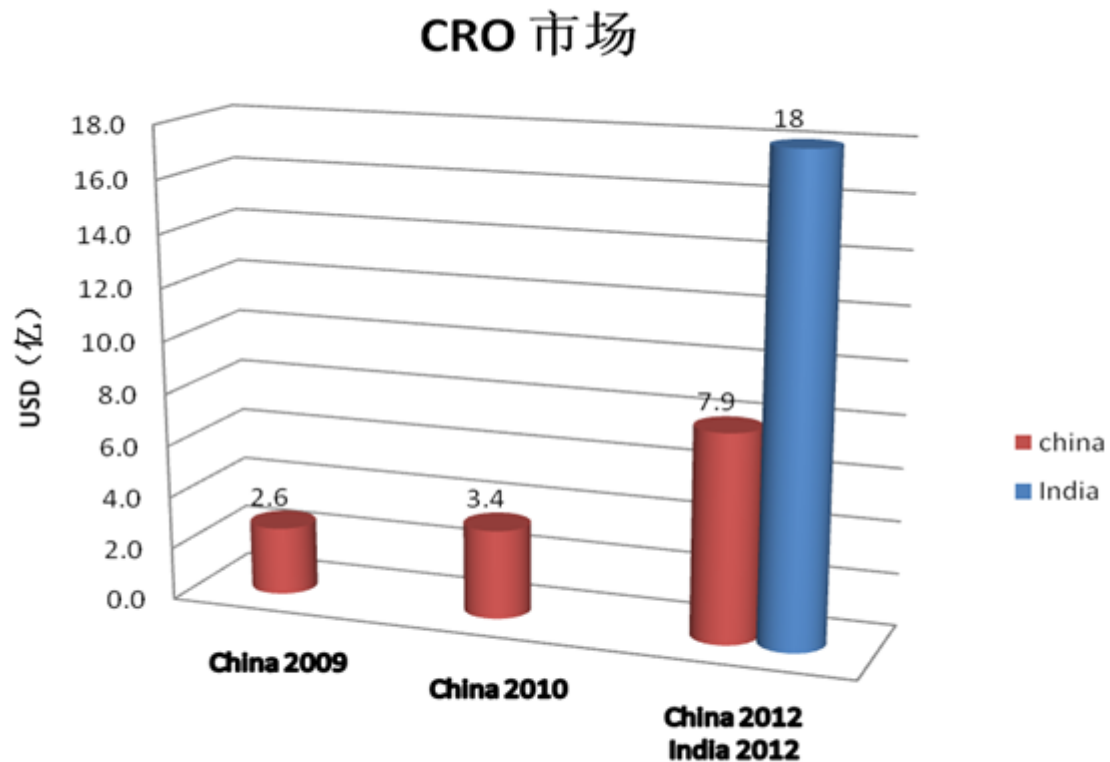


Global Clinical Trials Outsourcing Summit 14-16 May Seoul, Korea

## India is Becoming the Global Hub for Clinical Drug Development

- 8000亿卢比, 1,8 Billion US\$ industry 50,000 employees
- Global clinical contracts about 45Billion\$ 450 亿美元
- 25% annual increase
- China CRO,

2009, 2.6亿 \$  
2010, 4.3亿 \$  
2012, 7.9亿 \$



注: 取自 Price Waterhouse Cooper 和 ASSOCHAM (印度工商联合会) 数据

## 中国的CRO 产业

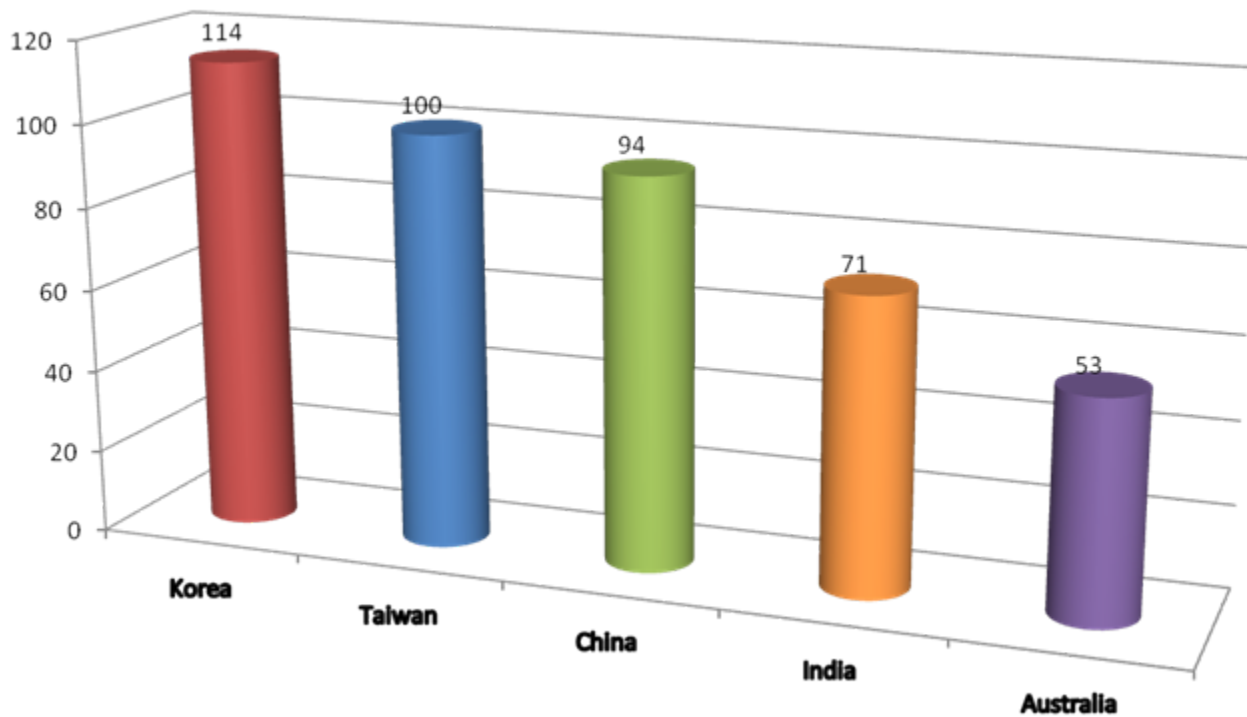
- ◉ 国外侵入 1996/1997 MDS, Quintiles, Covance
- ◉ 国内仿制药研发企业自己派生的, 主要是药证申报, 临床服务
- ◉ 国外回来建立的, 主要是药物发现, 化学合成, 临床前药理/毒理服务, 临床服务

## Current Situation of China CROs CRO 状态

规模小,服务单一,国际介入有限,多数为**3,6**类药

- Small in size/capability
  - About several hundred statewide, BJ has over 100
- Lack of international exposure
  - few known to the world, Wuxi, BioDura,
  - fewer, in the clinical, Excel, TigerMed,
- Limited recognition/acceptance by domestic pharmaceuticals
- Mostly in clinical development of drugs in Category 3 or 6

## CRO 平均客户数



Global Clinical Trials Outsourcing Summit, May 14-16, Seoul, Korea



## CRO 面临的主要境况，挑战

- 药物低研究经费
  - In US a phase II 数千万\$，
  - In China, 几百万RMB
- 现行药政法规 缺陷
  - 化药1-6类中3,6类居多,一个品种几十个申报(盐酸洛美利嗪 60多家)
- 制药行业对CRO 认同有限,拖欠费用普遍
- 自身水平, 人才流失
- 资质认证, 质量标准
- 知识产权,

## 境况,挑战 \_ continued

### 药政申报限制\_ CTA 申请漫长

| Country/<br>Region   | Government | Clinical trial approval time                               | Note                                       |
|----------------------|------------|--|--|
| China<br>(main land) | SFDA       | For new drug: 6-8 months<br>For Category 6 drug: 10 months | Actual approval time<br>is often over 1 yr |
| India                | DCGI, DGFT | For Category A: 2-3 months<br>For Category B: 3-5 months   |  |
| South Korea          | KFDA       | 3-4months  | In parallel with<br>IRB/EC(3-4 months)     |
| Taiwan               | MOH        | 2.5-3 months   |  |
| Singapore            | HAS        | 1.5 months   | In parallel with<br>IRB/EC(1.5 months)     |

## 境况,挑战\_ continued

- 低成本难以维系 ( in avg. < 1/5 of US cost) \_ *Drug Discovery Today, 2006, by Roman Boutillier*
- 药物研究法律,伦理 (7 death in an aids drug trial)

The market will become even more competitive  
How we survive and grow?

- ◉ 国际大的CRO 发展 \_ capacity and capability \_ size does matter!
- ◉ “全能型服务” 是关键, 并购, 联盟是途径

## Major Western CROs Are Madly Expanding in China

- PPD-Excel 伊格斯, PPD-保诺  
and then PPD itself, bought by Hellman & Friedman/Carlyle 3.9B\$
- INC acquired Kendle International 232 M\$
- InVentiveHealth Inc acquired Pharmanet
- Nautic bought Omnicare's clinical service (Thecome) 200M\$





- **CRO 受到投资界热捧 \_ 给CRO 功过并购,上市融资发展带来契机**

Though business up and down over the past 3-5 yr,  
成长空间大  
公司估值不高



通过收购, 或联盟, 迅速纵向一体化  
不仅限于同行, 也有跨行的,

- (Covance 收购 Lily 的R&D 50M\$)

优秀的**CRO** 发展离不开合作联手

- Merck \_ Pimaral
  - Bayer \_ Parexel
  - 先声 – 泰格
- 

## 国内**CRO** 业不甘寂寞 – 联盟成为强化服务和融资的渠道

- 康龙化成并购维通博际 (Pharmaron acquitted Bridge Lab, from drug discover to preclinical )
- 桑迪亚 (chemical synthesis), 联友制药(API, scale up) , 华大天源 (medicinal chemistry, biologic discovery, high throughput, screening)

## Continued

中国生物技术外包服务联盟(ABO) 整合了10多家外包机构

- \_ 品牌共享,协作营销, 新药研发,临床前, 临床研究,注册申报,外包生产... “一站式服务”

Wuxi recently acquired two CROs in Shanghai' (上海杰诚医药科技, 上海津石医药科技, MedKey/ Jiecheng Med-Tech Development

Going public (TigerMed) \_ for financing to quickly expand/occupy the market

- Mostly involved in Innovative drugs development Global multicenter trials
- 与跨国CRO相比，具有性价比高、本地化操作,执行力和效率高
- 泰格营业收入从 2009年 6,279.29万元  
2011年 19,326.38万元
- 年均复合增长率为75.44%。



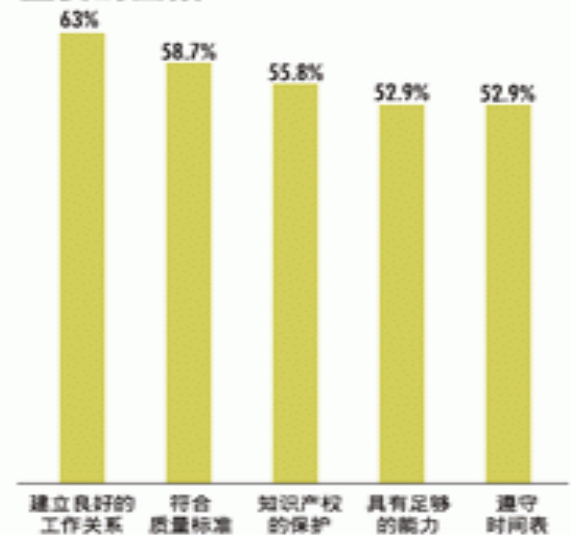
对于大多数，没有和“大户”人家联姻的，又  
没有能力通过上市融资 扩张的  
– how we survive and grow



## Top five attributes, that pharmaceutical are looking for

- Therapeutic expertise
- Low cost
- Global footprint
- CRA quality
- Upfront contingency planning

图3：对于医药研发外包业务非常重要的因素



数据来源: BioPlan 调查, 可多选

## Striving for Survival and Growth

- 提高自身能力,  
*get into global trials*  
*work with Western pharma/biotech for its China projects*  
liaised with Western CROs  
SOP/system/language

## 促进药政申报环境改变

- CTA approval process can take over a year
- Preclinical pharm/tox, 3,6 month stability data are required to be done from China
- Exit/entry restrictions/permit  
samples (bio, blood, tissues) complicated/duplicated  
procedures of application



## Promote Industry Standard

- CRO 产业推广质量标遵,操作规范
- 争取国际认证 (FDA inspection, and EMEA/international accreditation,
- CROU, IS9000
- 业务发展上 \_“傍大款”
- 联合产业链，上下游，纵向一体化，一站式，全服务
- 提供客为客户/项目定制的服务，研发联手，风险共担等

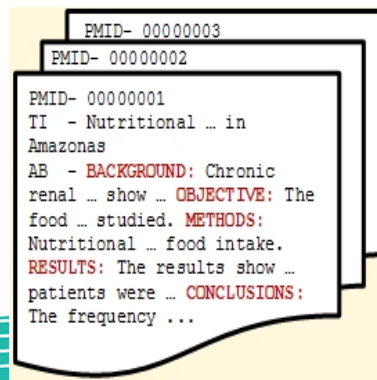
## 规范化? How, and to what standard ?

### 临床CRO 规范化/标准化面临的挑战

- ◉ 行业/协会自行出面, 组织 \_ CROU is making good effects now  
“合同研究组织临床服务管理规范”, (但是1很难以一家, 一本标准的推行来达到, 2 搞入门资质审定亦不实际)
- ◉ 操作比较好的, 服务Major Pharma 及国际项目多的CRO 带头提倡/推行质量提升的运作/标准
- ◉ 行业内避免因价格竞争而造成操作/规范/质量降低
- ◉ 药监部门要对不良操作事件/公司予以曝光

## 规范操作/标准化的核心是认真推行GCP

- 培训，检查，证书？
- **GCP** \_ 不是本条款去背的，是在操作实践中自觉尊崇的原则
- **ICF**，（内容，形式，操作）如何切实保障受试者的权益



## 改善 GCP 环境, China GCP Practice History

- 1998, Regulation of Drug Clinical trials
- 1999, Regulation of Drug Clinical Trials \_revised
- 2003, After China became WTO member (12, 2001),  
The items in the Regulation that were not in compliance with the ICH-GCP were removed or modified.
- Revised Drug Clinical Trials Quality and Guideline (GCP),  
published 09, 2003



## **GCP Deficiency \_ general situation** 中国GCP状态

*The current major hurdles: ICH-GCP compliance \_ in both the regulatory and industry practice*

*China falls behind, US/European countries, and developing counties (Asian countries) in general and in specific stage of drug development .*

**“China Drug Clinical Development \_Current Status and Development”  
Forum, 2009**

Organizer: SFDA Medicine Economic Inst, China Prescription Drugs, et al.



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## **GCP Deficiency – in regulatory oversight** **药政监管部门的缺陷**

**Regulatory agency focuses on site accreditation of the study hospital/sites (facility/equipments, education/academic recognition)**

**Less oversight/enforcement on training, GCP practice in trial operation and management.**



## Current GCP Practice \_at the study sites

SFDA accreditation of study sites \_ the only regulatory requirement for conducting clinical trials.

- Policy of site accreditation, 02, 2004
- At present, about 356 study hospital/sites, with a total of 1900 therapeutic areas accredited by SFDA
- Currently, all sites accredited before 2007 are under review.

**药物临床试验机构资格认定证书**  
CERTIFICATE FOR MEDICAL INSTITUTION CONDUCTING  
CLINICAL TRIALS FOR HUMAN USED DRUG

证书编号: 0174  
Certificate No.:

医疗机构: 广东省人民医院  
Institution: Guangdong Provincial People's Hospital

地址: 广东省广州市中山二路 106 号  
Address: No.106, Zhongshan Er Road, Guangzhou, Guangdong

认定专业: 心血管、肿瘤、皮肤、风湿免疫、呼吸、内分泌、  
Certified Therapy Area:

血液、烧伤、肝病、医学影像 (诊断)

经审查, 符合药物临床试验机构资格认定的要求。特发此证。  
After review the above-mentioned medical institution is qualified to  
conduct clinical trials.

有效期至 2010 年 11 月 15 日  
This certificate remains valid until

Date for Issuing 2007 年 11 月 15 日

国家食品药品监督管理局制  
PRINTED BY STATE FOOD AND DRUG ADMINISTRATION

## Current GCP Practice \_at the study sites (cont'd)

Regulatory accredited sites, limited mostly  
in top tier hospitals in major cities  
60% in BJ and Shanghai  
\_ subjects/patients are not as available as  
expected (competing trials, “professional”  
volunteers)

Clinical data collection/management, in  
general, preliminary, irregular, except  
limited sponsored by few MNC or major  
CROs



## Current GCP Practice \_ Training

- Extensive GCP training by regulatory agencies (State and Provincial levels), and associated institutions,
- Reported thousands of physicians, nurses, staff are trained,
- “Training certificates” issued as qualification for participating in clinical trials.



## Current GCP Practice \_ Training

- **Is it enough?** 目前的培训是不够的
- Content/scope of the training,  
inconsistent  
mostly, introduction of the GCP history/concept, 1-2 days to a couple of wks)
- Many clinical staff who were trained  
are not participating/retiring,  
newer/younger physicians/med graduates/nurses participating  
in the trial operations, without proper training.



**Example: Wrong information are dispersed by authentic institution**

<http://www.cSCO.org.cn/> Chinese Society of Clinical Oncology  
中国医学科学院, 协和医科大, 肿瘤医院, 中国临床肿瘤协会



Professional

English

Public

**China GCP Training** – wrong information is being dispersed,  
“GCP” that has been deemed incompatible with the ICH-GCP and  
international practice

<http://www.csc.org.cn/gcp/class/zhn002.htm>

Authentic GCP training



## 药物临床试验管理规范 (GCP)

药品临床试验管理规范 (GCP)

国家药品监督管理局令 (第 13 号)

一九九九年九月一日发布

### 目 录

第一章 总 则

第二章 临床试验前的准备与必要条件

第三章 受试者的权益保障

.....

Drug Clinical Trials Regulation (GCP)

State Drug Administration Reg No. 13

1999-09-01

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Chapter 1, General Introduction

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Chapter 3 .....

.....



## *A Specific Example:*

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**A pilot BE Study of 24 subjects for US NADA  
done in a China phase I center (Jan. 2010)**

**8/25 source doc/ICF/CRF were reviewed, 7 over 8 (87%) have GCP problems, e.g.**

- *missing signatures or dates on ICF, (physician's, patients' or witness')*
- *subjects enrolled with exclusion items (e.g. OTC drug, over-weight, under weight etc) with no explanation, no PI waiver*

## **Representative Problems - ICF process**

### **知情同一的操作**

- **Signature/date missing**
- **Singing on different dates**
- **Timing of consent,**  
    signing on the same date of dosing
- **Old version,**  
    not the update ICF, were signed by the subjects
- **Singing on ICF having different test drug info**
- **Different ICF were consented in multicenter studies**

## **Representative Problems – ICF content**

### **知情同意内容代表性问题**

- **Terminology, too difficult to understand (e.g. “drug abuse”)**
- **Content/format**
  - Poor layout,
  - No subtitles, or too condense
  - Repetition,
  - Overly long

## **Representative Problems – ICF Content(cont'd)**

知情同意内容代表性问题

- **Key Info missing**

**Risk and benefits of alternative therapies are not sufficiently disclosed.**

**Placebo consequence of not being treated are often not given fully**

(Declaration of Helsinki requires to, if subjects have a chance of receiving placebo)



## Representative Problem - IRB Issues

### 伦理委员会代表性问题

- IRB are hospital specific, each hospital/site uses its own
  - Redundant and difficult in global MCT
- IRBs are chaired/influenced by Academician, Director, KOLs in the hospital, who are often the PI
- IRBs are not regulatory empowered, mostly function as protocol reviewer, and often an approval is given with minor suggestions without any further oversight.
- Amendment, modification, notification are not properly done
- Inexperienced IRB may add extra hurdle for trial approval

## Representative Problems - Operational 操作中代表性问题

- ◉ **Add or enroll more patients,**  
do not follow the protocol, at any point of the study without IRB amendment or notification
- ◉ **Patient Diary** \_ incomplete, or retrofitted by the hospital/CRA's, by memory or simply for the sake of completing the report at the closure.  
(FDA is encouraging ePRO to safeguard the data integrity)

## **Representative Problems - Operational (cont'd)**

### **操作中代表性问题**

- **Others**

- Bio-samples (blood, urine, tissues) are taken by the hospital for other research purposes without acknowledgement of sponsor, or consent from the subject/patients
- Subjects/patients are used for other studies (by graduates, nurses, psychoanalysts)

## Geopolitical Factors

### - State/Provincial Projects

- Often a drug project is initiated /supported by governments (state/provincial) e.g.,
  - “Project 863”, “Project 973”
  - State Science/Tech Projects 国家科技重大专项,

All the parties involved in such projects including the IRB would like to “see” the project go through smoothly



## Geopolitical Factors – cont'd

- Downside of strong Government Financial Support \_  
Government becomes a cheerleader for a drug, the project or the company,

Even if the **result are uncertain objectively**\_ likely, a permissive result along the R&D processes all the way through the regulatory approval;

## Geopolitical Factors – cont'd

It is not yet clear from outside China:

How well or thoroughly  
the regulatory agency is ready to **truly embrace**  
the kind of **transparent processes**  
that are necessary for faster **genuine progress**  
in  
new drug development and  
for  
confidence in that progress  
to be without reservation elsewhere.

*- Drug Discover Today -*



## Others

- **Subject rights/safety/liability/insurance**

Insurance and liability litigation

- **IP protection**

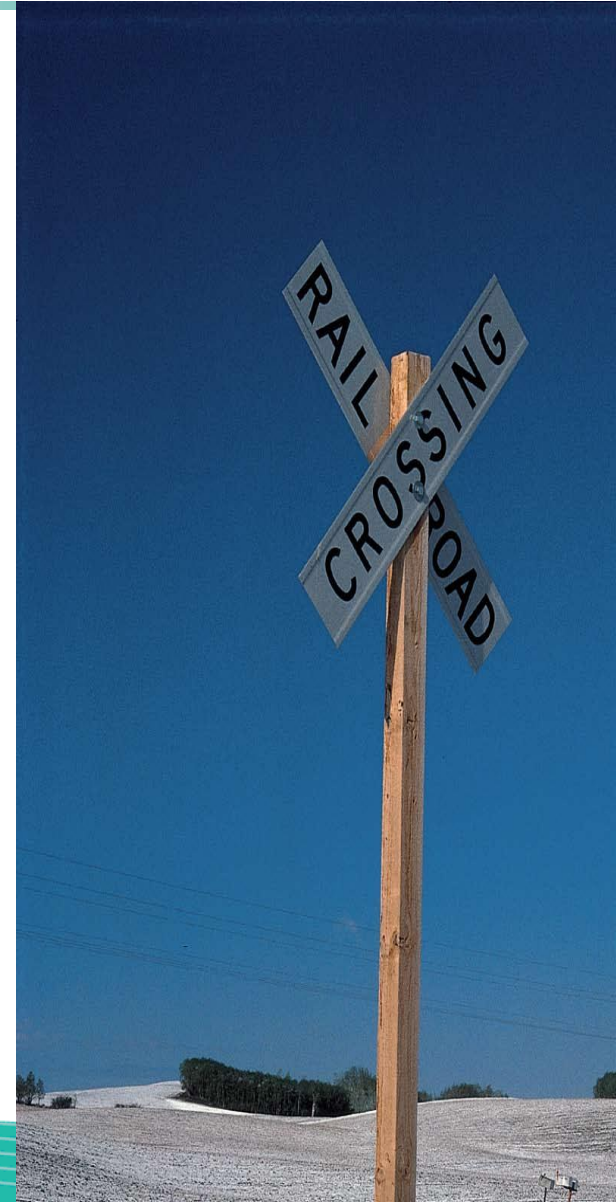
- IP infringing, allegations, a serious concerns,  
Western IP law firms in Shanghai and Beijing are now actively pursuing in China.
- NCEs in development stage, entering clinical(in US) , however modified agents by Chinese (actually “me-too”, “me-better” “NCEs” are going on competing for approval  
e.g., at the moment, several diabetic, oncology, anti-infectious NCEs of this type are going through clinical stages  
arguably even, who is the original NCE drug developer, if these “NCEs” were approved first in China

## To improve China GCP

Regulatory oversight/enforcement of GCP

\_ by which government (MOH, or SFDA?) on  
which part of practice/operation of the clinical drug  
development

Make GCP practice compatible with the international,  
e.g., via multicenter global trials to eventually  
make the data acceptable by US/EC.



## To improve China GCP

- IRB to be empowered to enforce GCP practice
- The regulatory body to oversee and improve the IRB practice.

IRB, central or regional, “independent” to the hospitals

IRB shall impose oversight on data integrity rather than leaving it to be produced by investigator/CRO via “QA” solely by themselves.

- Headquarter in Exton, PA
- Bio-analytical, biomarker, DMPK \_ Malvern PA,
- Pharmaceutical, formulation R&D \_ Exton, PA
- Clinical (phase I center) \_ Hackensack, NJ
- Clinical (CRO management, data/statistics) \_ Exton, PA

Frontage extended business in China  
(Shanghai, 2006)





## Frontage Services in China (Shanghai, Beijing, Zhengzhou) 方达在中国的业务

- Phase I centers in **Zhengzhou** (120 beds) and in **Changchun** (72 beds)
- Bio-analytical, pharmaceutical/tox, formulation, CMC, GMP manufacturing (**Shanghai, Beijing**)
- Early phase focused services (first in human, Poc)
- Services for US ANDA (BE/FDA filing), GMP/CMC consulting

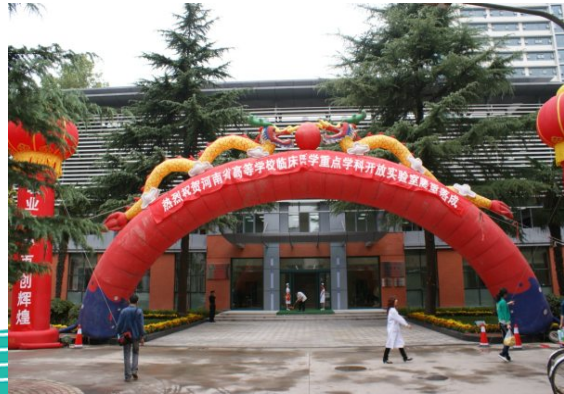
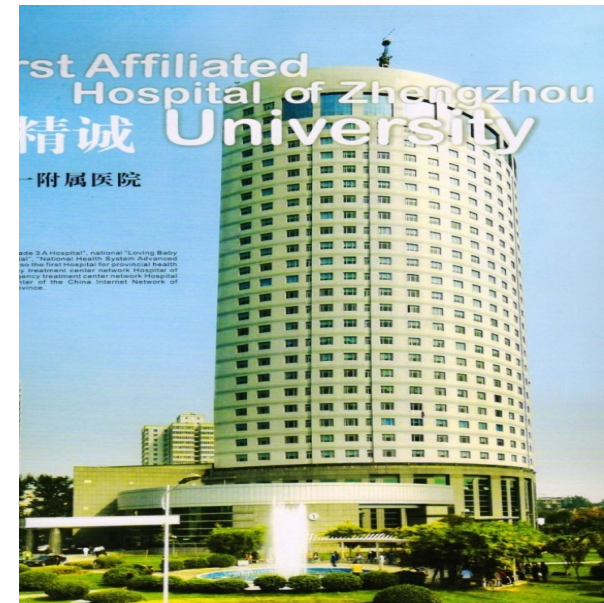


## Leveraging the Strengths on Both Sides

### Services of US quality at China cost

联合两边的优势以中国的价格提供高质量的服务

- Phase I sites in Hackensack NJ, US and Zhengzhou/Changchun China
- Same operation system (clinical, bio-analytical, SOPs)
- Chinese staff to be trained in the States, US staff coming to work at Zhengzhou site.



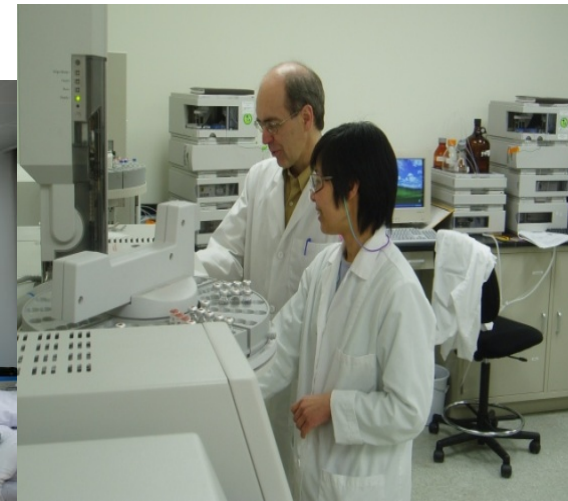


## Leveraging the Strengths on Both Sides

### Services of US quality at China cost

联合两边的优势以中国的价格提供高质量的服务

- BE study data to be submitted for FDA and China SFDA registration
- - pilot BE in China and the Pivotal in the States for FDA registration
- - now, Pivotal BE done in China for FDA ANDA submission
- Six FDA approved ANDA from China, Frontage has done 5 of them



**THANK YOU FOR SHARING  
OUR THOUGHTS**

