Cases and Opinions on Clinical Trials by Japanese Pharmaceutical Companies in China

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March 22, 2012

Development Status of Japanese Pharmaceutical Companies in China

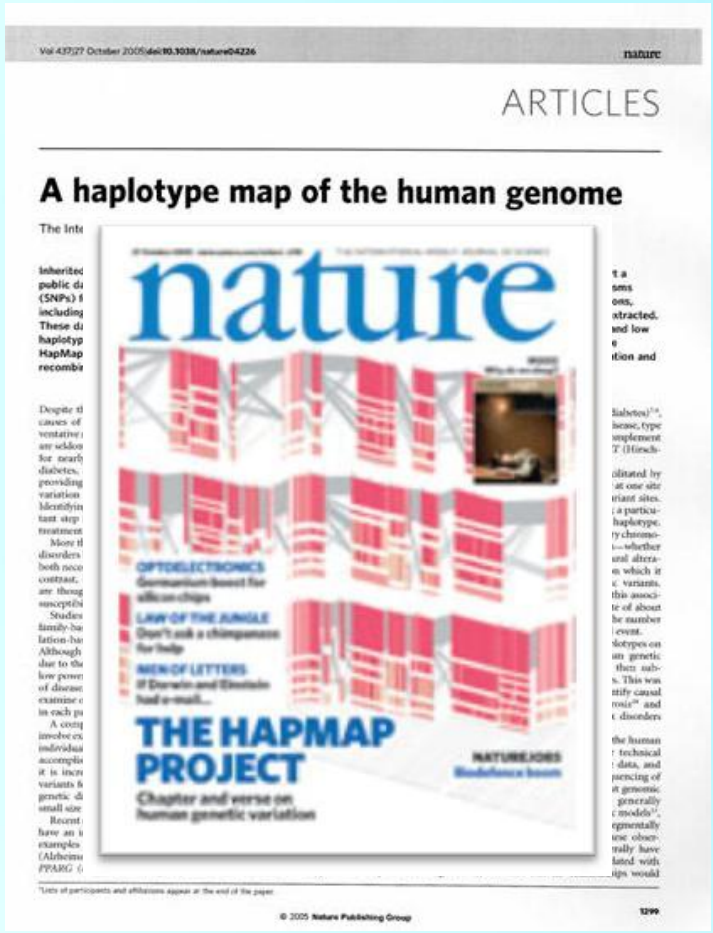
Cases on Clinical Trials by OBRI

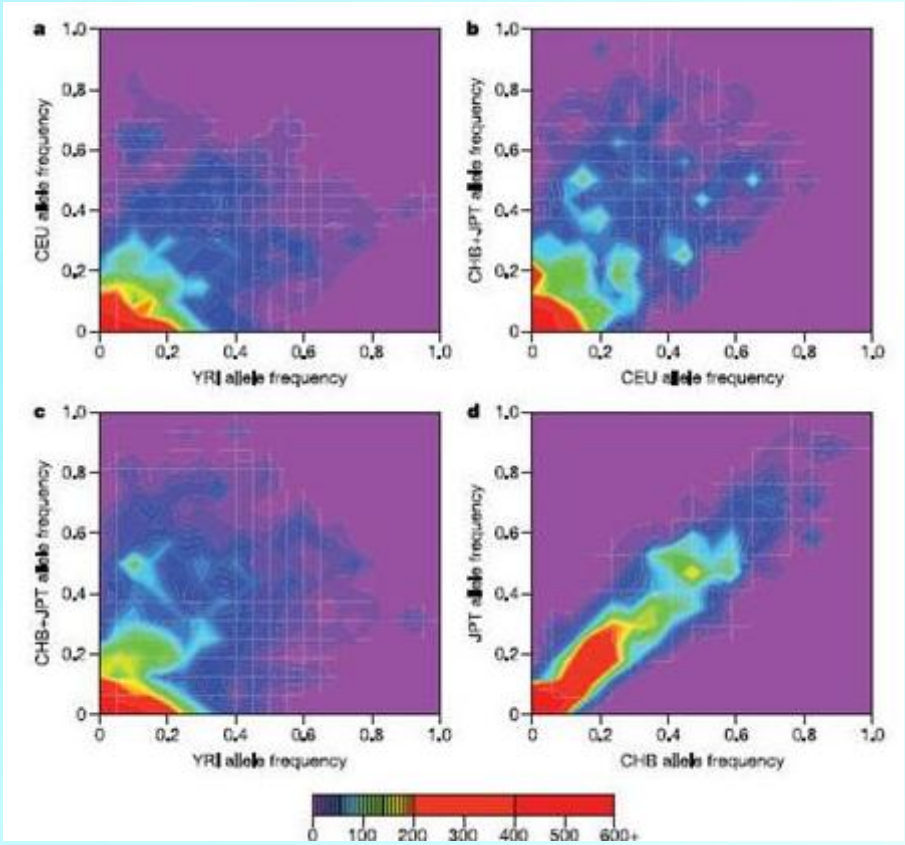
Opinions on Development Status in China

Development Status of Japanese Pharmaceutical Companies in China

Merit for Conducting MCTs in Japan and China

Chinese and Japanese are very similar in genes

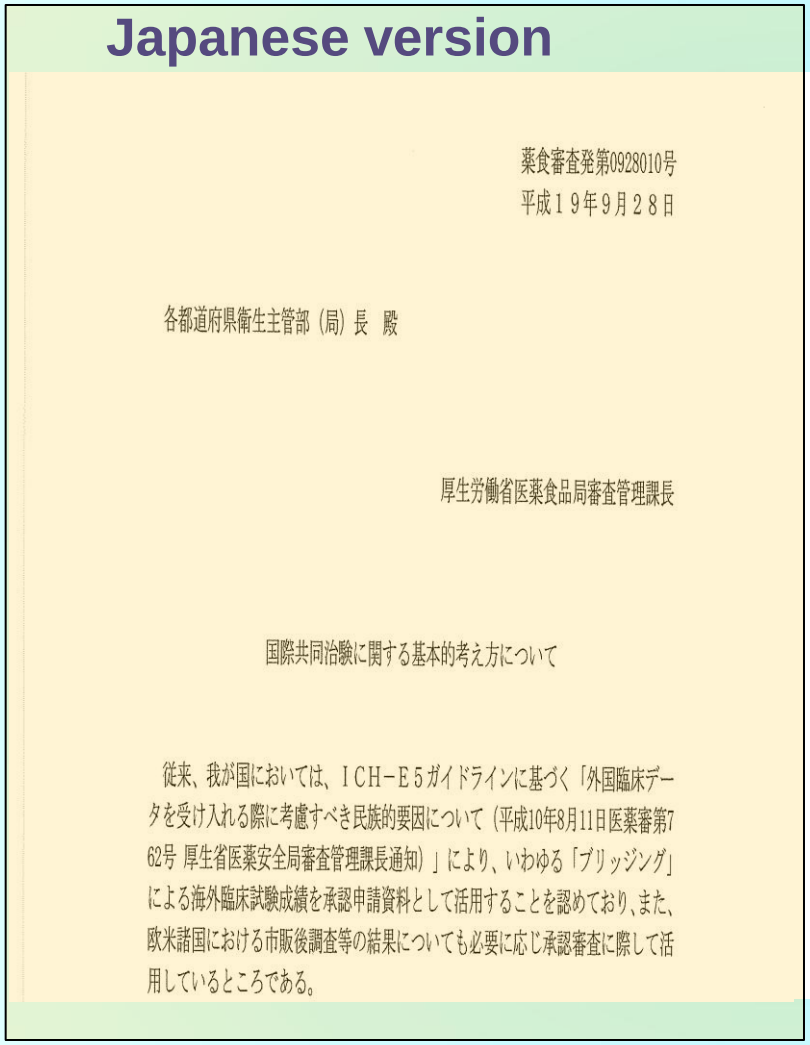




Nature 437: 1299-1320 (2005)

Japanese Basic Principles on Global Clinical Trials

Japanese version



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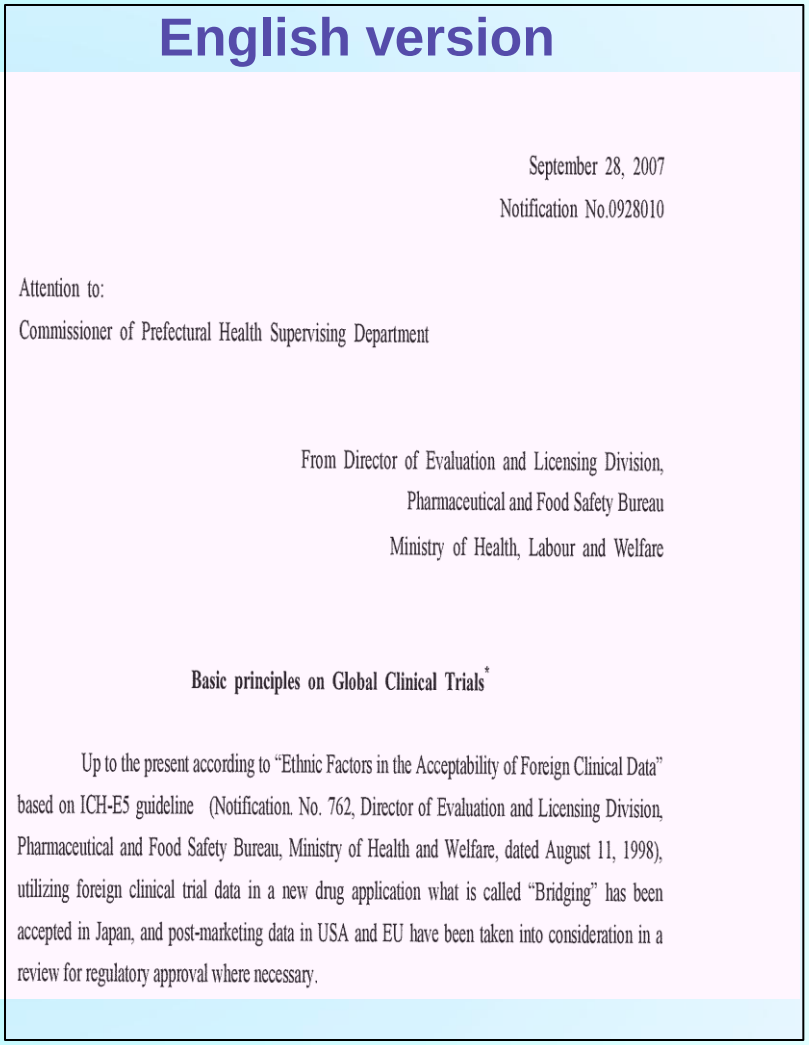
各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

国際共同治験に関する基本的考え方について

従来、我が国においては、ＩＣＨ－Ｅ５ガイドラインに基づく「外国臨床データを受け入れる際に考慮すべき民族的要因について（平成10年8月11日医薬審第762号 厚生省医薬安全局審査管理課長通知）」により、いわゆる「ブリッジング」による海外臨床試験成績を承認申請資料として活用することを認めており、また、欧米諸国における市販後調査等の結果についても必要に応じ承認審査に際して活用しているところである。

English version



September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Basic principles on Global Clinical Trials*

Up to the present according to "Ethnic Factors in the Acceptability of Foreign Clinical Data" based on ICH-E5 guideline (Notification. No. 762, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign clinical trial data in a new drug application what is called "Bridging" has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.

Japanese:http://www.pmda.go.jp/operations/notice/2007/file/0928010.pdf
English　:http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf

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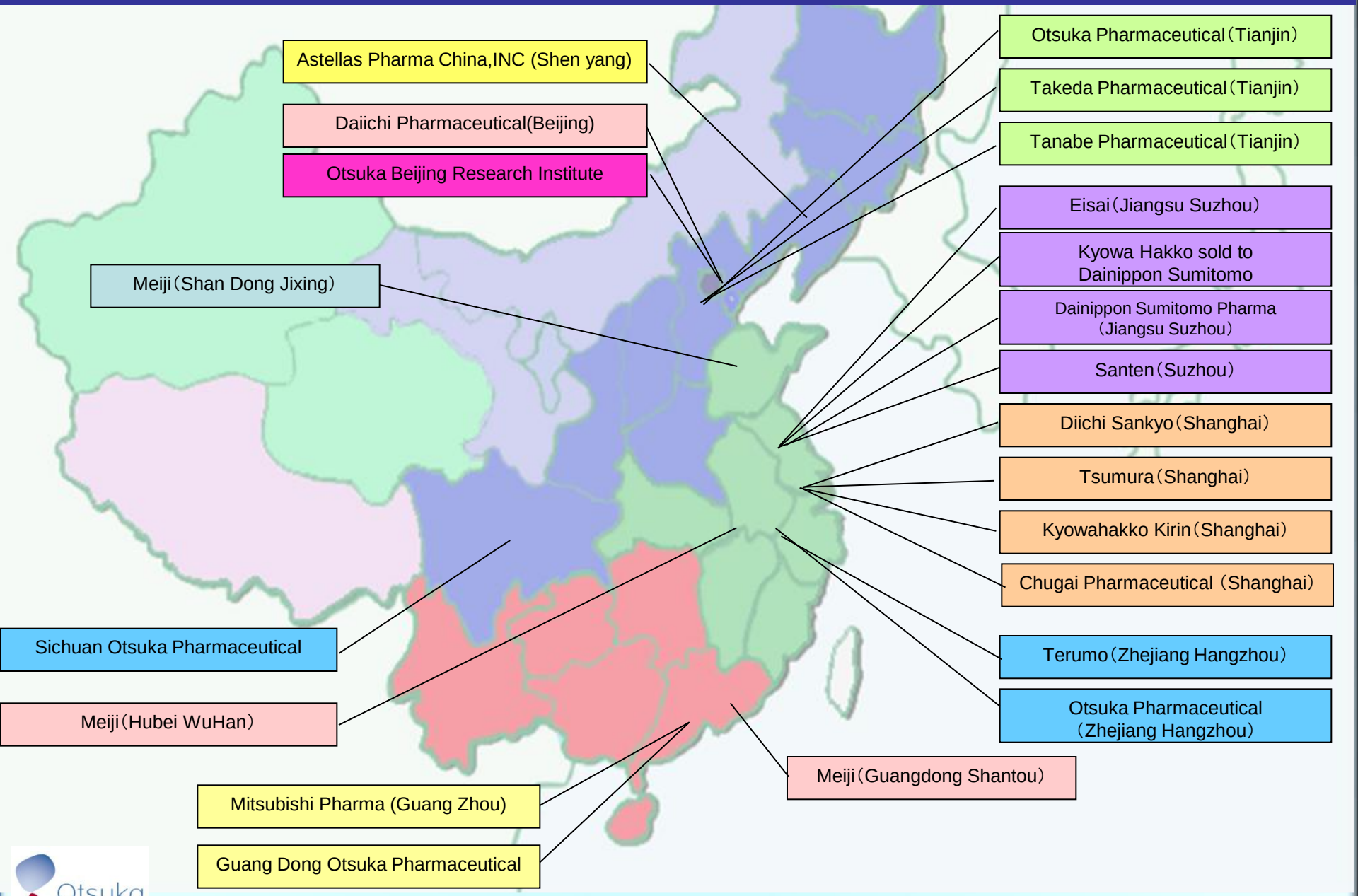
Japanese Pharmaceutical Companies in China (China local corporation)

1	Eisai China Inc	18	China Otsuka Pharmaceutical Co., Ltd
2	Kirin Kunpeng (China) Bio-Phramaceutical Co.,LTD	19	Otsuka Pharmaceutical Group Zhejiang Otsuka Pharmaceutical Co., Ltd
3	Takeda Pharmaceutical (China) Co., Ltd.	20	Guang Dong Otsuka Pharmaceutical Co., Ltd
4	Tianjin Takeda Pharmaceutical Company Limited	21	Sichuan Otsuka Pharmaceutical Co., Ltd
5	Sumitomo Pharmaceutical (Suzhou) Company Limited	22	Suzhou Otsuka Pharmaceutical Co., Ltd
6	Asahi Kasei Management (Shanghai) Company Limited	23	Mitsubishi Pharma Research & Development(BeiJing)
7	Kowa(Shanghai) pharmaceutical consulting Co.,Ltd	24	Mitsubishi Pharma Research & Development(GuangZhou)
8	Santen Pharmaceutical Co., Ltd	25	Kyowa Hakko Pharmaceutical Technology (Shanghai)Co.,Ltd
9	Chugai Pharmal(ShangHai)Consulting Co., Ltd.	26	Shanghai Tsumura Pharmaceutical. Co.,Ltd
10	CHUGAI Pharmaceutical Beijing Co., Ltd	27	Tianjin ROHTO Herbal Medicine Co., Ltd
11	Teijin Pharma Shanghai Consulting Co.,LTD	28	Nitto denko (Shanghai) pharmaceutical consulting Limited
12	Senju Pharmaceutical Science & Technology(BeiJing)Co.,LTD	29	Shanghai Ajinomoto amino acid limited company
13	Taiho Pharmaceutical of Beijing Co.,Ltd.	30	Eiken Shanghai Co.,Ltd.
14	Daiichi Sankyo Pharmaceutical (BeiJing)Co.,	31	FUSO TEIYAKU QINGDAO CO., LTD
15	Daiichi Sankyo Pharmaceutical (ShangHai)Co.	32	SUMMIT PHARMACEUTICALS CHINA LTD
16	Astellas Pharma China,INC.	33	Beijing Konishi Medical Consulting Co., Ltd
17	Otsuka Beijing Research Institute	34	Shantou Meiji pharmaceutical limited company
		35	HM Science Beijing Inc.

Japanese Medical Device Companies in China (China local corporation)

1	Hitachi medical equipment (Beijing) Co., Ltd.	10	Shanghai Kohden Electronic Medical Instrument Co., Ltd
2	Olympus (Beijing) sales and Service Company Limited	11	SHANGHAI KOHDEN MEDICAL ELECTRONIC INSTRUMENT CORPORATION
3	Asahi medical equipment (Hangzhou) Company Limited	12	Nihon Kohden Trading (Shanghai) Co., Ltd.
4	Asahi medical equipment (Hangzhou) Trading Company Limited	13	FUJIFILM (China) Investment Co.,Ltd
5	Toshiba Medical Systems (China) Co., Ltd.	14	Sony (China) Co., Ltd.
6	Toray Medical(Qingdao)Co.,Ltd	15	Canon (China) Co., Ltd
7	Beijing Shimadzu Medical Equipment Co	16	Konica Minolta medical printing equipment (Shanghai) Company Limited
8	Shimatsu International Trading (Shanghai) Company Limited	17	SHANGHAI KANON INTERNATIONAL TRADING CO.,LTD
9	Beijing Fukuda Denshi Medical Instruments Co.,Ltd		

The Distribution Map of Japanese Pharmaceutical Companies in China



Registration applications from Japanese Enterprises (2009)

Products & Applicants

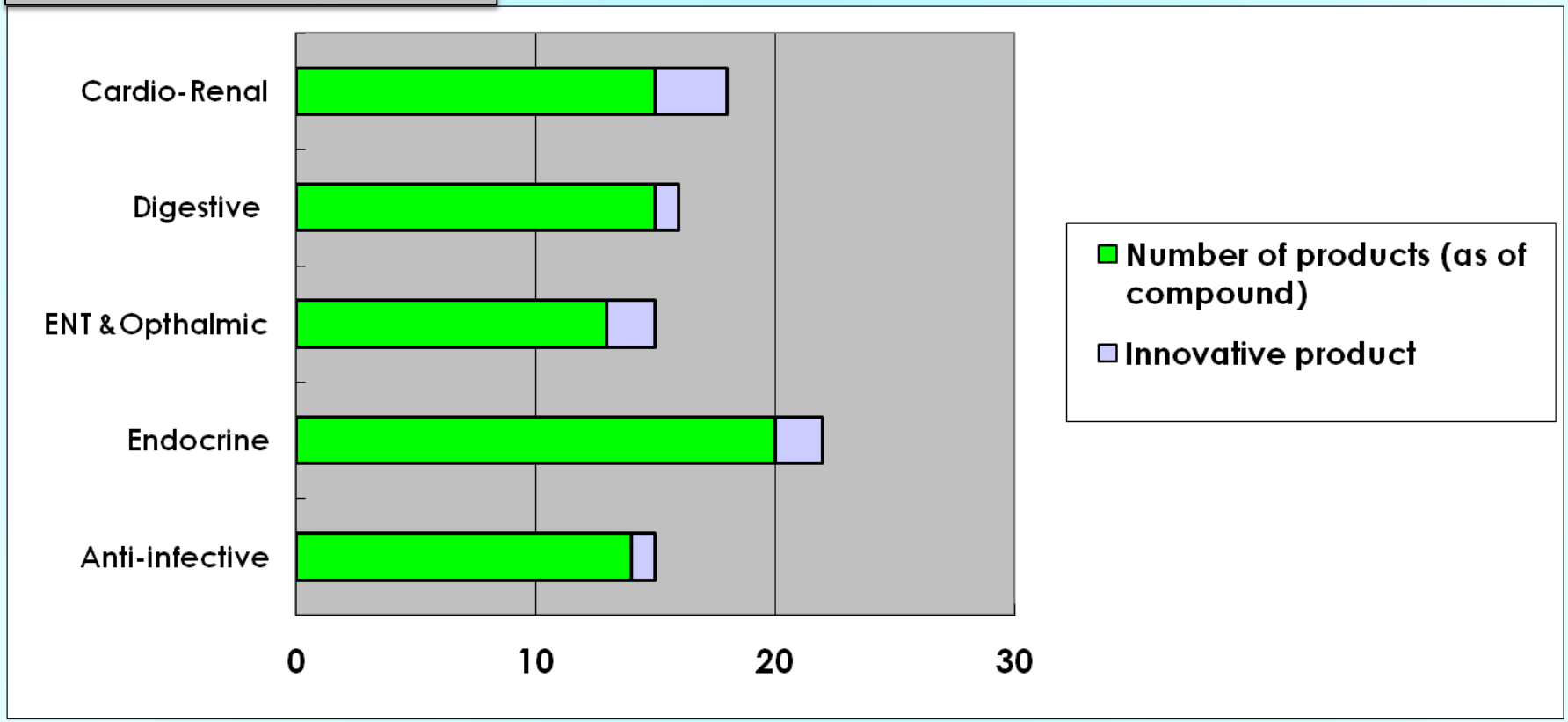
Product： **129 compound**

Applicants: **more than 50**

Average： **2.58 product per applicant**

Registration applications from Japanese enterprises (2009)

By Indication



Japan Application by Using Foreign Clinical Trail Data

Product	DETRUSITOL (Tolterodine)	NULOTAN (Losartan)	HERCEPTIN (Trastuzumab)	CRAVIT (Levofloxacin)
Company	Pfizer	Banyu	Chugai	Daiichi Sankyo
Approval	April, 2006	2006年4月	2008年2月	2009年4月
Study Type	Asian Study	April, 2006 Asian Study	Asian Study	Chinese Study
Countries (Area) in Asian	JP/KR	JP/HK/SNG/ Malaysia	JP/KR/CN/TW	CN
Application category	New active ingredient	New function	New function /New dosage	New dosage/New formulation

Cases on Clinical Trials by OBRI

OBRI Milestone

Medicine name	Registration classification	Indication	SFDA permission day in China
Abilify	Chemicals 3.1	Schizophrenia	June, 2007
Pletaal	Chemicals 3.4	Prevention of the cerebral infarction recurrence	February, 2008
Samsca	Chemicals 1.1	Hyponatremia	September, 2011
Adacolumn	Medical device	Active inflammatory bowel disease (IBD)	September, 2011

Clinical trial progress of OBRI

(Since 2004 to February, 2012)

Completed	7 projects(number of the clinical trials: 17)
Ongoing	5 projects(number of the clinical trials: 7)
Planning	8 projects(numbe of the clinical trials: 10)

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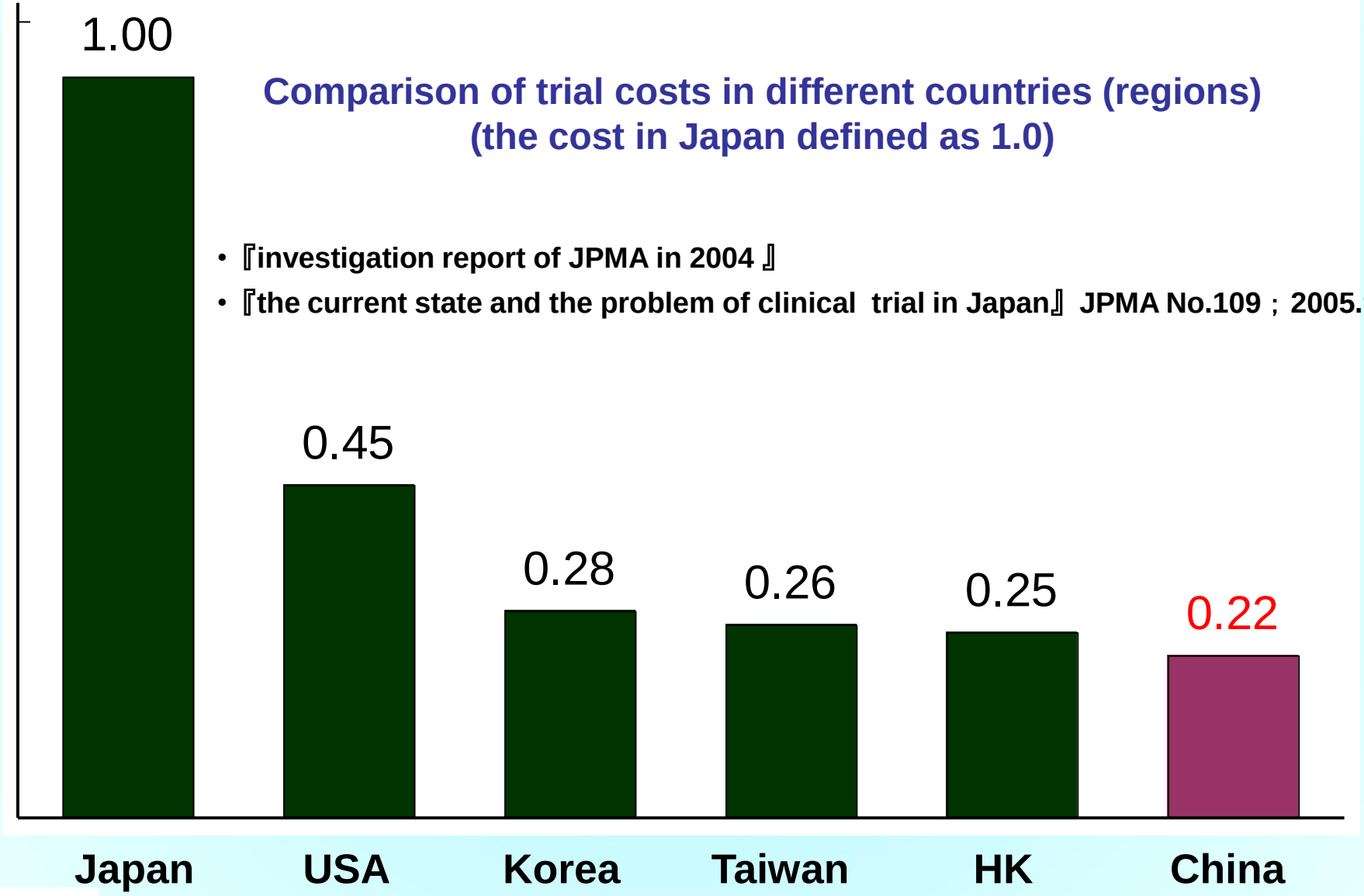
Characteristic of Clinical Trial in China

■Lower Clinical trial cost

■ The speed of subject enrollment is fast

■ High quality (strict management is necessary)

Substantial Cost Savings



Comparison of trial costs in different countries (regions)
(the cost in Japan defined as 1.0)

- 『investigation report of JPMA in 2004 』
- 『the current state and the problem of clinical trial in Japan』 JPMA No.109；2005.9

Fast enrollment is one of the characteristics in China

Example

CSPS

(Cilostazol Stroke Prevention Study)

12 Sites
720 Cases
6 Months

Related paper was published by Lancet in 2008

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Comparison between Chinese Pletaal CSPS clinical trial data and Japanese data

Rate of stroke recurrence

China

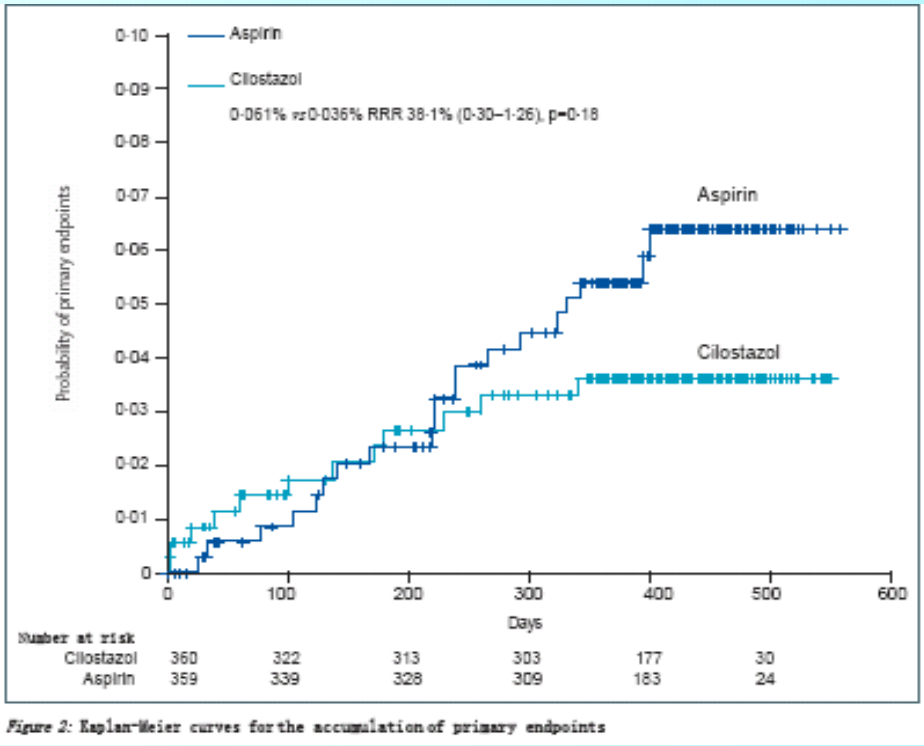
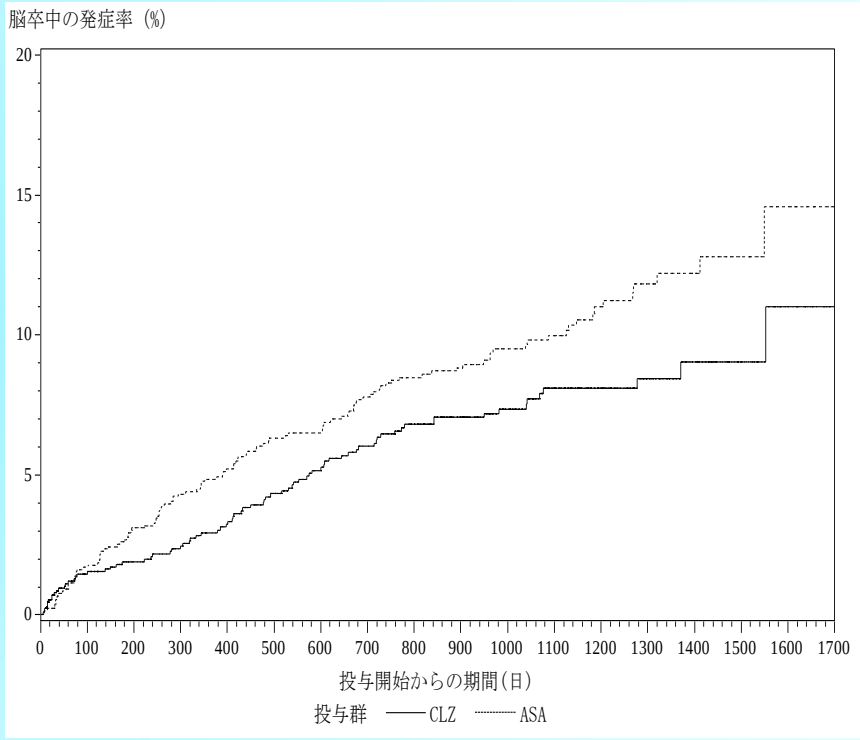


Figure 2: Kaplan-Meier curves for the accumulation of primary endpoints

Japan

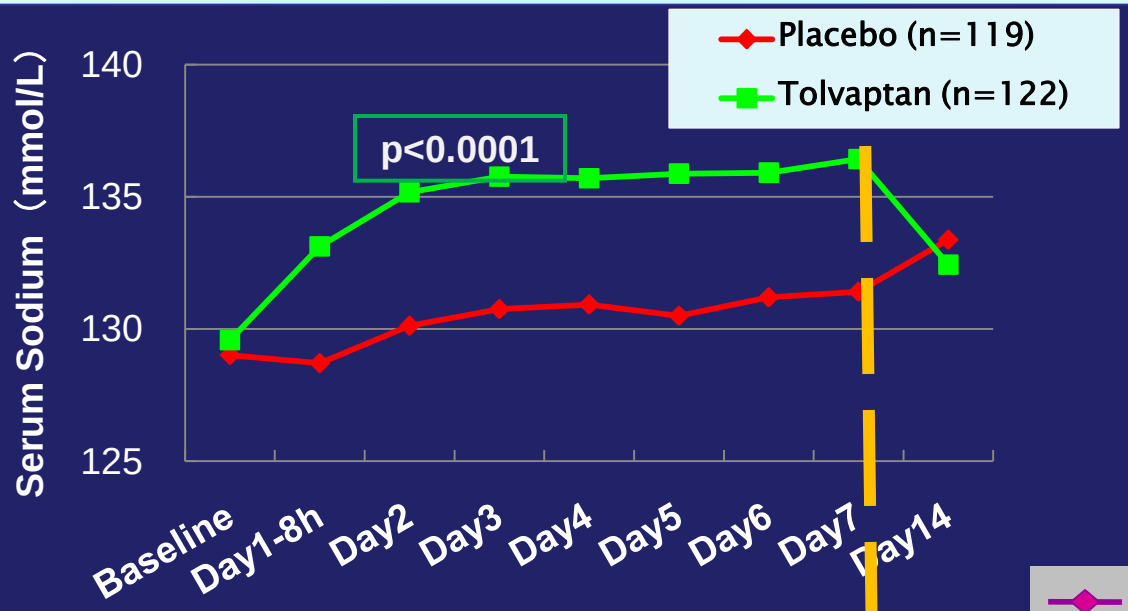


CSPS	n=720
Total	32
Pletaal	12
Aspirin	20

CSPS II	n=2,672
Total	201
Pletaal	82
Aspirin	119

Comparison between Chinese Tolvaptan Ph 2 clinical trial data and Japanese data

China



EU and US SALT2

Quality of Clinical Trial In China

Quality guarantee (OBRI's experience with a Global trial):

OBRI attended a multinational clinical trial including 17 sites (in US and CHN (2 sites and 2 Lab.), and all received audit by an America Auditor

Audit feedback:

- Reliable source data and well trained study staff
  →Among 9 contries17 sites in this global study, China's data is integrate and reliable

Key factors to guarantee quality of clinical trial In China

- Frequent training and site monitoring
  →Smooth communication between site/ sponsor/ EC

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Key factors to the Success of CT in China

Investigator's Cooperation

◆ the IMP and the therapeutic area

◆safety and effectiveness as proved via overseas CT

◆ budget

◆ relationship with the investigator

◆academic support

◆MNC's advantage in terms of opportunities in academic exchange

Patient Recruitment

◆ # of the potential subjects

◆ coastal cities with Beijing &Shanghai as the central point

◆ PI' s reputation and impact

◆ appropriate inclusion

◆attractive compensations

◆appropriate inclusion and exclusion criteria

◆ proactive approach to issues

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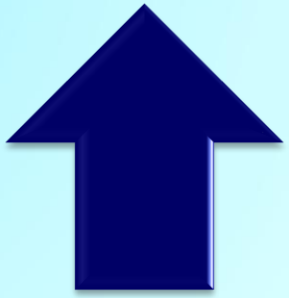
Today and Tomorrow--Clinical Trial In China

Opportunities

Lower cost

Rapid patient recruitment



Challenges

Slow regulatory process

Less experience in conducting clinical trial according to ICH GCP

Thoughts on Development Status in China

New Drug Application Prior Consultation System

New Drug Application Prior Consultation System

The time for IND approval is too long and it does not match international common practice and it also influences the global co-development schedule. Regarding this issue, the regulatory affair authorities and pharmaceutical companies already reached consensus and the relevant regulatory authorities are actively looking into reform policies.

The problem:
The government ‘s views: Too many applications, inadequately staffed, lacking of funds.
The industry’s view: Lack of complete prior consultation system.

Proposal:
Establishment of an effective prior consultation team with reference to the experiences of developed countries.
One or several times of prior consultations can take place.

Main advantages of prior consultation:
1 shortening the formal review time and improving the working efficiency of the reviewer.
2 helping pharmaceutical companies to prepare required and complete application documents, reducing the delay of approval caused by the request of supplementary documents.

Current Status and Future Prospects ー Clinical Trial in China

Although with the various uncertainties, we are confident that with the following improvements in the conducting environments, China will make more and more contributions to the new drug developments, both in Asia and the world.

- More transparent regulatory process
- Improving compliance with protocol and ICH GCP to obtain reliable clinical trial data
- Increasing in the number of experienced staff

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