China's Current State of Global Clinical Trials Conducted by Japanese Pharmaceutical Manufacturers

Shii Man

May 28th, 2010

Why Need Globalize R&D?

- **Expansion to regions with attractive R&D resources**
  - -Excellent human resources, high-level research/skills, government programs/support
- **R&D that addresses regional illnesses**
  - -Tropical diseases, viral diseases, malignant tumors, etc.
- **Selection of ideal companies**
  - -Incorporation of new compounds and technology

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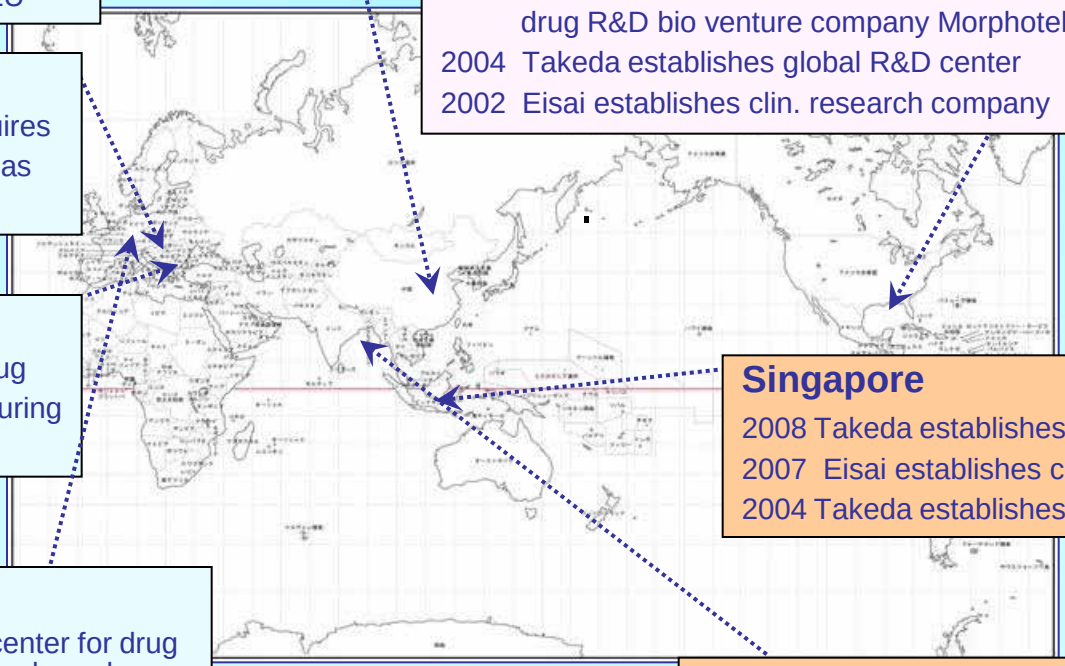
Global Expansion of Japanese Drug Company R&D (from 2000)

China
2009 Otsuka establishes new-drug R&D center in Shanghai
2003 Otsuak establishes clin. R&D center in Beijing

US
2009 Takeda relocates R&D headquarters responsible for global development strategy from Japan to US
2008 Takeda acquires Millennium as a subsidiary
Astellas relocates clin. R&D center from Japan to US
2007 Otsuka merges medical drug development and marketing strategy centers
Takeda establishes antibody drug R&D bio venture company
Eisai buys biopharma company MGI Pharma and antibody drug R&D bio venture company Morphotek
2004 Takeda establishes global R&D center
2002 Eisai establishes clin. research company

Europe
2005 Astellas reorganizes research center in EU

Germany
2008 Daiichi-Sankyo acquires a bio-drug company as a subsidiary



Czechoslovakia
2008 Otsuka buys bulk drug substance manufacturing company

Singapore
2008 Takeda establishes Asia-Oceania clin. R&D center
2007 Eisai establishes clin. research company
2004 Takeda establishes clin. research company

UK
2009 Eisai establishes a center for drug discovery, clin. research, and manufacturing in the EU
2007 Takeda buys bio venture company Paradigm Therapeutics

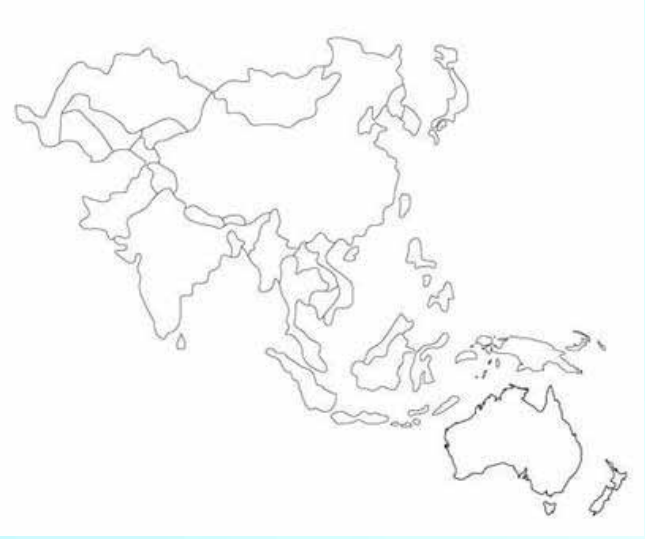
India
2008 Daiichi-Sankyo acquires Ranbaxy as a subsidiary
2007 Eisai opens manufacturing and research center

*Taken from each company's homepage

Asia, Pharma Market Growth

- A market with a huge population
- Vigorous momentum of economic development
- Rich resources of clinical cases
- potentially huge Pharma market

Global population	6.38 billion
Asian population	3.06 billion (48%
China	1.31 billion
India	1.06 billion
Japan	0.13 billion
ASEAN	0.56 billion



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Worldwide Top 10 Pharmaceutical Markets (1996-2010)

Predicted prescription and over-the-counter drug market size (unit: billion USD)

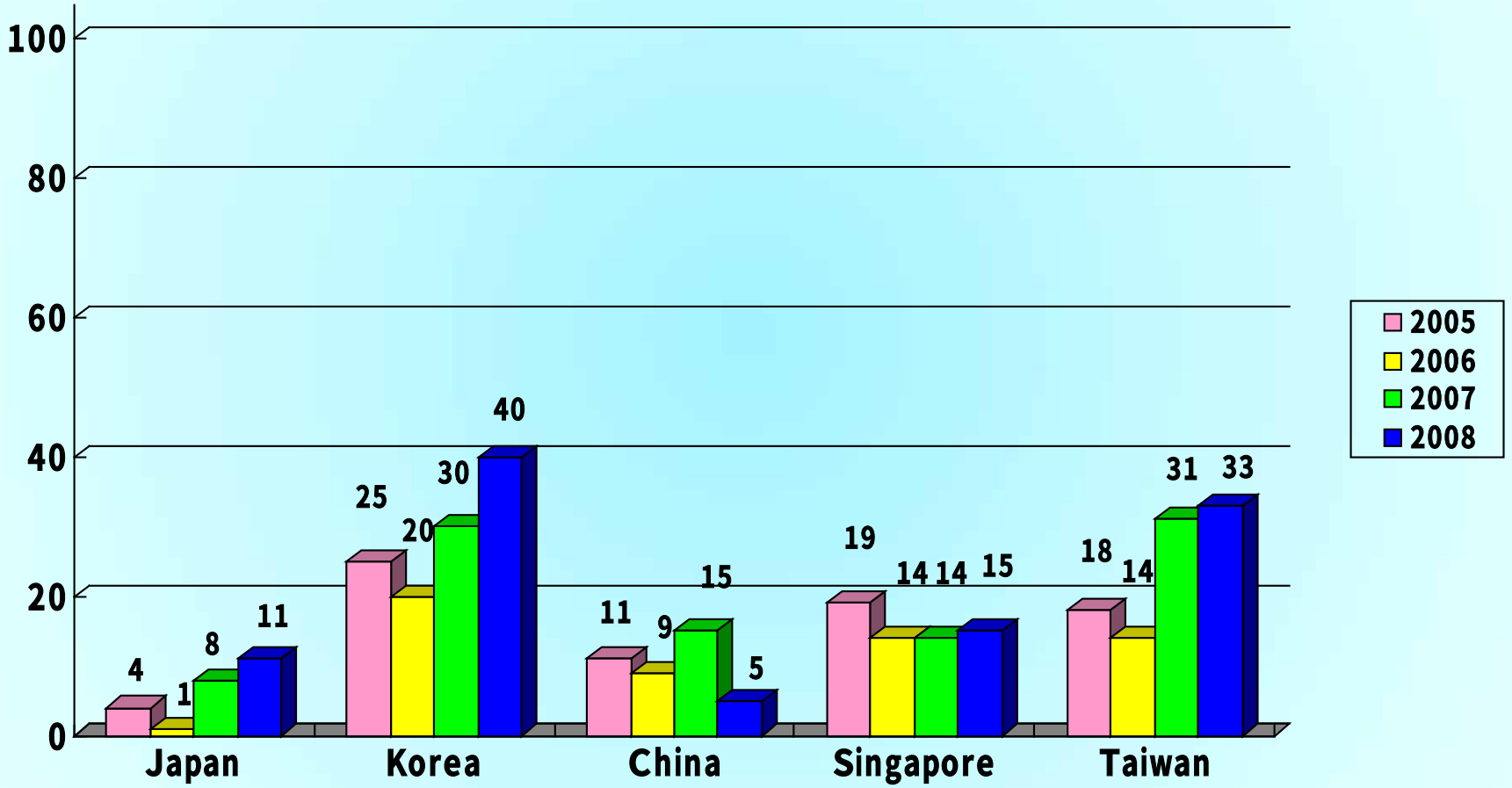
Rank	1996		2000		2005		2010	
1	USA	91	USA	150	USA	262	USA	466
2	Japan	52	Japan	58	Japan	65	Japan	81
3	Germany	20	Germany	17	Germany	24	Germany	37
4	France	18	France	17	France	21	France	28
5	Italy	10	UK	11	UK	16	China	25
6	Brazil	8.4	Italy	11	Italy	15	UK	24
7	UK	8.2	China	6.8	China	13	Italy	23
8	Spain	6.0	Brazil	6.0	Brazil	10	Canada	17
9	Korea	4.5	Canada	4.5	Canada	10	Spain	16
10	Canada	4.3	Spain	4.3	Spain	9.8	Brazil	15
11	China	4.3						

By the prediction of IMS conducted in Oct,2009, China's pharmaceutical market will reach 80 billions dollars scale in 2013,and becomes the third place in world pharmaceutical market

Source: IMS

Phase 2 Global Studies from 2005 to 2008

– Number of studies according to year of registration on Clinical Trials –



Phase 3 Global Studies from 2005 to 2008

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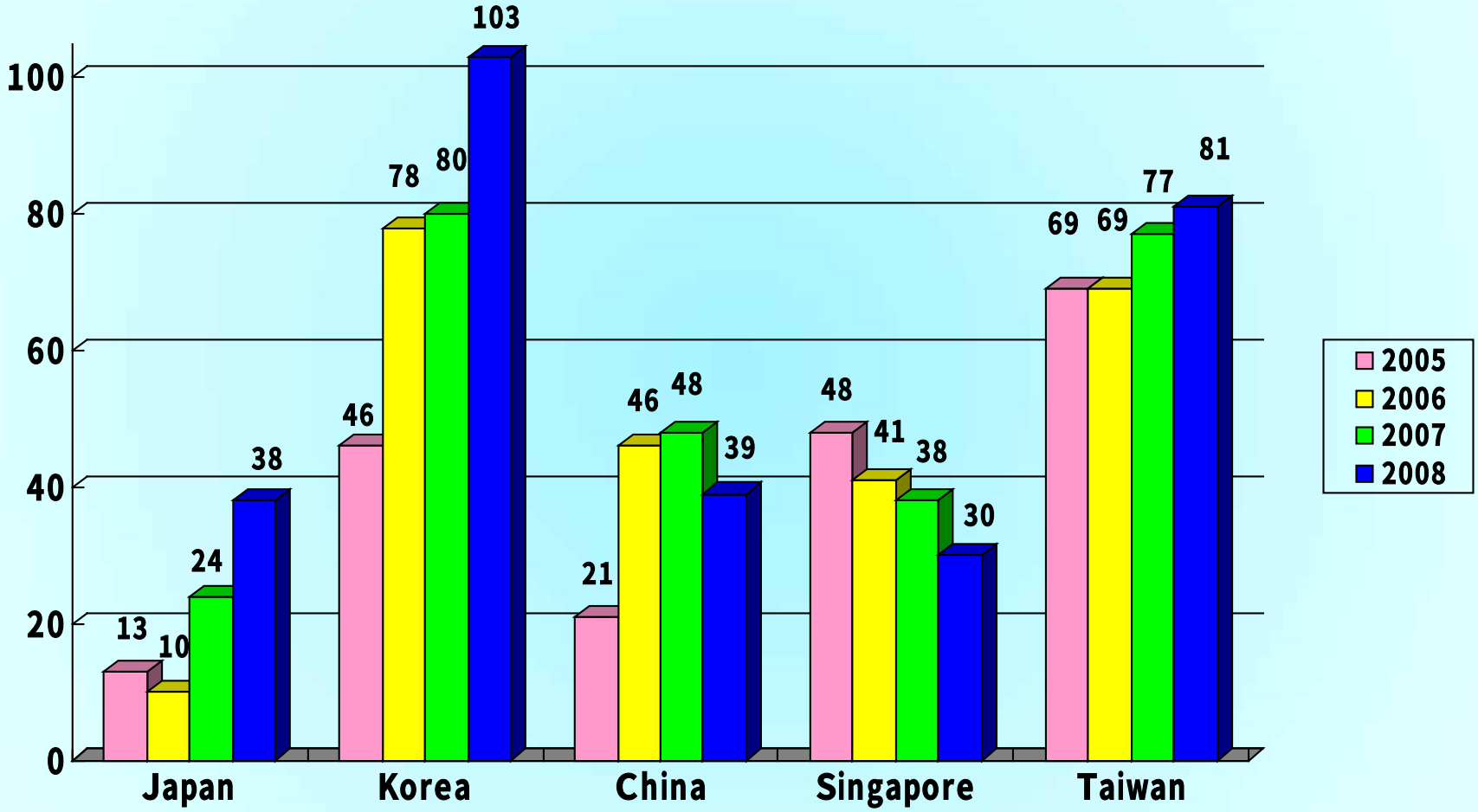


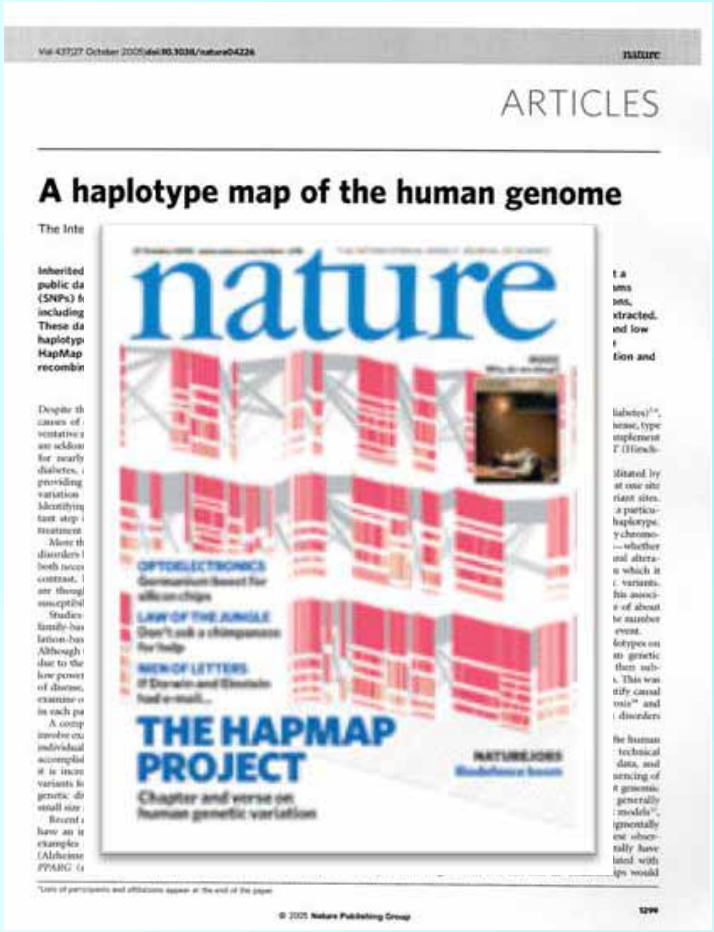
The Shift from Japan to China

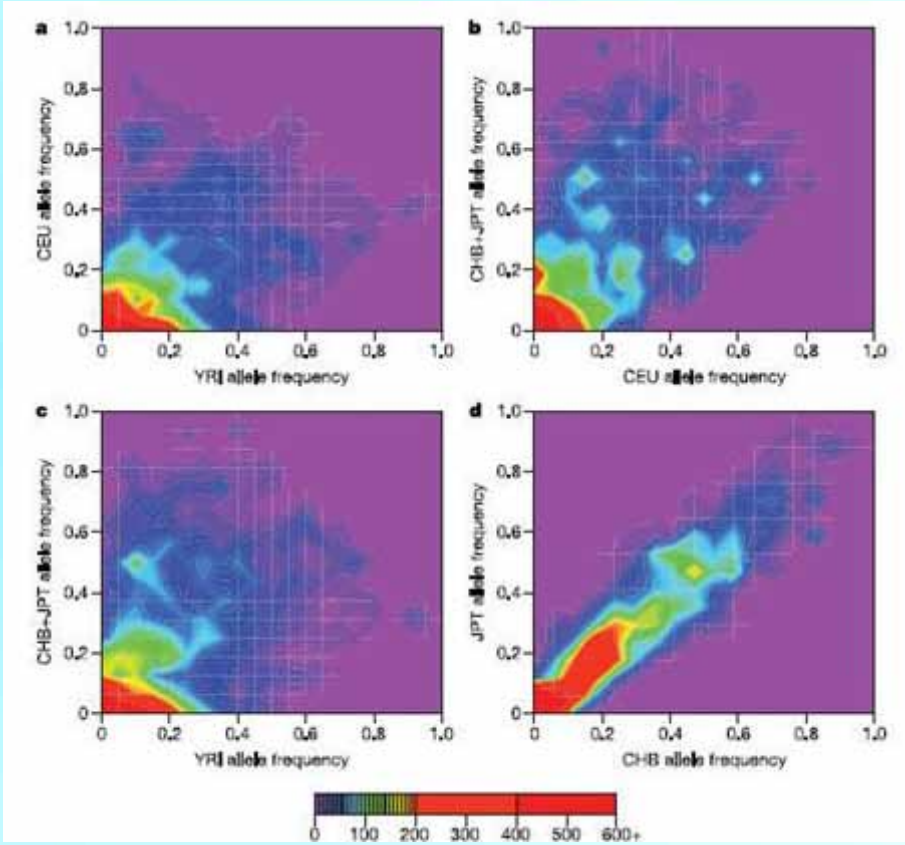
Relocation of research centers from Japan to China

Company	Home Country	Location in Japan	Year of Closure	
Bayer	Germany	Kyoto	2004	R&D center set up in China
Merck	US	Okazaki, Aichi Prefecture Kumagaya, Saitama Prefecture	2006	
Bayer	Germany	Kobe	2007	
GlaxoSmithKline	UK	Tsukuba	2007	
Pfizer	US	Taketoyo, Aichi Prefecture	2008	
Novartis	Switzerland	Tsukuba	2008	

The Asian Region Is Very Important for Conducting MCTs

Chinese and Japanese are very similar in genes

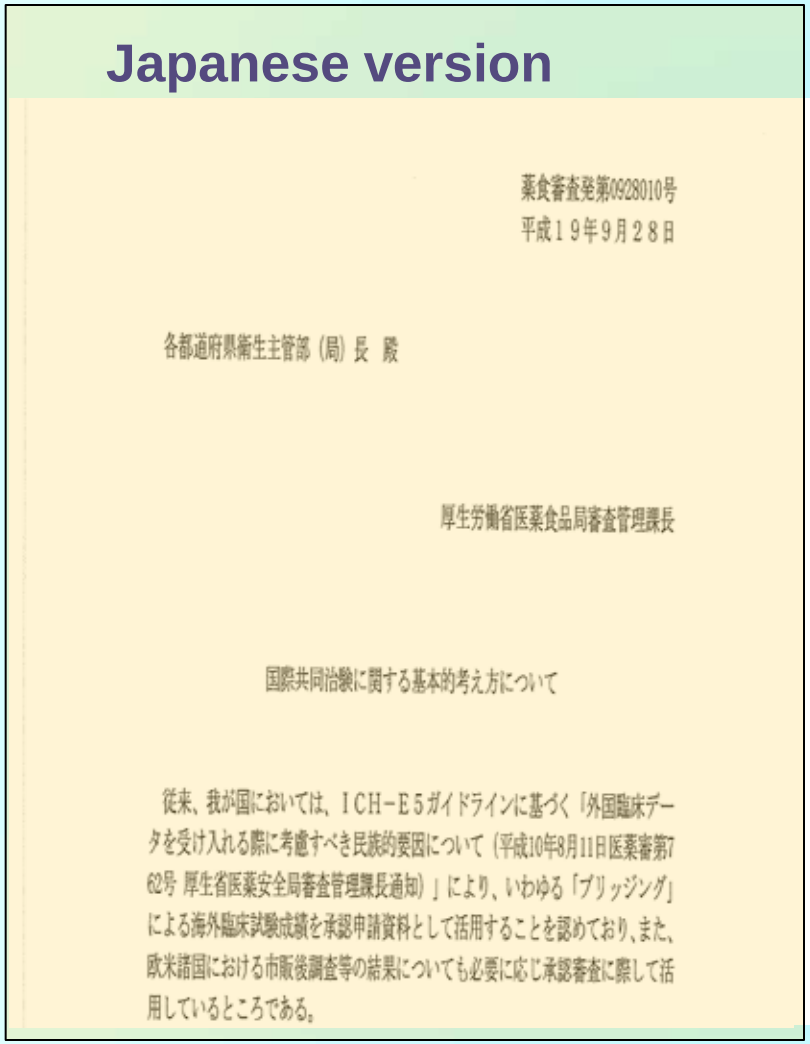




Nature 437: 1299-1320 (2005)

Basic Principles on Global Clinical Trials

Japanese version



薬食審査発第0928010号
平成１９年９月２８日

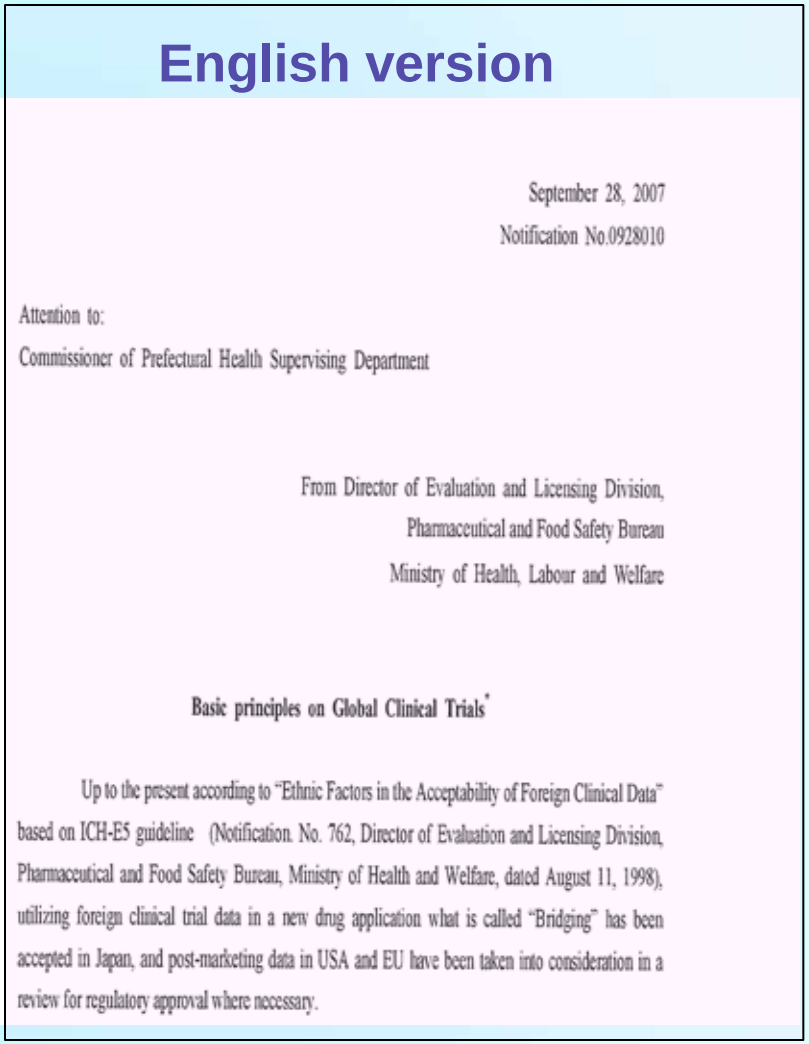
各都道府県衛生主管部（局）長　殿

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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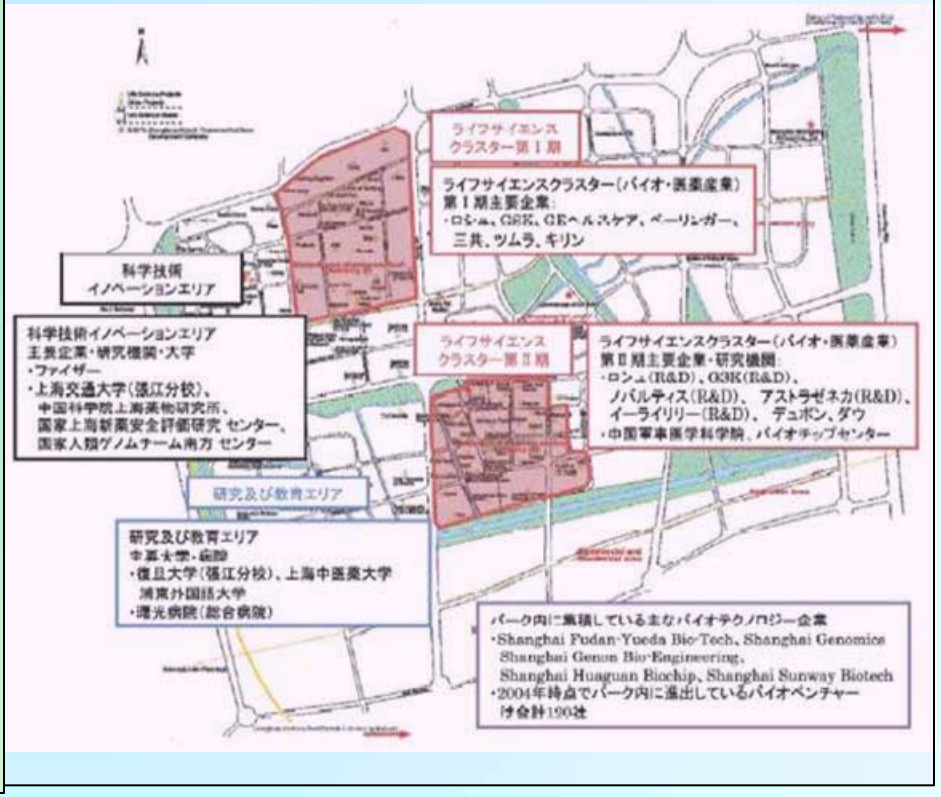
Chinese Govt. Actively Encourages MNCs to Establish R&D Centers in China

Zhongguancun Science and Technology Park, Beijing, China

China Medical City, Taizhou, china

Zhangjiang High-tech Park (North District), Shanghai, China
(Red frame: Bio Valley [Medicine Valley])



Source: Material from Zhangjiang Hi-Tech Park State Biotech &Pharmaceutical Industrial Base, Biotechnology Volume 26 Number 1, January 2008.
Based on "Chinese health biotech and the billion-patient market"

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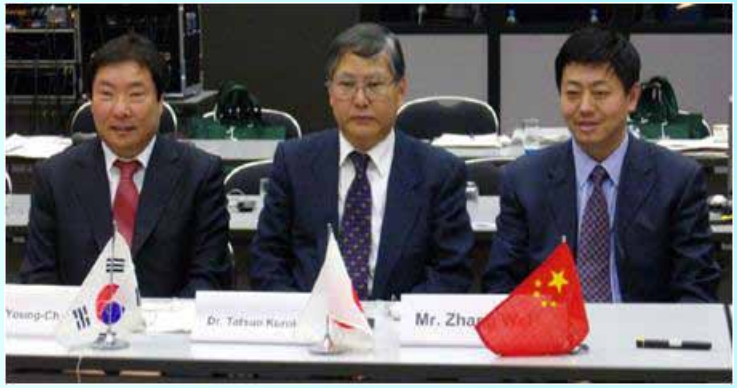
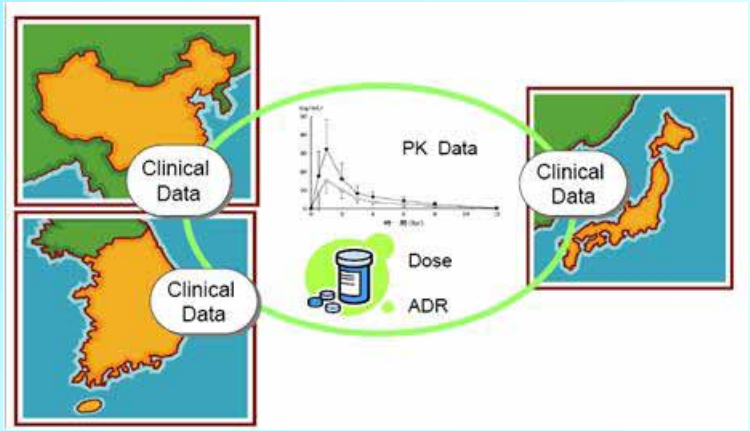
Regulatory Trends in CHN, JPN and KOR

April 2007: Joint Communiqué of Health Ministers



April 2008: Agreement at Director-General Level Meeting



August 2009: First meeting of Working Group

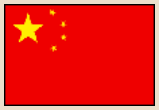
Open Ceremony of Japan-China Medicine information net

Japan-China Medicine information net ：http://www.cjpi.org.cn/

Japanese Pharmaceutical Manufacturers of JPAM-Beijing

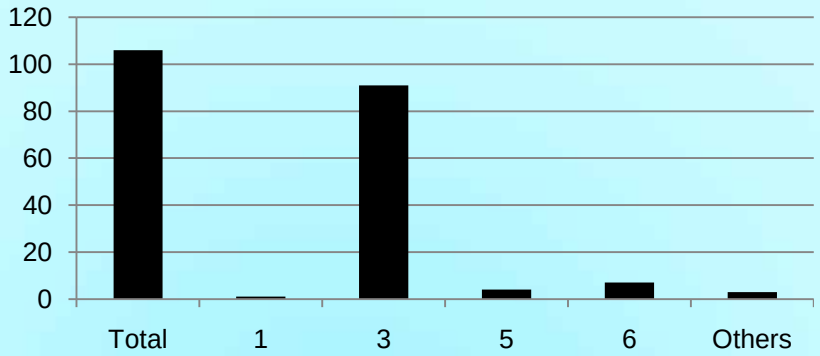
Kyowa Hakko Pharmaceutical Technology	Senju Pharmaceutical Co., Ltd.	Kowa(Shanghai)Pharma Consulting Co.,Ltd.
Otsuka Beijing Research Institute	Asahi Kasei Phama Corporation	Daiichi Sankyo Pharmaceutical(Beijing) Co.,Ltd.
KIRIN KUNPENG (CHINA) BIO-PHRAMACEUTICAL CO.,LTD	Minophagen Pharmaceutical Co.,Ltd.Beijing Office	Mitsubishi Beijing Research Institute
Santen Pharmaceutical Co., Ltd	Teijin Pharma.	Mingzhi Pharmaceutical Co., Ltd.
TAIHO Pharmaceutical (Beijing) Co.,Ltd	Eisai China Inc.	Daiichisankyo Pharmaceutical (Shanghai) Co. LTD
Sumitomo Pharmaceuticals(Suzhou) Co.,Ltd.	HM SCIENCE INC.	Daiichisankyo Pharmaceutical (Shanghai) Co. LTD
Tianjin Tanabe Seiyaku	NIPPON ZOKI PHARMACEUTICAL CO.,LTD.BEIJING OFFICE	Astellas Pharma. China, Inc.
Chugai Pharmaceutical Co., Ltd.	Tianjin Takeda Pharmaceuticals Co., Ltd.	Shantou Mingzhi Pharmaceutical Co., Ltd.
Nippon Chemiphar Co., Ltd.	NIPPON ZOKI PHARMACEUTICAL CO.,LTD.BEIJING OFFICE	

JPMA-Beijing Activated as the Bridge of Government Visit Activity Between Japan and China

Country	Communication Item
China 	◆ **Apr. 2009** Officials of MHLW，JPMA visited SFDA, CDE Topics: to know current policies and their future development trends of Chinese Authorities, and enhance communications between both countries, in order to promote mutual development. ◆ **Aug. 2009** SFDA Bureau of Investigation & Enforcement and MHLW, PMDA, JPMA Meeting . Topics：policies on supervision and auditing of marketed products in both countries. ◆ **Dec. 2009** 1.China /Korea/Japan Director-General Meeting on Pharmaceutical Affairs 2.China, Japan and Korea WG Meeting 3. Open Ceremony of Japan-China Medicine information net Topics: to promote scientific research cooperation under the legal background of each country, in the Joint Research Project on ethnic factors in clinical data, with a view to encouraging global development and sharing clinical data.
Japan 	◆ **Jan. 2009** Officials of MHLW，JPMA visited SFDA, CDE Topics：to know current policies and their future development trends of Chinese Authorities, and enhance communications between both countries, in order to promote mutual development ◆ **Aug. 2009** China, Japan and Korea WG Meeting Topics: to promote the Joint Research Project on ethnic factors, exchange information and other preparation work ◆**May. 2010** 1.China /Japan Bilateral Meeting 2. 2010 China-Japan Symposium on Global Clinical Trials and Ethnic Factors Topics: to promote dialogue and bilateral cooperation has been clarification of ethnic factors in clinical data, boosting the countries' multi-regional clinical development and sharing clinical data.

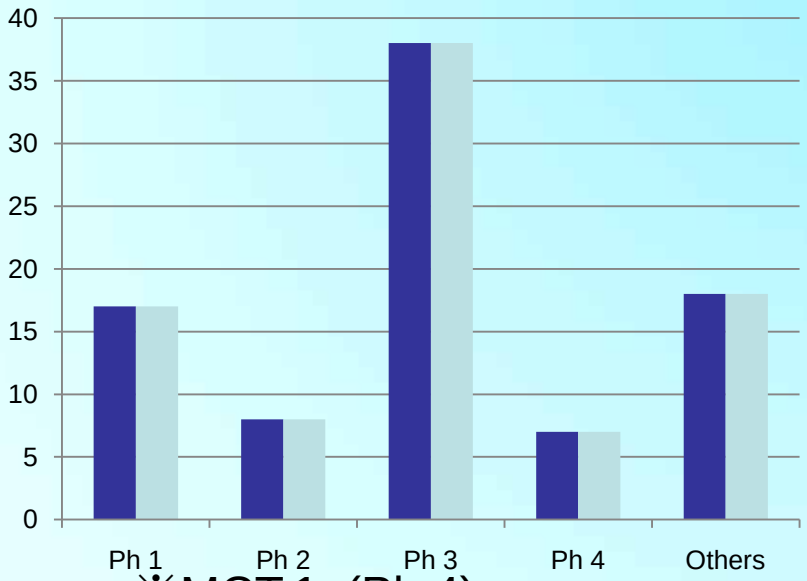
Marketed Drugs and Clinical Trials Conducted by Japanese Pharmaceutical Companies in JPAM-Beijing

Total Number of Marketed Products



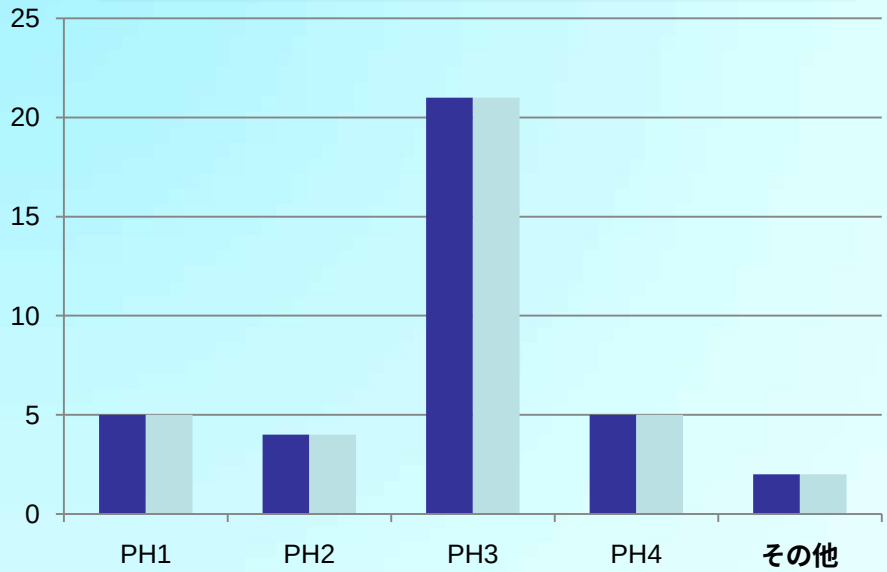
Registration Category

Number of Completed Clinical Trials



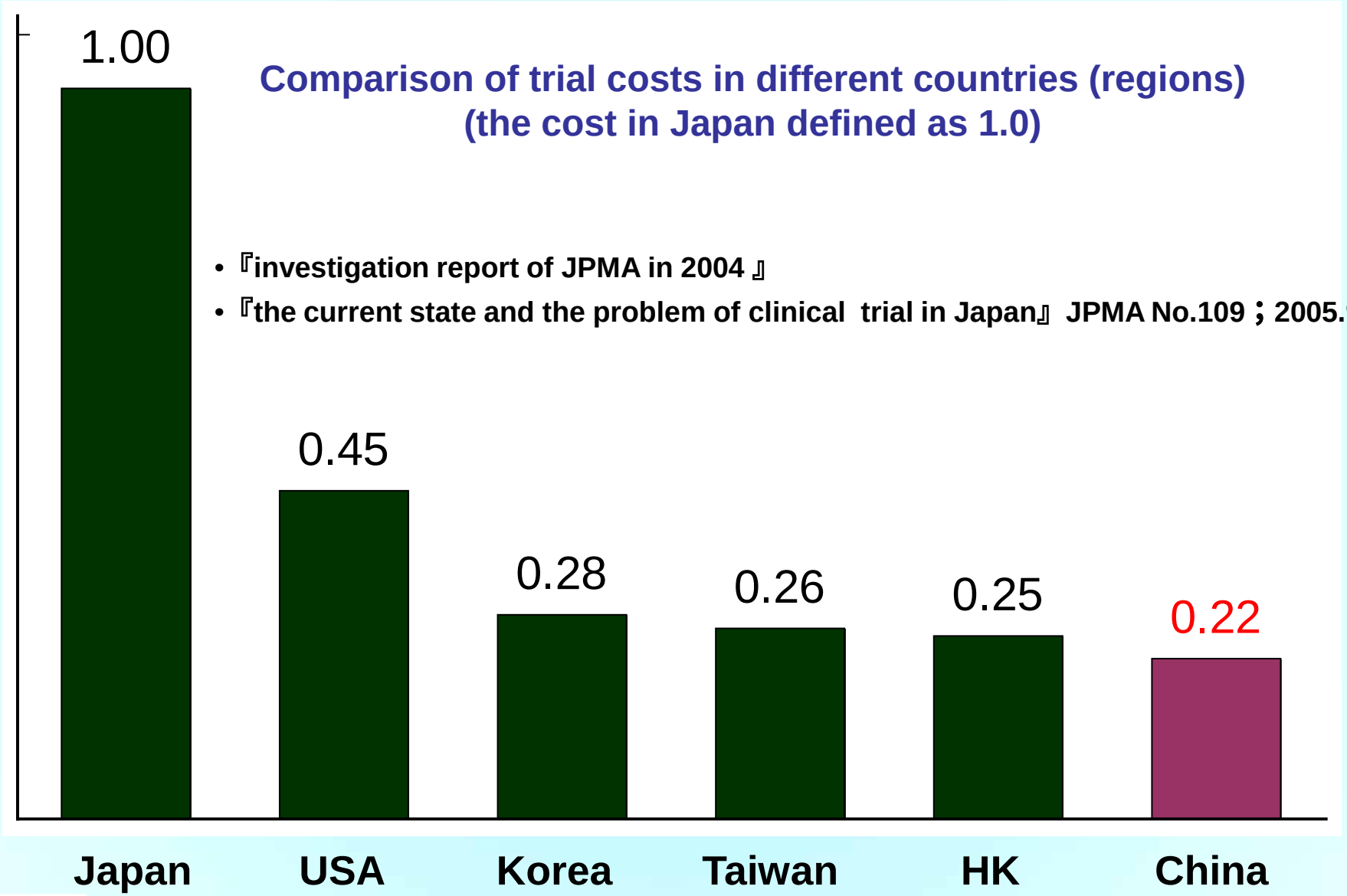
※MCT:1 (Ph 4)

Number of Ongoing Clinical Trials



※MCT:1 (Ph 2)、4 (Ph 3)

Substantial Cost Savings



Fast Enrollment Is the Character in China

Example

CSPS

(Cilostazol Stroke Prevention Study)

12 Sites
720 Cases
6 Months

Related paper was published by Lancet in 2008

China and Japan Data Comparison of Pletaal CSPS

Stroke Incidence rate(%)

China

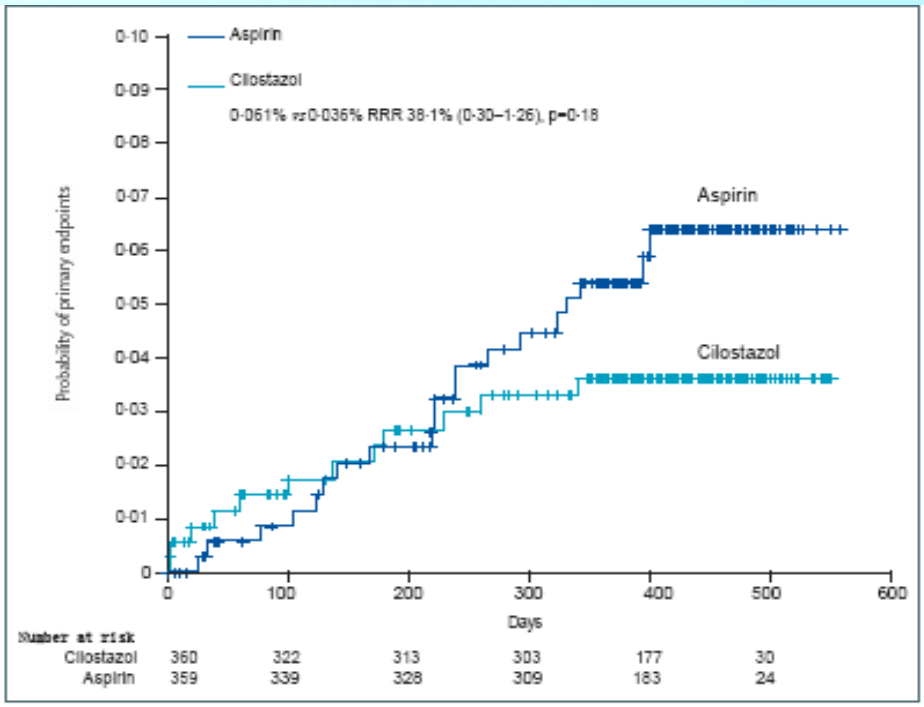
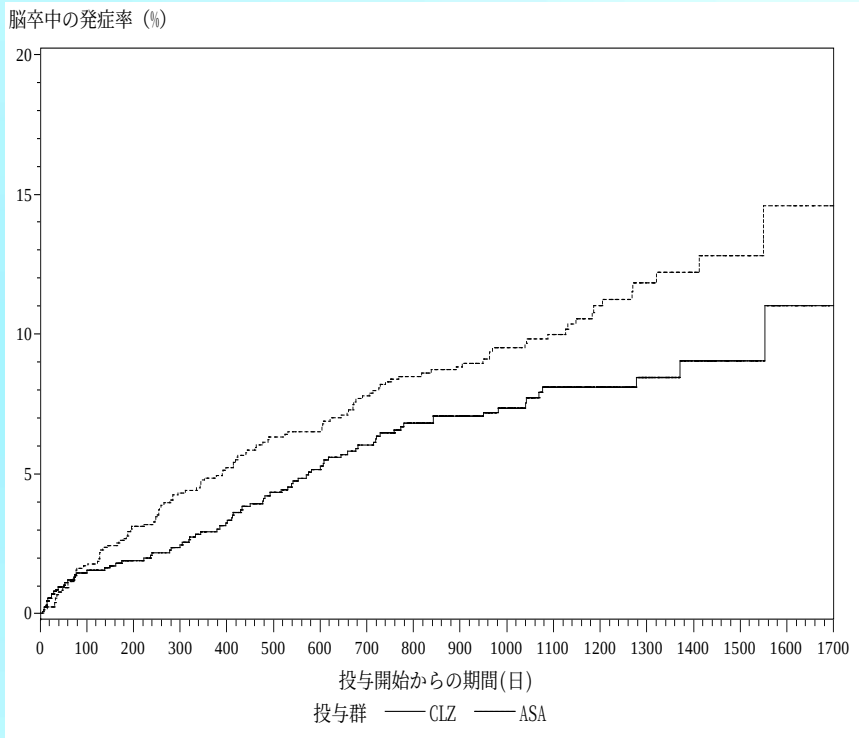


Figure 2: Kaplan-Meier curves for the accumulation of primary endpoints

Japan



CSPS n=720

Total	32
Pletaal	12
Aspirin	20

CSPS II n=2,672

Total	201
Pletaal	82
Aspirin	119

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Quality of Chinese Clinical Data

u Quality Assurance Activities (Experiences at OBRI)

Efforts done in 2 sites + 2 labs in China :

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

Audit feedback:

- u Reliable source data and well trained study staff
- u Among 12+ sites in this global study, China's data is integrate and reliable

Experiences of SFDA's Inspection

- Abilify PK: Dec., 2006 (after NDA submission)
- Dec., 2007 (after approval: on-site training of SFDA inspectors)
- Abilify Ph2: Dec., 2006 (after NDA submission)
- CSPS Ph3: Nov., 2007 (after NDA submission)
- OPC-41 Ph1/2: Mar., 2010 (after NDA submission)

Otsuka Review results: No critical/major findings

Japan Application by Using Foreign Clinical Trail Data

－ Centered in Asian Data －

Product	デトルシトール DETRUSITOL (Tolterodine)	ニューロタン NULOTAN (Losartan)	ハーセプチン HERCEPTIN (Trastuzumab)	クラビット CRAVIT (Levofloxacin)
Company	Pfizer 輝瑞	Banyu 万有	Chugai 中外	Daiichisankyo 第一三共
Approval	April, 2006	April, 2006	Feb, 2008	April, 2009
Study Type	Asian Study	Global Study	Global Study	(Domestic 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

Clinical Trials in China, Today and Tomorrow

Opportunities:

- Lower cost
- Larger patient pool
- Rapid patient recruitment

Challenges:

- Slow regulatory process
- Less experience in conducting clinical trial according to ICH GCP
- Blood/tissue export permit

Benefits of Conducting International Multicenter Trials

1. Country: Saving clinical research source
2. Doctor: Improving physician's professional competence
3. Patients：Obtaining new therapies
4. Industry: Promoting new drug development

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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Time for Examination and Approval of Clinical Trials (IND)

IND

review

Communication

China	6M+2M(review meeting)
Japan	1M
Korea	2M
Singapore	2M
Hong Kong	2M

Longer Period

DRUG REGISTRATION REGULATION-New Edition

1. w.e.f Oct 1, 2007

2. on-site inspections for Manufacturing Application on NDA application was added

3. allows “Special Examination”

Special Examination and Approval

◆Following requirements should be met:

1. New active ingredients and its preparation extracted from natural drugs, or preparation made of material from plant, animal and minerals, which have not been marketed in China ;

2. drug raw material and its preparations, and biological product that have not been marketed domestically or outside China ;

3. new antiviral drug for AIDS and drug used for diagnosis and prevention of AIDS, cancer and orphan drug ;

4. new drugs which treat diseases for which there is no effective therapy.

Drugs satisfied requirements 1 and 2 will be applied in IND phase.

Drugs satisfied requirements 3 and 4 will be applied in NDA phase.

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Advantages to Obtain Special Examination and Approval

- **Pre-consultation is available.**
- **Shorter technical evaluation:**

  IND：90 Days→80 Days

  NDA：150 Days→120 Days

- **Supplemental information can be submitted.**

International Multi-Center Clinical Trial

◆ **Article** 44

1. The drug used for an international multi–center clinical study shall be one already registered in a foreign country or in phase II or phase III clinical trials.
2. SFDA may request the applicant to firstly conduct the Phase I clinical trials in China;
3. During a study conducted in China, the Applicant shall report to SFDA any serious adverse events or unexpected adverse events which occur in any countries
4. Upon the completion of the study, the Applicant shall submit the complete clinical study report to SFDA
5. Data generated from an international multi–center clinical trial used for drug registration in China, shall be in accordance with the relevant provision of this *Regulation*, and the applicant shall submit the complete research information of the study

Outlook for Drug Development in Asia

- Accelerated interaction/information exchange between regulatory authorities

- Progression of specific clinical development projects within the drug industry

If the industry and the regulatory authorities unite their efforts in tackling issues, we will be able to achieve things that we couldn't in the past.

Thank you!