Clinical Trials in Asia : Growing role of Asia in global clinical drug development

1st International workshop ASGO, Aug. 1, 2010

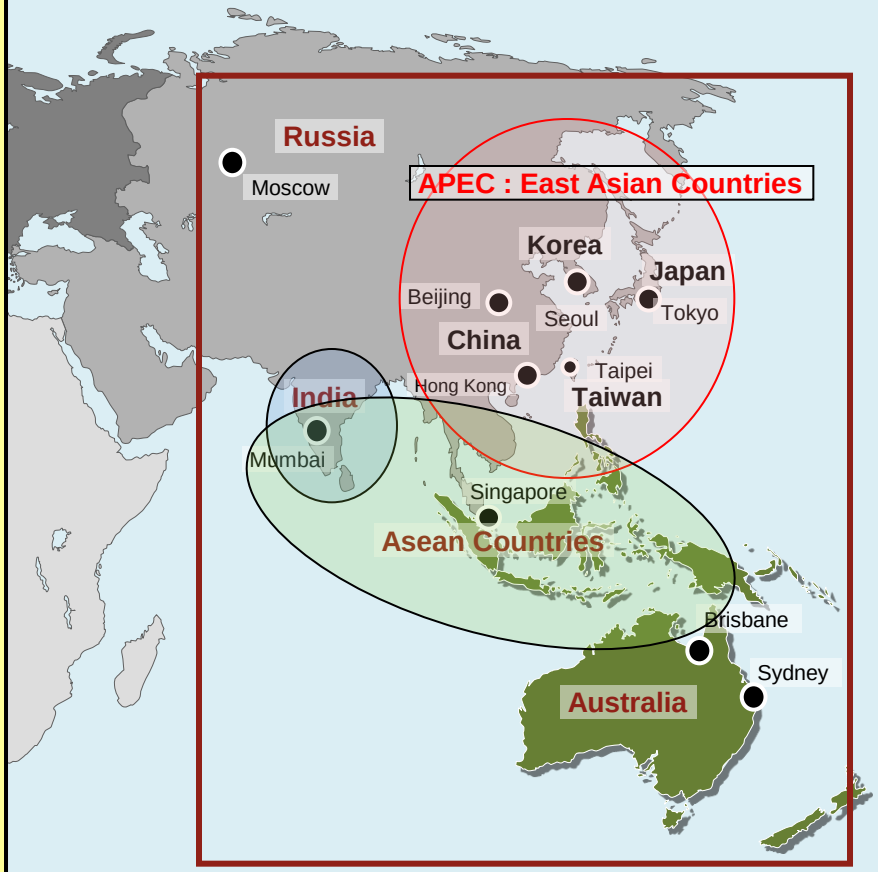
Sang-Goo Shin, MD
President, Korea National Enterprise for Clinical Trials/MIHWAF
Professor of Clinical Pharmacology, Seoul National University Hospital, Korea

KoNECT 국가임상시험사업단
Korea National Enterprise for Clinical Trials

Asia : APEC - East Northern Asian Countries

APEC – East Northern Asian Countries

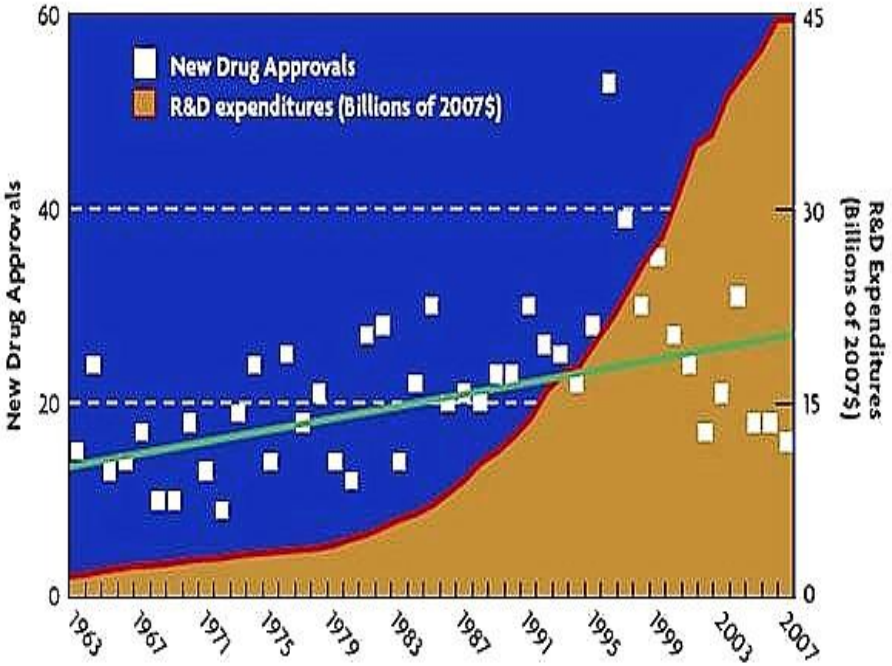
- **Why are these countries so important and interesting?**
- **Huge patient Population**(3 billion**) & Economic Potential**
  - China : 1.3 billion population
  - India : 1.2 billion
  - Japan : 120 million
  - Korea : 50 million
  - Taiwan : 25 million
- **Access to global expertise and talent**
  - Japan and China ranks top 5 in publication in scientific journals
  - High IT technology (Japan, Korea, Taiwan, India)
- **Global Pharmaceutical Marketplace** will change by 2015
  - Growing marketplace (China 32% growth in 2008)
  - Asia sales will exceed EU sales
  - Top 3 market will be US, China and Japan
  - **Domestic Pharmaceutical R&D industries (Japan, China, Korea, India)**
  - **Conservative perspectives on ICH-E5 (relatively unique ethnicity)**



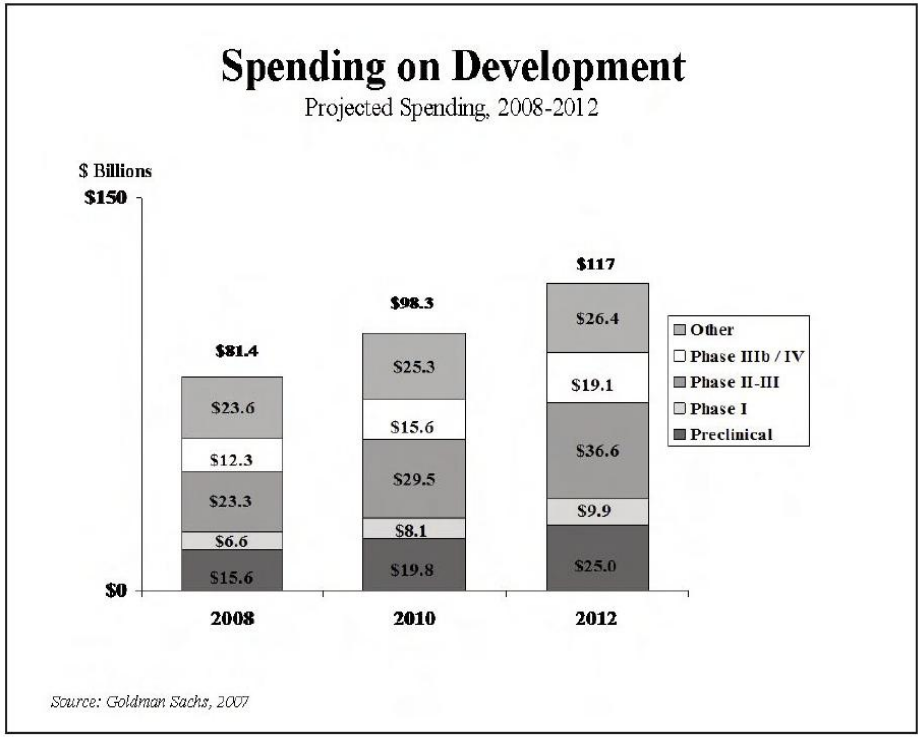
R&D Cost vs. New Drug Output

NEW DRUG OUTPUT CONTINUES TO STAGNATE, WHILE R&D COSTS REMAIN HIGH

New Drug Approvals and R&D Spending



Source: Tufts Center for the Study of Drug Development, PhRMA



Source: Goldman Sachs, 2007

ICH – new wave of clinical development

November 2003: *ICH6*	Sixth International Conference on Harmonisation, Osaka, Japan
November 2000: *ICH5*	Fifth International Conference on Harmonisation, San Diego, USA
July 1997: *ICH4*	Fourth International Conference on Harmonisation Brussels, Belgium
November 1995: *ICH3*	Third International Conference on Harmonisation Yokohama, Japan
October 1993: *ICH2*	Second International Conference on Harmonisation Orlando, USA
November 1991: *ICH1*	First International Conference on Harmonisation Brussels, Belgium

ICH Global Cooperation Group

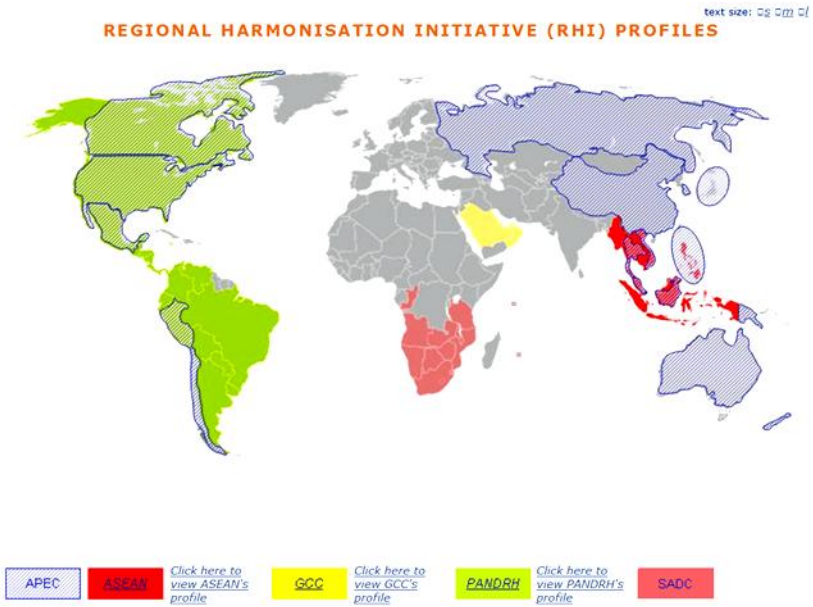
- start as a subcommittee of ICH from 1999
- cooperative activity with RHI groups from 2004

Expanded GCG

ICH Meetings June 8-12, 2008

- Participation of individual countries for first time
- Distinct and complementary to participation of official RHI representatives

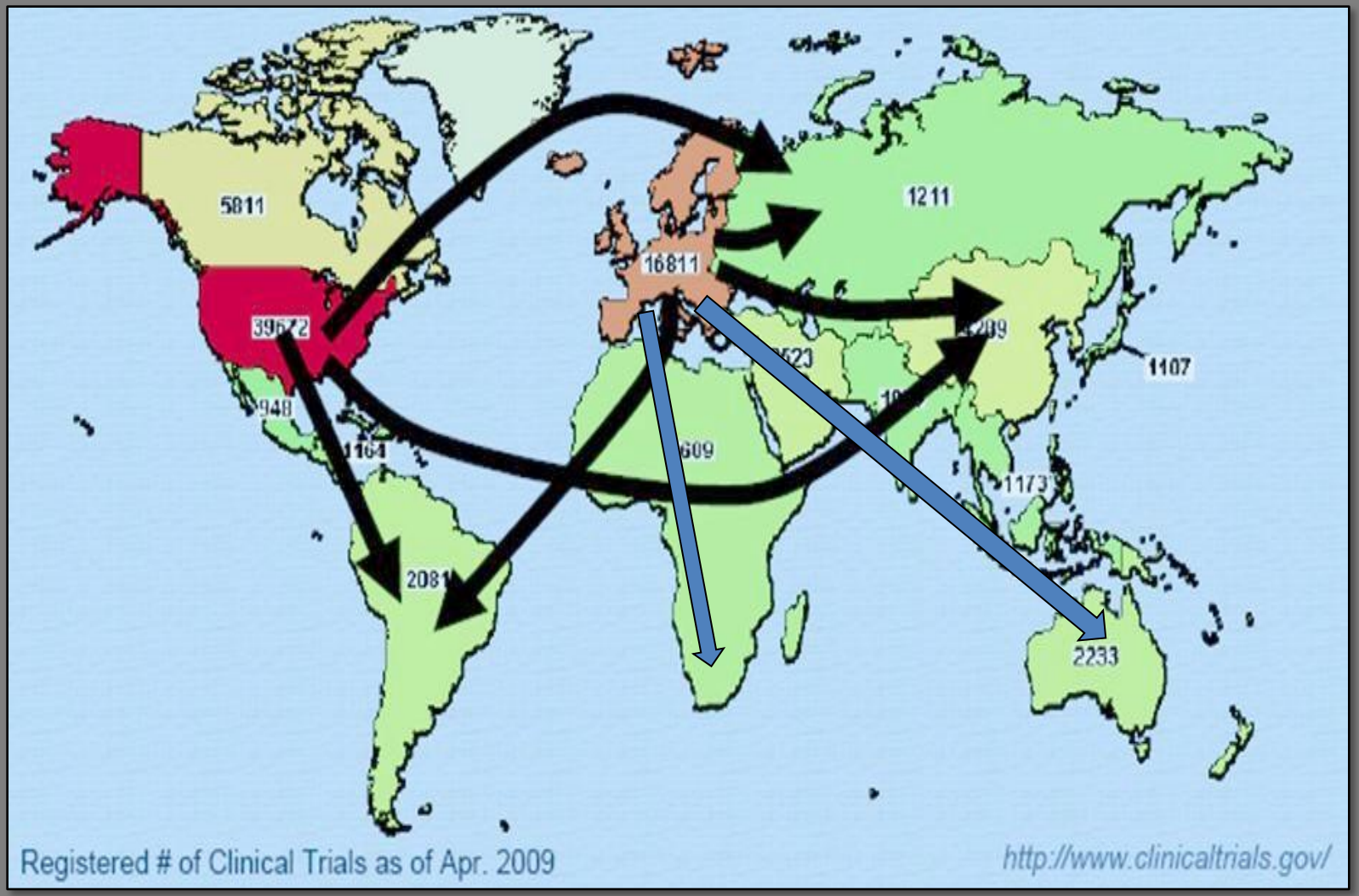
- Australia
- Brazil
- China
- Chinese Taipei
- India
- Korea
- Russia
- Singapore



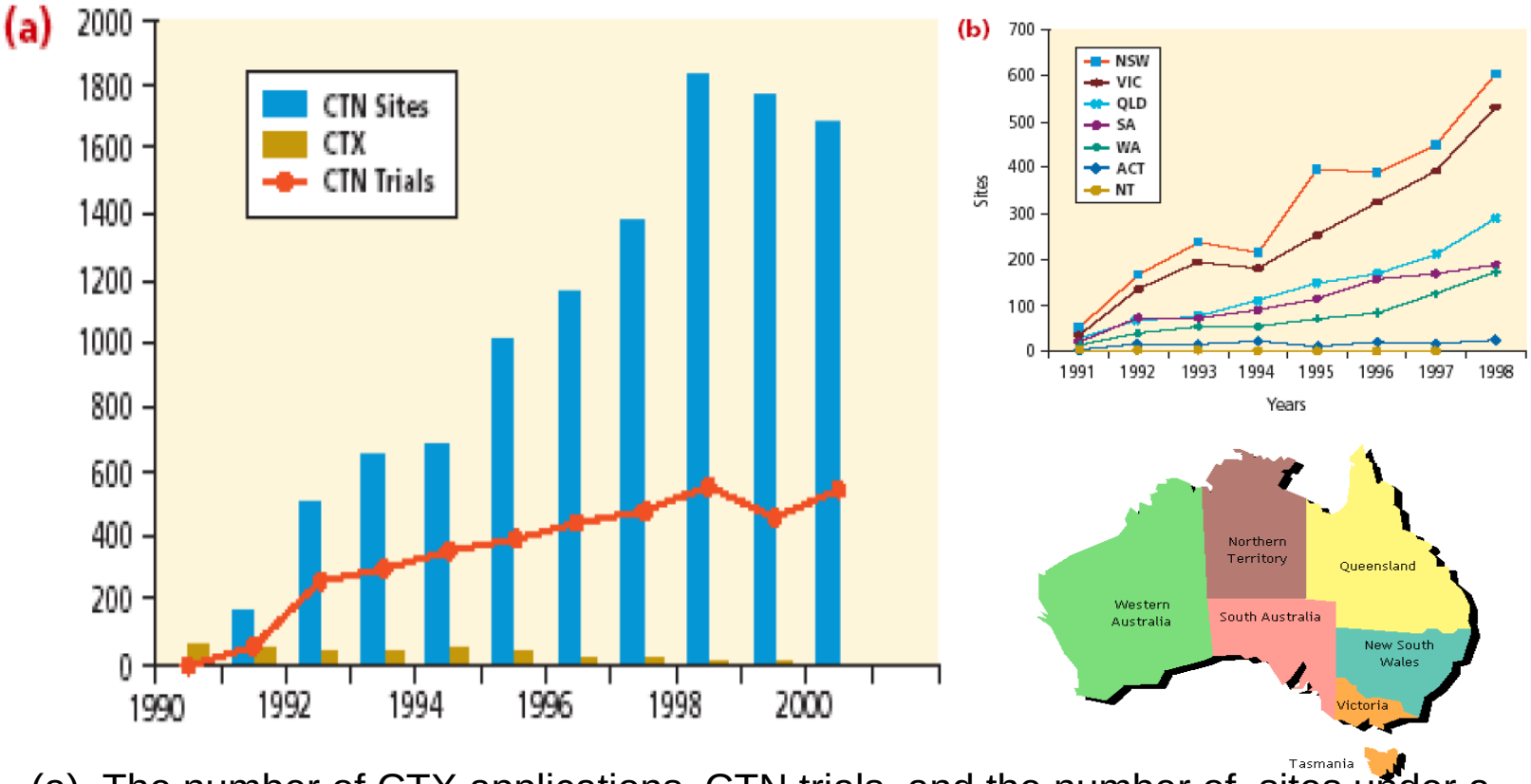
www.ich.org

Drift (Creation) of Clinical Trials to Emerging Regions, - 1990s

Big Shift after ICH-GCP consolidation



Australian Globalization in Clinical Trials during 1990s



(a) The number of CTX applications, CTN trials, and the number of sites under a true CTN process in Australia (1990~2000)

(b) Federal and Regional support for globalization in clinical trials

Foreign Clinical Investigators working on US IND during 1980-1999

Table 2
Clinical Investigators Working Under IND Regulations in Selected Countries.
Fiscal Year 1991 to 1999

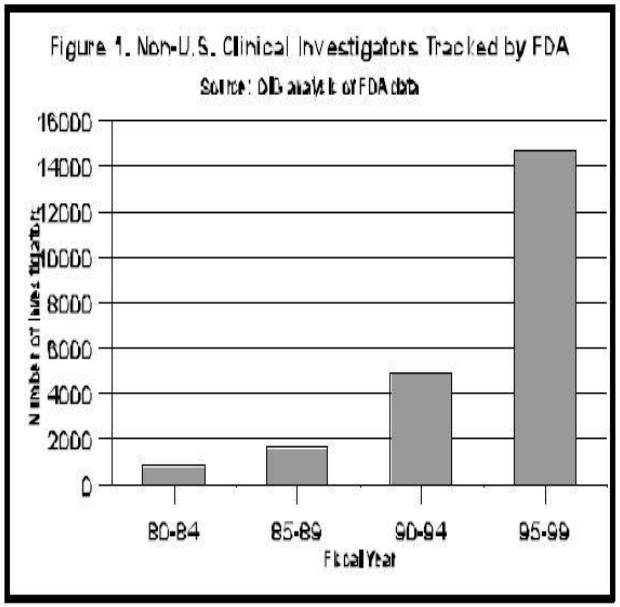
Country	91-93	94-96	97-99
Argentina	6	122	271
Brazil	16	52	187
Hungary	9	35	161
Mexico	29	48	187
Poland	4	100	190
Russia	0	5	170
Thailand	1	2	24

Source: OIG analysis of FDA data

Source: FDA Form 1572

Office of Inspection General Reports, 2002

In 1980, just 41 foreign clinical investigators conducted drug research under an IND. By 1990, that number grew to 271, and by 1999, to 4,458. The growth of these foreign clinical investigators has been particularly sharp in recent years (see figure 1). As mentioned previously, although FDA's database does not capture the growth of foreign investigators who have submitted data in NDAs, the number of foreign clinical investigators FDA tracks under INDs has increased sharply.



- 28 countries in 1990 to 79 countries in 1999

What was the great concern in East Asian Countries in 1990s ?

- Eastern Northern Asian Countries' requirement for new drug registration : local trials (ethnic sensitivity), Good Clinical Practice (informed consent – cultural difference?)

At the 1996 DIA Workshop on GCP *(from left to right) : Sang Guo-wei(China), Sang-Goo Shin(Korea), Carl Becker(Kyoto), K.Tsutani(Nippon), T. Tanigawa(MHLW), Herng-Der Chern(Taiwan), Robert Teoh(Singapore)*

Barriers for early globalization in east northern Asian countries after consolidation of ICH E5(foreign data acceptability), E6(GCP)

Simultaneous Global Development Barriers List

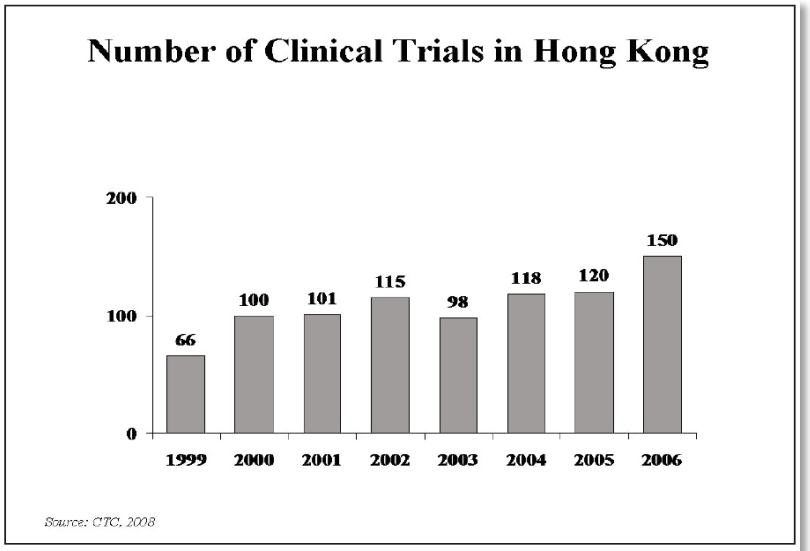
	Region or Country Relevance				
Barrier	**CH**	**JP****	**KO**	**CT**	**AP**
1.1. Regulatory requirements: dossier content					
Requirement for country-specific phase I (PK) study	X	X		X*	
Requirement for bridging study			X*	X*	
Requirement for local registration study	X	X	X*	X*	X
Requirement for data showing optimal dose(s) for local patients		X			
Requirement for minimum number of patients from country	X				
Requirement for source country approval to complete dossier	X		X	X	X
CMC and GMP requirements beyond ICH (NDA) and/or CPP requirements (eg, in lieu of conducting PAIs)	X		X		X
Other differing regulatory standards					X

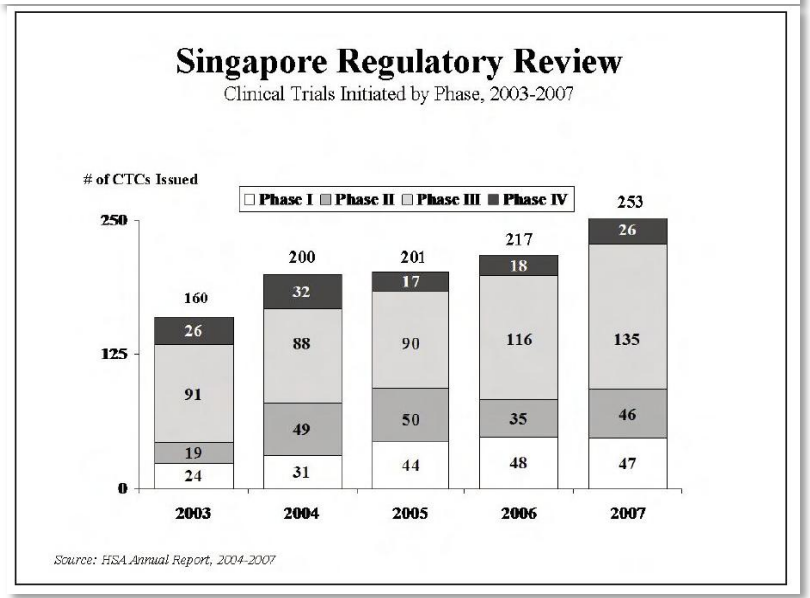
Saillot et al. Drug Information Journal 339;45, 2009

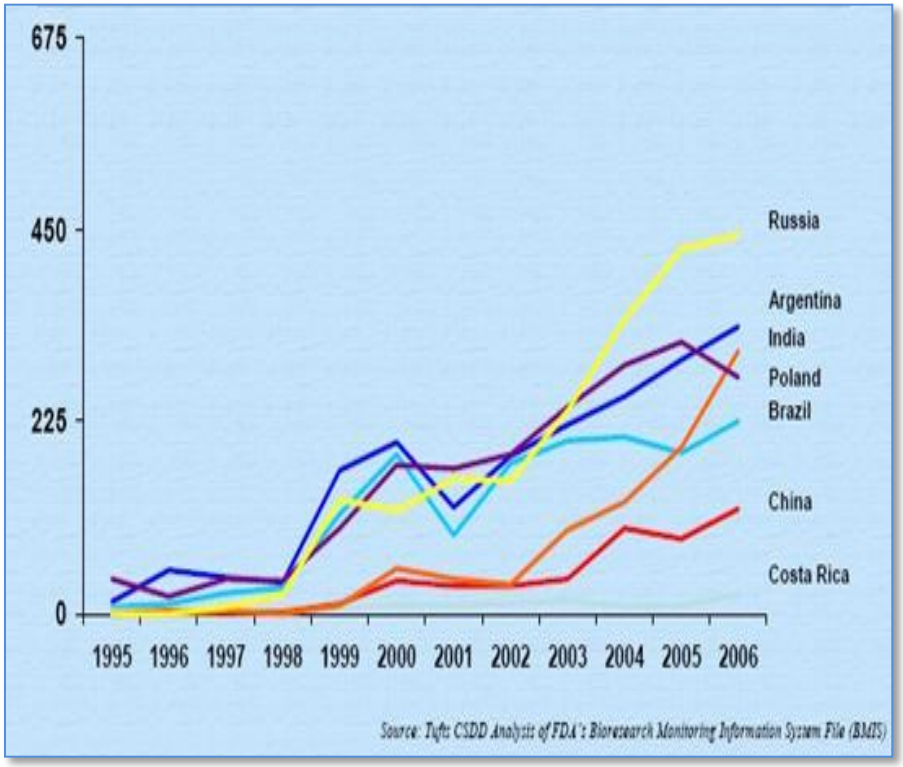
**** Step by step clearances for questions in extrapolation of foreign data (PK study in Japanese, then Dose-Response study)**

Rather early globalization of Singapore, Hong Kong, India in Asian Countries

- No local study requirement for New Drug Registration







- Provost et al, DIA 2009 : Growth of Investigator filed 1572 form, latency of east Asian countries

European Medicines Agency
Inspections

London, 23 September 2009
Doc. Ref. EMEA/INS/GCP/58632/2009

Clinical trials submitted in marketing authorisation applications to the EMEA:

Overview of patient recruitment and the geographical location of investigator site

2005-2008

- The data are recorded against the year in which the MAA was submitted. The patients would actually have entered the trials in preceding years (probably 1-5 years earlier in many cases),

- The data collection period (2005-2008) is very short and the major trends are undoubtedly taking place over a longer term. The widespread information on increases in clinical trials in Asia has probably not yet been reflected in the MAAs or involves trials that will not all be included in MAAs. Maybe a bias in the data is because the pharmaceutical companies may prefer to conduct (part of) their pivotal trials in the key EU and North American markets.

Number of Patients in Pivotal study by sub-region

**cis=Russia, Ukraine, Georgia etc(Commonwealth Independent stats)

No patients per region	2005	%	2006	%	2007	%	2008	%	Total	%
EU/EEA/EFTA	**32,090**	**37.0**	**49,960**	**44.2**	**55,667**	**44.1**	**42,024**	**28.6**	**179,741**	**38.0**
Comprising:										
EU-15/EEA	27,822	32.1	30,714	27.2	42,894	34.0	27,561	18.7	128,991	27.3
EU-10	3,412	3.9	16,601	14.7	11,016	8.7	11,706	8.0	42,735	9.0
EU-2	656	0.8	2,146	1.9	1,251	1.0	2,447	1.7	6,500	1.4
Switzerland	200	0.2	499	0.4	506	0.4	310	0.2	1,515	0.3
North America	**37,117**	**42.8**	**33,389**	**29.6**	**41,810**	**33.2**	**55,165**	**37.5**	**167,481**	**35.4**
Comprising:										
Canada	3,477	4.0	3,919	3.5	6,231	4.9	4,454	3.0	18,081	3.8
USA	33,640	38.8	29,470	26.1	35,579	28.2	50,711	34.5	149,400	31.6
ROW	**17,585**	**20.3**	**29,637**	**26.2**	**28,628**	**22.7**	**49,948**	**33.9**	**125,798**	**26.6**
Comprising:										
Africa	523	0.6	1,938	1.7	2,061	1.6	9,962	6.8	14,484	3.1
Middle East/Asia/Pacific	1,694	2.0	9,925	8.8	7,801	6.2	17,458	11.9	36,878	7.8
Australia/New Zealand	1,560	1.8	1,892	1.7	2,663	2.1	1,219	0.8	7,334	1.6
CIS	664	0.8	6,939	6.1	2,731	2.2	6,677	4.5	17,011	3.6
Non-EU/Eastern Europe	69	0.1	862	0.8	1,202	1.0	1,370	0.9	3,503	0.7
Central/South America	13,075	15	8,081	7	12,170	10	13,262	9	46,588	9.8
Total	***86,792***	***100***	***112,986***	***100***	***126,105***	***100***	***147,137***	***100***	***473,020***	***100***

Table 2: Number of patients in pivotal trials submitted in MAAs to the EMEA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World). These 3 global regions are also shown split into their component sub-regions.

Countries more than 0.5% patients out of EU countries

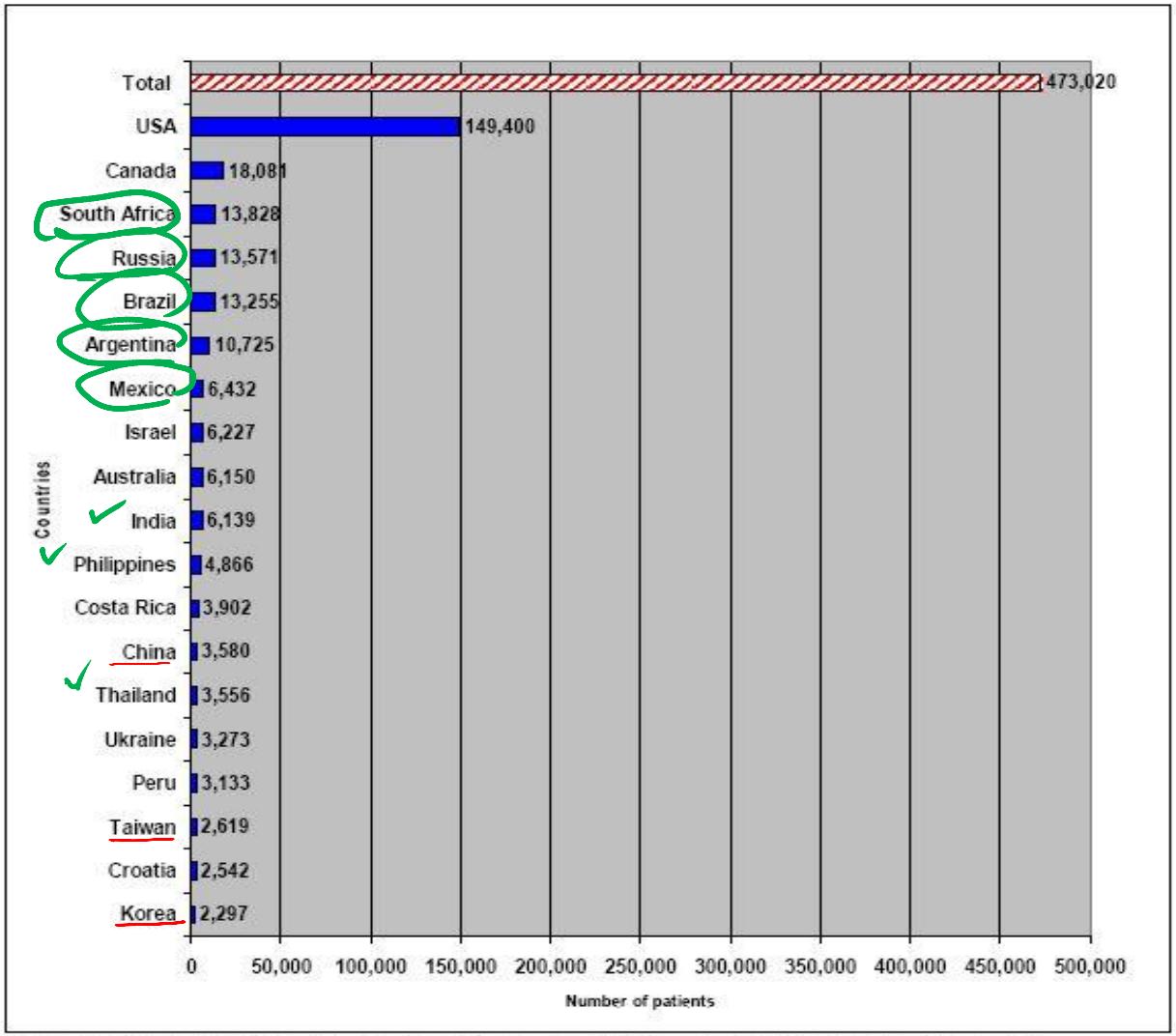
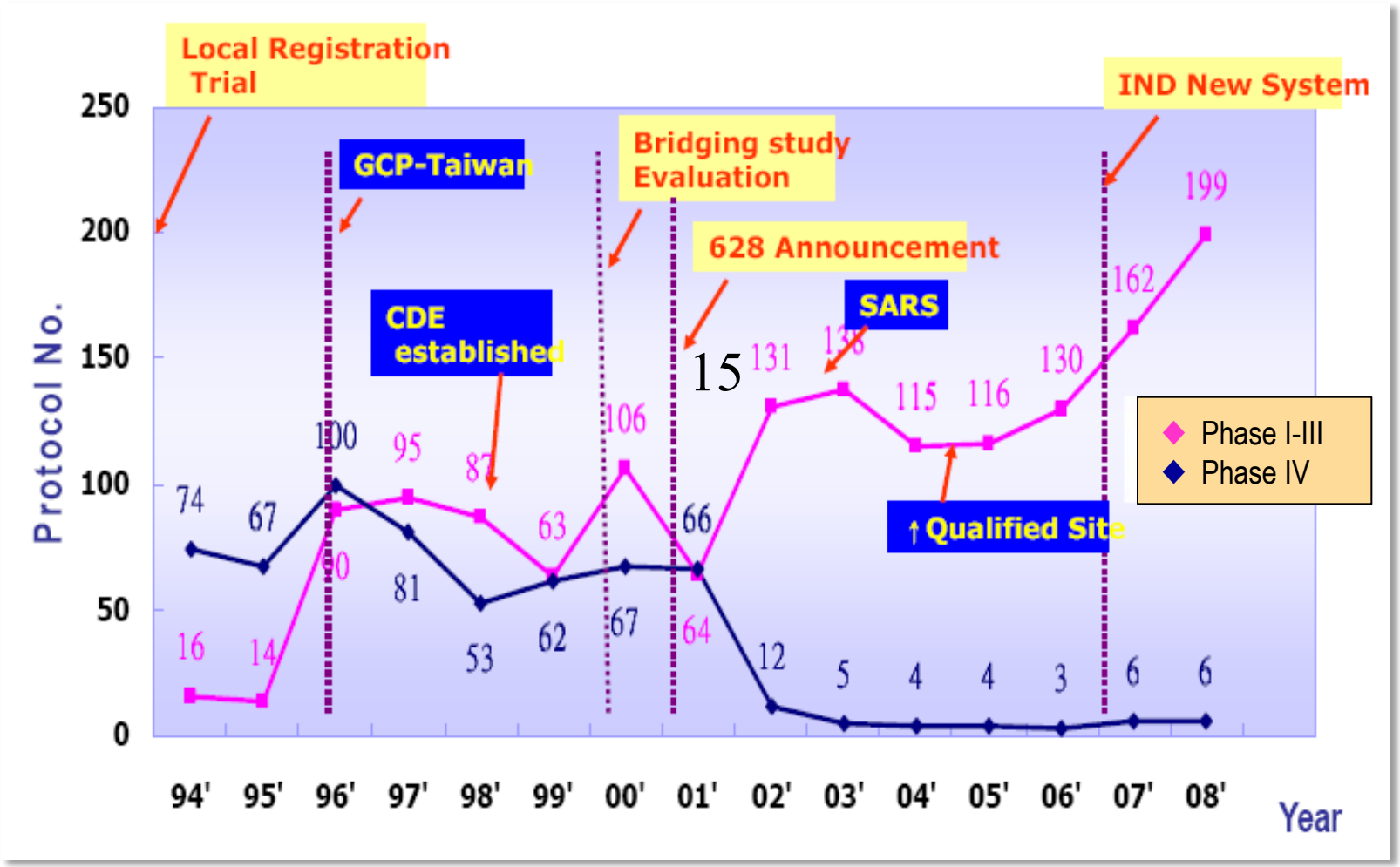


Figure 5: Third countries with at least 0.5% of patients in the pivotal trials included in the MAA submitted to the EMEA during the 2005-2008 period

- **Recent Governmental Initiatives for Globalization in East Northern Asian Countries**

- **Statistics of Global Clinical Trials in ENA Countries**

Taiwan : Impact of Regulatory Approval Process and Timeline on Clinical Drug Development Activities



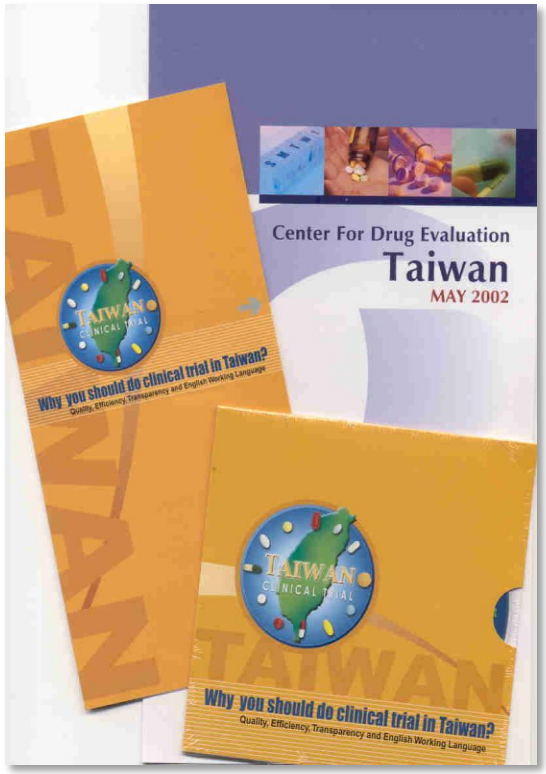
Source: HD Chern: IFPMA Meeting, Kuala Lumpur, 2008

Taiwan : Emphasis on high standard Regulatory environment & fostering Clinical trial Infrastructure

- Independent Review body(CDE) for IND & NDA review
- GCRC supporting program in 7 Hospitals

- Centralized "Joint IRB" among 6 University Hospitals for Multi-region/center study review

- Active player for APEC Network on Regulatory Science/Harmonization
- Establishment of Taiwan tFDA(2009)
- Price incentives(10%) for global trial in Taiwan



Taiwan : Multi-regional clinical trials, - source/CDE Taiwan

Clinical Trial Statistics
- Multinational Trials among INDs

	2004		2005		2006		2007		2008	
	P	S	P	S	P	S	P	S	P	S
Single Site	32	32	24	24	11	11	21	21	34	34
Multiple Sites	25	88	10	43	22	74	20	81	16	49
MN Trials	62	196	86	284	100	337	127	479	155	599
% MN Trials, P	52.10%		71.70%		75%		75.60%		75.60%	
Total	119	316	120	351	133	422	168	581	205	682

P: Protocol; S: Sites

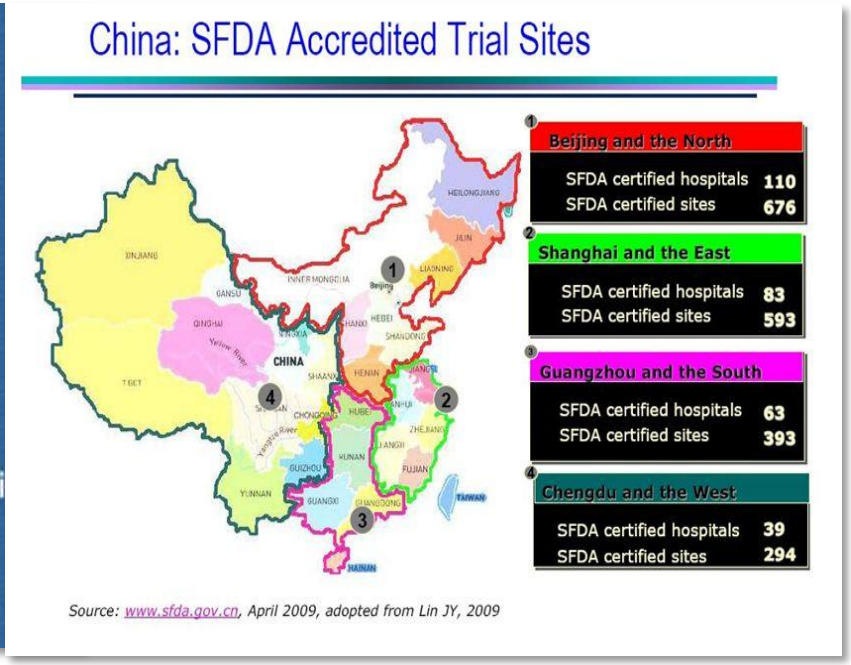
Source: CDE 2009

China : Regulatory changes & Quality assurance of Infrastructure

- **ICH – GCP Adoption : 1999**
- **Site certification Program including Hong Kong**

– 1998 by SFDA
– 2004 by SFDA and Ministry of Public Health
– 2009 re-certification by SFDA and Ministry of Public Health

- Basic requirements
  - Hardware construction
    - Office: necessary equipments :online, telephone, fax... ...
    - Document room
    - Drug room
  - Software construction
    - investigators should have been accepted GCP and regulation trai
    - Establish items of systems and SOPs for clinical trial
  - Site organization office manage the clinical trial in every site

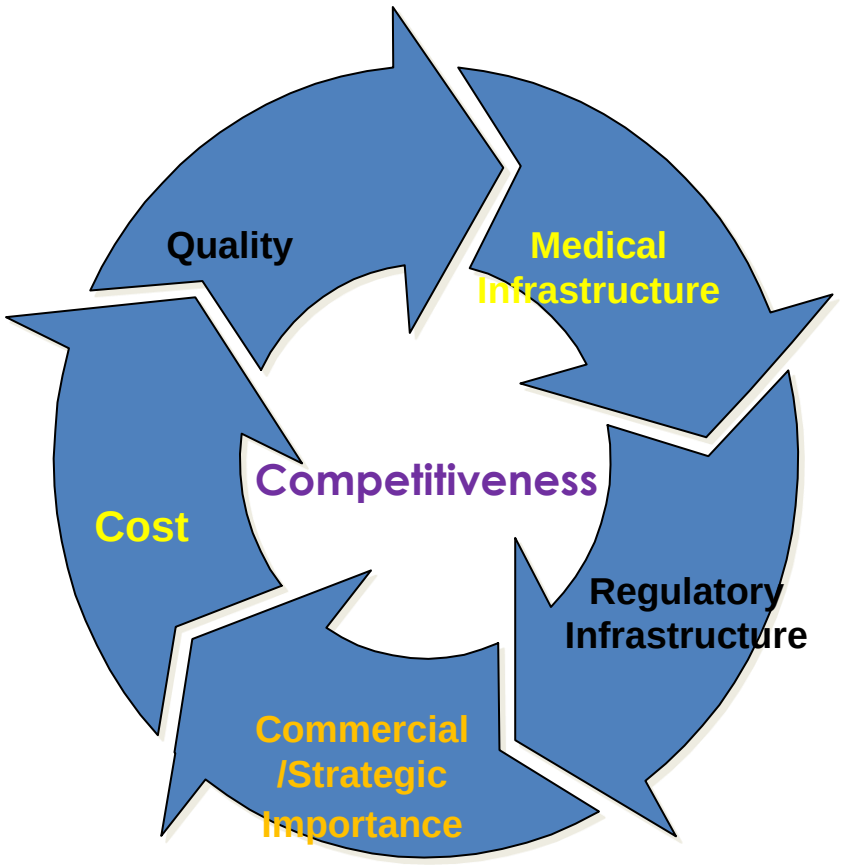


- **Regulatory changes for multi-regional trials in China**

China : Regulation for Multiregional Trials

- **Pre-condition and rules**
  - Differentiation technical requirements and evaluation , especially CMC between IND and NDA
  - Phase I study again among Chinese population for some trials
  - At least three countries involved, with PI in abroad and same protocol
  - Drug already marketed abroad, or at least Phase II trial or Phase III trial has already commenced abroad
  - Etc.
- **Evaluation and Approval Timelines**
  - Dossier Receiving : 5 days
  - Provincial DA Primary Evaluation : 30 days
  - **QC Lab's tests : 60 days, Bio-products : 90 days**
  - CDE technical Evaluation for CTA : 90 days
  - SFDA administrative approval : 30 days

Pharma Decision Parameters for Clinical Research Site : Interest on ENA as an Emerging Sites



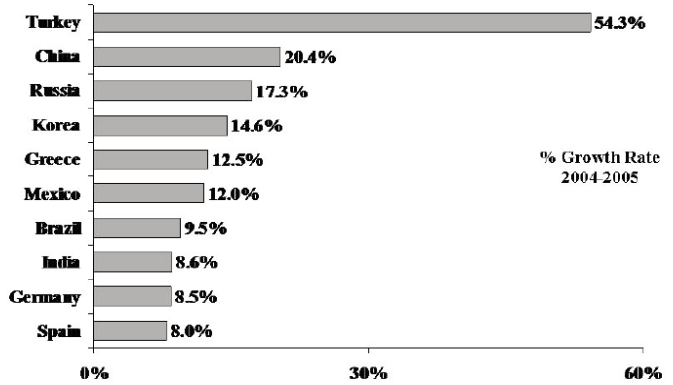
Top 10 Pharma Markets

2003, 2007, 2011

	2003 Rankings	2007 Rankings	2011 Rankings
1	United States	United States	United States
2	Japan	Japan	Japan
3	Germany	France	France
4	France	Germany	Germany
5	Italy	Italy	China
6	United Kingdom	United Kingdom	United Kingdom
7	Spain	Spain	Italy
8	Canada	Canada	Brazil
9	Brazil	China	Canada
10	China	Brazil	Spain

Ten Fastest Growing Pharmaceutical Markets

2004-2005



Source: IMS Health, Intel 360, 2006

Investment mainly in China : market potential and strict regulation (?), healthcare investment by Chinese government

Expansion of Global Companies Establishing Research and Development Bases in Asia

Company	Descriptions	Timing
AstraZeneca	Established a **research base** in Shanghai	2002
Novartis	Established an **R&D center** in Shanghai with an investment of 100 million dollars	2007
GSK	Set up an **R&D center (CEDD)** in neurodegenerative disease in Shanghai	2007
Roche	Established an **R&D center** in Shanghai	2004
Merck	Established a **research based collaboration** in India	2006
Pfizer	Established an **R&D center** in Shanghai	2005
Eli Lilly	**R&D investment** in China	2007

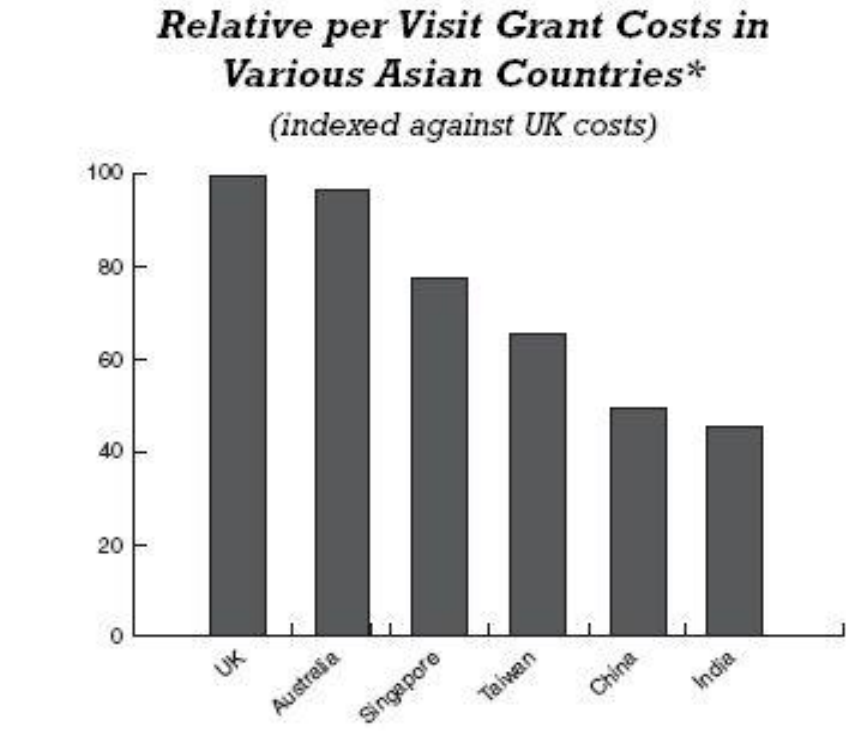
Source: Becoming a More Competitive "Drug Discovery Venue" —The Current State of the Pharmaceutical Industry, and Problems Therein— (May 2005, Office of Pharmaceutical Industry Research)

India : Rapid Expansion of Gross in Clinical Trials

- Rapid growing model country since 2000
- Size of Population : 5 major Cluster
  - Delhi : 15,335,000 population
  - Bombay : 18,337,000
  - Chennai
  - Hyderabad
  - Bangalore
- High level of Infrastructure in big city (Medical, IT etc.)
- Language; English, Low trial cost
- Governmental support: R&D Tax deduction, Regulatory support – fast CTA

Cost Index : Asian Countries

Source : Parexel source book 2009/2010



* UK=100 base

Source: TTC

India Clinical Trials Costs One-Tenth of US Costs?

In India, a first-rate academic medical center charges approximately $1,500 to $2,000 per case report, less than one tenth the cost at a *second-tier* center in the United States.

Source: JP Garnier, "Rebuilding the R&D engine in big pharma," Harvard Business Review, 2008; 86:68-76

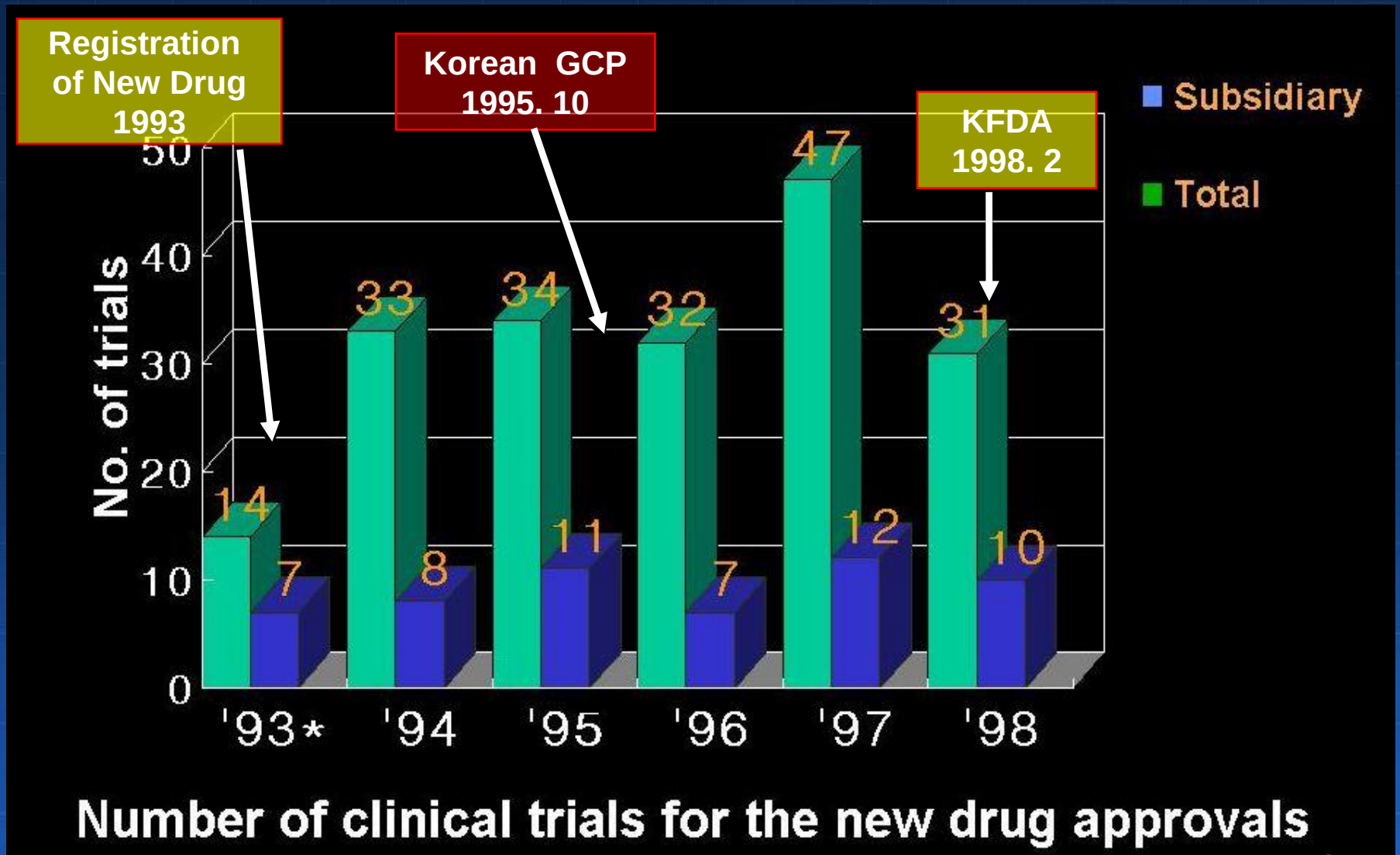
India : Status of various categories in India : 2005-2009

S.No	Subject	Year 2005* (Jan-Dec)	Year 2006* (Jan-Dec)	Year 2007* (Jan-Dec)	Year 2008* (Jan-Dec)	Year 2009 (Jan- Dec)
1	New Drug Applications	1200	1500	1600	1750	1753
2	Global Clinical Trials	100	170	300	350	262
3	Market Authorization of Vaccines and Biotech	10	50	40	45	137
4	Medical Devices	0	300	450	400	936
5	Diagnostic Kits including Test License	250	350	400	850	878
6	Export NOCs	2000	2100	1800	2350	3371
7	Test License	3700	5000	5500	7200	8215
8	Blood Bank License	200	225	280	275	630
9	Import Registration	300	450	400	475	418
10	Import License / Dual use	2300	2400	2000	1950	4291
11	BE NOC for exports	100	400	600	1300	1915
	Total	**10160**	**12945**	**13370**	**16945**	**22806**

*** This does not include other applications like NOC for manufacturing of trial batches of drug, correspondence with various ministries/dept., sate drug controller authorization, parliament matters & other misc. letters**

Clinical Trials requirement for registration in Korea

- **due to questionable ethnic difference ?**



Number of clinical trials for the new drug approvals

Korea : Major regulatory changes and Streamlining of IND (120 days to 30 days?) in early 2000s

- **KGCP revision, as of January 4, 2000**

  Harmonize with ICH-E6 guideline

- **Adoption of the Bridging Concept (E5)**

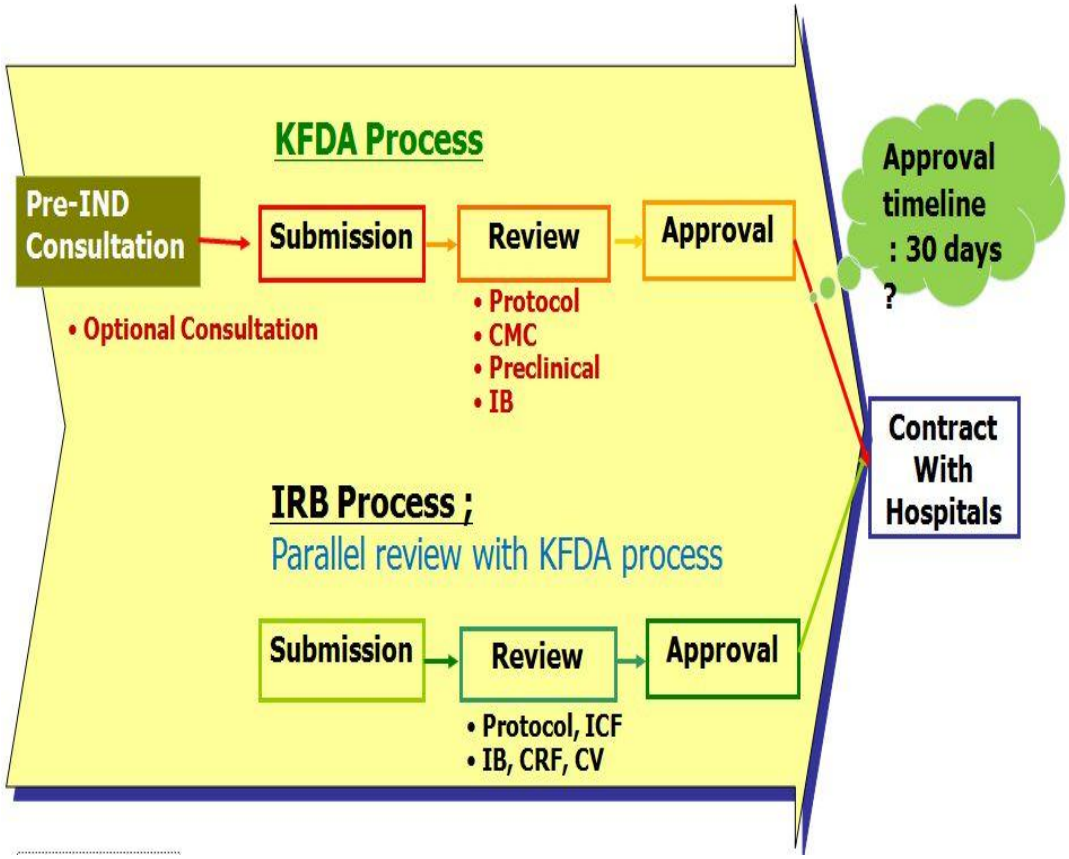
  Diverse bridging strategies ; BS or early global involvement

  Effective since 2001 for NDA

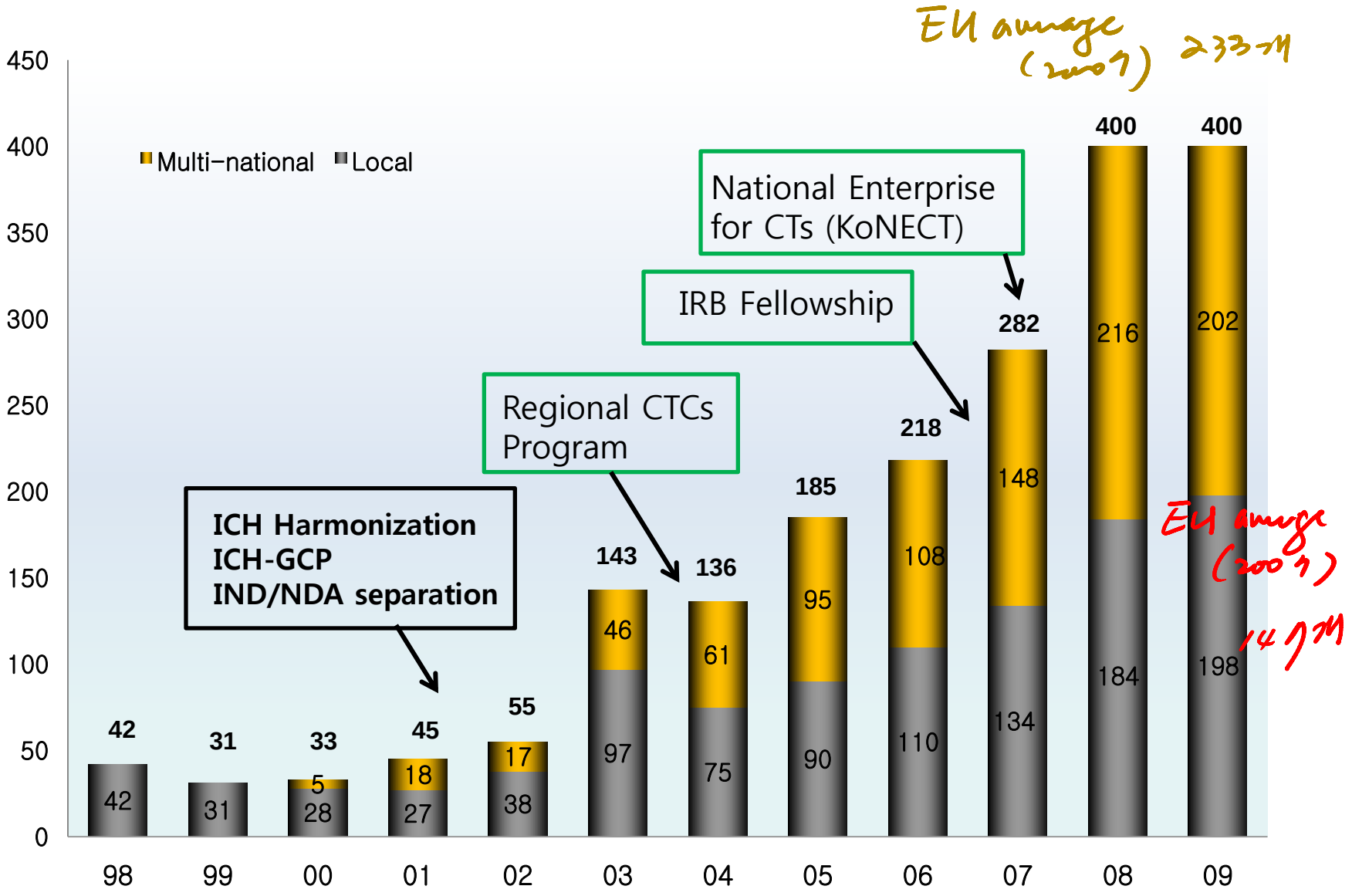
- **Separation of IND from NDA**

  Participation in global study permitted in any stage

  Effective since 2002



Korea : Clinical Trials Approved by KFDA

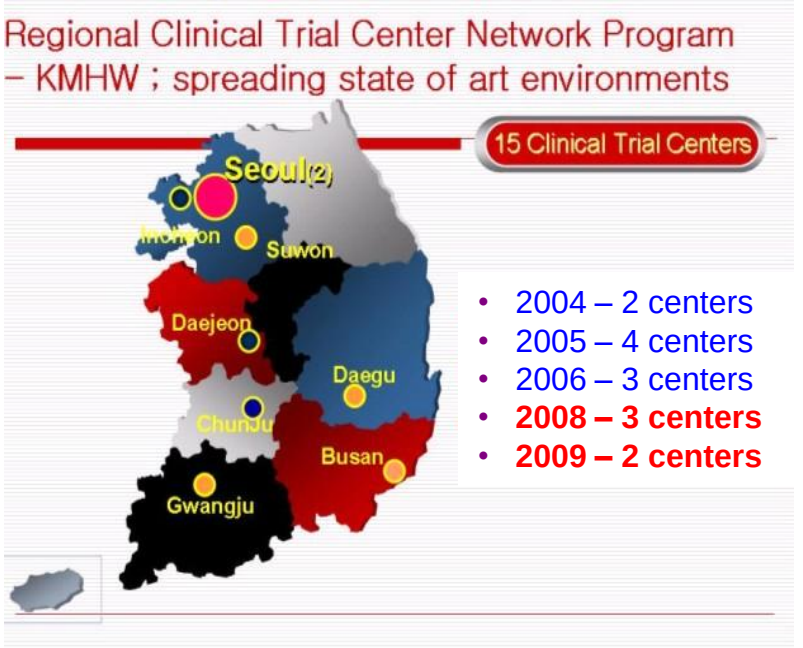


Korea : Government starts to support Clinical Trials & Clinical Researches

- Government-support for new drug discovery & development by MOST(1991-), MOHW later

- **Regional Clinical Trial Centers supporting program by MOHW (2004-)**

  - similar to US NIH-GCRC supporting program
  - 14 centers of excellence till 2009
  - supporting ~ US$ 4 million per center
  - same amount of matching fund from each Institution.



KoNECT as the national integrative supporting program, 2007. 12

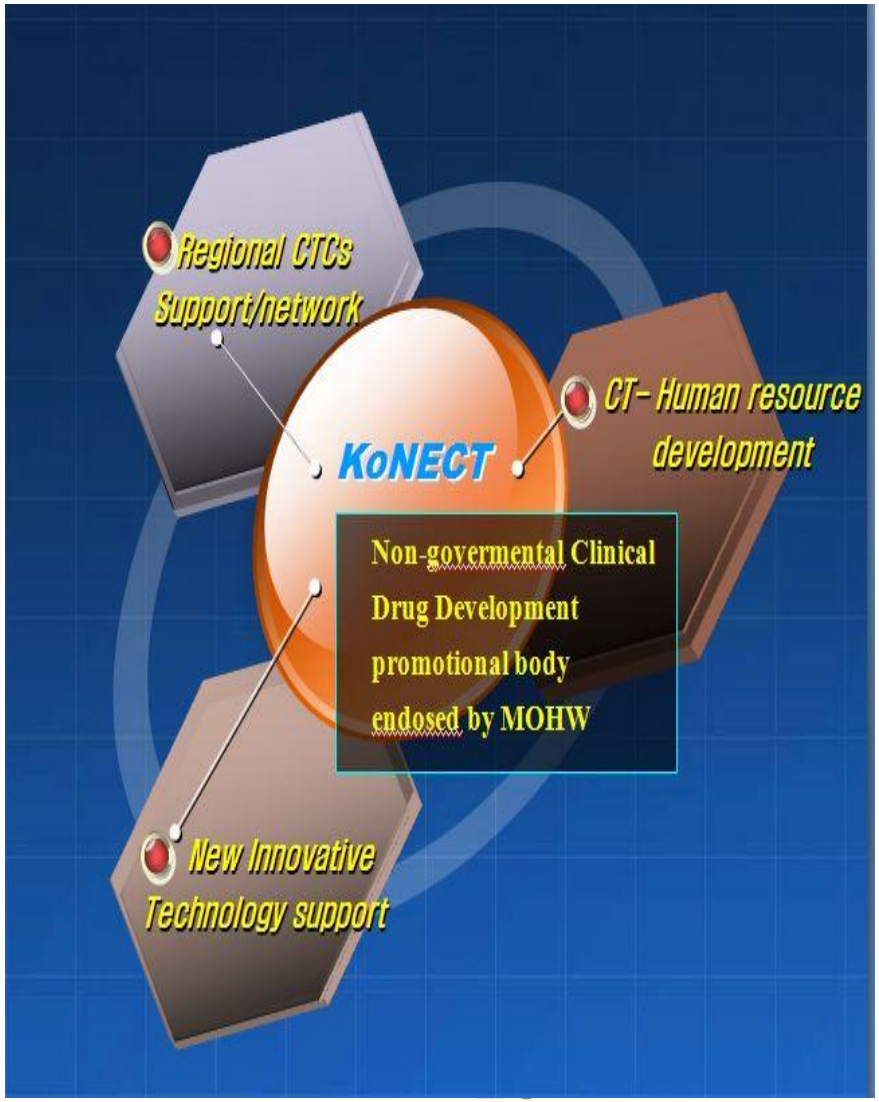
ORGANIZATION

★ **International Technical advisory committee**

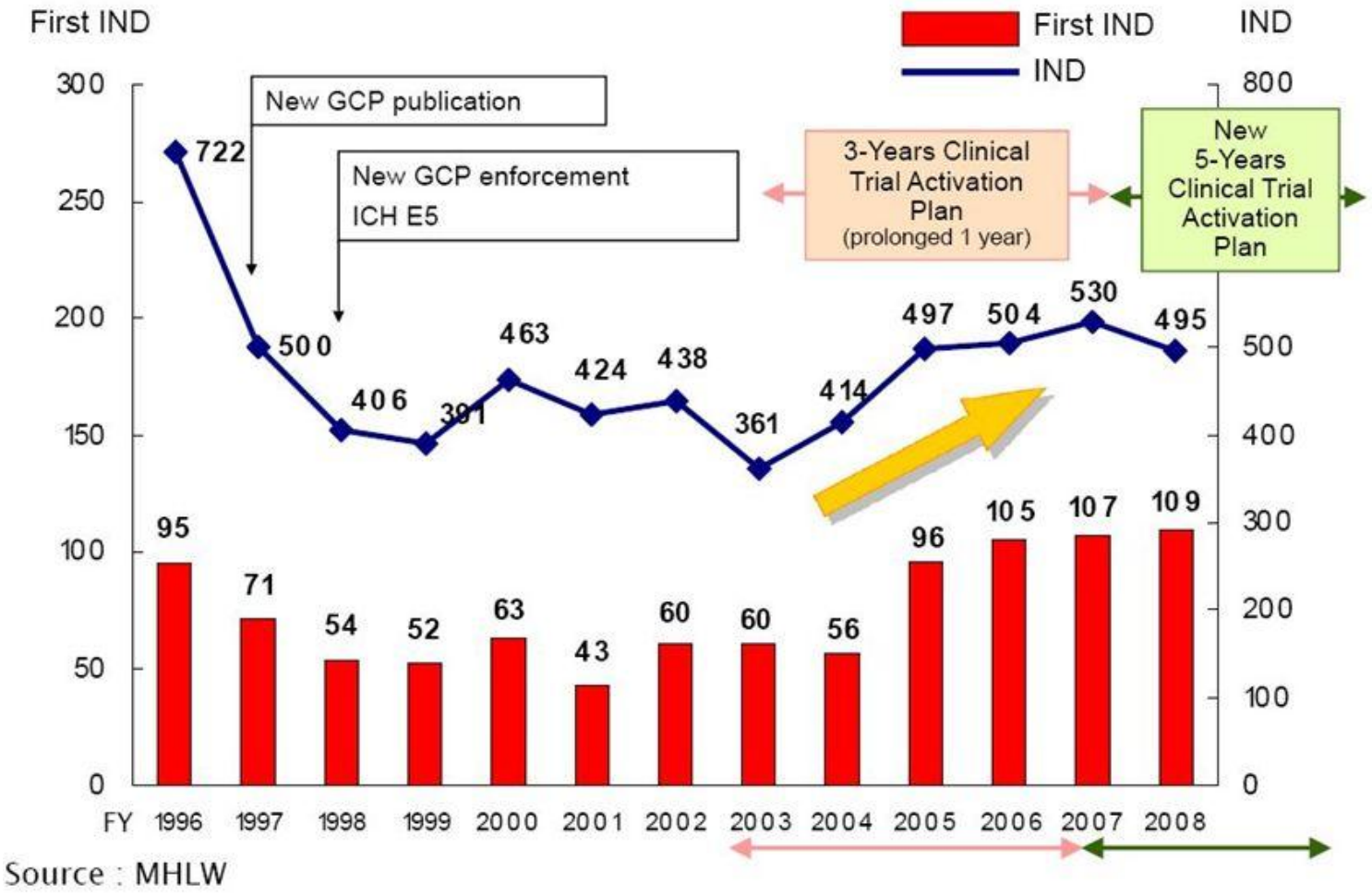
- **Prof.Nadarajah Sree Haran**
- **Dr.Adam Cohen**, Centre for Human Drug Research, CEO
- **Prof.Kyoichi Ohashi**, Oita Univ.
- **Prof.Masahiro Takeuchi**, Kitasato University School of Pharmaceutical SciencesDivision of Biostatistics & Division of Pharmaceutical Medicine
- **Dr.Stephen Phua**, Agenix CEO & Managing Director
- **Dr.Richard L.Lalonde**, Pfizer Global Research & Development, Vice President, Global head of Clinical Pharmacology
- **Prof.Trevor M. Jones**
- **Prof.Stuart R.Walker**, CMR Vice President & Founder

In Collaboration with

MIHWAF	Ministry for Health, Welfare and Family Affairs	kotra	Korea Trade-Investment Promotion Agency
KFDA	Korea Food & Drug Administration	KAIRB	Korean Association of Institutional Review Boards
KHIDI	Korea Health Industry Development Institute	KACTC	Korea Association of Clinical Trials Center



Japan : Suffering in new drug development, especially clinical development

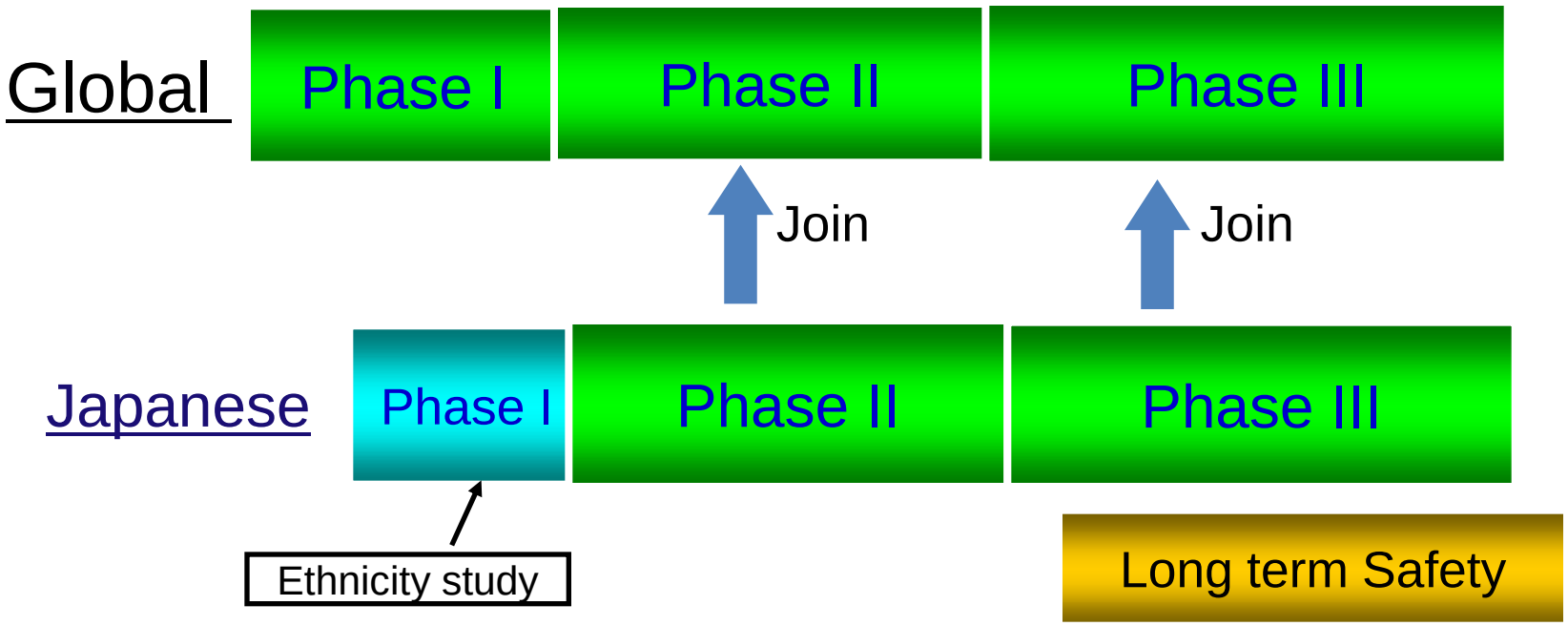


Source : MHLW

Early initiation Clinical study in Japan
- Global Trial Guidelines, 2007

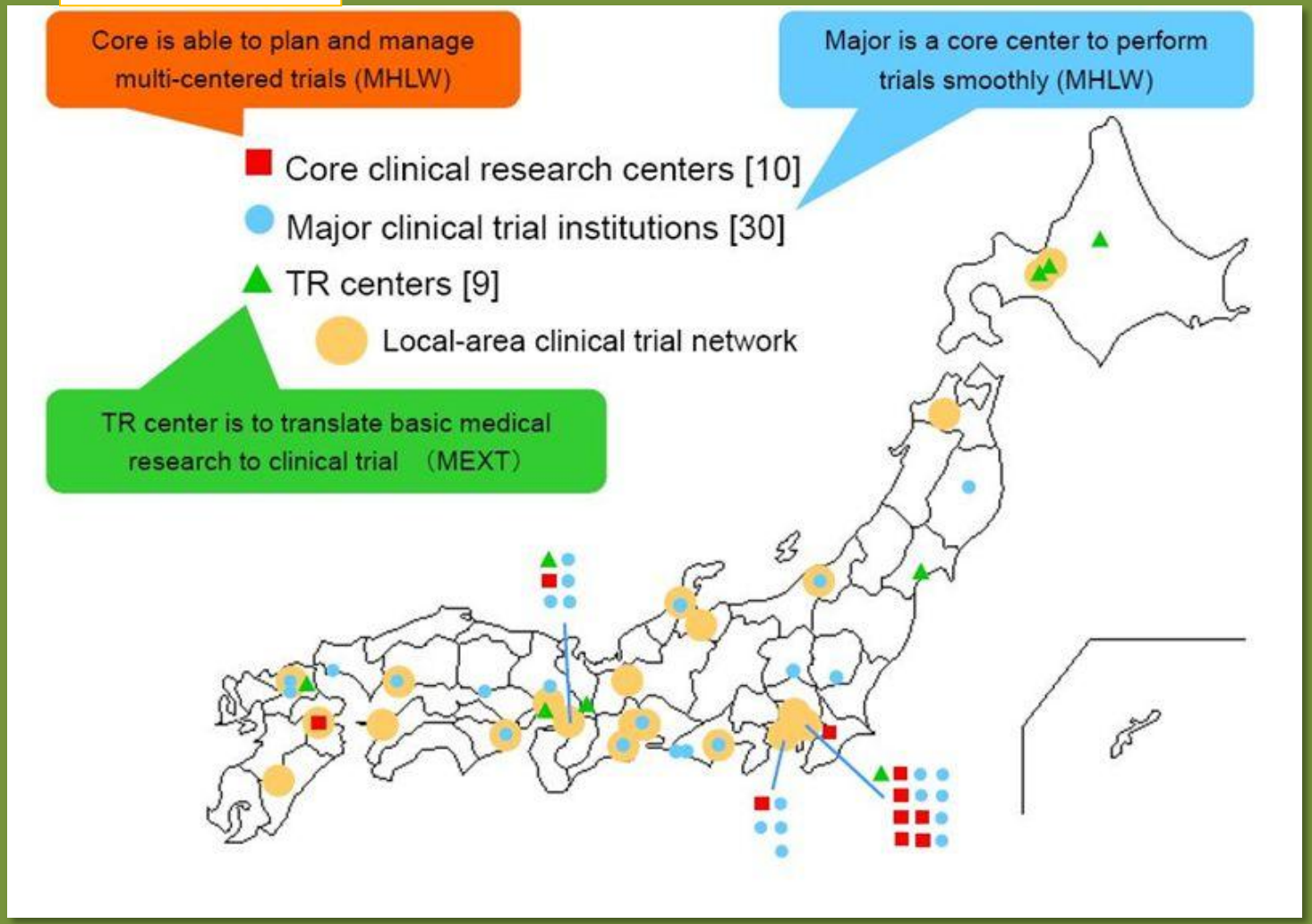
VOLUME 87 NUMBER 3 | MARCH 2010 | www.nature.com/cpt

- highly recommend multinational company to initiate clinical trials in Japan as early as possible, parallel to western region to resolve drug-lag and increase possibility to join Simultaneous Global Clinical Development



Clinical Trials Activation 5 yrs Plan (2007-2011) : as a part of ICR Projects

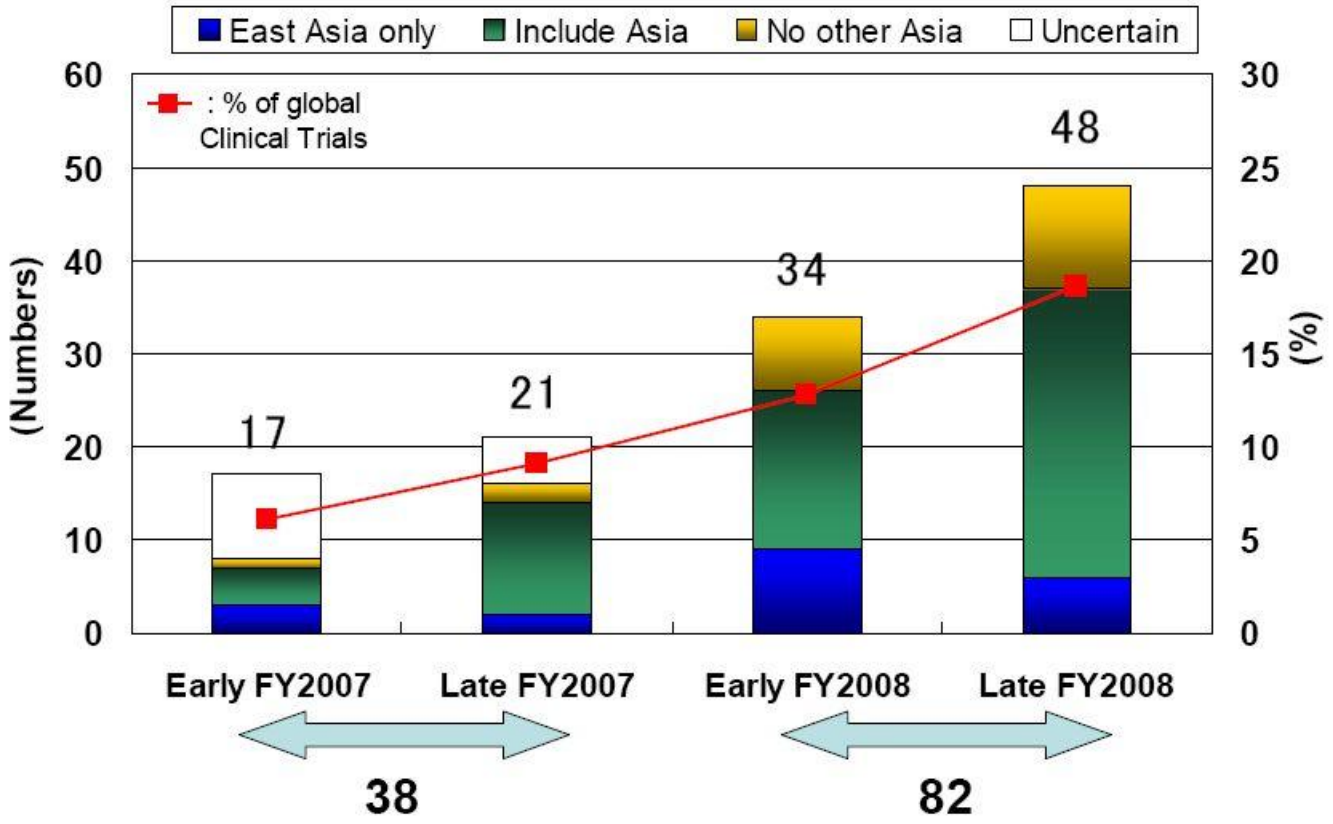
1.75 bn￥/ yr



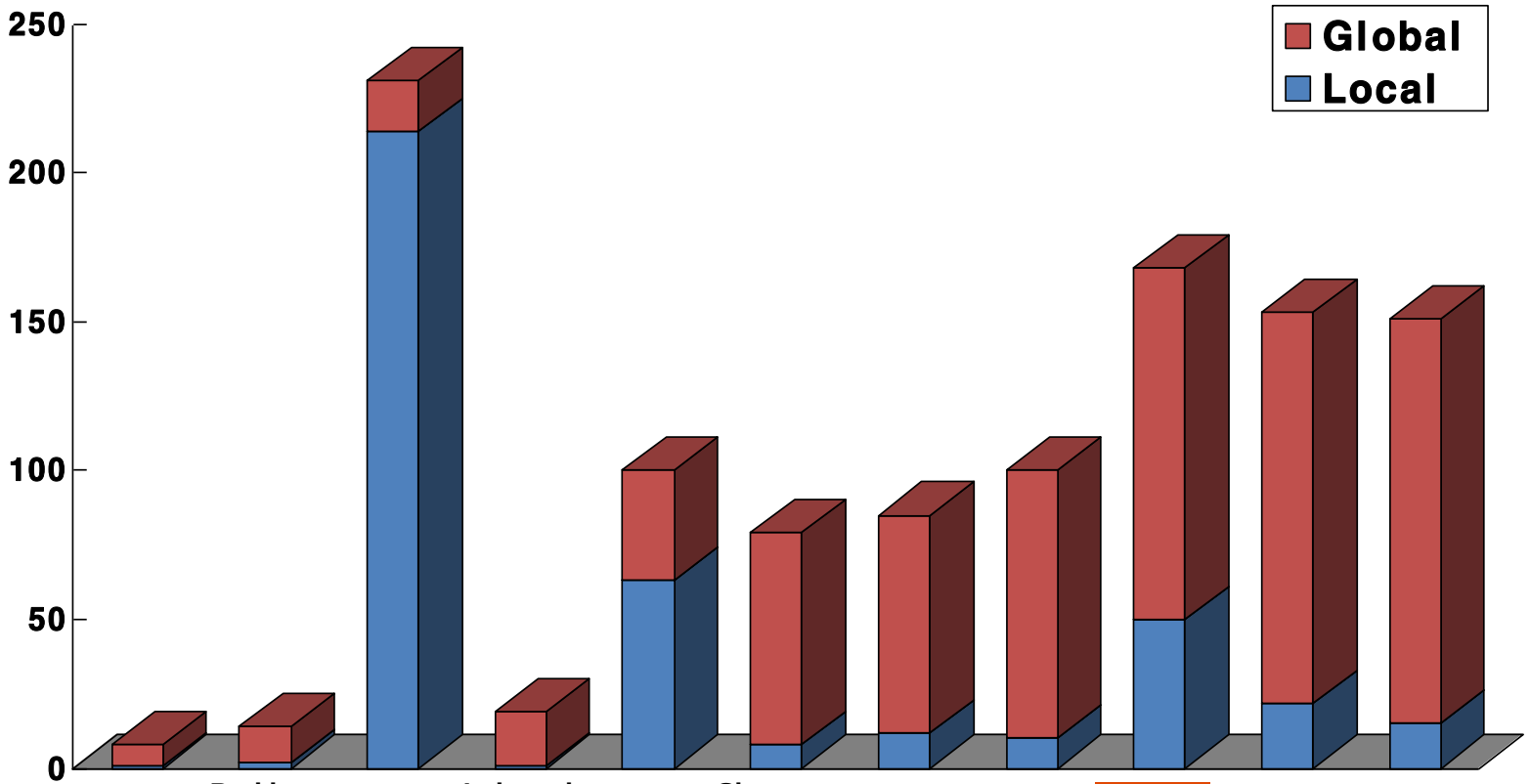
Recent Multinational Clinical Trials in Japan

Trends of Global Clinical Trials including Japan

- Operational Regions -



Local vs Global Trials in Asian Countries



	Vietnam	Parkistan	Japan	Indonesia	China	Singapore	Thailand	HK	Korea	Taiwan	India
Global	7	12	17	18	37	71	73	90	118	131	136
Local	1	2	214	1	63	8	12	10	50	22	15

Sources, Hong Kong Univ. CTC : www.clinicaltrials.gov (Oct06)

Trends in the globalization of Clinical Trials

- Nature Review/Drug discovery 2008. 1 (2007. 4)

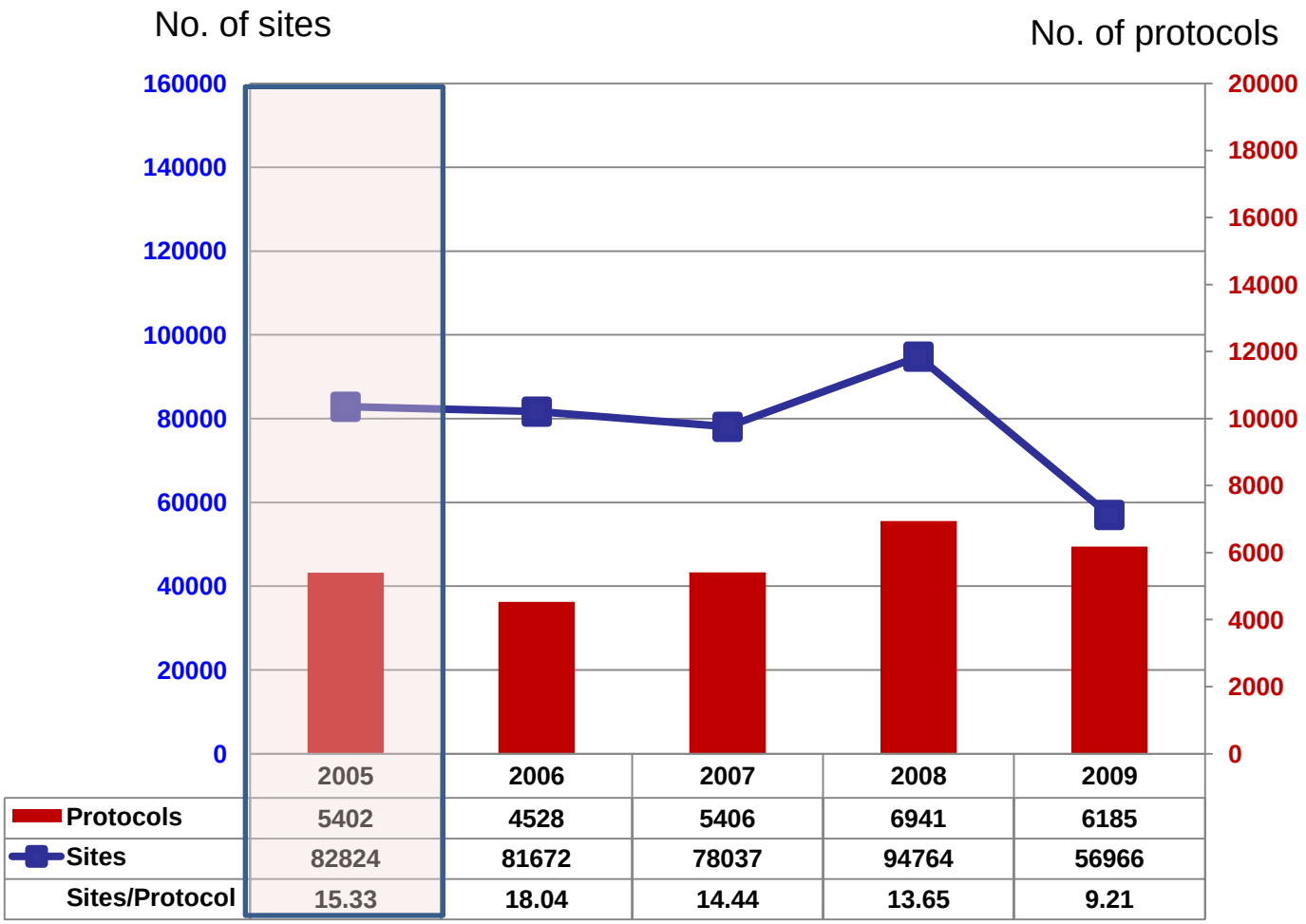
Table 1 | **Country trends in participation in biopharmaceutical clinical trials**

Rank	Country	Number of sites	Share (%)	ARAGR (%)	Trial capacity	Trial density
1	United States	36,281	48.7	-6.5↓	43.7	120.3
2	Germany	4,214	5.7	11.7↑	10.9	51.2
3	France	3,226	4.3	-4.0↓	9.6	50.3
4	Canada	3,032	4.1	-12.0↓	8.6	92.2
5	Spain	2,076	2.8	14.9↑	6.8	46.4
6	Italy	2,039	2.7	8.1↑	6.7	34.6
7	Japan	2,002	2.7	10.3↑	33.4	15.7
8	United Kingdom	1,753	2.4	-9.9↓	7.6	29.1
9	Netherlands	1,394	1.9	2.1↑	6.8	85.0
10	Poland*	1,176	1.6	17.2↑	5.3	30.9
11	Australia	1,131	1.5	8.1↑	5.4	54.4
12	Russia*	1,084	1.5	33.0↑	5.8	7.7
13	Belgium	986	1.3	-9.4↓	5.2	94.8
14	Czech Republic*	799	1.1	24.6↑	4.5	77.6
15	Argentina*	757	1.0	26.9↑	4.8	19.0
16	India*	757	1.0	19.6↑	5.8	0.7
17	Brazil*	754	1.0	16.0↑	5.1	4.0
18	Sweden	739	1.0	-8.6↓	5.1	81.0
19	Mexico*	683	0.9	22.1↑	4.0	6.2
20	Hungary*	622	0.8	22.2↑	4.1	62.5
21	South Africa*	553	0.7	5.5↑	4.3	11.9
22	Austria	540	0.7	9.6↑	3.8	65.1
23	China*	533	0.7	47.0↑	5.3	0.4
24	Denmark	492	0.7	9.2↑	4.4	90.3
25	South Korea*	466	0.6	17.9↑	3.4	9.5

*Countries in emerging regions. ARAGR, average relative annual growth rate. Trial capacity is the number of sites in the country involved in large trials (20 or more sites) divided by the number of large trials in the country. Trial density is the number of recruiting sites on April 12th 2007 divided by the country population in millions.

- **Global Competitiveness/challenges of Asian Countries in industry sponsored trials**

Trends of Global Clinical Trials according to clinicaltrials.gov. (Industry Sponsored Trials only)



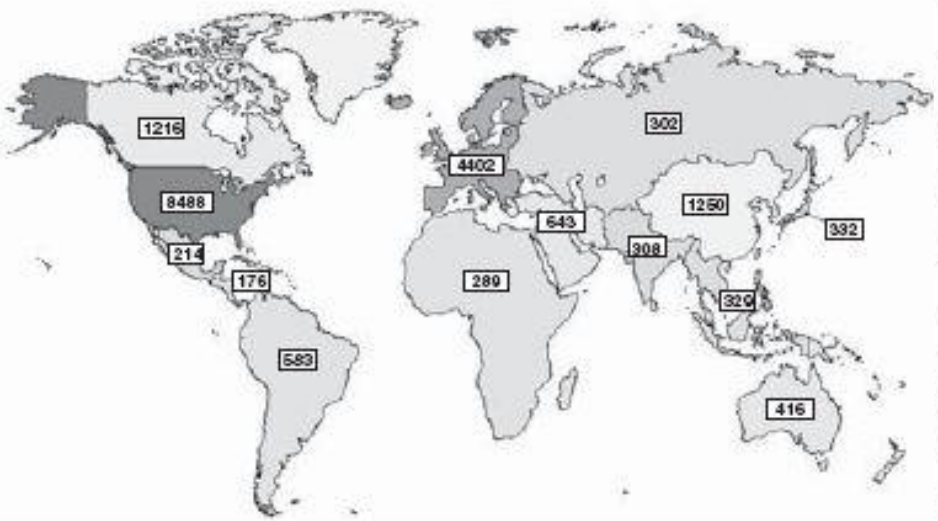
	2005	2006	2007	2008	2009
Protocols	5402	4528	5406	6941	6185
Sites	82824	81672	78037	94764	56966
Sites/Protocol	15.33	18.04	14.44	13.65	9.21

- Source: www.clinicaltrials.gov, 2009 12. 31

Trends of Industry Sponsored Trials in EA countries : 2005 - 2008

Parexel/KoNECT Reports, Dec 2009

Worldwide clinical trials, as first entered into ClinicalTrials.gov, in 2008



Worldwide Clinical Trials First Entered in Each Calendar Year, 2005-2008

Regions	2005	2006	2007	2008	% of Worldwide Trials (2008)
Worldwide	13,007	10,947	13,508	17,052	—
Africa	395	325	289	289	1.7%
Asia*	1,458	1,428	1,724	2,189	12.8%
China	142	200	280	334	2.0%
India	138	201	218	275	1.7%
Japan	242	194	233	332	2.0%
So. Korea	113	202	316	366	2.2%
Taiwan	454	184	240	336	2.0%
Central America	183	154	149	176	1.0%
Europe	3,348	2,940	3,590	4,402	25.9%
Middle East	357	547	610	643	3.8%
North America	7,262	6,262	7,482	9,289	54.5%
Pacifica	531	406	396	416	2.5%
South America	211	381	421	583	3.5%

*includes trials counted in China, India, Japan, Korea and Taiwan

Clinical Trials Activities in each Countries(Industry Sponsored Trials only, rank as no. of sites)

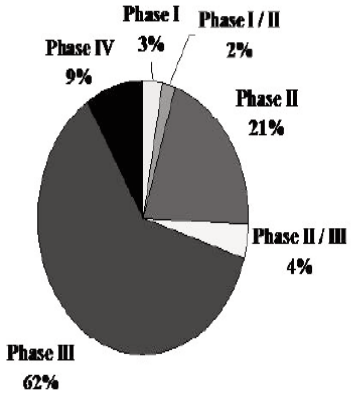
Source: www.clinicaltrials.gov, 2009 12. 31

	2005			2006			2007			2008			2009		
1	US	39920	48.20%	US	35072	42.94 %	US	34207	43.83 %	US	44080	46.52 %	US	26042	45.71 %
2	Germany	4545	5.49%	Germany	5359	6.56%	Germany	5683	7.28%	Germany	5666	5.98%	Germany	3707	6.51%
3	Canada	4407	5.32%	France	4338	5.31%	France	3298	4.23%	France	4243	4.48%	France	2440	4.28%
4	France	3606	4.35%	Canada	3878	4.75%	Canada	2729	3.50%	Canada	3606	3.81%	Canada	2028	3.56%
5	UK	2454	2.96%	UK	2551	3.12%	Spain	2255	2.89%	Italy	2471	2.61%	Japan	1747	3.07%
6	Italy	2439	2.94%	Spain	2316	2.84%	Italy	2137	2.74%	Spain	2439	2.57%	Italy	1499	2.63%
7	Spain	2052	2.48%	Italy	1991	2.44%	Japan	2046	2.62%	UK	2394	2.53%	Spain	1481	2.60%
8	Japan	1694	2.05%	Japan	1688	2.07%	UK	2041	2.62%	Japan	2326	2.45%	UK	1398	2.45%
9	Australia	1601	1.93%	Poland	1614	1.98%	Russia	1757	2.25%	Poland	1889	1.99%	Russia	1186	2.08%
10	Netherlands	1323	1.60%	Russia	1549	1.90%	Poland	1728	2.21%	Russia	1839	1.94%	Poland	1030	1.81%
11	Poland	1288	1.56%	Australia	1333	1.63%	Australia	1337	1.71%	Australia	1401	1.48%	Australia	861	1.51%
12	Belgium	1258	1.52%	Belgium	1293	1.58%	Belgium	1197	1.53%	Belgium	1335	1.41%	Korea	842	1.48%
13	Sweden	1203	1.45%	Netherlands	1141	1.40%	India	1022	1.31%	India	1330	1.40%	China	822	1.44%
14	Denmark	921	1.11%	Brazil	1047	1.28%	Hungary	950	1.22%	Netherlands	1273	1.34%	India	816	1.43%
15	Russia	892	1.08%	Argentina	1034	1.27%	Czech republic	874	1.12%	Brazil	1130	1.19%	Belgium	767	1.35%
16	Czech republic	888	1.07%	Czech republic	985	1.21%	Brazil	872	1.12%	Czech republic	1051	1.11%	Netherlands	644	1.13%
17	South Africa	798	0.96%	India	963	1.18%	Netherlands	861	1.10%	Sweden	956	1.01%	Czech republic	603	1.06%
18	Norway	734	0.89%	Hungary	840	1.03%	Argentina	780	1.00%	Hungary	898	0.95%	Brazil	554	0.97%
19	Hungary	732	0.88%	Austria	804	0.98%	Ukraine	733	0.94%	Argentina	855	0.90%	Hungary	542	0.95%
20	Brazil	714	0.86%	Sweden	774	0.95%	China	690	0.88%	Korea	847	0.89%	Mexico	532	0.93%
21	Finland	647	0.78%	Mexico	773	0.95%	Korea	678	0.87%	Mexico	825	0.87%	Sweden	507	0.89%
22	Mexico	611	0.74%	South Africa	733	0.90%	Sweden	668	0.86%	China	813	0.86%	Argentina	420	0.74%
23	Argentina	588	0.71%	Ukraine	703	0.86%	Mexico	659	0.84%	Romania	800	0.84%	Israel	415	0.73%
24	India	548	0.66%	Israel	667	0.82%	Austria	633	0.81%	South Africa	779	0.82%	South Africa	393	0.69%
25	Switzerland	461	0.56%	Korea	659	0.81%	Israel	608	0.78%	Ukraine	733	0.77%	Romania	388	0.68%
26	Austria	447	0.54%	China	590	0.72%	South Africa	561	0.72%	Israel	691	0.73%	Ukraine	382	0.67%
27	Israel	407	0.49%	Denmark	538	0.66%	Romania	517	0.66%	Austria	575	0.61%	Taiwan	372	0.65%
28	Greece	371	0.45%	Romania	462	0.57%	Taiwan	504	0.65%	Denmark	526	0.56%	Austria	371	0.65%
29	China	367	0.44%	Finland	418	0.51%	Finland	471	0.60%	Finland	523	0.55%	Denmark	330	0.58%
30	Taiwan	359	0.43%	Switzerland	381	0.47%	Denmark	454	0.58%	Taiwan	467	0.49%	Finland	321	0.56%
31	Korea	344	0.42%	Slovakia	379	0.46%	Slovakia	385	0.49%	Bulgaria	460	0.49%	Slovakia	314	0.55%
32	Portugal	344	0.42%	Taiwan	369	0.45%	Switzerland	352	0.45%	Turkey	428	0.45%	Turkey	270	0.47%

Trials by Phase : comparison between emerging and developed countries

Trials by Phase in India

Drug and Biological Trials Listed on Clinicaltrials.gov

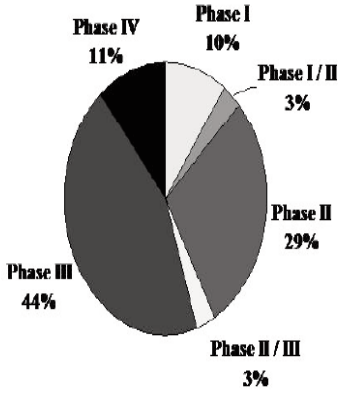


Note: numbers may not add up to 100% due to rounding

Source: CenterWatch Analysis of clinicaltrials.gov, December 7, 2008

Trials by Phase in the United Kingdom

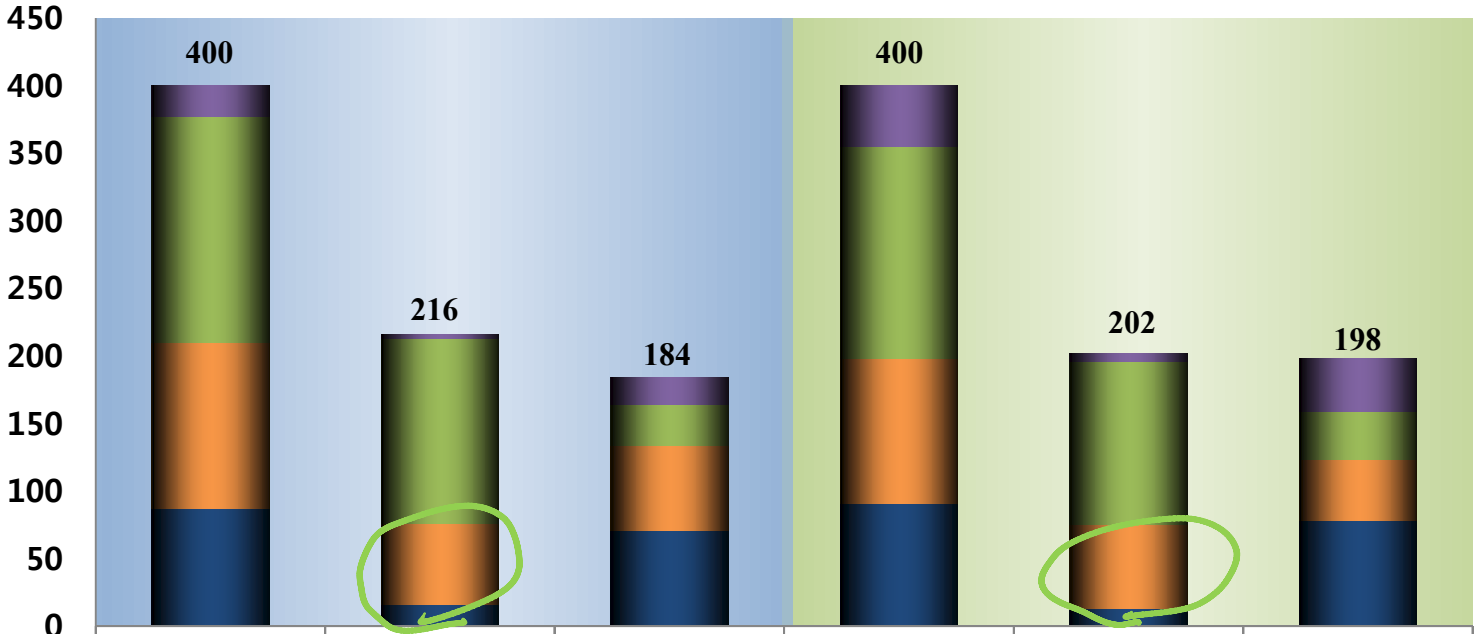
Drug and Biological Trials Listed on Clinicaltrials.gov



Note: numbers may not add up to 100% due to rounding

Source: CenterWatch Analysis of clinicaltrials.gov, December 7, 2008

Characteristics of Clinical Trials in Korea, 08-09



	2008			2009		
	Subtotal	Multinational	Domestic	Subtotal	Multinational	Domestic
Phase Ⅳ	23	3	20	45	6	39
Phase Ⅲ	167	137	30	157	121	36
Phase Ⅱ	123	60	63	107	62	45
Phase Ⅰ	87	16	71	91	13	78

Geographic trends of 'first time in human' trials

1 January 2005 – 30 June 2009
Phase 1 industry-sponsored clinical trials, received by ClinicalTrials.gov

Regions+	2005	2006	2007	2008	1H2009	% Growth of Trials (2005-2008)	% of Worldwide Trials (1H09)
Worldwide	**480**	**704**	**1116**	**1675**	**1051**	**249%**	**--**
China	2	7	7	11	8	450%	.76%
Hong Kong	2	3	4	4	4	100 %	.38%
Japan	5	25	36	47	25	840%	2.4%
Korea, Republic of	1	4	12	17	11	1,600%	1.0%
Taiwan	4	5	4	7	6	75%	.57%
Russian Federation	6	3	6	6	3	0%	.29%
India	2	6	7	10	12	400 %	.95%
Singapore	2	6	4	16	12	700%	.95%

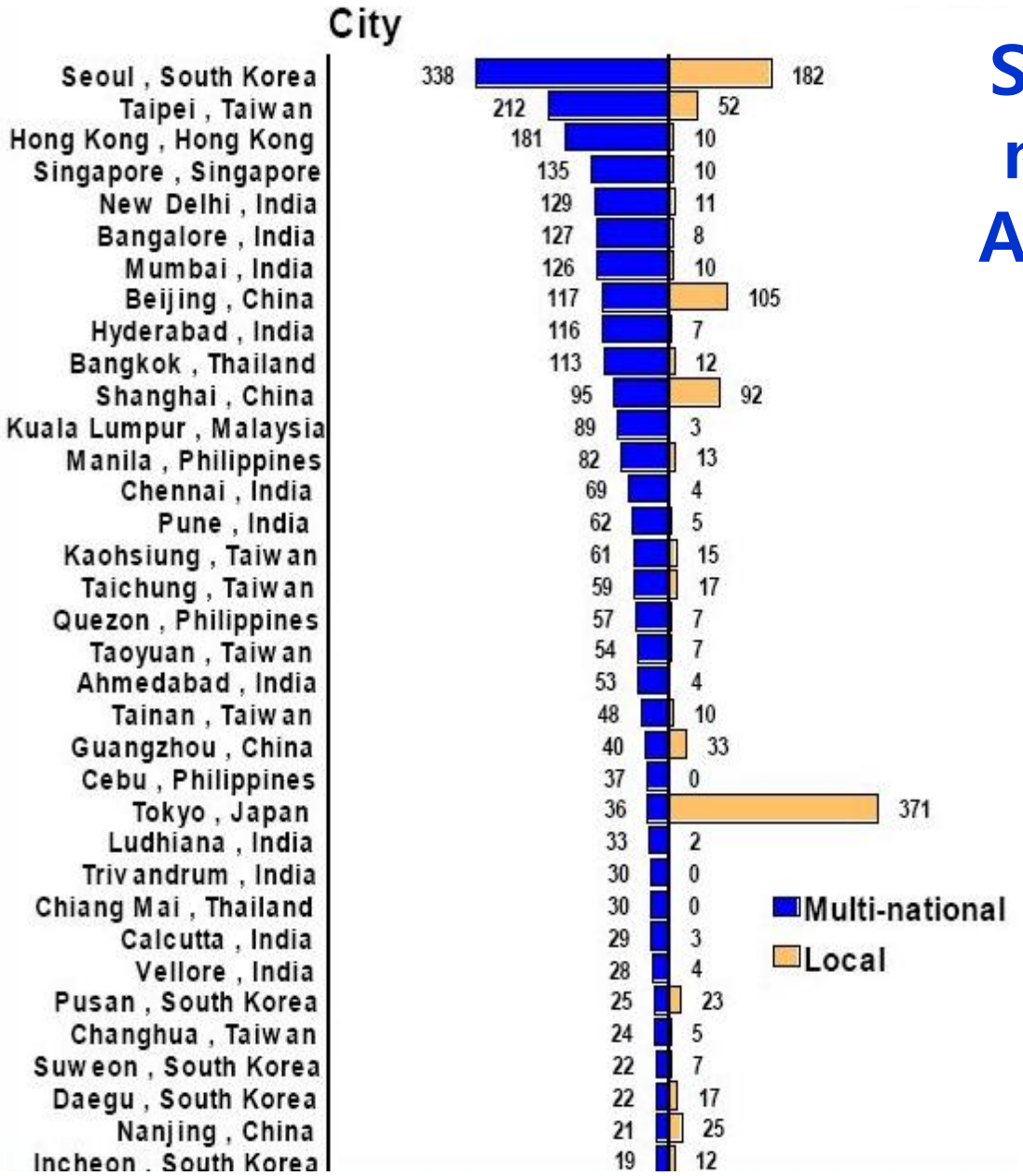
Therapeutic Area distribution in Asian Trials

Figure 16 - 2008 Trial Activity by Therapeutic Category[166]

Category	China	India	Korea	Singapore	Russia	Average for 5 Countries
Oncology	30%	24%	29%	32%	28%	29%
Cardiovascular	37%	21%	13%	11%	23%	21%
Endocine/Metabolic	6%	16%	10%	NA	11%	11%
CNS	4%	12%	10%	6%	11%	9%
Antinfective	3%	5%	7%	NA	6%	5%
GI	0%	5%	4%	3%	2%	3%
Respiratory	7%	6%	4%	NA	5%	5%
Musculoskeletal	1%	1%	4%	NA	1%	1%
Hematology	0%	1%	4%	NA	1%	1%
Rheumatology	2%	3%	3%	NA	3%	3%
Total Above Categories	**91%**	**93%**	**87%**	**52%**	**91%**	**83%**

Comparison of Korea's Multinational Trial/Local Trial Activity with Global Trial Therapeutic Area**

	FDA-regulated INDs* (% of total)	Korean Trials (% of total)
Oncology	836 (14.7%)	117 (29%)
Cardiovascular	368 (6.5%)	53 (13%)
Endo/Metabolism	424 (7.4%)	39 (10%)
Anti-Infective/Ophth.	435 (7.6%)	34 (9%)
Psychiatry	296 (5.2%)	29 (7%)
Respiratory	272 (4.8%)	17+ (4%)
Gastrointestinal	315 (5.5%)	16 (4%)
Rheumatology	536++ (9.4%)	11 (3%)
Hematology+++	244 (4.3%)	14 (4%)
Neurology	533 (9.4%)	11 (3%)
Dermatology#	398 (7%)	8 (2%)
Urology##	398 (7%)	11 (3%)



Seoul has been the most active city in Asia in clinical trials since 2006

Clinical Trial Magnifier Vol. 1:5 May 2008
(www. ClinicalTrialMagnifier.com)

The chart includes the number of study sites for both multi-nationally (ranking measure) and locally conducted industry sponsored clinical trials in the top 50 most active Asian cities.

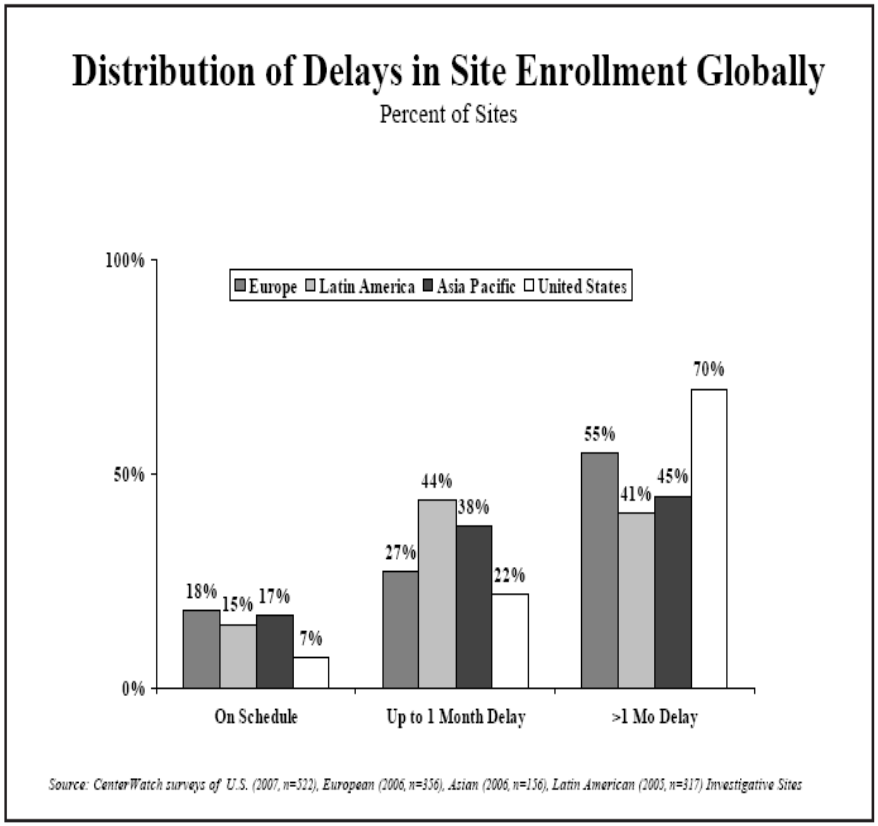
Top 30 Cities in Industry sponsored Trials (No. of Sites)

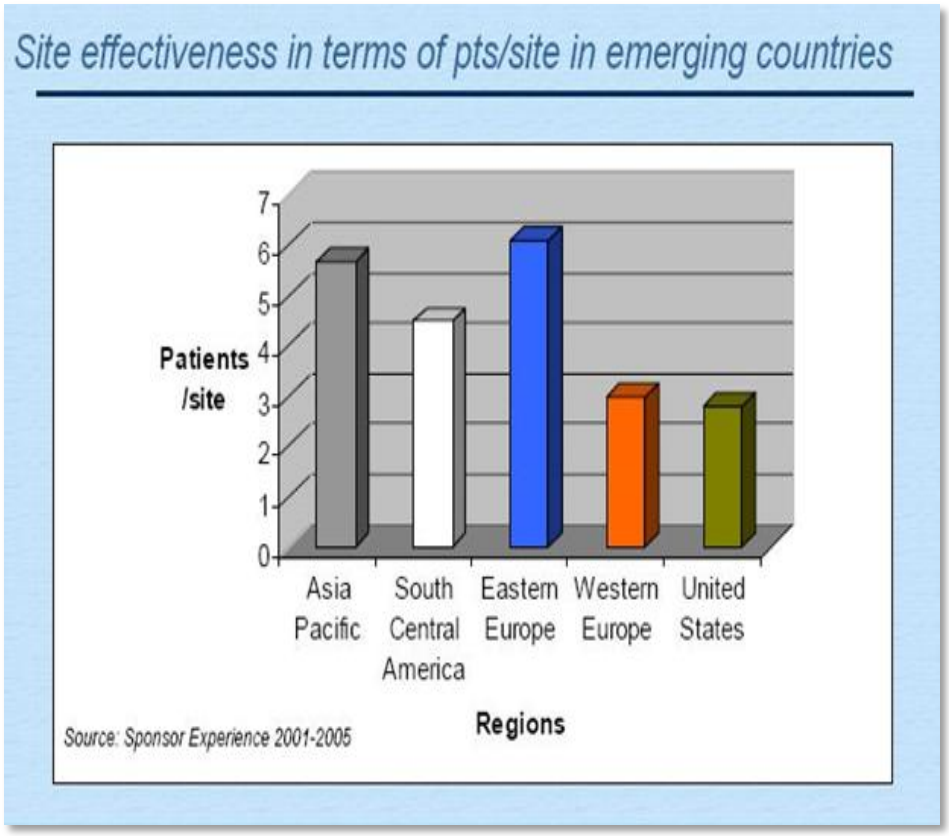
❖ Source: www.clinicaltrials.gov, 2009 12.31

	2005			2006			2007			2008			2009		
1	Houston	672	0.81%	Houston	617	0.76%	Houston	754	0.97%	Houston	820	0.87%	Houston	563	0.99%
2	New York	655	0.79%	New York	572	0.70%	New York	643	0.82%	New York	731	0.77%	San Antonio	447	0.78%
3	Chicago	558	0.67%	Moscow	527	0.65%	Berlin	597	0.77%	San Antonio	685	0.72%	**Seoul**	**436**	**0.77%**
4	Los Angeles	543	0.66%	Berlin	511	0.63%	Boston	523	0.67%	Berlin	627	0.66%	New York	415	0.73%
5	Philadelphia	536	0.65%	London	477	0.58%	Moscow	520	0.67%	Dallas	604	0.64%	Berlin	408	0.72%
6	Boston	535	0.65%	Dallas	469	0.57%	San Antonio	513	0.66%	Los Angeles	585	0.62%	Dallas	377	0.66%
7	Dallas	513	0.62%	Chicago	462	0.57%	Chicago	505	0.65%	Philadelphia	578	0.61%	Boston	372	0.65%
8	Atlanta	471	0.57%	Philadelphia	460	0.56%	Dallas	496	0.64%	Boston	556	0.59%	Moscow	350	0.61%
9	London	459	0.55%	Madrid	452	0.55%	Philadelphia	460	0.59%	Moscow	556	0.59%	London	328	0.58%
10	San Antonio	458	0.55%	Boston	451	0.55%	Los Angeles	452	0.58%	Chicago	516	0.54%	San Diego	321	0.56%
11	San Diego	447	0.54%	San Antonio	421	0.52%	London	413	0.53%	San Diego	513	0.54%	Los Angeles	316	0.55%
12	Berlin	438	0.53%	Barcelona	411	0.50%	Madrid	394	0.50%	London	502	0.53%	Philadelphia	303	0.53%
13	Birmingham	422	0.51%	Birmingham	406	0.50%	**Seoul**	**381**	**0.49%**	Atlanta	494	0.52%	Madrid	293	0.51%
14	Toronto	421	0.51%	Los Angeles	402	0.49%	Barcelona	380	0.49%	Birmingham	487	0.51%	Chicago	284	0.50%
15	St. Louis	395	0.48%	Toronto	379	0.46%	Atlanta	371	0.48%	Madrid	463	0.49%	Paris	283	0.50%
16	Cincinnati	394	0.48%	Baltimore	366	0.45%	Toronto	353	0.45%	Paris	458	0.48%	Miami	279	0.49%
17	Montreal	394	0.48%	Atlanta	364	0.45%	Birmingham	341	0.44%	Cincinnati	449	0.47%	Cincinnati	267	0.47%
18	Portland	390	0.47%	Miami	352	0.43%	San Diego	340	0.44%	Miami	437	0.46%	Toronto	267	0.47%
19	Madrid	386	0.47%	San Diego	346	0.42%	Miami	334	0.43%	**Seoul**	**435**	**0.46%**	Birmingham	264	0.46%
20	Baltimore	378	0.46%	Montreal	342	0.42%	Cincinnati	328	0.42%	Barcelona	423	0.45%	Baltimore	258	0.45%
21	Barcelona	373	0.45%	Paris	317	0.39%	Baltimore	318	0.41%	Baltimore	420	0.44%	Barcelona	257	0.45%
22	Moscow	370	0.45%	Cincinnati	312	0.38%	Paris	318	0.41%	Toronto	403	0.43%	Atlanta	249	0.44%
23	Pittsburgh	345	0.42%	Phoenix	309	0.38%	St. Louis	310	0.40%	Indianapolis	365	0.39%	Phoenix	237	0.42%
24	Indianapolis	341	0.41%	St. Louis	308	0.38%	Portland	294	0.38%	Montreal	362	0.38%	Austin	217	0.38%
25	Paris	338	0.41%	**Seoul**	**306**	**0.37%**	Cleveland	292	0.37%	Portland	355	0.37%	Montreal	216	0.38%
26	Miami	338	0.41%	Buenos Aires	296	0.36%	Rochester	292	0.37%	Phoenix	354	0.37%	Portland	212	0.37%
27	Rochester	337	0.41%	Indianapolis	294	0.36%	Nashville	282	0.36%	Nashville	340	0.36%	Nashville	205	0.36%
28	Seattle	327	0.40%	Portland	285	0.35%	Columbus	280	0.36%	St. Louis	339	0.36%	Rochester	204	0.36%
29	Phoenix	312	0.38%	Cleveland	282	0.35%	Montreal	279	0.36%	Tampa	335	0.35%	St. Louis	200	0.35%
30	Nashville	308	0.37%	St. Petersburg	280	0.34%	Indianapolis	278	0.36%	Austin	331	0.35%	Indianapolis	190	0.33%

58위 - Seoul	**198**	**0.24%**

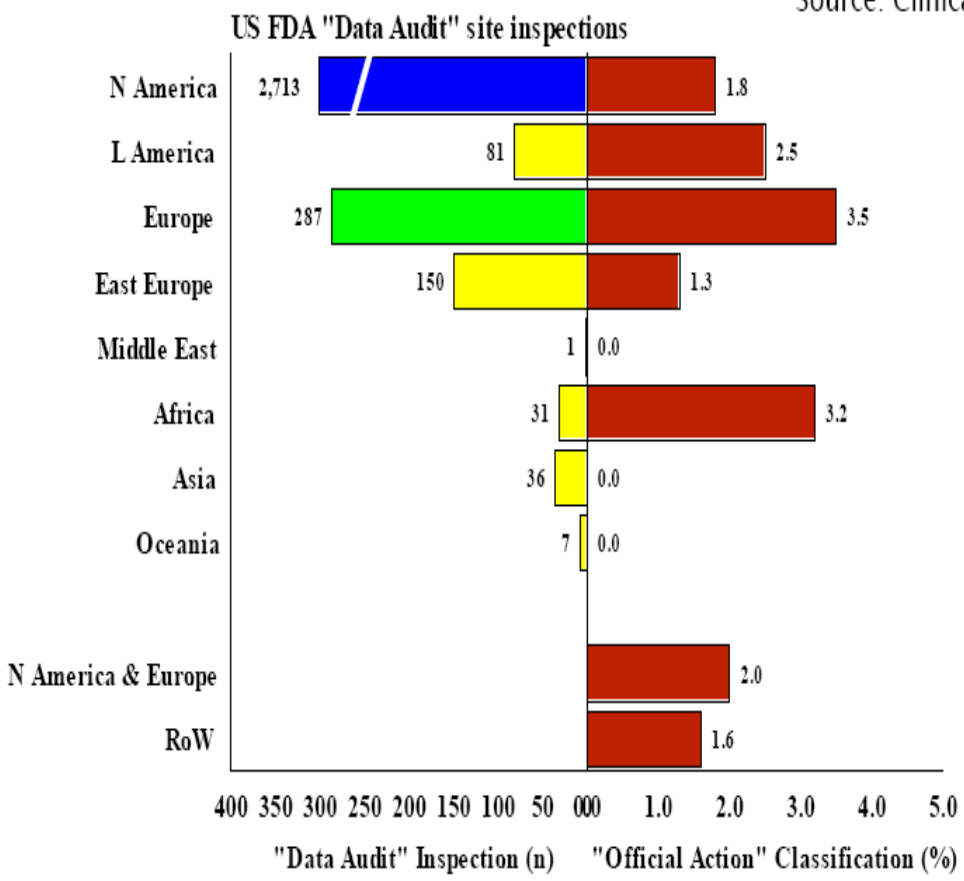
Competitiveness : Asia's growing role - Performance





DIA 2009, San Diego

Competitiveness : Performance - FDA site inspection/global



Source: Clinical Trial Magnifier Vol. 2:4 Apr 2009
www.ClinicalTrialMagnifier.com

Figure 7. Number of US FDA Data Audit site inspections between 1997 and 2008 by geographic region; the proportion of inspections classified as Official Action is also provided. Values from Table 4.

Increasing Involvement of Asia in Early Phase Trials

(2007 DIA meeting, vice president of Wyeth)

Wyeth's New Phase II Initiative

Among large international pharmaceutical companies, Wyeth is making the largest push into India. The company is planning to decrease the number of sites it works with for a typical phase II program from 50 to 100 to about 10 to 20. India will play a major part in this initiative.

Europe. "We are moving our entire clinical trial program, not just phase II but overall ratios, closer to what industry is, which is about 55% core countries, 45% rest of world. Asia Pacific we think will be about 25%, and most of that's China and India," said Maguire. Wyeth will have enrolled 500 to 1,000 subjects in their trials in India this year.

Pfizer CRS (CORE Research Sites) and GSK Center of Excellence

CORE(Center Of Research Excellence) Research Site

- Pfizer's new Strategy for Phase II projects : 50% of Phase IIs trials will be conducted at CRS sites
- 9 Institutions(Consortium) as CRS until 2010
  ▶ currently in 7 countries : US, Canada, Mexico, Poland, Argentina, South Korea (Consortium), India
- **Korea : Seoul National, Asan Medical Center, Samsung Medical Center, Yonsei Univ. (2008.5)**
- 2008 May ~ Dec : 2 Phase I and 10 Phase II trials in Korea

GSK Center of Excellence

- Therapeutic area
- 4 Institutions of Korea are involving many therapeutic area: Seoul National, Asan Medical, Yonsei Univ. Catholic Med.
- 2008 : 4 Phase Ⅰ and 8 Phase Ⅱ trials in Korea

Challenges :

CMR International September, 2005

Harmonisation

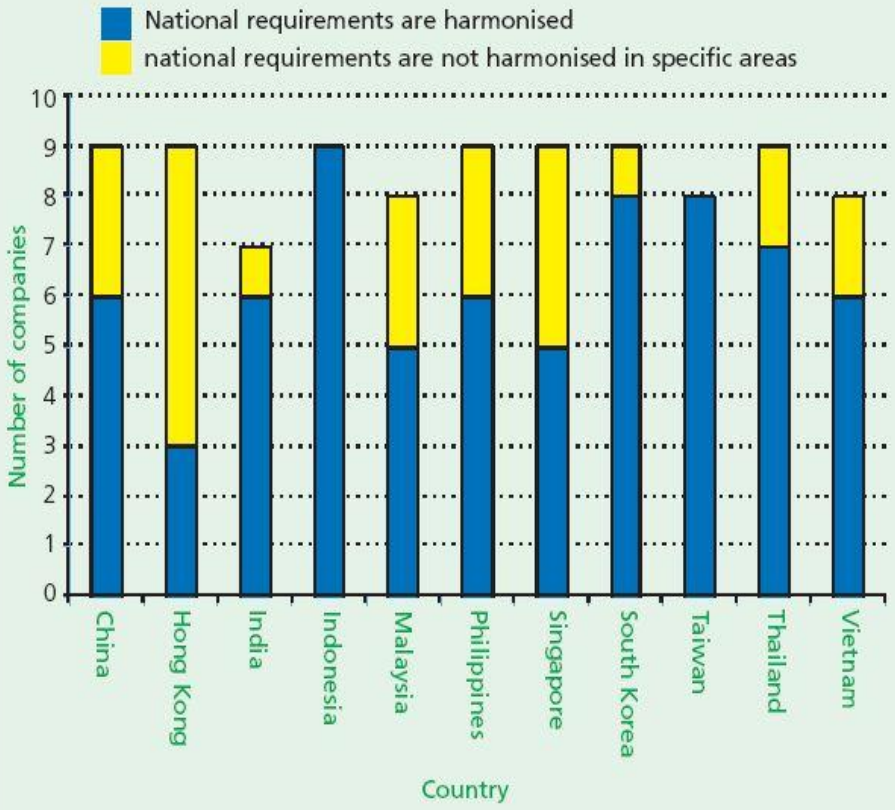
Lack of harmonisation of technical requirements for testing pharmaceutical products can lead to duplication of effort and a waste of valuable resources.

Companies were asked for their views on the extent to which national requirements, in the region, are harmonised with, or differ from, international (ICH, WHO) guidelines. The results are shown in Figure 8.

Whilst companies support the ASEAN initiatives to promote regional harmonisation this has resulted in ICH guidelines being 'adapted' rather than being 'adopted' unchanged. The divergence of technical guidelines from the international norm could lead to difficulties and delays in registering important new products in the region and act as a deterrent if companies feel that costly additional testing may be demanded.

Figure 8

Harmonisation of national requirements with international (ICH, WHO) guidelines



Challenges : Globalization Issues

- Regional variation in genetic background, standard care and social ecology
- Selection of patients in multi-regional/national trials
- **Regulatory barriers**
- **Regulatory oversight of international clinical research**
- **Training and experience of clinical investigators, human resources of clinical trial related professionals**
- **IRB / EC quality and efficiency**

N ENGL J MED 360;8 NEJM.ORG FEBRUARY 19, 2009

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Ethical and Scientific Implications of the Globalization of Clinical Research

Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D.

ETHICAL AND SCIENTIFIC QUESTIONS RAISED BY GLOBALIZATION

In our opinion, multiple approaches are needed to address concerns raised by the globalization of clinical research (Table 2). In general, the goal is to foster innovation and access to therapies while ensuring that clinical research is conducted in populations in proportion to the potential uses of the products after approval. Also, it is essential to create a robust framework to ensure the integrity of research, wherever it takes place.

European Medicines Agency

London, 5 December 2008
Doc. Ref. General-EMEA/228067/2008

EMEA strategy paper: Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications.

Doc. Ref. EMEA/CHMP/EWP/692702/2008

The current reflection paper indicates that in particular extrinsic factors, such as medical practice, disease definition and study population, may influence the applicability of foreign data to an EU setting. These factors are also identified in the ICH E5, which highlights the importance of this guideline in the planning of worldwide clinical studies. The current paper identifies specific issues based on experience specific to the EU population and should be regarded as a reinforcement of the ICH E5.

In conclusion, this paper speaks in favor of an in-depth, prospective analysis of potential extrinsic and/or intrinsic factors when conducting a clinical trial in a certain region. The outcome of such analyses may facilitate for regulatory assessors the decision whether certain clinical trials conducted in a specific area of the world are relevant to the EU setting or if there are reasons to perform additional clinical trials within the EU.

Thank you for attention