Expectations of Asian Collaboration and Contribution to New Medicines

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JPMA

Key Words for JPMA

The pharmaceutical industry contributes to improve the health and wealth of people all over the world, through the effort to develop innovative and useful pharmaceuticals, and deliver them to patients.

(http://www.jpma.or.jp)

Japan-Originated Drugs Sold Overseas (Sales over $500m)

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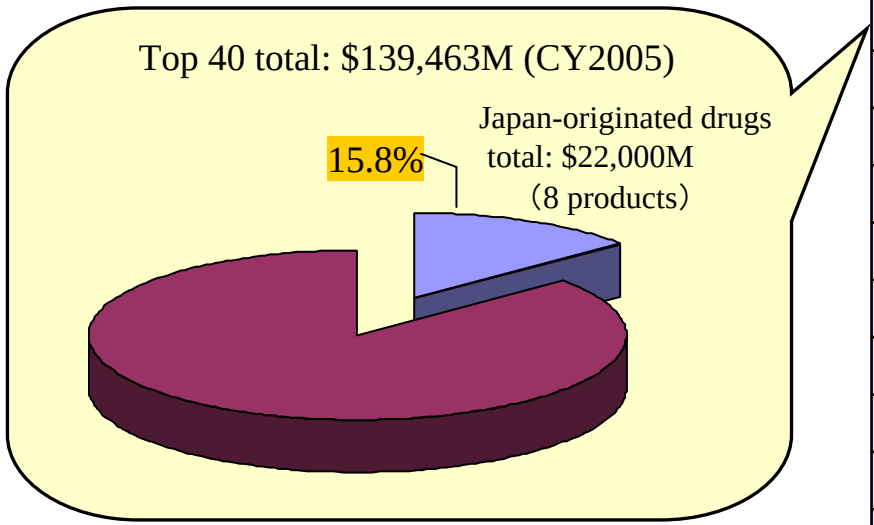
CY1997 **($m)**

Ranking	Product	Company (Developed by)	Sales
3	Mevalotin	Sankyo	2,748
8	Gaster	Yamanouchi	1,708
15	Leuplin	Takeda	1,181
29	Takepron	Takeda	857
30	Herbesser	Tanabe	848
Japan-originated Drugs Total		5	7,342

CY2003 **($m)**

Ranking	Product	Company (Developed by)	Sales
3	Takepron	Takeda	5,142
6	Mevalotin	Sankyo	4,746
26	Harnal	Yamanouchi	2,247
32	Leuplin	Takeda	1,989
33	Cravit	Daiichi	1,954
43	Actos	Takeda	1,660
44	Clarith	Taisho	1,656
47	Blopress	Takeda	1,616
54	Pariet	Eisai	1,406
58	Aricept	Eisai	1,323
82	Prograf	Fujisawa	975
86	Campto	Yakult	938
99	Gaster	Yamanouchi	827
117	Sevofrane	Maruishi	712
145	Basen	Takeda	532
149	Meropen	Sumitomo	511
150	Cefzon	Fujisawa	507
Japan-Originated Drugs Total		17	28,741



Source: Pharma Future No.163, Utobrain 2006
Reference: OPIR research paper No.23 2004.10

Trend for Clinical Trial Notification in Japan

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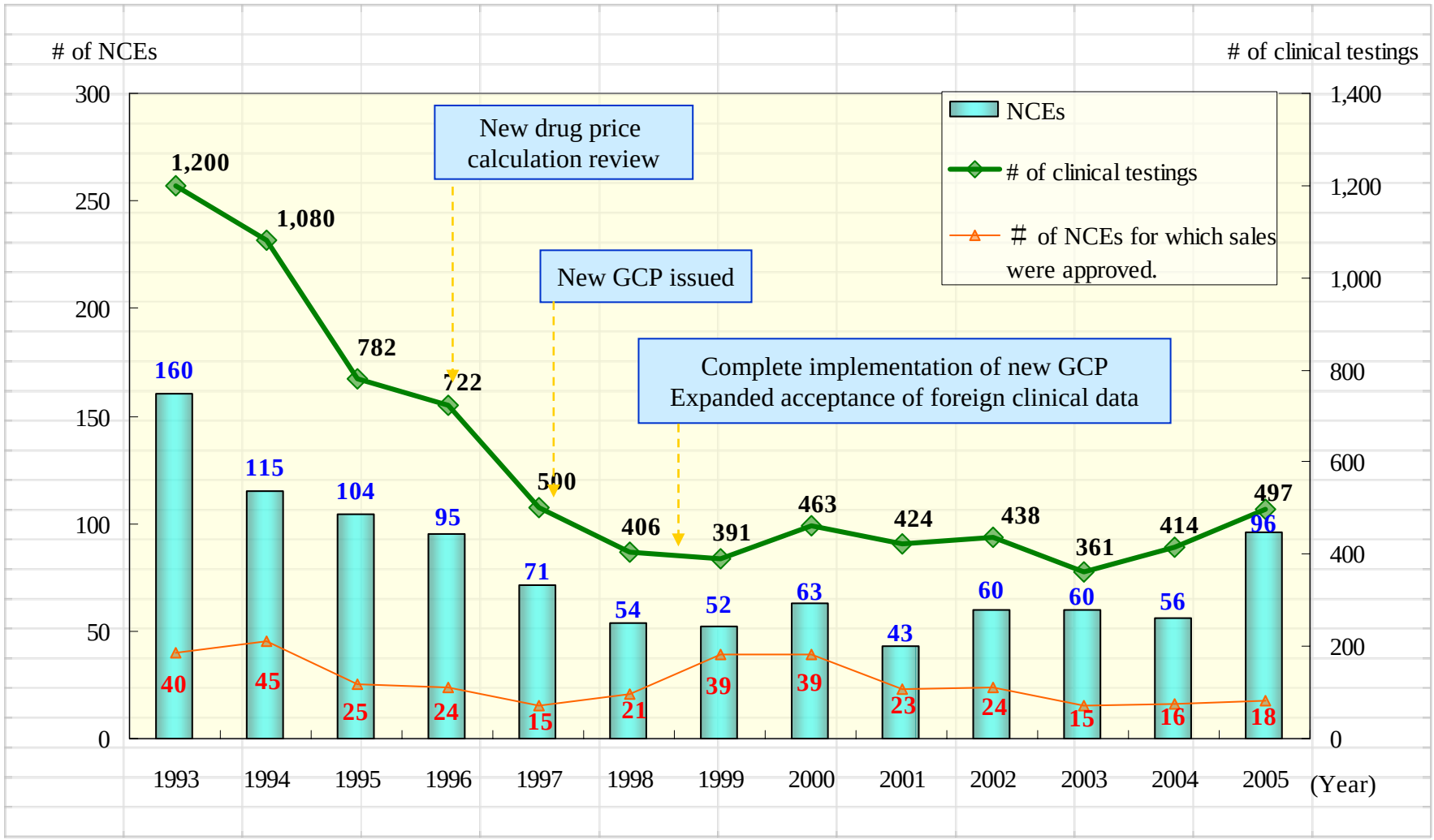
Clinical trials in Japan are declining



Source: *Yakumu Koho*

Development status of Japanese pharmaceutical companies

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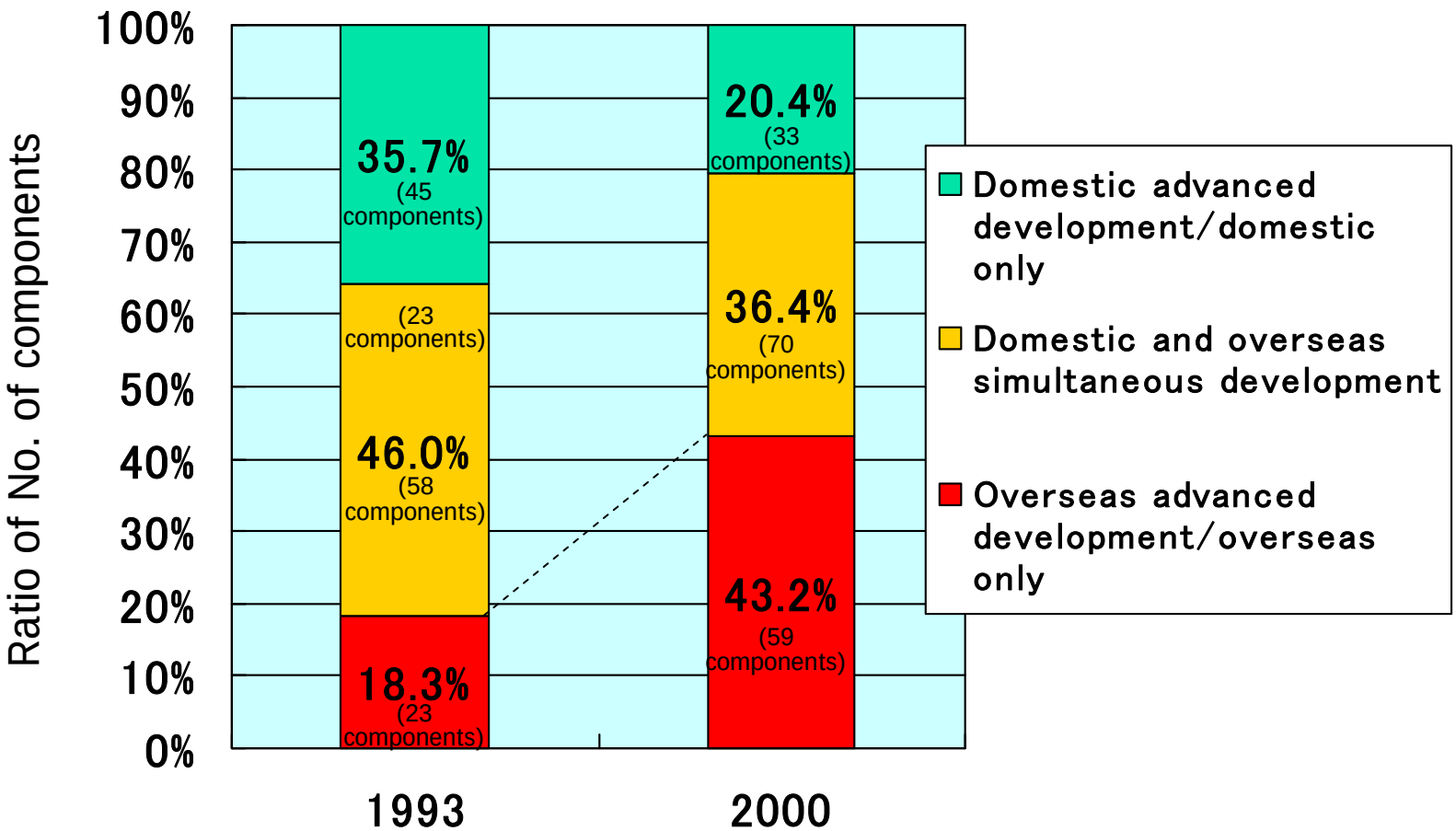
Actual status of overseas advanced development



Source: Office of pharmaceutical Industry Research, JPMA

Problems and current status of clinical trials in Japan

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Quality	**Markedly improved**	**Over-quality**
Speed	**Partially improved**	**Ads for recruiting subjects** **Contribution of CRC, SMO, CRO**
Cost	**Markedly increased**	**Abovementioned costs** **Frequent visits by CRAs**
J-GCP	**Improved very little**	

Current status of clinical trials in Asia (1)

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Patient Recruitment

Indication	Recruitment Rate (pts/site/mth)		
	Asia*	EU	US
Hepatitis B	2.4	0.3	0.3
Acute MI	4	2	2
Acute MI	2.5	2	2
Pain relief	5	2.5	3

* Except for Japan and China

Source: Quintiles Translational（partially modified）

Current status of clinical trials in Asia (2)

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Development Costs

Hypothetical protocol for treatment of patients with mild to moderate essential hypertension

		China Mainland	Korea	Chinese Taipei	**Hong Kong**	**Singapore**	Thailand	Malaysia	Japan
Costs of facilities and investigators*		0.18	0.29	0.26	0.27	0.27	0.19	0.21	1
Costs of CRO	Costs incurred before starting trial	0.24	0.27	0.27	0.23	0.23	0.24	0.27	1
	Regulation-related costs	0.48	0.27	0.16	0.16	0.14	0.17	0.18	1
	Monitoring cost	0.24	0.27	0.27	0.24	0.24	0.24	0.27	1
Total		0.22	0.28	0.26	0.25	0.25	0.21	0.23	1

Comparison estimated by a large size CRO

*In Japan, these costs correspond to clinical trial/research costs and investigator drug management cost at participating institutions.

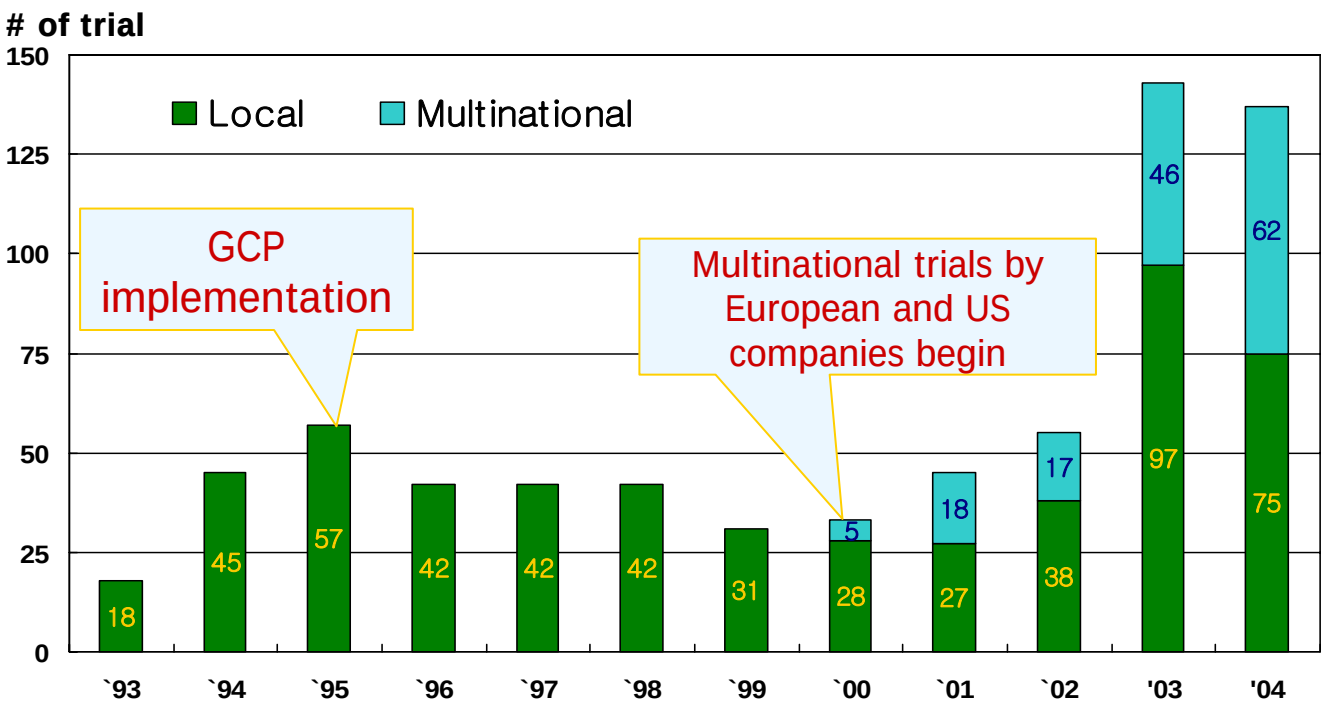
Source: Study Result by Drug Evaluation Committee, JPMA (2004)

Current status of clinical trials in Asia (3)

Trend in Korean Clinical Trial Notification & Taiwanese Clinical Trial Approval

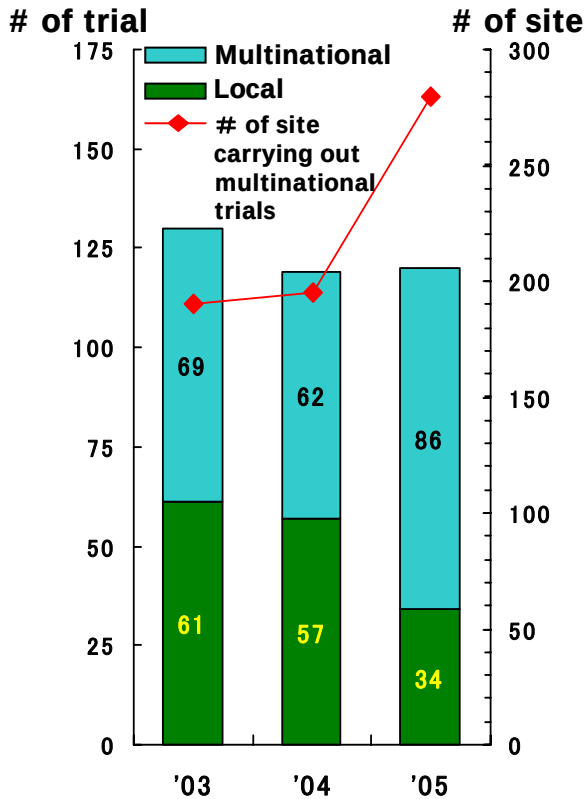
Rapid increase of clinical trials in Korea since 2003
Many multinational trials are Phase III and Phase IV

Korea



Source: KFDA Data

Chinese Taipei



Source: CDE Data, Taiwan

Results of JPMA Investigation in Asia: Fall 2004

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- Clear awareness of the pharmaceutical industry as a customer
- Key infrastructure such as Clinical facilities and Clinical Trial Centers have been established
- Multi-national CROs have expanded their business all around Asia
- Many Asian clinical sites can conduct clinical trials of good quality (inspected several times by sponsors or the FDA)
- Clinical studies characterized by fast patient recruitment with less cost
- Multi-national clinical studies have increased since introduction of ICH-GCP or domestic GCP in conformity with ICH-GCP in Asian countries following the ICH-GCP agreement in 1996

Source: Study Result by Drug Evaluation Committee, JPMA (2004)

Situations of key medical institutions involved with clinical researches and trials in the U.S., South Korea and Chinese Taipei

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	Core Center	Clinical Research / Trial Center
U.S.	NIH clinical center	GCRC / CRC Approx. 80 facilities
South Korea	Clinical research centers 9→15 facilities (up to '14)	Accredited clinical trial centers 109 facilities
Chinese Taipei	General clinical research centers 15 facilities	Qualified hospitals 134 facilities

Stagnation of Clinical Research Activities in Japan

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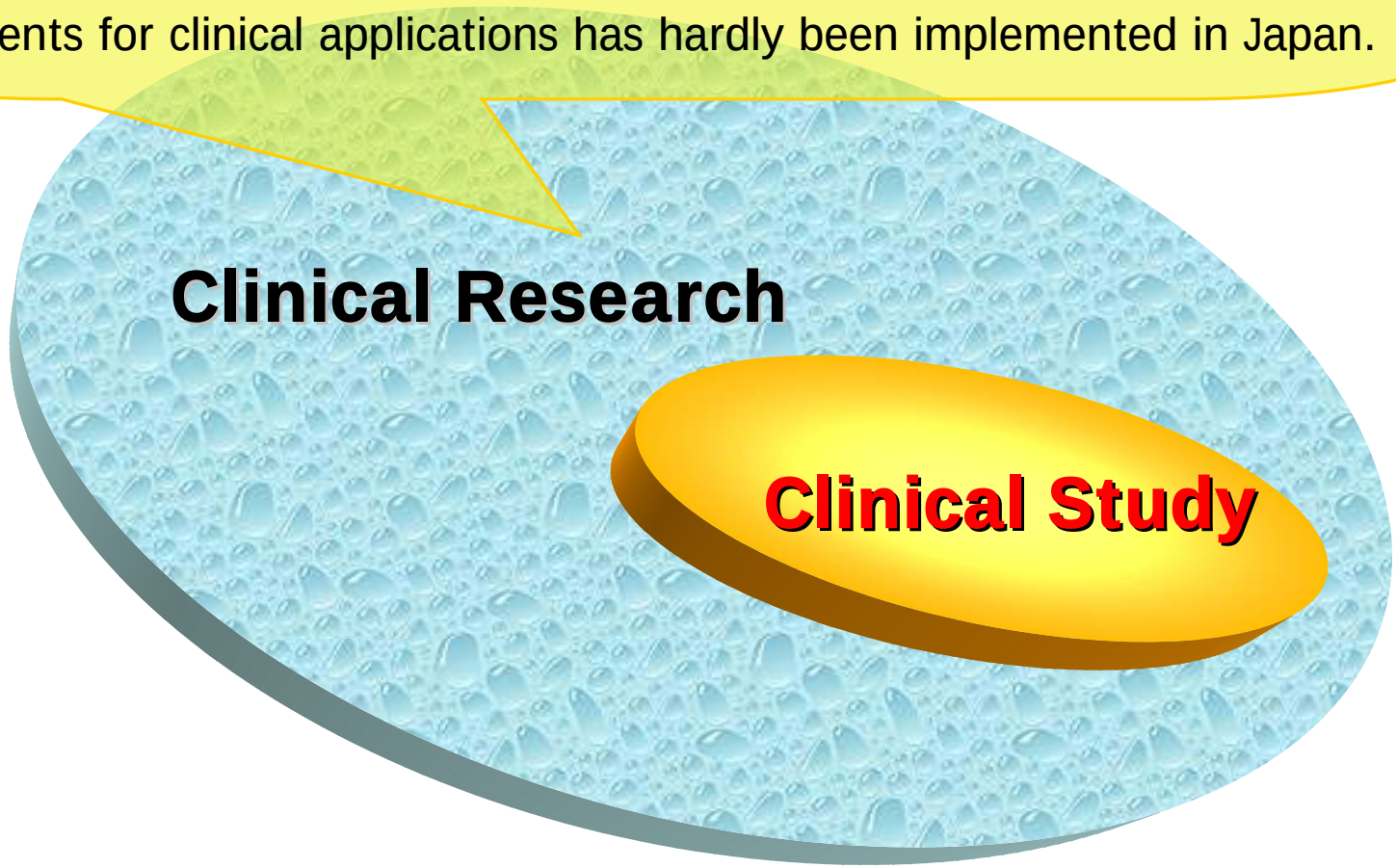
Current situation in Japan:

Due to the lack of an appropriate infrastructure for clinical research, clinical research of high quality aimed to develop new diagnoses and treatments for clinical applications has hardly been implemented in Japan.



Administrative initiatives to improve the clinical trial environment in Japan:
- Major initiatives -

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- **3 Year Plan for Clinical Trial Activation:**
  FY2003～2005
  MHLW, MECSST

- **Planning for Next Clinical Trial Activation :**
  Including Clinical Research Infrastructure Improvement
  FY2006
  MHLW, MECSST

- **Clinical Research Infrastructure Improvement Plan:**
  FY2006～2008
  MHLW

Ethnic Similarity in Asia (1)

Distribution of HBV genotype

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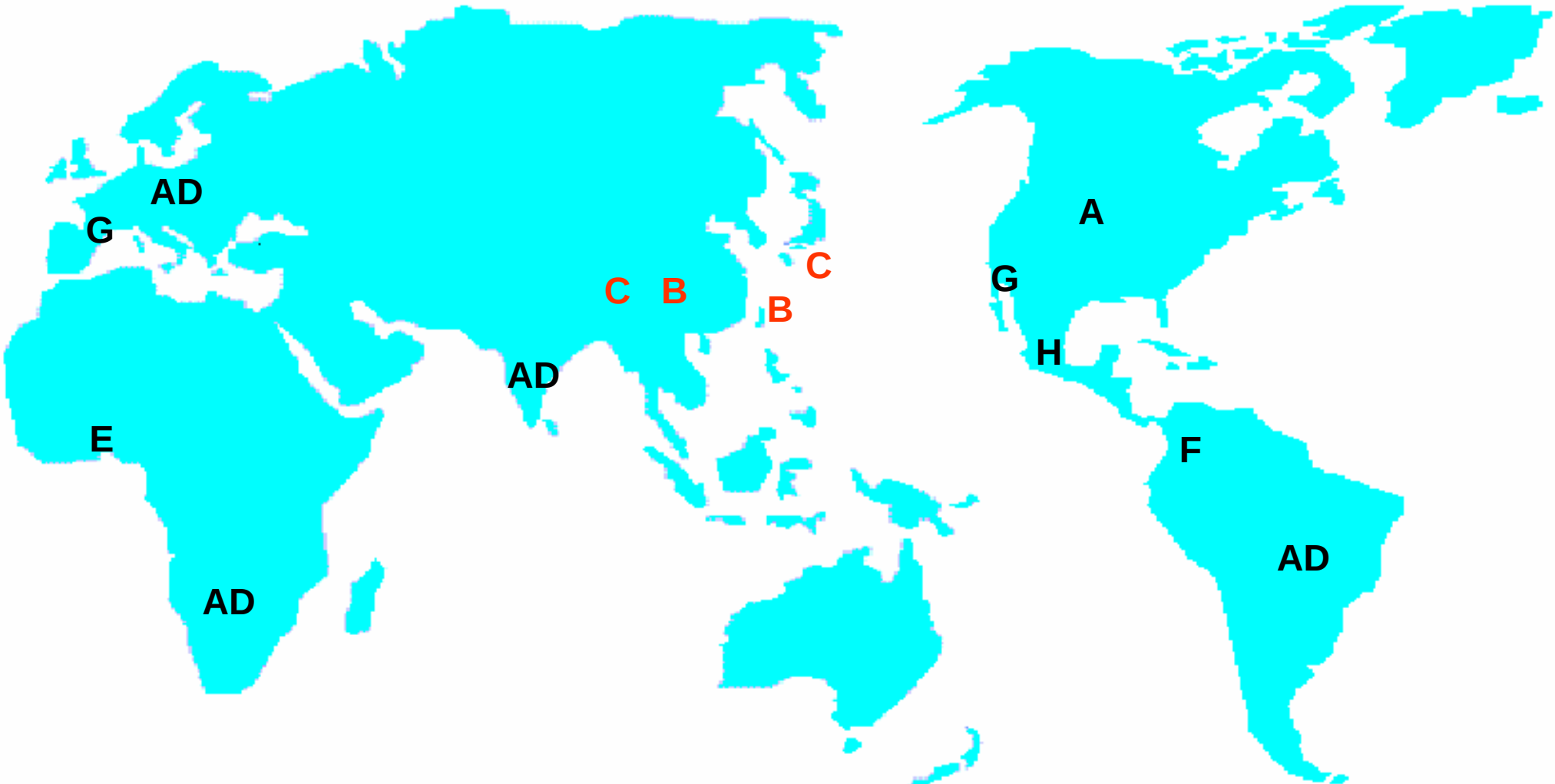

Source: KAN･TAN･SUI 49(4): 425–430 (2004) (modified)

Ethnic Similarity in Asia (2)

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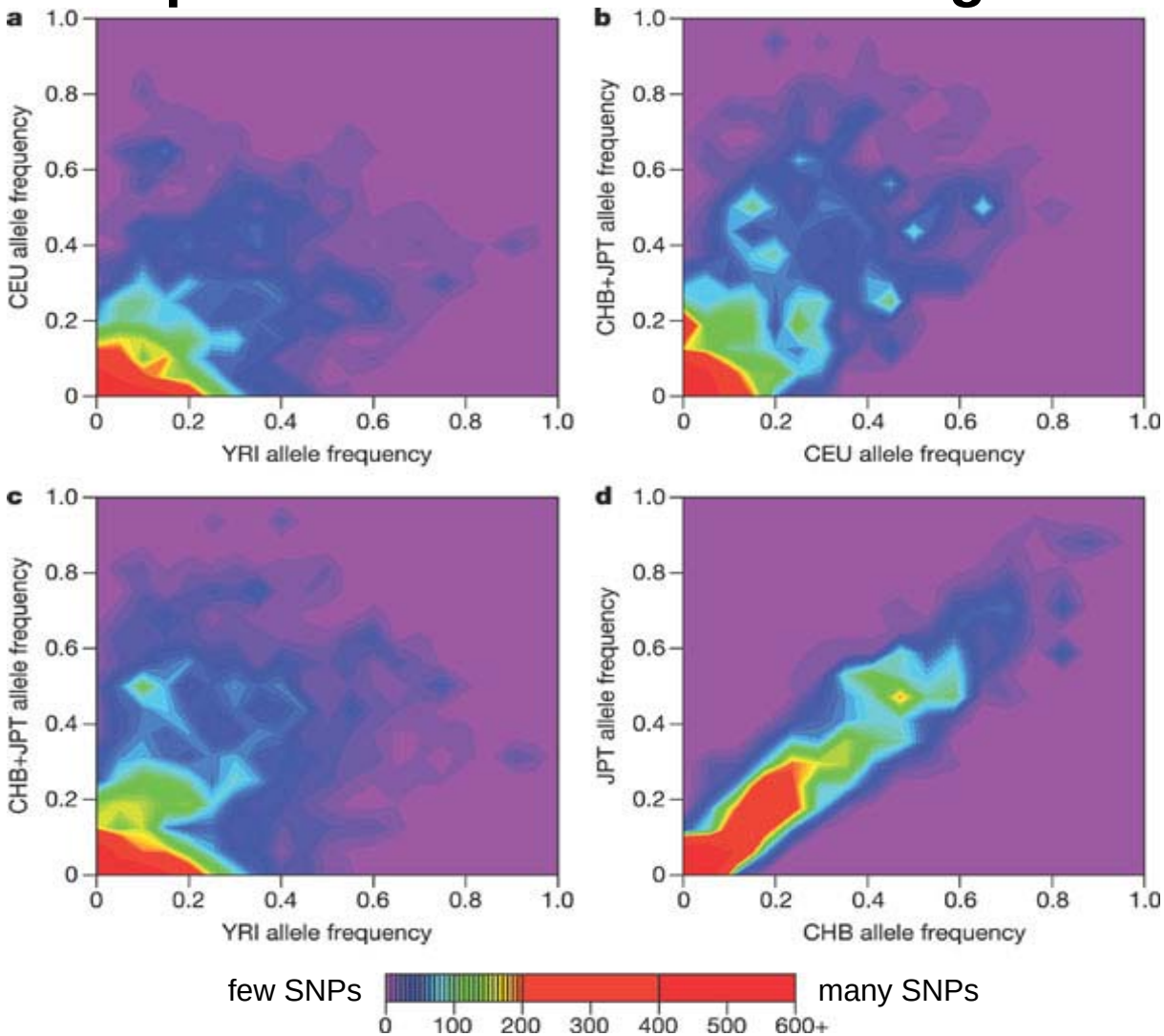
Comparison in terms of human genomes



Source: Nature 437, 1300-1320(2005)

Ethnic Similarity in Asia (3)

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Height & Weight

		Male		Female	
		Height	Weight	Height	Weight
Chinese	Adult	169.7cm	67.7kg	158.6cm	59.6kg
Japanese	40's	169.3cm	68.2kg	155.7cm	54.5kg
	50's	165.7cm	64.6kg	153.0cm	54.6kg

Life expectancy

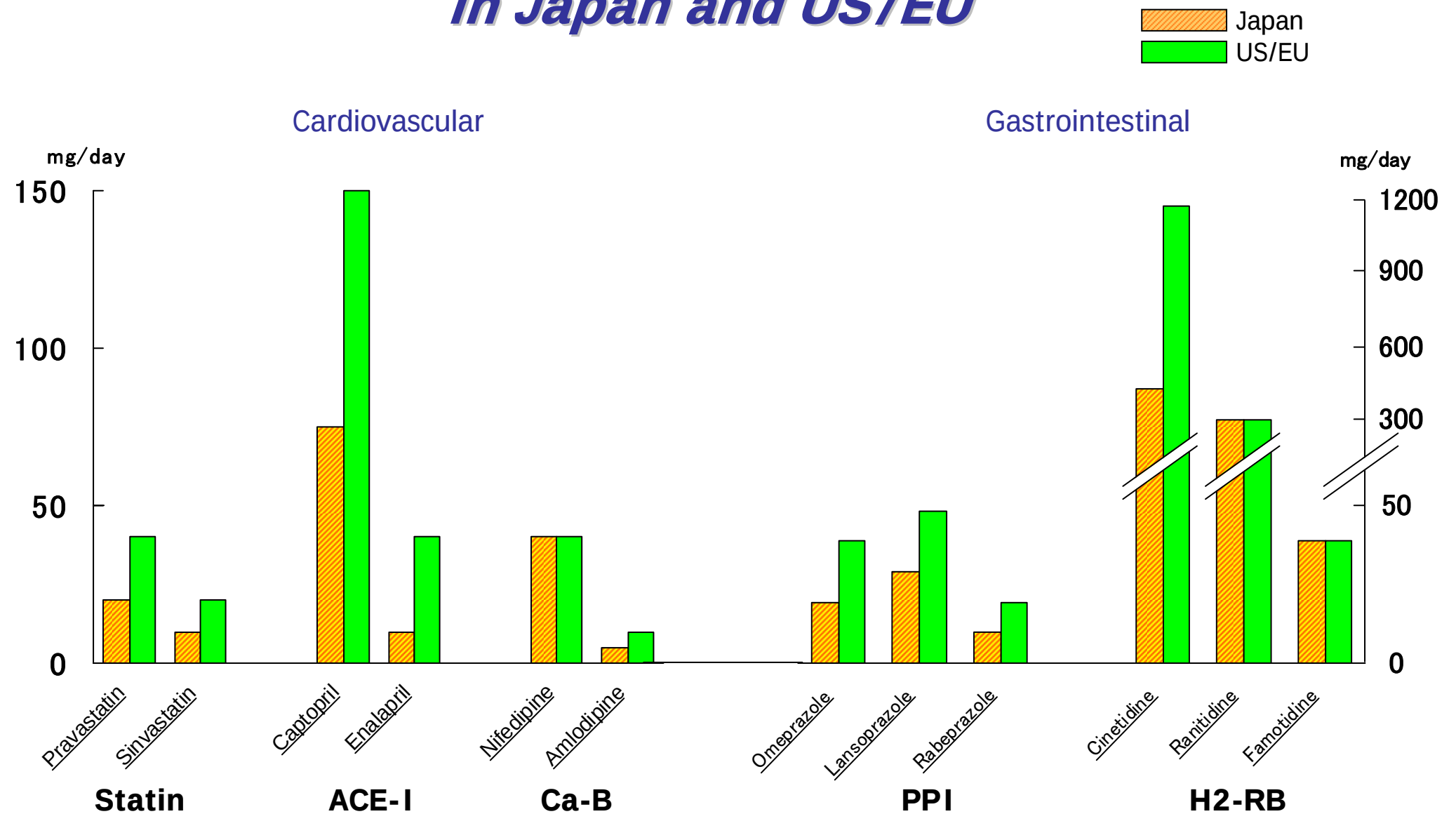
Japan		Hong Kong	
Male	Female	Male	Female
77.6	84.6	78.0	83.9

Cause of death

	1	2	3	4	5
Hong Kong	Cancer (33.0%)	Heart disease (16.3%)	Brain disease (10.5%)	Pneumonia (8.9%)	Sudden accident/ Poisoning (5.6%)
Japan	Cancer (31.0%)	Heart disease (15.3%)	Brain disease (13.6%)	Pneumonia (8.8%)	Sudden accident (4.1%)

Source: J.Clin.Therap.Med. 22, 597-606 (2006)

Comparison of Max. Daily Doses in Japan and US/EU



Differences in views on optimal doses between Japan and Europe/US

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Using Captopril as an example

1971 Separated teprotide (nonapeptide) from snake toxin and synthesized it

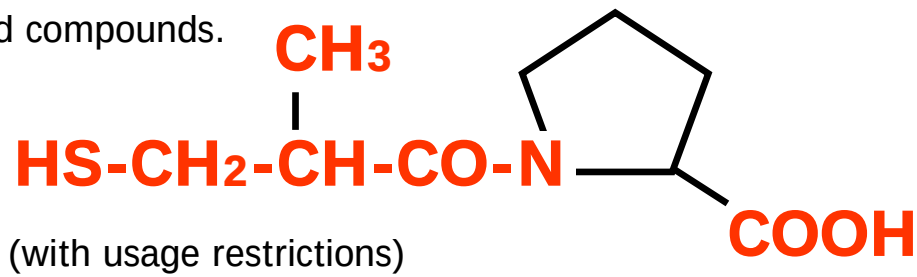
Pyr-Trp-Prp-Arg-Pro-Gln-Ile-Pro-Pro

1973 Administered teprotide intravenously to healthy people and hypertension patients

1973 Launched R&D of oral ACE-I

1974 Discovered lead compounds

1975 Synthesized captopril. Succeeded in optimizing lead compounds.



1977 Clinical trial of captopril

1981 Squibb: Obtained approval as a hypotensive agent (with usage restrictions)

1982 Sankyo: Obtained approval as a hypotensive agent (no usage restrictions)

1985 Squibb: Usage restrictions are lifted

~ 150 mg ~ 75 mg ~ 37.5 mg ~

└ High incidence of adverse drug reactions

└ Usage restrictions

Source: Jap.J. Pharmacol 125, 104-106 (2003)

Views on optimal dosage: Image

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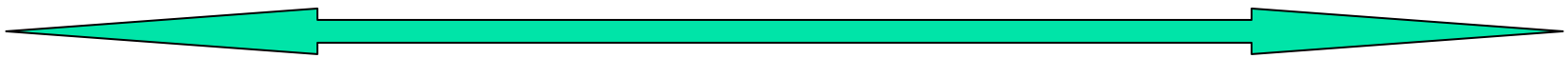
Other countries in Asia

South Korea Chinese Taipei

Japan



Accept doses used in Europe and the US

Seek doses suited to own country
Rigorous process to determine optimal dosage

It's about time we begin considering doses suited for us

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The Purpose of ICH

- Ensure a more timely introduction of new medicinal products to patients
- Contribute to the protection of public health
- Lead to a greater mutual acceptance of research and development
  to reduce and obviate the need for duplicate testing
- Maintain safeguards on quality, safety and efficacy

Source: ICH website (modified)

The Situation of Clinical Trials in Asia

- **Quality : ICH-GCP**
- **Speed**
- **Cost**
- **Ethnic Similarity**

⇨ **It is natural for Asian countries to collaborate.**

Role of Early Clinical Trials

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- Comprehensive clinical assessment for establishment of a late clinical trial plan
  - Tolerability, safety and pharmacokinetics
  - Effects of meals and drug interactions
  - Evaluation of the efficacy and therapeutic doses
- Determinants for a global development strategy
  - Evaluation of the similarity between Japanese and non-Japanese in terms of tolerability, safety and pharmacokinetics

    → global cooperative trials or regional trials
- Selection of projects with a high probability of success

→ Important stage for development strategy and investment decisions

The aim is to enable implementation of early clinical trials in Asia under the same strategy.

Problems for Japan's in collaborating with Asia

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Clinical trial

- J-GCP different from ICH-GCP: Essential documents, contracts, safety information, reliability survey, management
- Small number of patients enrolled for each site
- Distinct safety assessment method
- Rigorous views on optimal dosage

Scientific advice

- Not implemented in a timely manner

→

- **There are numerous problems that must be actively resolved in order for Japan to participate**
- **Actively promote country -country dialogues in Asia**

Promote approach to collaboration and mutual acceptance in Asia

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- **Clinical data for NDA : acceptance**
- **GCP inspection : acceptance, recognition (MOU)**
- **P-IV study : usage, acceptance**

Aim at attaining even more comprehensive mutual acceptance in the future

So as to efficiently provide new therapeutic means to citizens of various countries

Existence of Unmet Medical Needs

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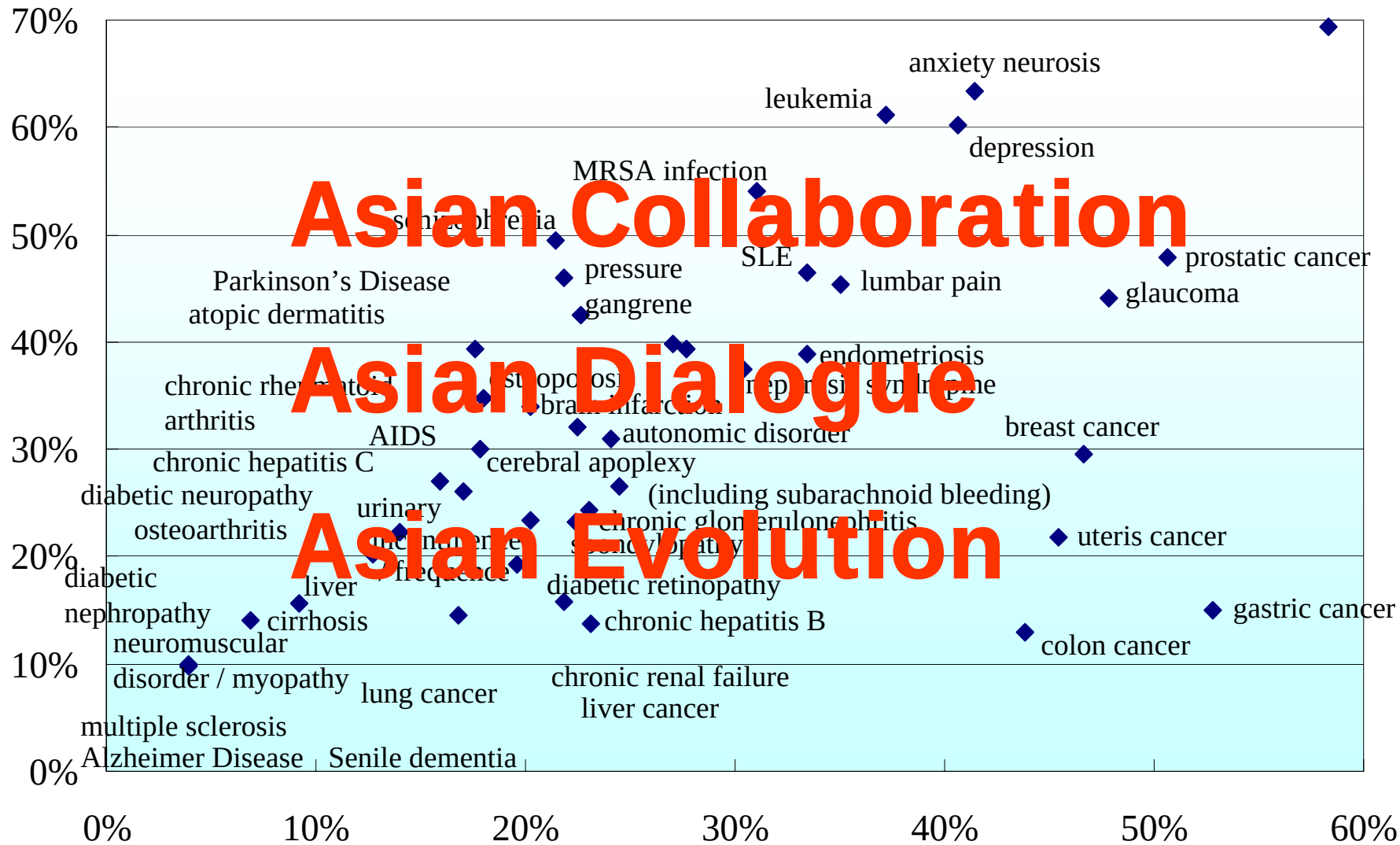

Subject: Doctors (128 responses)

Source: Japan Health Sciences Foundation: Domestic Fundamental Technology Research Report – Medical Needs Outlook in 2010 (2000)