Strengthening cooperation with Indonesia and among ASIA

– highlighting Multi Regional Clinical Trials (MRCT) –

(Pharmaceuticals and Medical Devices Agency)

Why do we need to promote international cooperation ?

Globalization of Pharmaceuticals:
Drug development, Manufacturing, Marketing,
Safety information

Regulatory challenges:
Goal: to promote / protect our people's health
under the borderless situation
A regulatory agency can cover all task?

international cooperation

Overall Goal: from "For our people" to
"For world people"

Indonesia - Japan

インドネシアは日本の真の友人

WAWANCARA KHUSUS

PM Abe: Indonesia Sahabat Sejati Jepang

JAKARTA, KOMPAS — Indonesia menjadi satu dari tiga negara di Asia Tenggara yang dikunjungi Perdana Menteri Jepang Shinzo Abe dalam rangkaian kunjungan pertamanya ke luar negeri sejak dilantik pada Desember 2012. Abe dijadwalkan tiba di Jakarta, Jumat (18/1) ini, dan akan bertemu dengan Presiden Susilo Bambang Yudhoyono.

Kompas mendapat kesempatan mewawancarai PM Abe secara tertulis sebelum kunjungannya tersebut:

Apa arti penting kawasan Asia Tenggara, khususnya Indonesia, bagi Jepang?

AFP

Shinzo Abe

amanan, khususnya dengan negara-negara ASEAN yang diprediksi menjadi sebuah komunitas ekonomi besar, sangatlah esensial demi kestabilan dan kesejahteraan seluruh kawasan ini.

Kunjungan ke Asia Tenggara kali ini bertujuan memperdalam hubungan dengan negara-negara

kontribusi bagi perkembangan Indonesia dengan memanfaatkan teknologi tinggi dan kebudayaan unik yang merupakan "kekuatan Jepang" dan "ke-Jepang-an", agar dapat membawa kedua hal ini pada pertumbuhan ekonomi kedua negara kita. Saya tak berhenti berharap, investas

Kompass,
Jan. 18, 2013

Prime Minister Abe visited Indonesia in his first oversea trip.

◘ PMDA International Strategic Plan (February, 2009)

1. Strengthening of cooperation and building of collaborative relations with the United States (US), the European Union (EU), Asian countries, and relevant international organizations

◘ PMDA International vision (November 2011)

PMDA EPOCH TOWARD 2020

a. Secure the highest level ***E***xcellence in ***P***erformance

b. Maintain close ***P***artnership with the ***O***rient for common benefits

- Cooperation to improve the level of medical products regulation across Asia
- Communication of information and opinions to the world as a member of the Asian community

・・・・・ to concentrate on partnering with the countries in East Asia (China and South Korea) and Southeast Asia (such as Indonesia) for the time being.

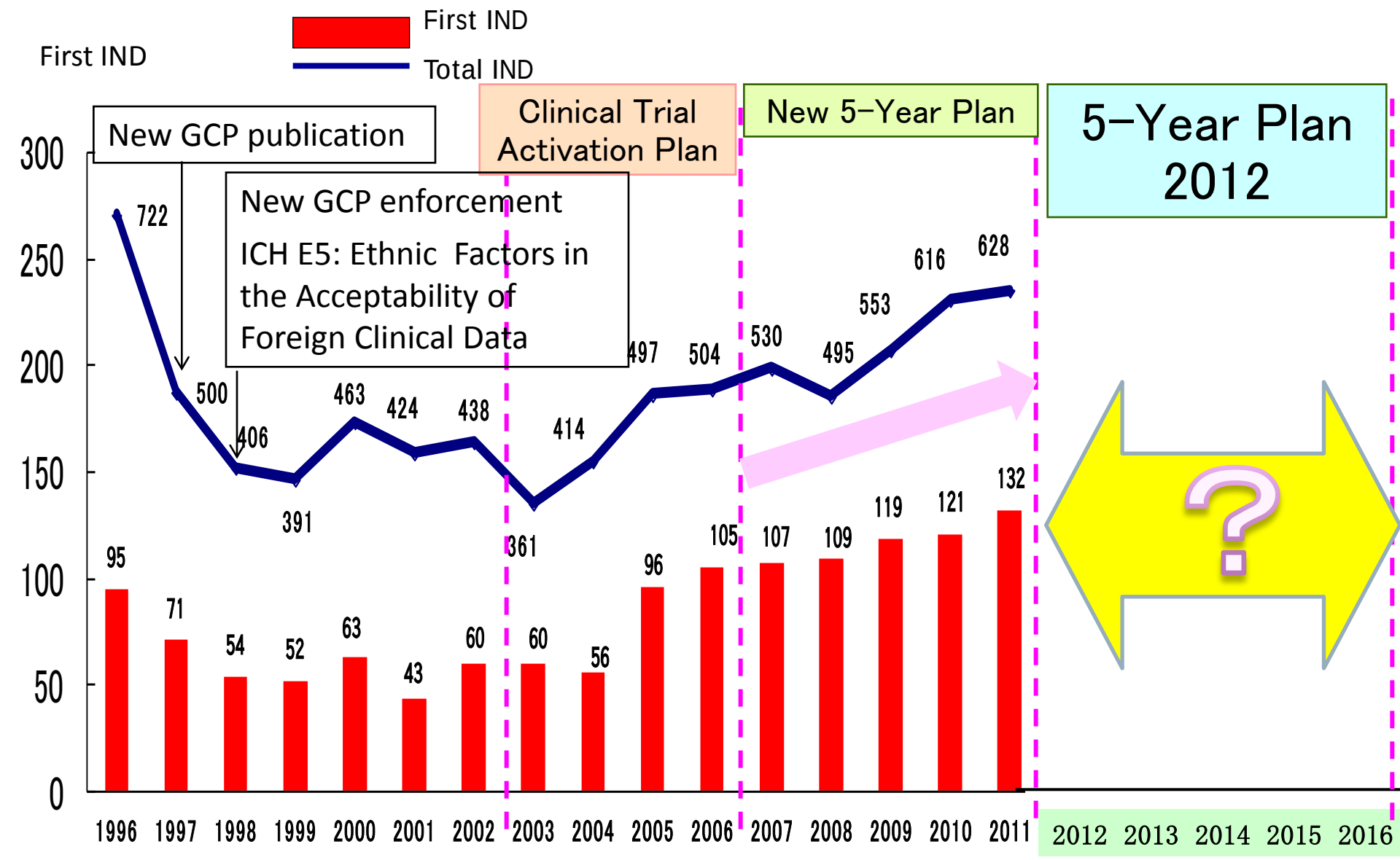
c. Actively ***C***ontribute to International Regulatory ***H***armonization

Background & Challenges to promote MRCT?

1. Background
- To provide patients with innovative drugs rapidly
- To collect clinical data efficiently

2. Challenges
- To improve circumstances to conduct Clinical trial
- To design MRCT whose data can be utilized by regulatory authorities
- To promote international cooperation

Number of IND Notifications in Japan



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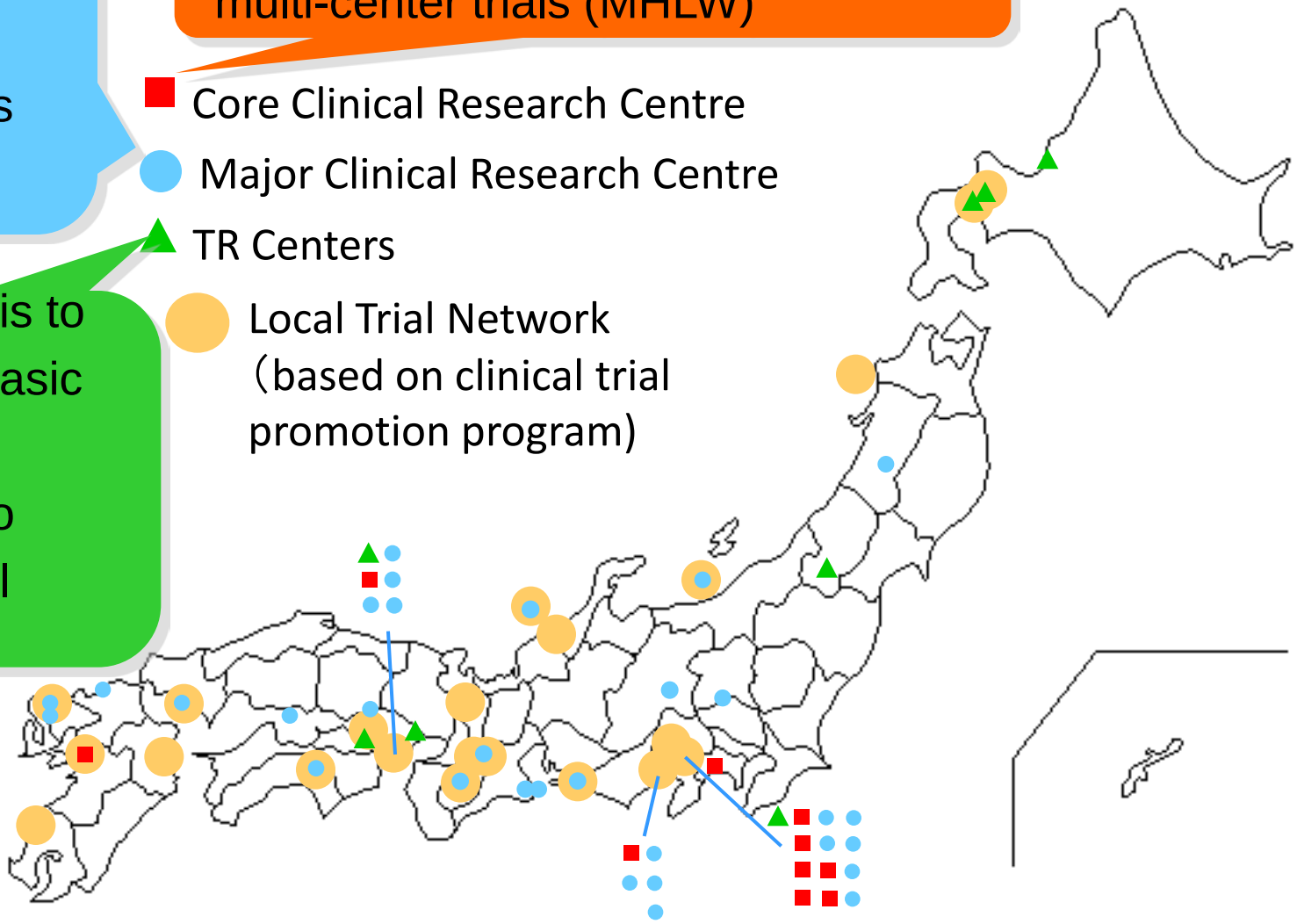
Nation-wide network of TR/clinical trial centers

MCRC is a center to smoothly perform trials (MHLW)

CCRC is able to plan and manage multi-center trials (MHLW)

TR center is to translate basic medical research to clinical trial (MEXT)

- Core Clinical Research Centre
- Major Clinical Research Centre
- TR Centers
- Local Trial Network (based on clinical trial promotion program)



Public Promotion of Clinical Trial and Encouraging Participation
-Japan Primary Registries Network(JPRN)-

http://www.mhlw.go.jp/topics/bukyoku/isei/chiken/index.html

Since Oct.2007

Public

1. Keep public well informed
2. Avoid publication bias
3. Utilize negative data
4. Promote subject recruitment

WHO-ICTRP

MHLW

- Promotion
- Regulation and guidance

National Institute of Public Health
Search Portal Site

- Portal site management
- Promotion
- Coordination with 3 sites of clinical trial registry
- coordination with WHO-ICTRP

JPRN

UMIN
Clinical Trial Registry

- System management
- investigator initiated trials
- Promotion

http://www.umin.ac.jp/ctr/index-j.htm

JMA
Centre for Clinical Trials

- Sponsor-investigator trials
- Promotion

https://dbcentre2.jmacct.med.or.jp/ctrialr/

JAPIC
Trial Information System

- System management
- Company initiated trials
- Promotion

http://www.clinicaltrials.jp/user/cte_main.jsp

Investigator or company

5-Year Clinical Trials Vitalization Plan 2012

March 30, 2012 MEXT / MHLW

1. **Further leap and independence of clinical trial sites based on the past 9 years' activation plan**

2. **Measures toward the creation of innovative drugs, medical devices etc. originating in Japan (Innovation)**

Creation of Early-Stage and Exploratory Clinical Trial Centers

(FY2011-2015)

Goal: Perform world-leading clinical trials to create innovative drugs and medical devices originating in Japan

Basic research → Pre-clinical → **Early-stage development** → Late-stage development → Application

Support this stage

Create infrastructure for FIH and POC clinical trials in key areas

Subsidy: JPY510M (approx. $6.38M) / year/ center

<Example of key areas>
- Oncology
- Neurology, Psychiatry
- Cardiovascular Diseases

- Experienced investigators, CRCs and other staff
- Capacity to cope with unexpected SAEs
- Necessary diagnostic equipment etc.

Conduct FIH and POC studies as investigator-initiated CTs

Research grant: JPY150M (approx. $1.88M) / year/ center

Support the cost for:
- Study drug manufacturing (GMP compliant)
- Protocol drafting
- Data management
- PMDA's consultation (R&D Strategy, CTs)

etc.

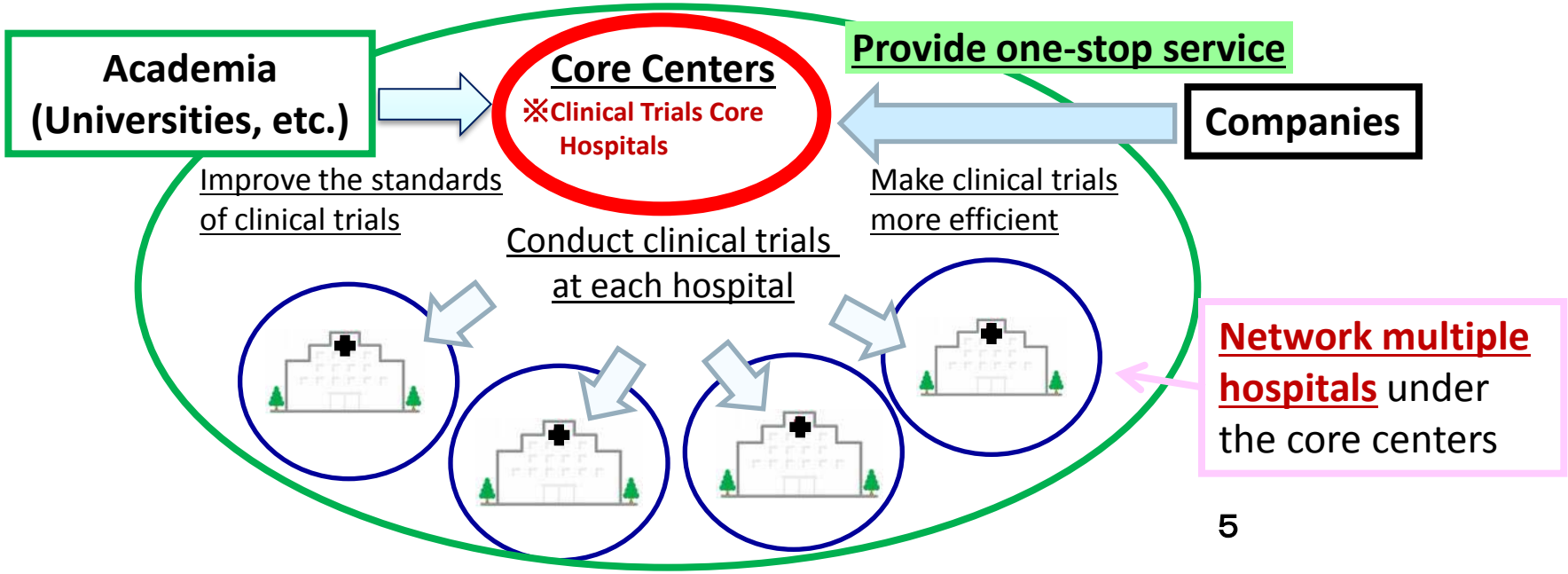
Accelerate development with infrastructure subsidy and research grant

MHLW's Efforts to Promote Medical Innovation

Creation of Clinical Trials Core Hospitals

【 Actions Taken by MHLW 】

- **Set up the core centers, such as Clinical Trials Core Hospitals**
- **Network a multiple number of hospitals** under the core centers
- **Provide one-stop service for clinical trial sponsors**
- **Actively conduct clinical trials for intractable diseases etc.**



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Background & Challenges to promote MRCT?

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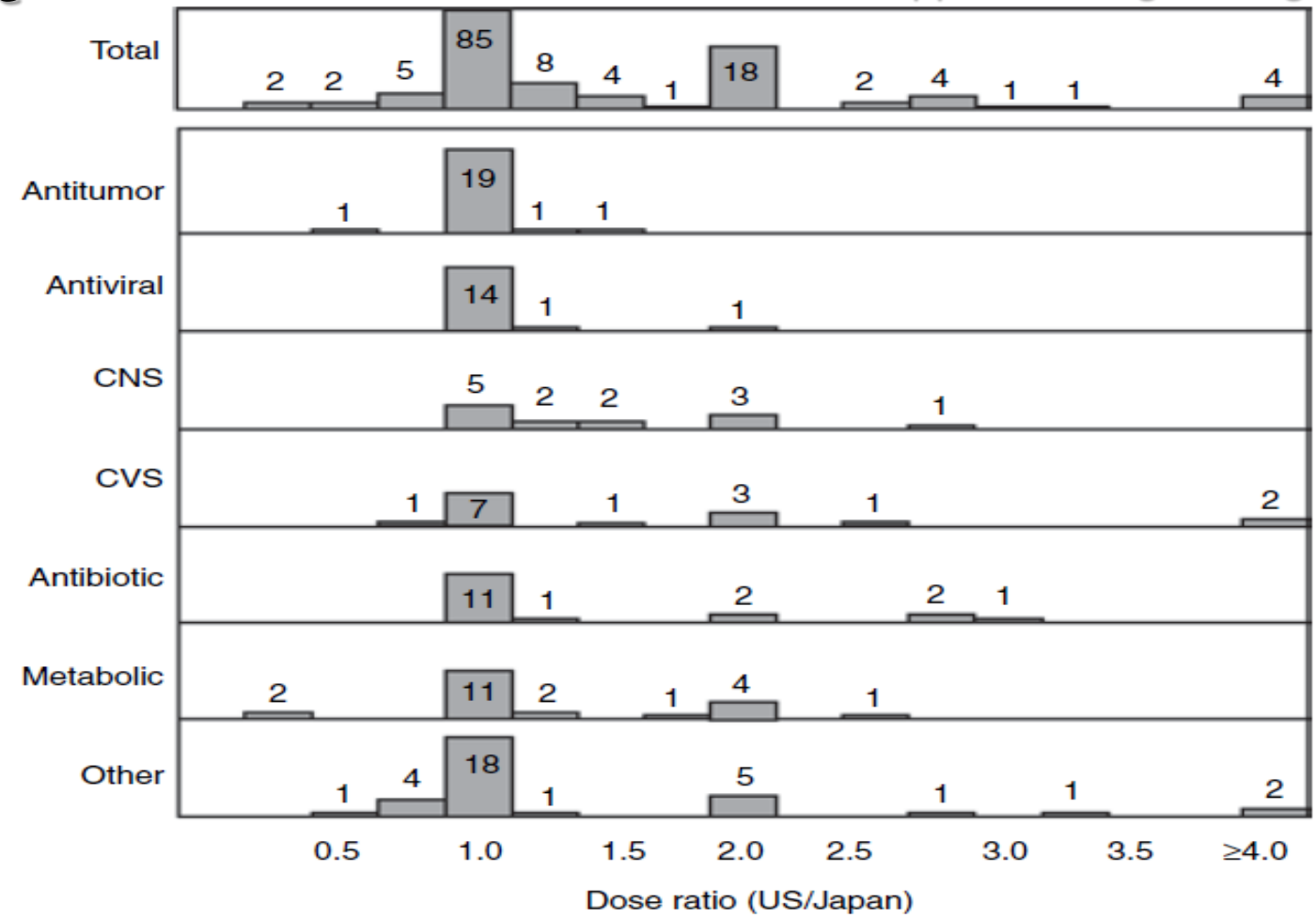
   - To promote international cooperation

Dose difference by region

For 32 % of drugs, US/EU dose was ≥ 2 times higher than Japanese dose

Approved drugs during 2001-2007



Arnold FL et al., Clin Pharmaco Therapeut., 87: 714-720, 2010

Japanese have higher risks of drug-induced Interstitial lung disease (ILD) than foreign population

Table 2 Comparison of the incidence rates of drug-induced lung disease in Japan and abroad

	Japan	Overseas
Gefitinib	3.98% (4,473 Japanese cases, AstraZeneca's cohort study)	0.3% (23,000 US cases, FDA Approval Letter)
Leflunomide	1.81% (3,867 Japanese cases)	0.017% (861,860 overseas cases)
Bleomycin	0.66% (3,772 Japanese cases)	0.01% (295,800 global cases)

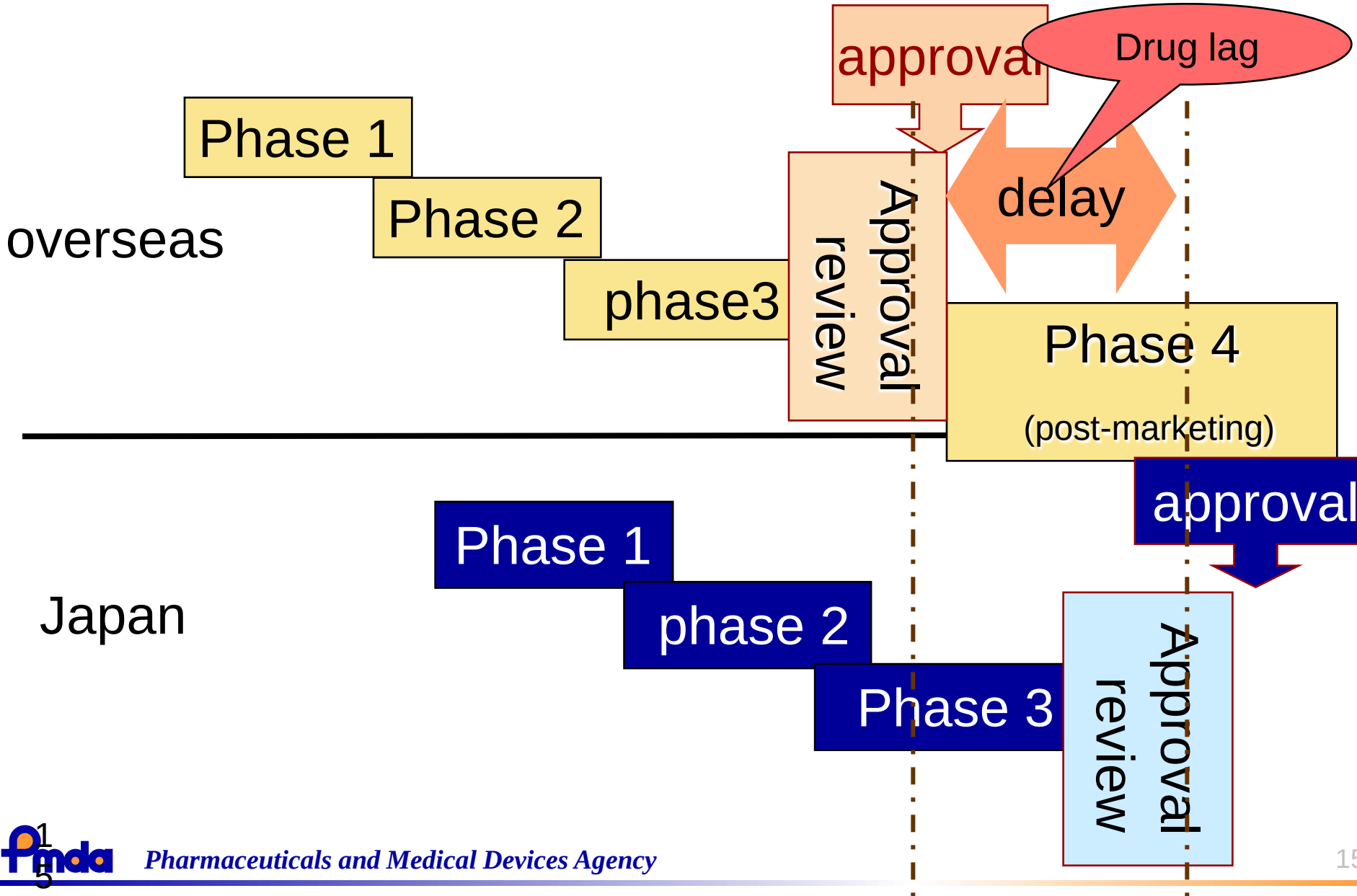
The incidence rate is markedly higher in Japan than abroad for any of the causative agents.

Azuma A, Japan Med Associate J, 50: 405-411, 2007

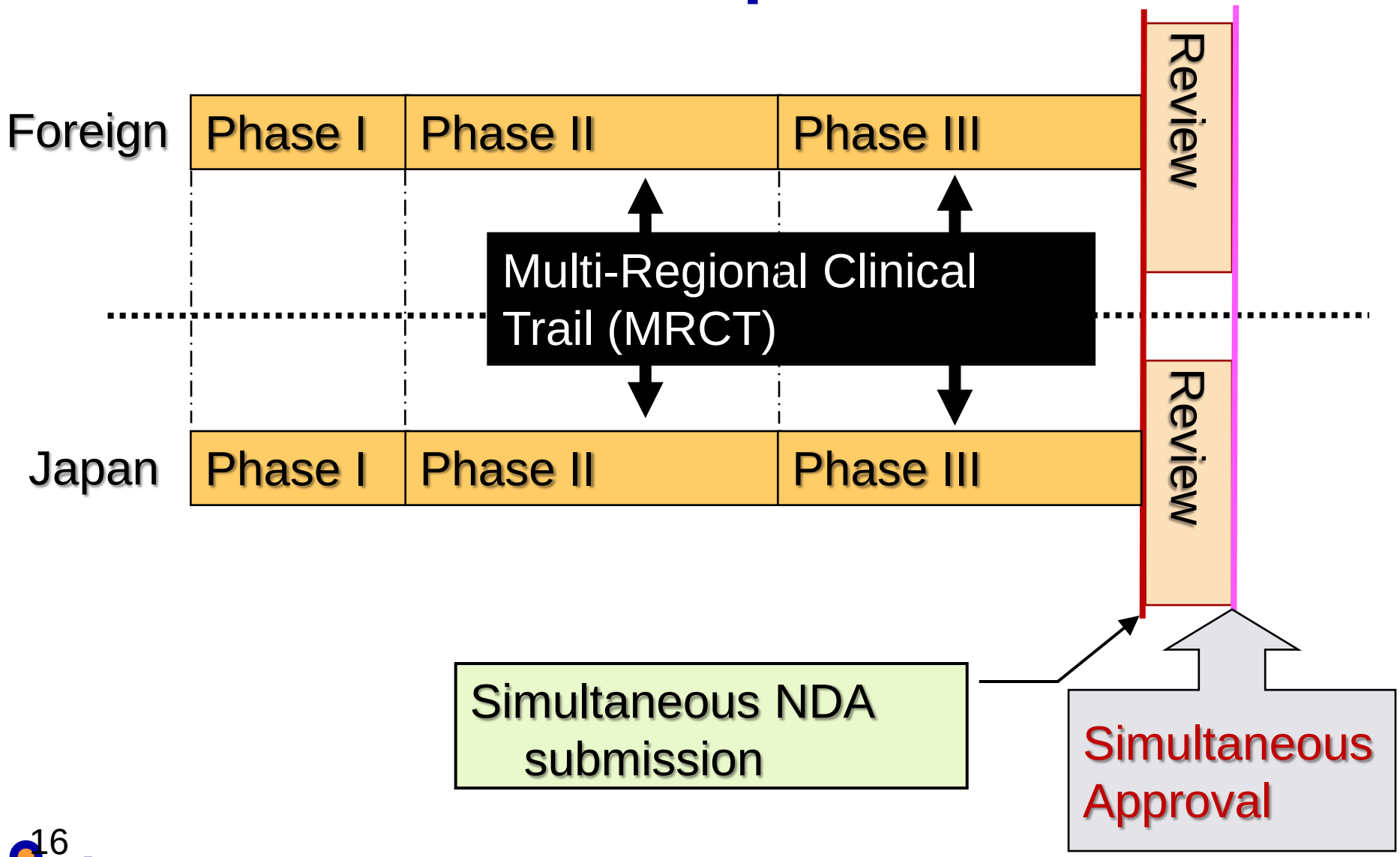
Serious cases of ILD have been reported.
5 death cases in 3 month after launch.
16 ILD cases in 3412 patients enrolled in the survey

"Box Warning" in the label were revised to increase the precaution level about ILD

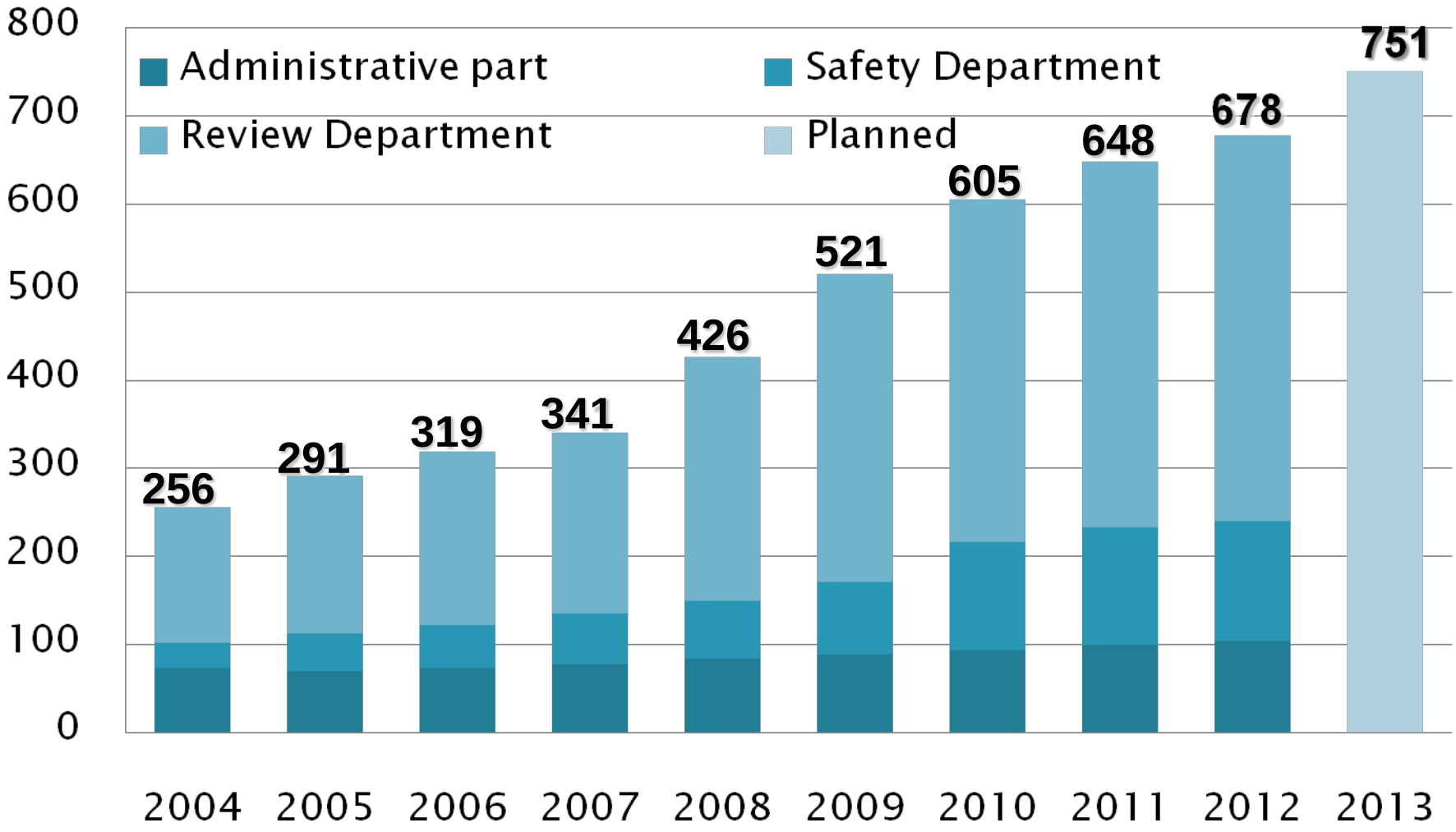
Should all data be obtained domestically?



Simultaneous Global Drug Development



PMDA Staff Size



Median Total Review Time for New Drugs

		2007	2008	2009	2010	2011
Standard	Target (month)	–	–	19	16	12
	Result (month)	20.7	22.0	19.2	14.7	11.5
Priority	Target (month)	–	–	11	10	9
	Result (month)	12.3	15.4	11.9	9.2	6.5

Guidance: Basic Principles On Global Clinical Trials

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

Describe basic principles for global clinical trials including Japan at the present time.

－One of Key Messages－

- Promote to conduct global clinical trials more appropriately in consideration of ethnic factors

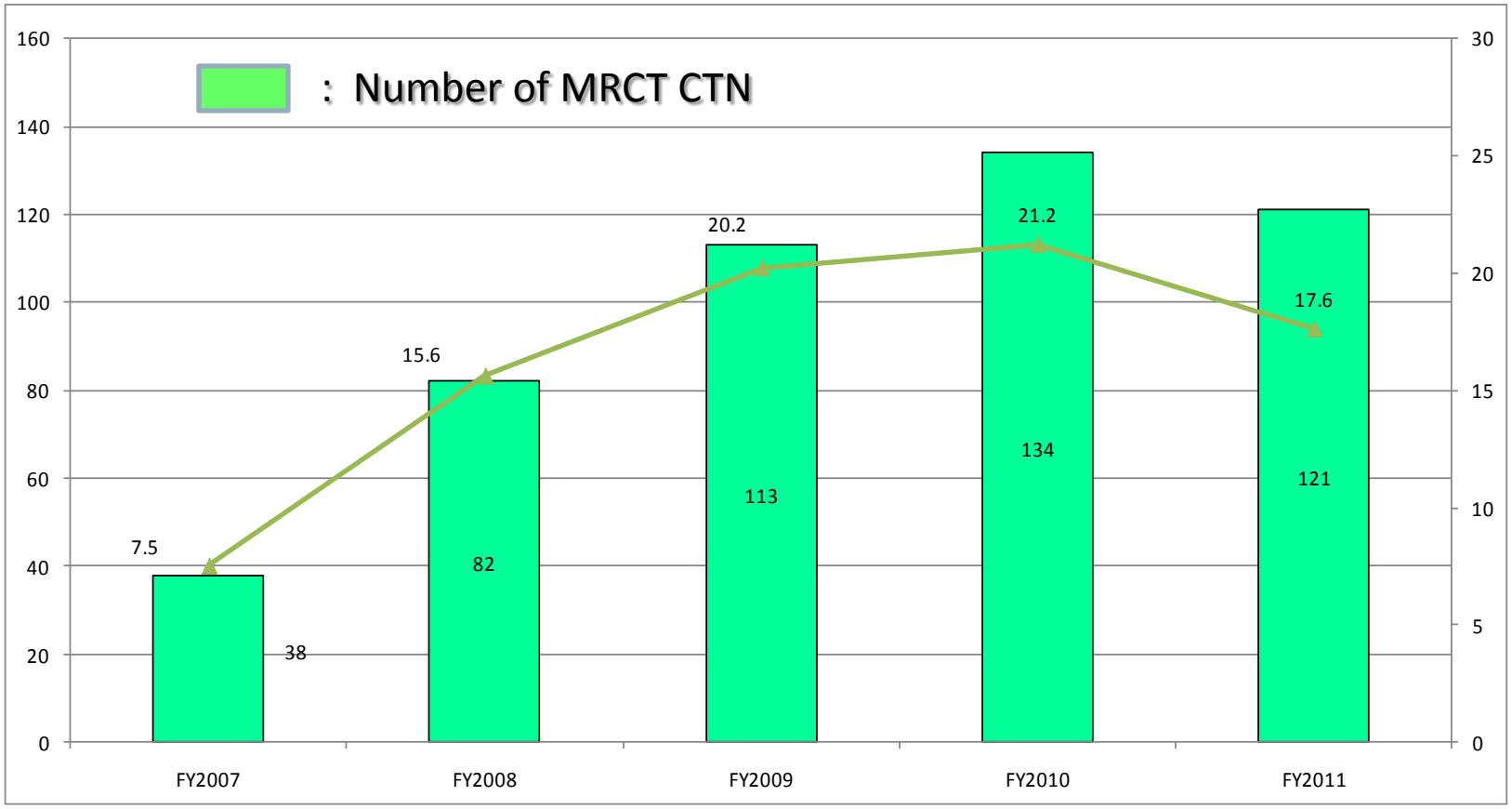
- Impacts -

✓ Markedly increase numbers and % of clinical trial notification (CTN) of MRCTs including Japan

✓ Promotion of sample size considerations in scientific arena

- Kawai, N et al, An Approach to Rationalize Partitioning Sample Size Into Individual Regions in a Multiregional Trial, *Drug Info. J.* 42, 139-147 (2008)
- Quan, H et al, Sample size considerations for Japanese patients in a multi-regional trial based on MHLW guidance, *Pharmaceut. Statist.* Published Online: Jun 4 2009 4:09AM 10.1002/pst.380 (2009).

Trends of MRCTs Including Japan
- % of MRCTs in Clinical Trial Notifications -



Approved cases based on GCTs

2006	2007	2008	2009	2010	2011	2012	
Tolterodine	Losartan	Trastuzumab	Insulin - glulisine	Peramivir	Dabigatran	Denosumab	
			Tadalafil	Everolimus	Trastuzumab	Aripiprazole	
				Panitumumab	Pramipexole	Olanzapine	
				Travoprost/ Timolol	Edoxaban	Exenatide	
				Temsirolimus	Dasatinib	Crizotinib	
				Laninamivir	Indacaterol	Budesonide / Formoterol	Atomoxetine
				Nilotinib	Linagliptin	Esomeprazole	Aflibercept
					Gefitinib	Formoterol	Insulin - degludec
					Everolimus	Axitinib	Glycopyrronium
						Budesonide / Formoterol	Pazopanib

Red: Asian GCT

- 36 applications were approved as of Nov 1, 2012

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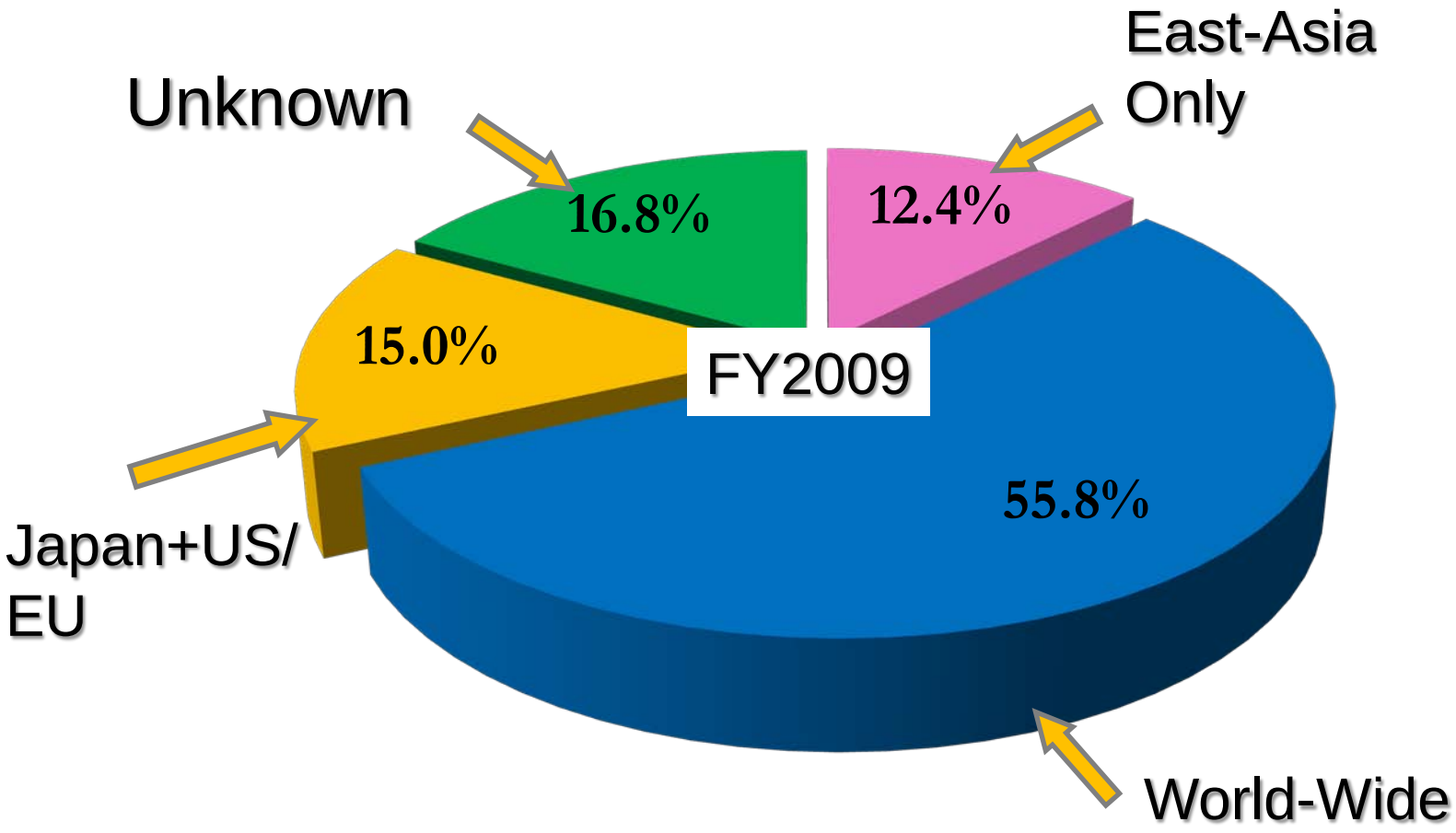
Operational Regions of Global Clinical trials including Japan in FY2009



How about South East Asian Countries including Indonesia?

Release of information regarding approval review of new drugs

- **“Review Reports”** that describe the details and results of reviews are released on PMDA’s website.
- as well as **“Summaries of Product Application”** that summarize submitted data by pharmaceutical companies.

Some review reports are translated into English. Unfortunately the summaries are available only in Japanese.

on the Medical Product Information page of PMDA website

- Information Related to Drugs
http://www.info.pmda.go.jp/info/syounin_index.html

- Information regarding the application review of new drugs (listed deliberation products basis)
http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html

- Information regarding the application review of new drugs (listed in the order of the Brand Name (Applicant Company)
http://www.info.pmda.go.jp/shinyaku/shinyaku_hanbaimei_index.html

- the release of re-examination reports of new drugs
http://www.info.pmda.go.jp/saishinsa/saishinsa_hanbaimei_list.htm

Medical Products Information on website

Review Reports of New Product Applications | Pharmaceuticals and Medical Devices Agency

Japanese ▸

Pharmaceuticals and Medical Devices Agency, Japan

Font size

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Home > Services of PMDA > Drug and Medical Device Reviews > Approved Products > Review Reports of New Product Applications

Services of PMDA

- Drug and Medical Device Reviews
  - Outline
  - Approved Products
    - List of Approved Products
    - Review Reports of New Drug Applications
    - Package Inserts Database (in Japanese)
  - Regulations and Procedures
  - Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug (PDF)
  - Record of Consultations on Pharmacogenomics/Biomarkers
- Post-marketing Safety
  - Outline
  - Safety Information
    - MHLW Pharmaceuticals and Medical Devices Safety

Review Reports of New Product Applications

The following English translations of review reports are intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese originals and the translations, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of the English versions.

New Drugs

The review reports are selected for translation among those of drugs with a new active ingredient that recently received marketing approval, in consideration of relevant factors including the novelty and priority.

- Clozaril (Clozapine) (PDF)
- Januvia/Glactiv (Sitagliptin Phosphate Hydrate) (PDF)
- Xolair for subcutaneous injection (Omalizumab [Genetical Recombination]) (PDF)
- Remitch (Nalfurafine Hydrochloride) (PDF)
- Pirespa (Pirfenidone) (PDF)

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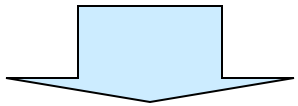
Collaboration in East-Asia

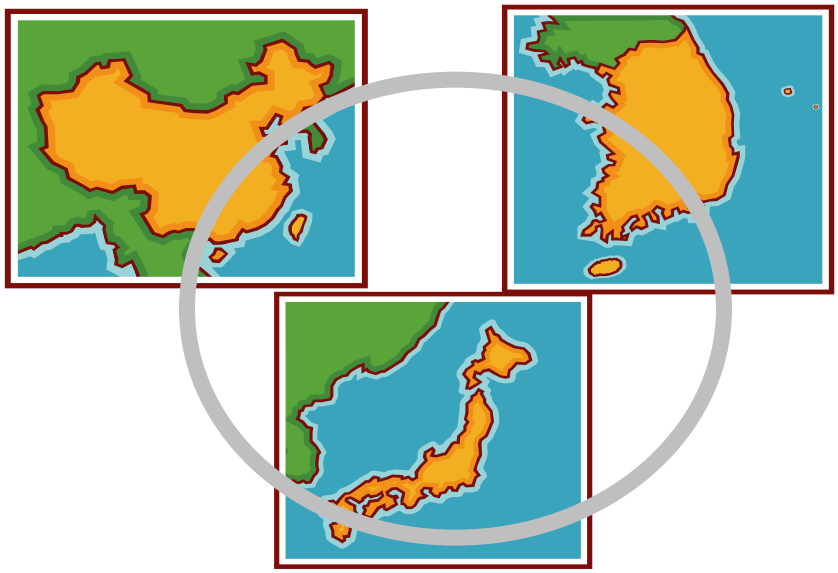
Background:

- In the era of globalization of Drug Development
- The necessity of evaluation on ethnic factors
- East Asian Advantage
  - Ethnic Similarities in China/Korea/Japan East-Asia
    - Genetic similarities
    - Cultural similarities (e.g.; chopsticks countries)
  - Improvement of clinical trial environment in East-Asia
  - Emerging drug market in East-Asia



To develop better drugs through collecting clinical data efficiently in East-Asia, Regulatory collaboration among China/Korea/Japan is important

China/Korea/Japan Tripartite Cooperation



Health Ministers' Joint Statement among China, Korea & Japan (April 8, 2007)

April 2008 Tokyo

Dec. 2009 Beijing

Sep. 2010 Seoul

Nov. 2011 Tokyo

China-Japan-Korea Tripartite Cooperation

Outcome of the 4ht meeting on Oct. 31, 2011

Research on ethnic factors

- In order to assess ethnic difference in PK, a single protocol that controls extrinsic factors should be employed and uniformly applied to the study populations. With some compounds, formerly reported ethnic differences in PK were found to be not existent under controlled conditions.
- Because polymorphisms of the relevant genes affects PK of a drug, it is recommended to know genotypes of study subjects and take them into consideration before evaluating the clinical data.
- DG agreed to continue further research on ethnic factors from the view point of PK and PD analysis

Information exchange on clinical trials

- DG recognized that the project is very important in terms of promoting mutual understanding of the regulatory frameworks for clinical trials in the three countries.
- DG agreed that WG further proceeds its work and information exchange on clinical trials among the three countries.

MRCT guideline

- DG recognized that the project proposed by China is also meaningful to strengthen the cooperation among Korea, China and Japan.
- DG agreed that China will coordinate the WG's work to make guidelines on regional clinical trials with close cooperation with Korea and Japan.
- For that purpose, DG agreed that China will make the concept paper in cooperation with Korea and Japan.

Activities on ethnic factor research in East Asia

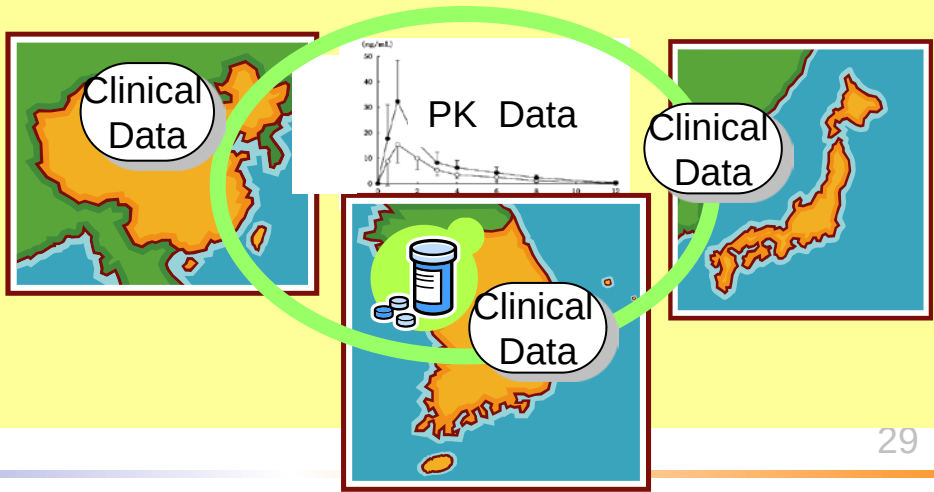
1 Activities of Japan

- FY2008 Collecting available PK data of Chinese, Korean and Japan and review the data
- FY2009-2010 Conducting Prospective PK study Including Chinese, Korean and Japanese in order to compare ethnic difference more precisely

- Budget: approximately total 400M Yen (=4M $)
- PK for several marketed drugs is planned to measure
- PK is measured by use of validated methods

2 Activities of Korea, China & Japan Tripartite Cooperation

- Collecting available data and discussing ethnic factors



“Reference Cases”

- “Basic Principles on Global Clinical Trials (Reference Cases)” was issued on Sep 5, 2012.
  - Based on recently accumulated scientific data and our experiences in consultation meetings and new drug review.
  - Reflect the outcome of cooperation in clinical trials among the regulatory authorities of Japan, China, and Korea

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“Reference Cases”

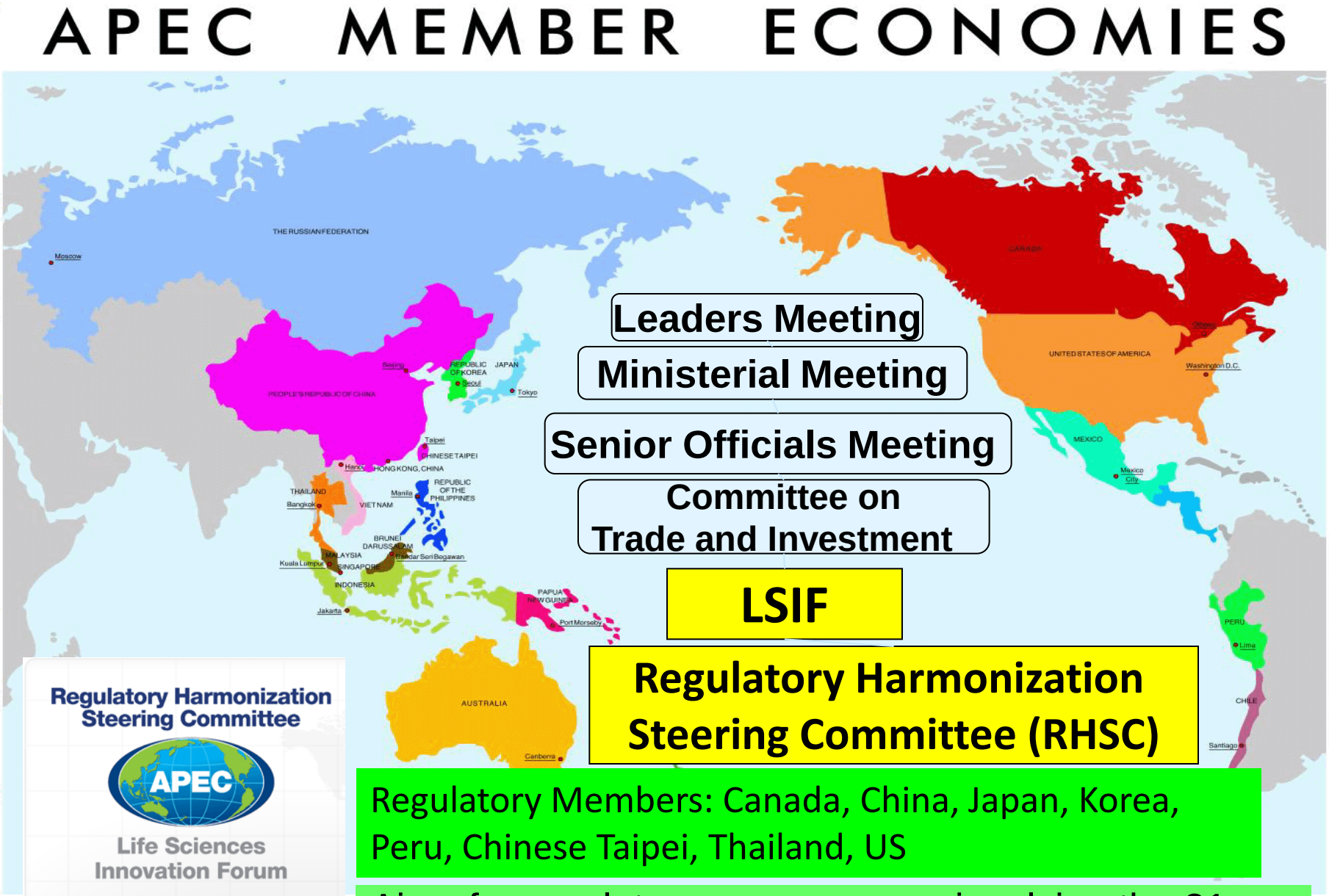
- Purpose of “Reference cases”
  - To promote further understanding of the former “Basic Principles” issued in 2007
  - To ensure Japan’s smooth participation in global drug development activities from an early stage
  - To ensure smooth and appropriate conduct of global clinical trials in East Asia
- 17 Q&As
  - 4 points to consider for global clinical trials in East Asia
  - 13 general points to consider on global clinical trials

China-Japan Symposium

To promote dialogue and cooperation between the agencies

2010 May	2011 March	2012 March
Global Clinical Trials and Ethnic Factors	IND, Pre-Consultation, GMP and DMF System	Contemporary Global Clinical Trials & Utilization MRCT, Consultation & GCP

APEC LSIF (Life Science Innovation Forum)



Regulatory Harmonization Steering Committee

APEC Life Sciences Innovation Forum

Regulatory Members: Canada, China, Japan, Korea, Peru, Chinese Taipei, Thailand, US

Aims for regulatory convergence involving the 21 member economies

Priority Work Areas

Project	Champion	Activity
Multi-regional Clinical Trials	Japan	Roadmap approved Workshop held in Seoul and Tokyo
Supply chain integrity	US	Established the expert working group
Good Review Practices	Chinese Taipei	Roadmap approved Workshop will be held in November
Good Clinical Practices	Thailand	Preparing questionnaire to compare the member economies' status of implementation
Combination Products	Chinese Taipei	Roadmap approved Workshop will be held in November
Biosimilars	Korea	Workshop held in April Discuss definition of terms
Pharmacovigilance	Korea	Roadmap approved Discussion focused on pharmaceuticals
Advanced Therapies	Singapore	Roadmap approved

PMDA leads discussion for the issues around ICH-GCP guideline implementation

- The voluntary-based activity
  - The Group of GCP experts from interested Regulatory agencies
- Objectives
  - Identify critical factors/propose a practical way for a proper implementation of ICH-GCP
- Participants (ex. From east Asia and ASEAN)

Japan PMDA *Group Leader*

Korea KFDA, Singapore HSA, Thai FDA, Indonesia BPOM, Malaysia DRA, Philippines DRA

PMDA Training Seminar

2010 November – December

PMDA's role in regulation, and Scientific review process on new drug applications biological applications

35 trainees participated from Indonesia, Singapore, China, Taiwan, Korea and Nigeria

2011 December

Pharmaceutical GMP inspection

27 trainees participated from Indonesia, Korea, India, ….

3rd PMDA Training Seminar

2013 January 21-25

Post-Marketing Safety & Relief Services

18 trainees :
- Korea
- Taiwan
- Indonesia
- Singapore
- Brazil
- Ukraine

http://www.pmda.go.jp/english/events/3rd_pmda_training_seminar.html

Trainings for individual Trainees

Medium-term training

- 2.5 months training for a SFDA reviewer – May～July 2010
- Three weeks' training for three KFDA officials on general issues - Dec 2011
- One month training for TFDA (Taiwan FDA) officials on Medical Devices – Feb 2012

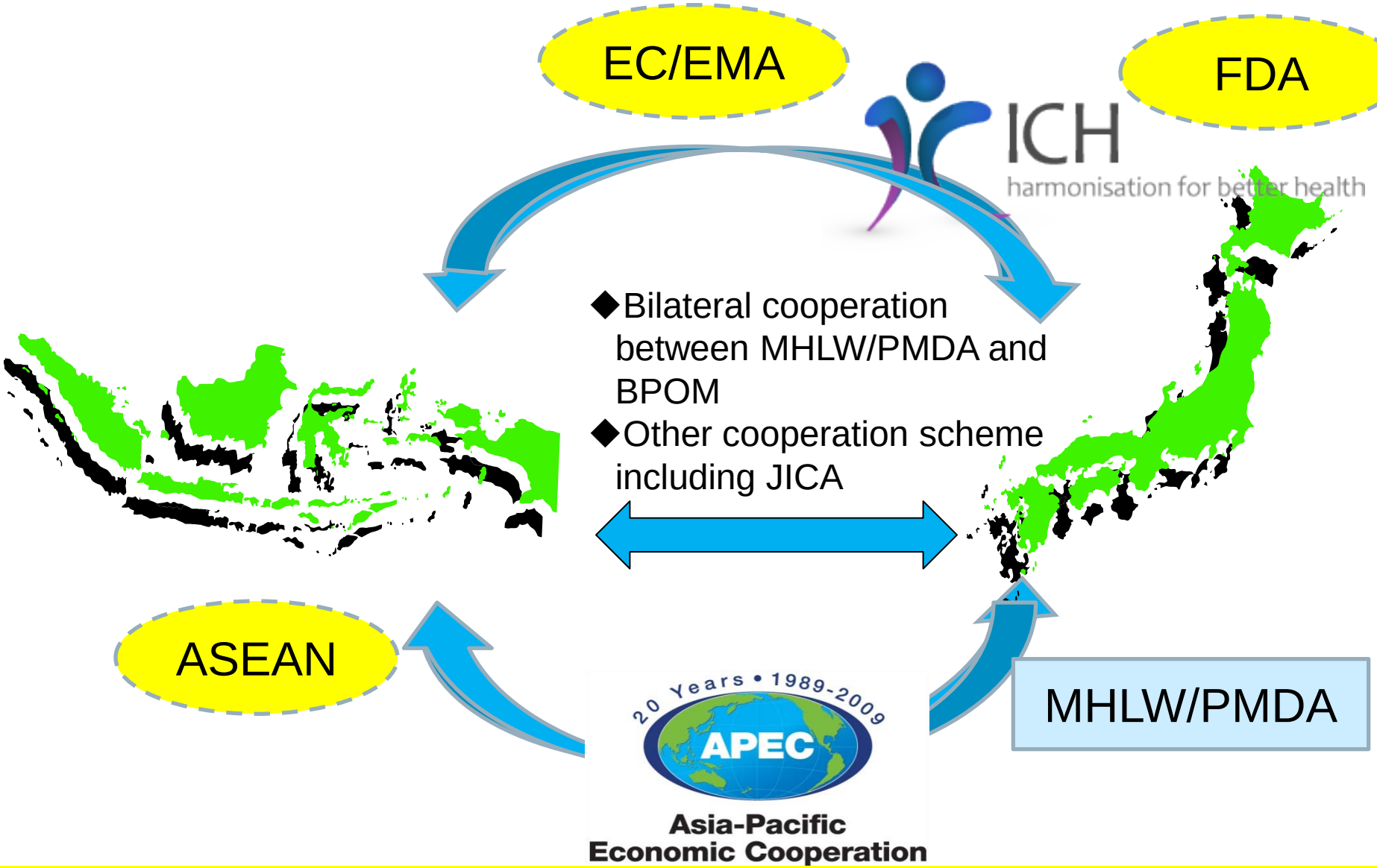
Dr. Kondo with Trainees from KFDA

Dr. Kondo with Trainees from Taiwan FDA

Cooperation through Japan International Cooperation Agency（JICA)

1. MHLW/PMDA dispatched long/short-term experts to BPOM from 2003 to 2012
2. MHLW/PMDA worked together with BPOM for workshops/seminar
3. MHLW/PMDA accepted trainees from BPOM

What's next ?



Work together for our people, Asia and the world!

- MHLW http://www.mhlw.go.jp/english/index.html
- PMDA http://www.pmda.go.jp/english/index.html
- Review Report http://www.pmda.go.jp/english/service/review.html
- Japanese Pharmacopoeia http://www.std.pmda.go.jp/jpPUB/index_e.html