Overview on Multi-Regional Clinical Trials in Japan from Sponsor's Point of View

– Advantages &Issues in MRCT involving China–

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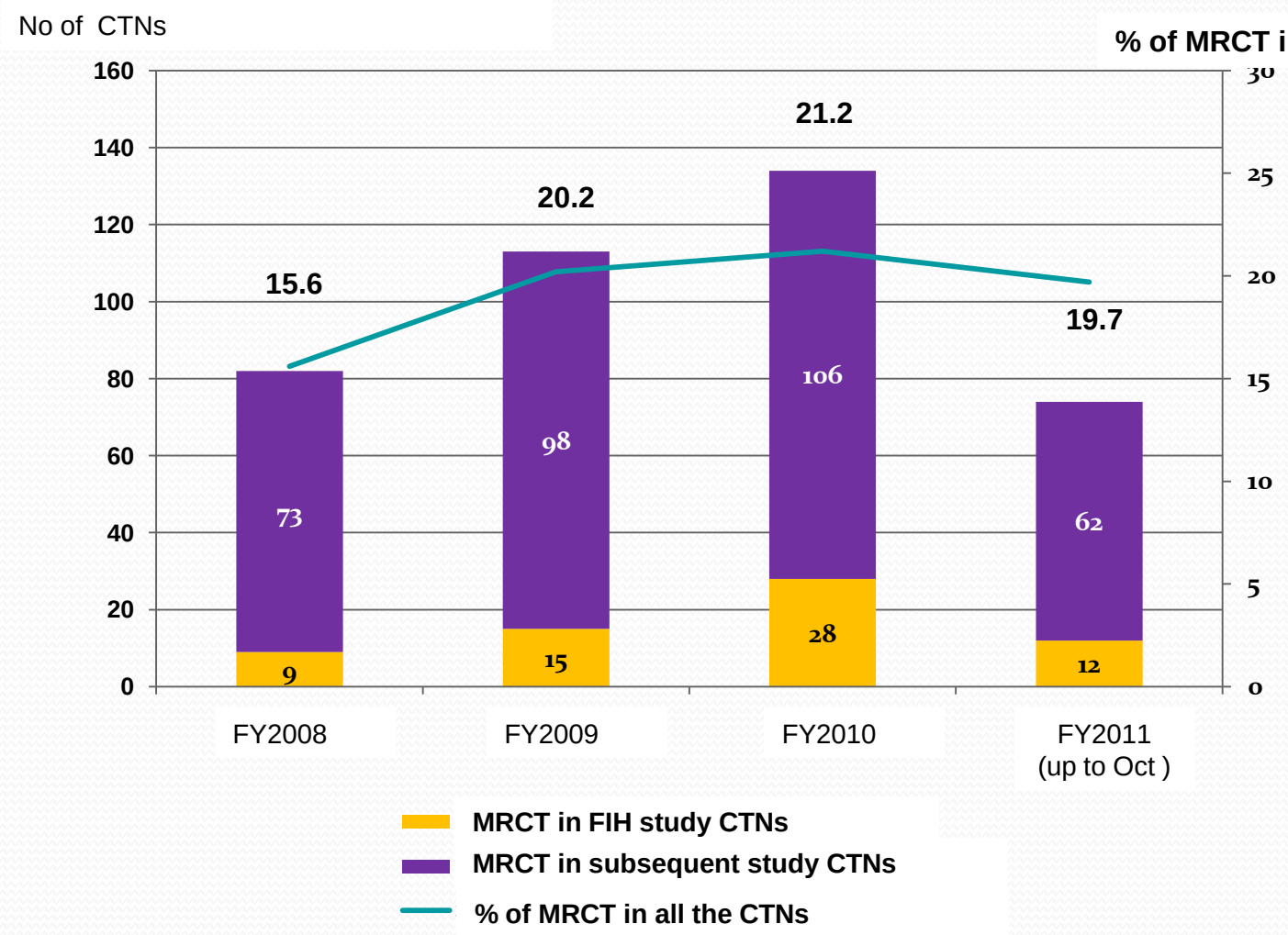
Agenda

1. Introduction
2. Multi-Regional Clinical Trials（MRCT）from sponsor's point of view
   Findings from questionnaire to 59 JPMA member companies conducted in 2010 and 2011
3. Advantages of MRCT involving China and successful cases
   - In general
   - Approval cases study
4. Issues in MRCT involving China
   - Issues in regulations and operations

Increasing Global and Asian Studies



Source: PMDA's publication

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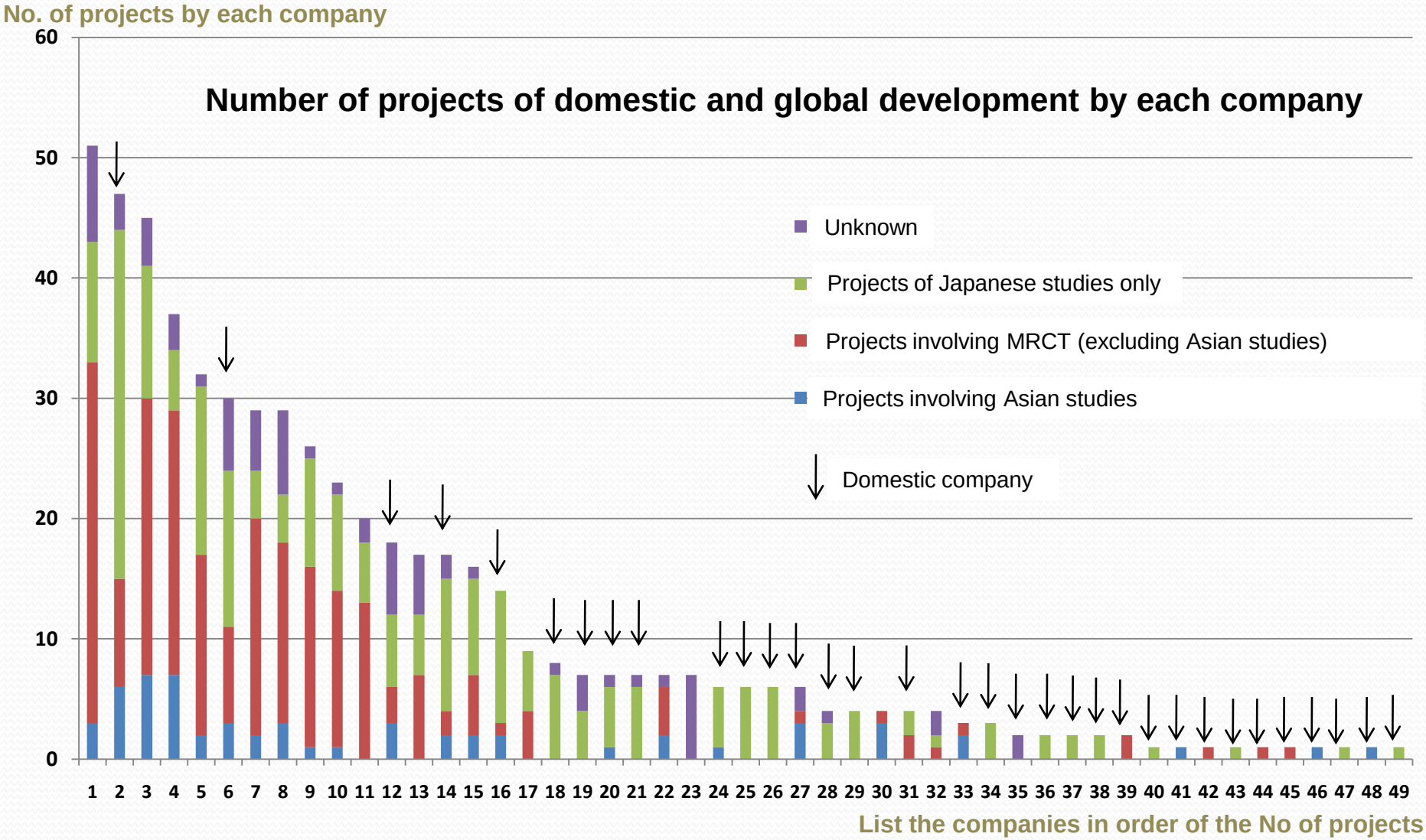
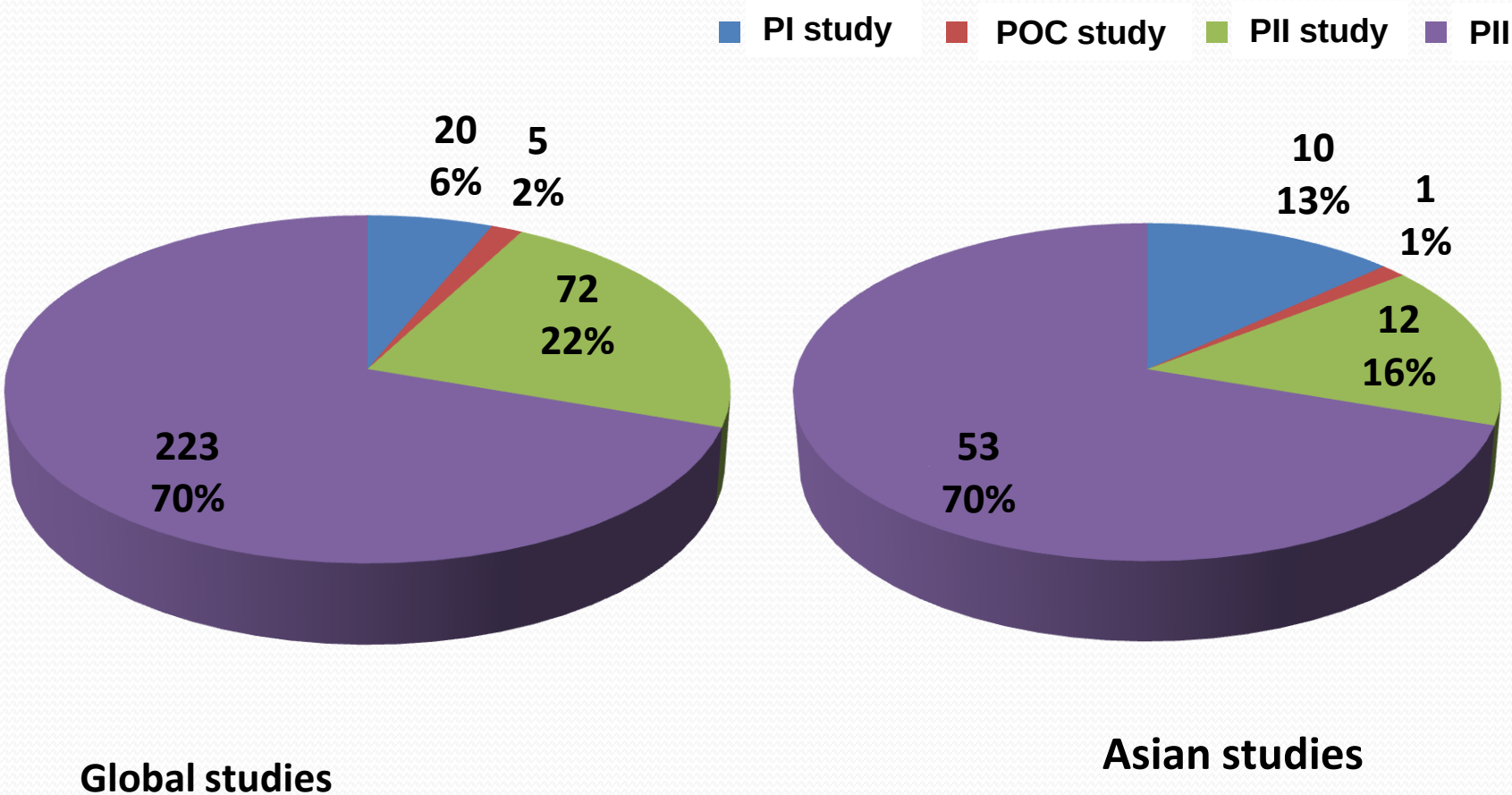
Ratio of Domestic/Global Development by Company



Data of 13 companies without development project excluded

Development Phase of Global/Asian Studies



Global studies

Asian studies

Conditions for Including MRCT in Submission Data Package in Constructing Development Strategy

- **Areas where MRCT is always considered**
  - **Basically all the areas　10 companies**
  - **Oncology　8 companies / CV　7 companies / CNS　6 companies**
  - **Others (Anti-infectives, anti-inflammatory, Urology, etc)**
  - **Orphan drugs　3 companies**
- **Reasons: Development efficiency (number of cases, cost, speed), launch accuracy, company strategy**
- **Conditions: No marked ethnic difference, no time restriction = good timing, similar evaluation criteria between Japan and overseas, large scale (long term) study**

Factors for Participating in MRCT in Each Development Stage – PI Study

Requirements/Factors for participating

* **Rapid information sharing and safety security among multiple countries can be assured.**
* **Conduct in Japan is difficult due to manufacture of investigational drug, etc.**
* **There is no time for preparation/conduct of PI study in Japan.**

Factors for not participating

* **It is essential to general PK data of the race in the relevant country/region**
* **Issue of cost in the stage where POC is yet to be determined**
* **Time required for procedures for clinical trial start**
* **It is more efficient to conduct the study at one site in one region**

Factors for Participating in MRCT in Each Development Stage – POC Study

Requirements/Factors for participating

* Diseases specific to Japan (Asia)

Factors for not participating

* **Issue of cost in the stage where POC is yet to be determined**
* **Time required for procedures for clinical trial start**
* **It is more efficient to conduct the study at one site in one region because POC study is usually conducted in a small number of subjects and it is difficult to examine the ethnic difference in the study to determine product profile**

Factors for Participating in MRCT in Each Development Stage – PII, III Studies

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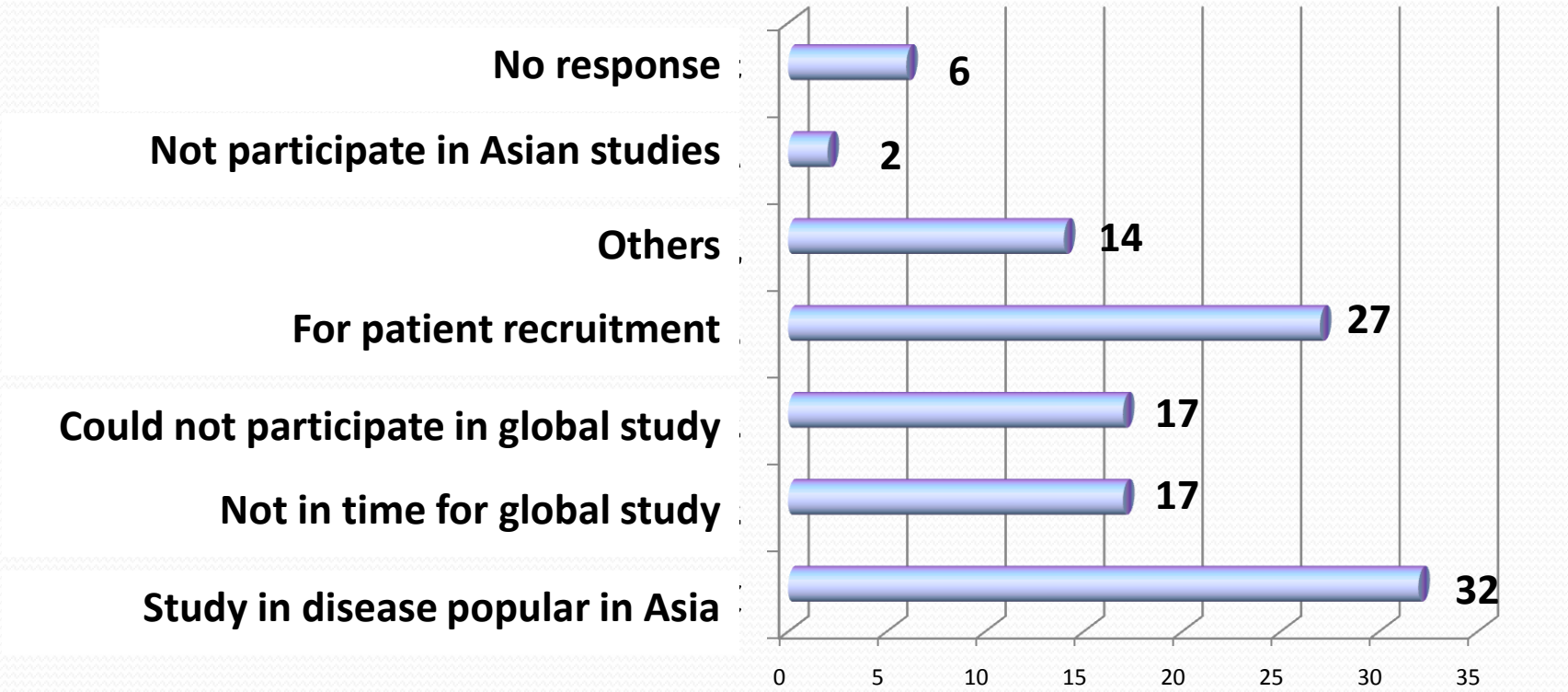
Requirements/Factors for participating

* Timing is suitable for participation.
* Launch accuracy, development speed and cost exceed the risk.
* No ethnic difference suggested in PK (whether difference in doses for approved drugs in the same class exists or not)
* Assurance of safety of the drug in higher doses
* Feasibility of the study conduct with unified protocol (evaluation method, investigational drug, medical practices) in Japan Number of Japanese patients with the disease
* Agreeability of the protocol with the regulators in terms of study design such as dosage, concomitant drugs, control drug, scale, duration and endpoints.
* Efficiency of patient recruitment – Particularly PIII studies

When to Plan Asian Studies



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Advantages of MRCT Involving China

Strategic point of view

* Cancer/hepatitis of similar disease background
* No ethnic difference
* No cultural difference
  - Share similar views on some issues
* Low cost, fast recruitment

Operational point of view

* Timely Communication as no time different
  - Quick action for any issue raised
* Sufficient support by Medical background staff and scientific and monitoring background staff to local monitoring team

Approvals Based on Submission Data Package

Including Asian Studies

Name of Drug	Indication	Approval
Tolterodine	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Apr.2006
Insulin glulisine	Diabetes mellitus	Apr.2009
Peramivir *	Type A and Type B Influenza virus infection	Jan.2010
Laninamivir *	Type A and Type B Influenza virus infection	Sep.2010
Edoxaban*	Prevention of venous thromboembolism after major orthopedic surgery	Apr.2011
Indacaterol	Chronic obstructive pulmonary disease (COPD)	Jul. 2011
Gefitinib	EGFR mutation-positive inoperable or relapsed non-small cell lung cancer	Nov.2011
Aripiprazole	Manic symptoms associated with bipolar disorder	Jan.2012

*: Not approved in USA

Clinical Data Package

- Japanese data
  - Phase I (healthy male subjects)
  - Phase II (influenzae virus infected patients)
  - Phase III
    - **Single dose Asian study (influenzae virus infected patients)**
    - Single and repeated doses study (at risk patients infected with influenzae virus)
- Overseas data
  - Phase I (healthy male subjects, patients with renal failure, the elderly)

Reasons for Adopting Asian Study

Reasons for adopting Asian study

- Seasonal disease ⇒ Completion of the clinical study in one season was challenged
- No marked difference between races
- Reduction in cost (Estimation: 30-60% reduction)

Reasons for selecting Korea and Taiwan

- Clinical stats of influenza is similar to that in Japan
- Study initiation in short time (seasonal disease)
  - IND period considered
- Number of collectable cases
  - Hundreds of cases expected to be collected in one season

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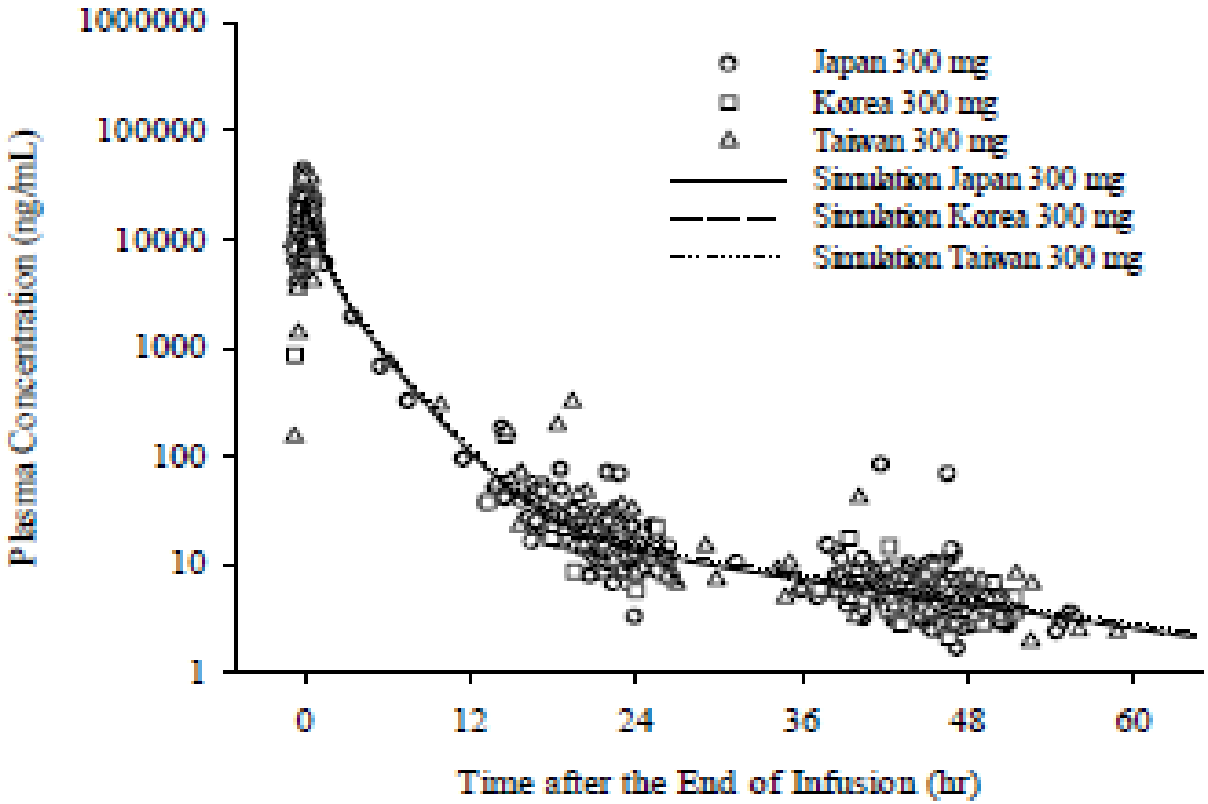
Pharmacokinetics following 300 mg single iv dose



Plasma concentrations of peramivir (actual measurements) in influenza virus infected patients and time plotted mean plasma concentrations in population of each region

○: Japan □: Korea △: Taiwan

Solid line: Mean plasma concentration simulation curve in Japanese population

Break line: Mean plasma concentration simulation curve in Korean population

Dotted line: Mean plasma concentration simulation curve in Taiwanese population

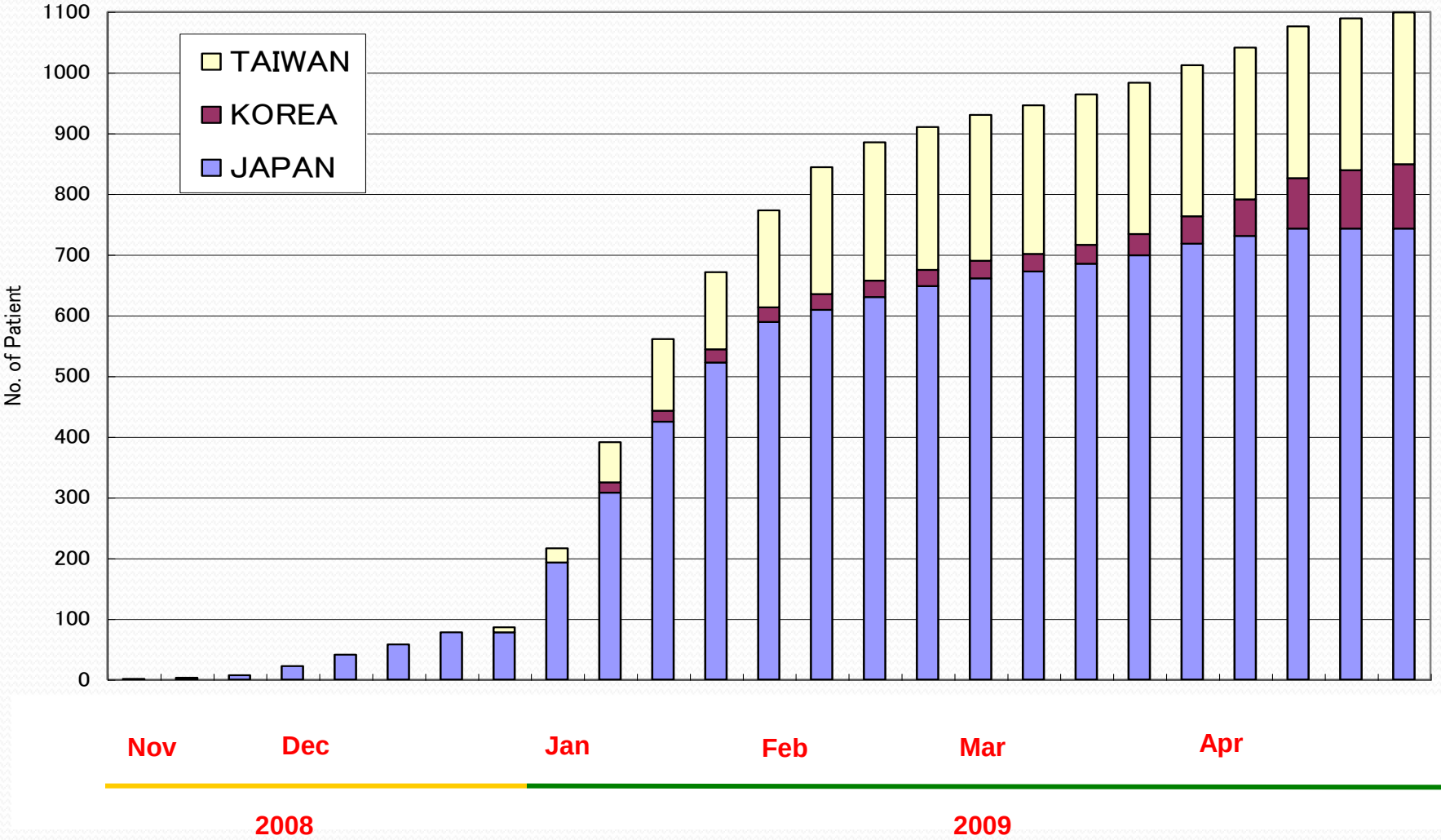
Summary and Results of Asian Study

Country	Japan	Korea	Taiwan
Target number of cases	1,050 (350 x 3 arms)		
	550	250	250
Registered number of cases	743	106	250
	1,099		

Factor for ↑	● Met seasonal epidemic ● GP sites ● RAT is common ● Phase 2 study	● Korean enterprise ● 2nd peak of epidemic	● Met epidemic ● GP referral ● ER participated ● Shionogi Taiwan
Factor for ↓		● Lost the first peak ● Less GP referral ● RAT is uncommon	● RAT is uncommon
Influenza Standard Therapy	● Anti-influenza drug	● Less use of anti-influenza drug ● RAT is uncommon	

RAT: Rapid Antigen Test

Weekly Patient Enrollment



Clinical Data Package

- Placebo controlled double blind comparison study (Asian study)
- Double blind long-term continuation study (Asian study)
- Non blind long-term continuation study with concomitant use of mood-stabilizing drug (Asian study)
- Non blind long-term continuation study with concomitant use of mood-stabilizing drug (Japan)

Overseas clinical data used as “referential data”

Case study 2 Aripiprazole (bipolar disorder)

Number of Cases for Efficacy Evaluation in Asian Pivotal Study

	Total	Aripiprazole group	Placebo group
Total	247	122	125
Japan	79 (32.0%)	39	40
China	56 (23.9%)	28	28
Taiwan	35 (14.2%)	17	18
Indonesia	15 (6.1%)	7	8
Malaysia	25 (10.1%)	12	13
Philippines	37 (15.0%)	19	18

Source: Review Report

- Asian study led by Japan was conducted in neurophychiatric area where ethnic difference is said to be relatively large
- For drugs like aripiprazole already approved in the West, conduct of such Asian study is beneficial in reduction in development time

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Issues in MRCT Involving China 1
- In perspective of regulations and operations -

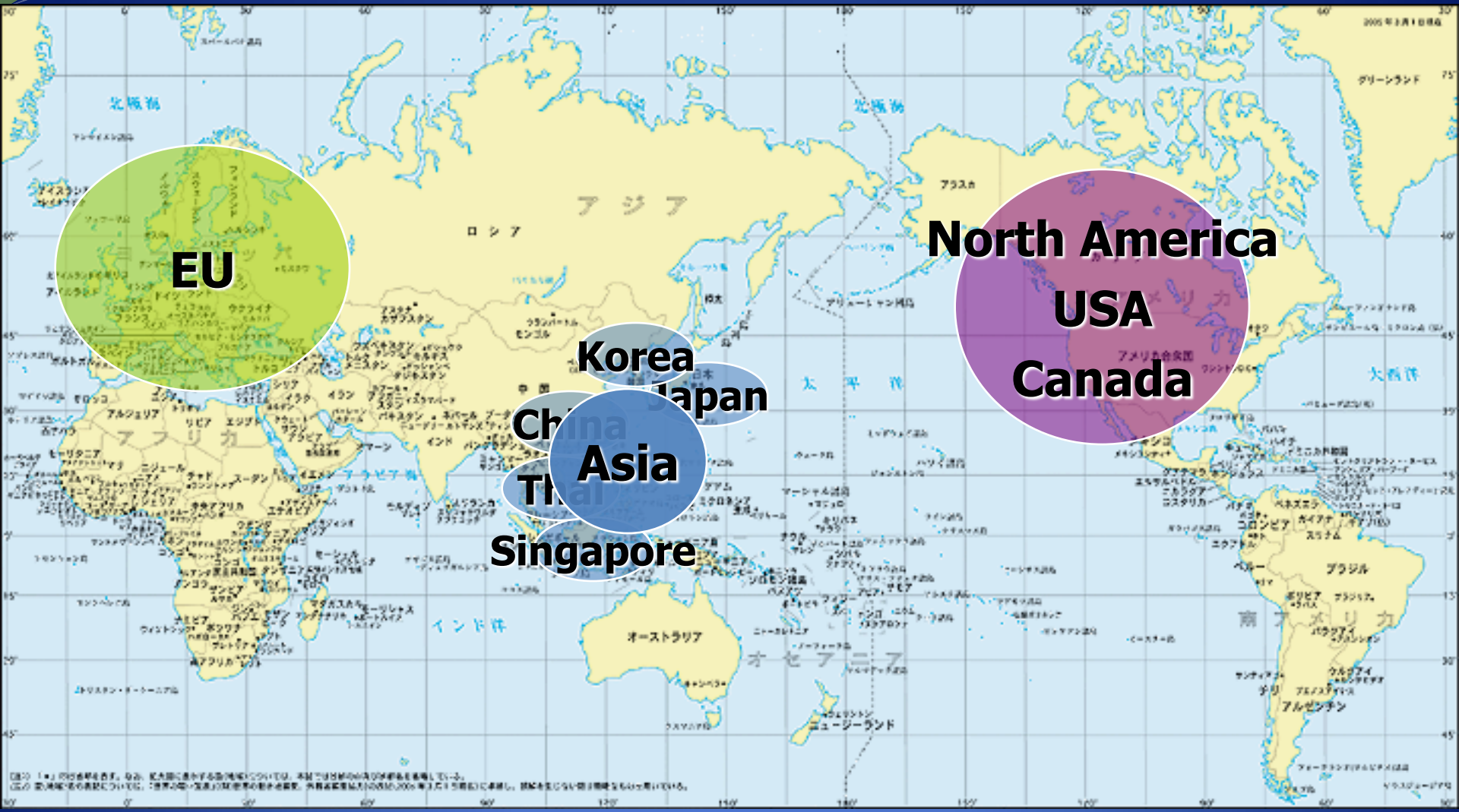
- Establishment of clinical trial/development consultation system
- Acceleration of issue of therapeutic guidelines in China (diagnosis, treatment, clinical studies)
- Reduction in CTA review time by differentiating IND (CTA) review system and NDA review system in China (submission dossier, review process and timeline) （difficult to progress in parallel in case of global study)

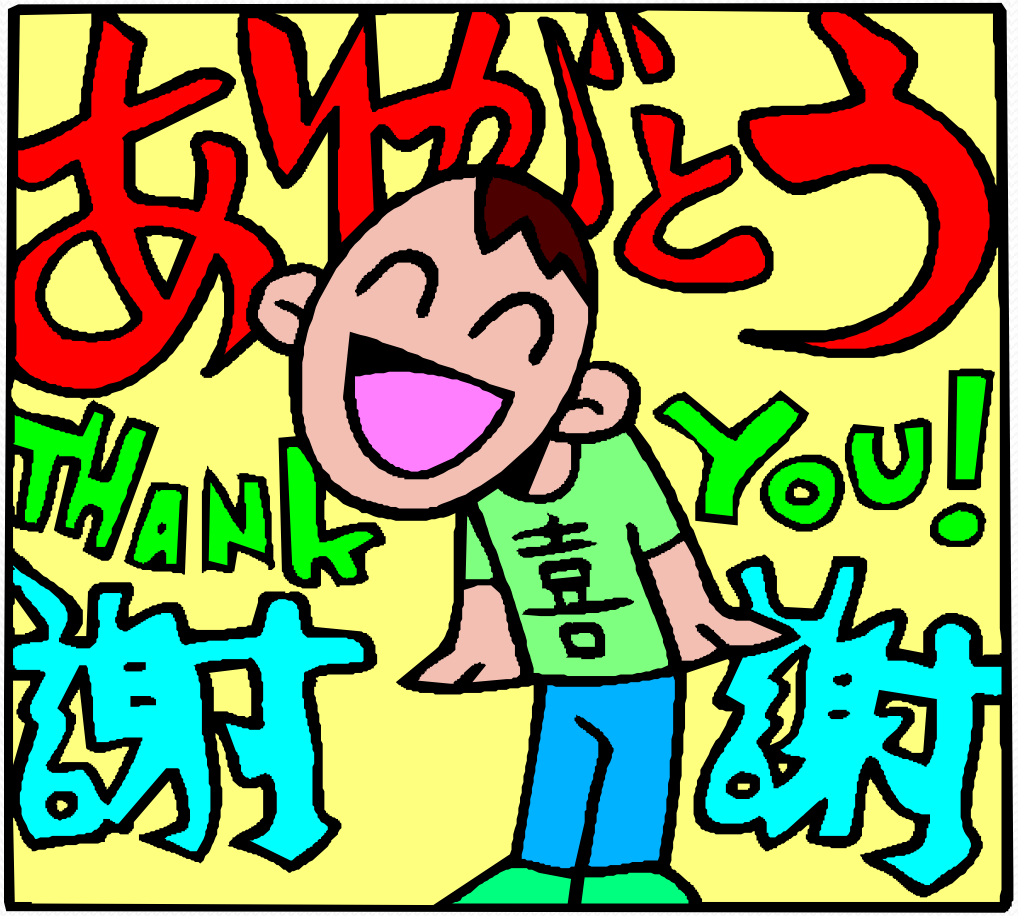
  Particularly, simplification of CMC dossiers and abolishment of submission of investigational drug sample in CTA
- Increase in Chinese CDE reviewers

Issues in MRCT Involving China 2
- In perspective of regulations and operations -

- In MRCT, investigational drug should be the drug registered in China or overseas or in PII or PIII stage. Acceptance of participation of China to FIH studies is requested.
- Only the drugs approved in China can be used as the control drug.
- Acceleration of EC, investigator & study nurse (coordinator) training in China
- Acceptance of dossiers in foreign language by Chinese agency

From Asia to Global





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