Review experiences of global clinical trials in Japan

Takahiro Nonaka, Ph.D

Office of New Drug V

Pharmaceuticals and Medical Devices Agency

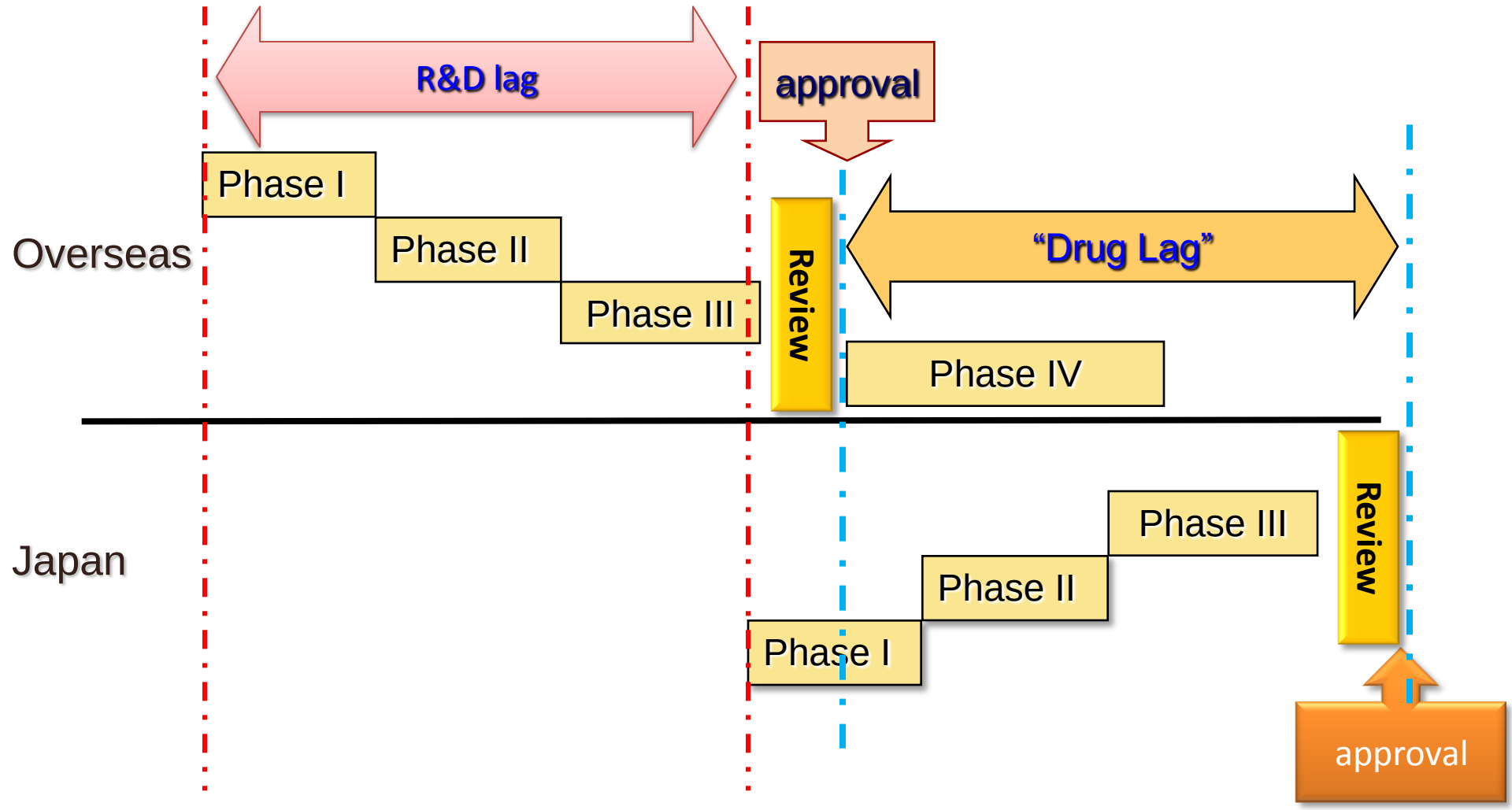
Disclaimer Notice

- The views and opinions expressed are those of the individual presenter and should not be attributed to PMDA.

Global drug development

- Purpose of global drug development
  - Prevention of unnecessary duplication of clinical trials
  - Efficient and cost-effective drug development
  - Solving the “drug lag” issues with global simultaneous drug development

Drug lag


R&D lag
approval
Phase I
Phase II
Phase III
Review
"Drug Lag"
Overseas
Phase IV
Japan
Phase III
Review
Phase II
Phase I
approval

Drug lag against USA

	FY 2006	FY 2007	FY 2008	FY 2009
Pre-application lag	1.2	2.4	1.5	1.5
Post-application (in review) lag	1.2	1.0	0.7	0.5
Drug lag (Sum)	2.4	3.4	2.2	2.0

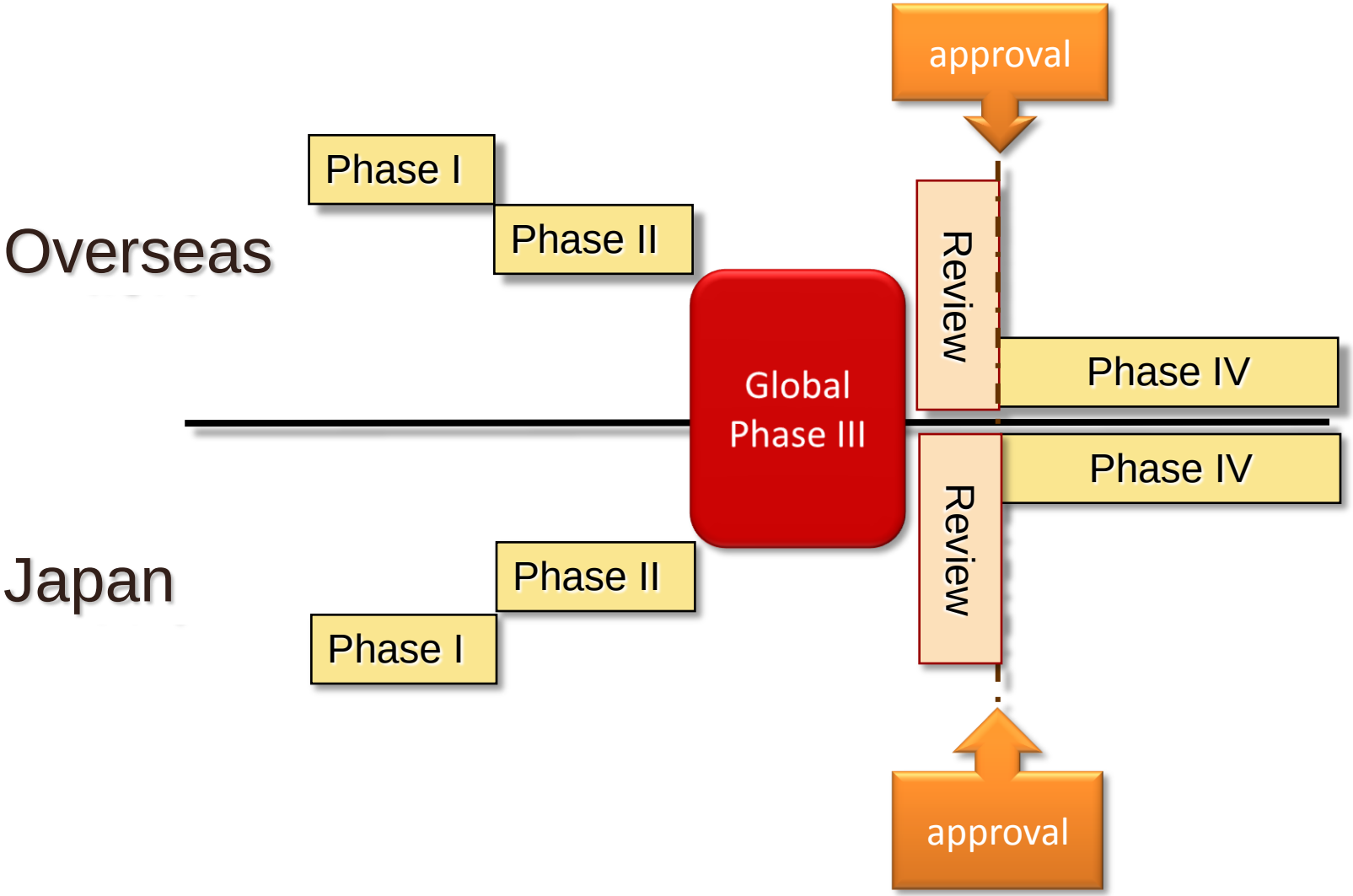
Provisional calculations

Pre-application lag : Median years of difference between USA/Japan application for each product

Post-application lag : Median years of difference between review time (USA/Japan) application for each product approved in Japan

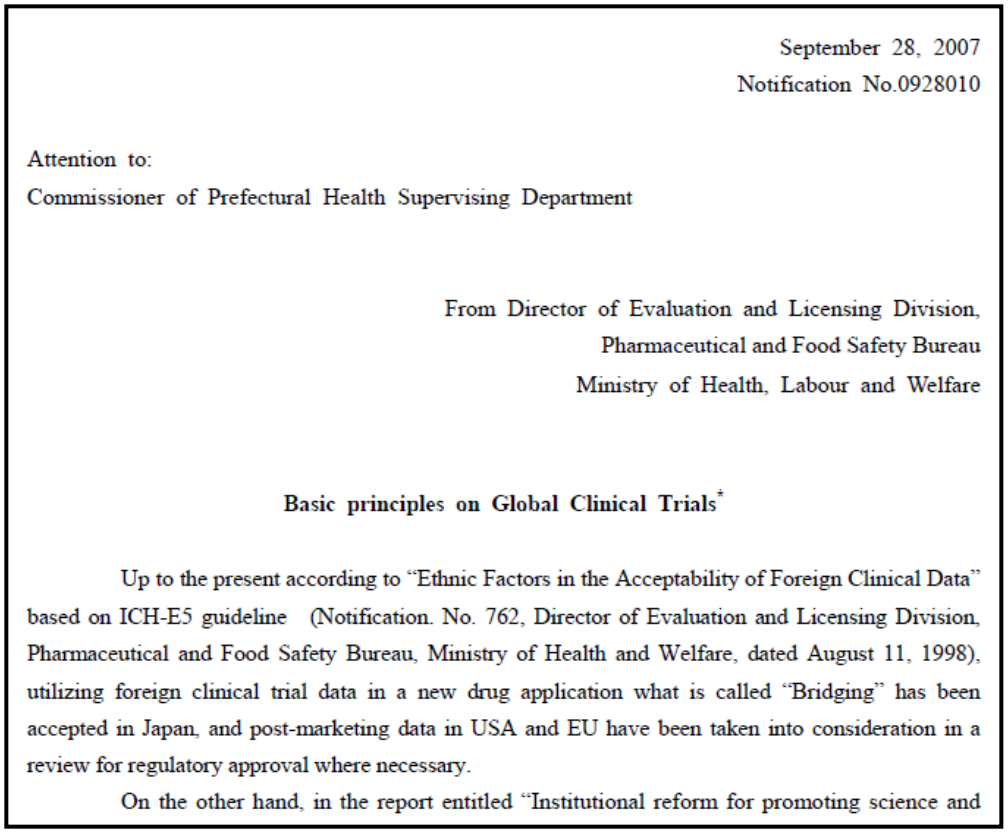
To resolve the drug lag

Global drug development



Guidance document (2007)

Basic principals on Global Clinical Trials



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.

On the other hand, in the report entitled "Institutional reform for promoting science and

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

Key message

- Encourage Japan's participation in global drug development
- Promote to conduct global clinical trials more appropriately in consideration with ethnic factors

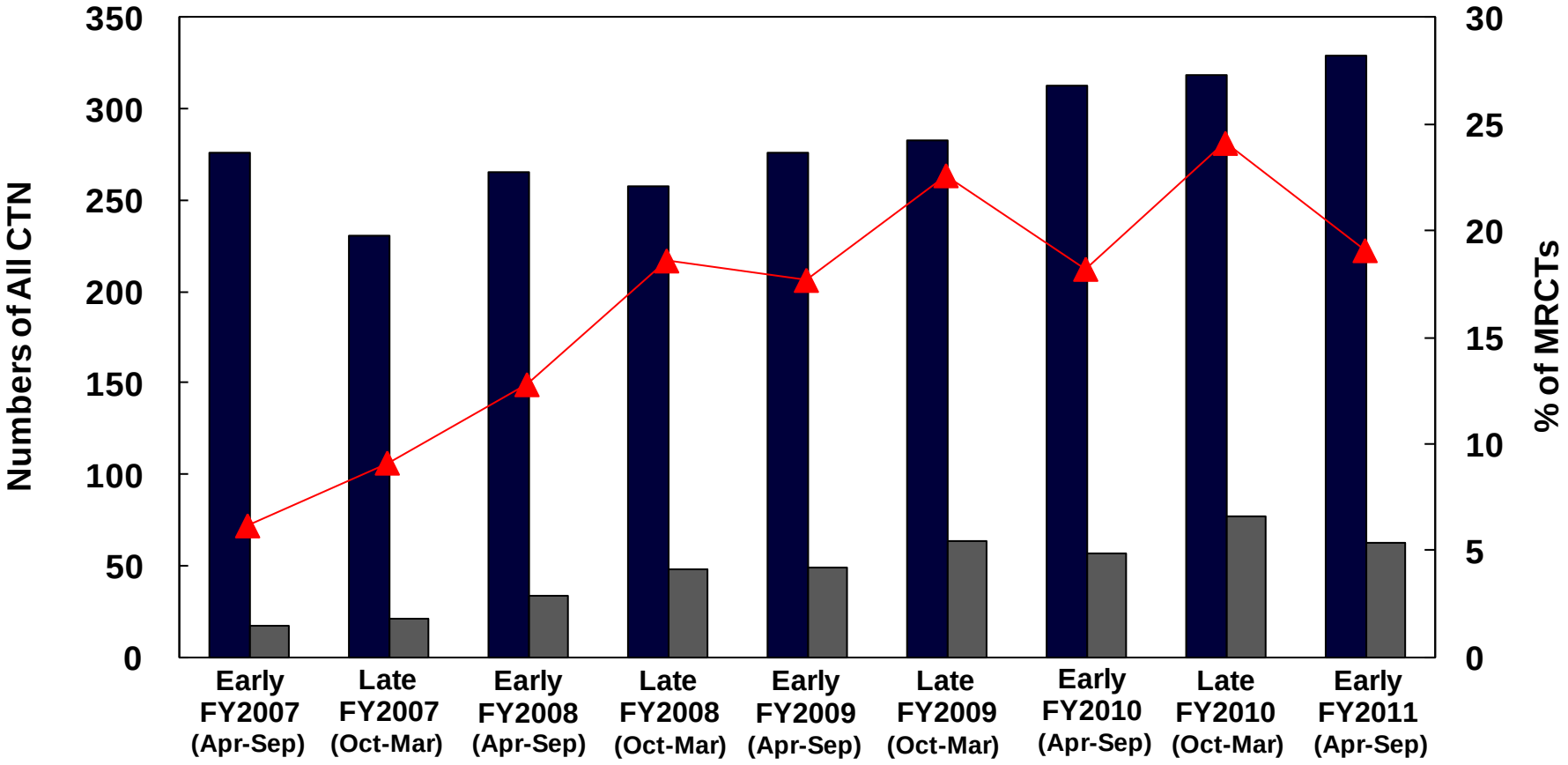
GCTs-based approval in Japan

Name of Drug	Indication	Approval
Peramivir *	Type A and Type B Influenza virus infection	Jan. 2010
Everolimus	Metastatic renal cell carcinoma	Jan. 2010
Panitumumab	Metastatic colorectal carcinoma with wild-type KRAS tumors	Apr. 2010
Travoprost/Timolol*	Glaucoma	Apr.2010
Temsirolimus (GC)	Advanced renal cell carcinoma	Jul. 2010
Dabigatran	Stroke and systemic embolism in patients with non-valvular atrial fibrillation	Jan. 2011
Trastuzumab	Metastatic HER2-overexpressing gastric cancer	Mar. 2011
Pramipexole	Parkinson's disease	Apr. 2011
Edoxaban*	Prevention of venous thromboembolism after major orthopedic surgery	Apr. 2011
Dasatinib	Chronic myeloid leukemia (CML)	Jun. 2011
Indacaterol	Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.	Jul. 2011
Linagliptin	Type 2 diabetes mellitus (adjunctive to diet and exercise)	Jul. 2011

- More experienced to review GCTs data
- Importance of East-Asian contribution is well recognized

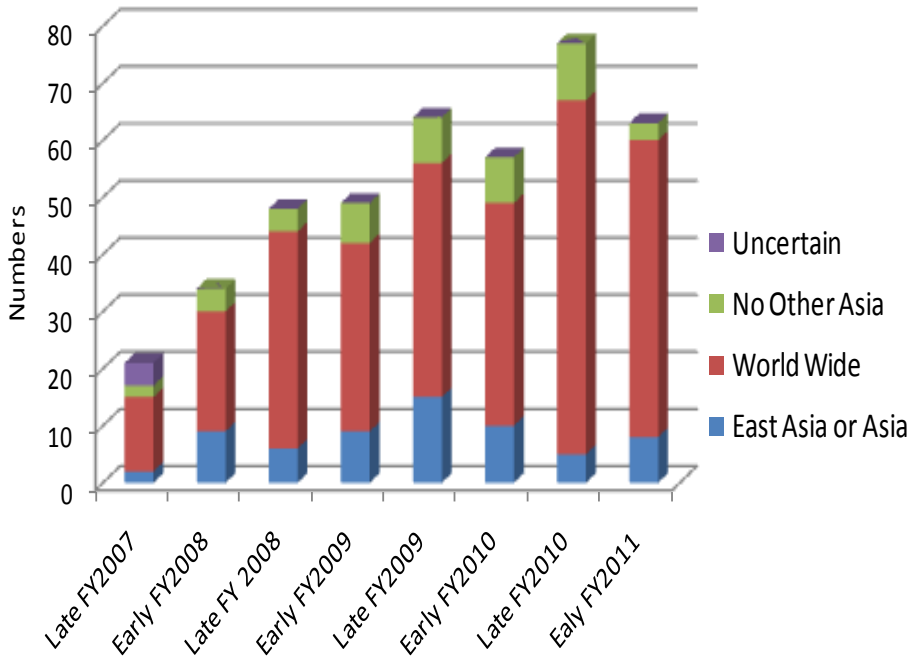
*: Not approved in USA

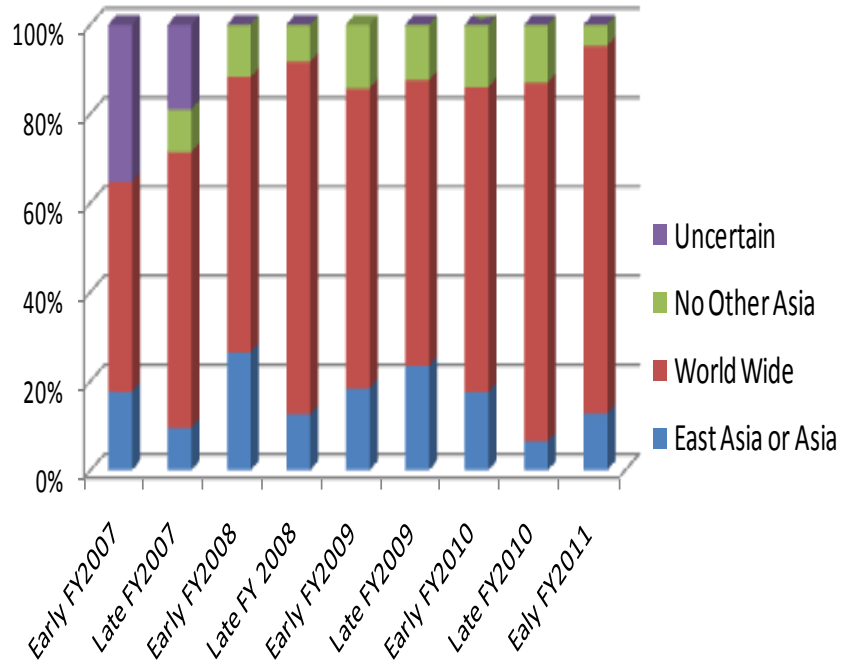
Trends of GCTs in Japan



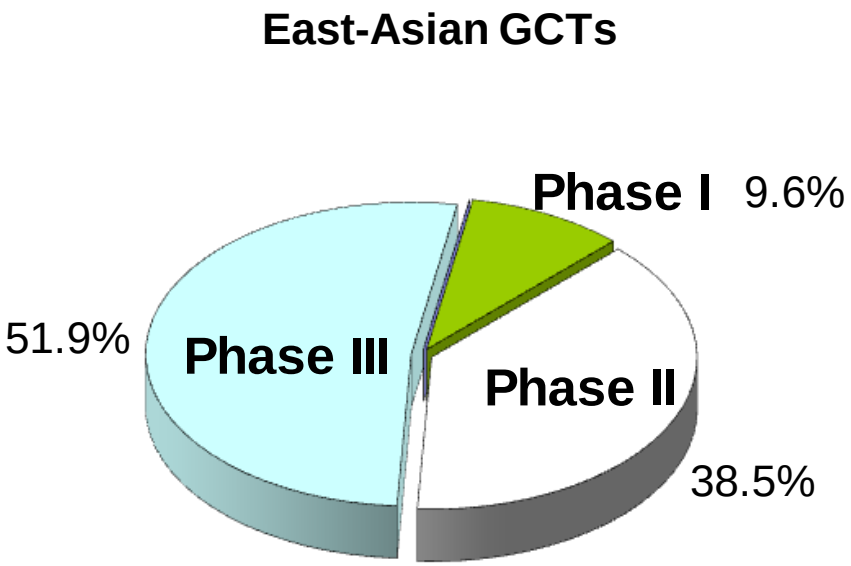
CTN: Clinical trial notifications
MRCTs: Used in the same meaning as GCTS

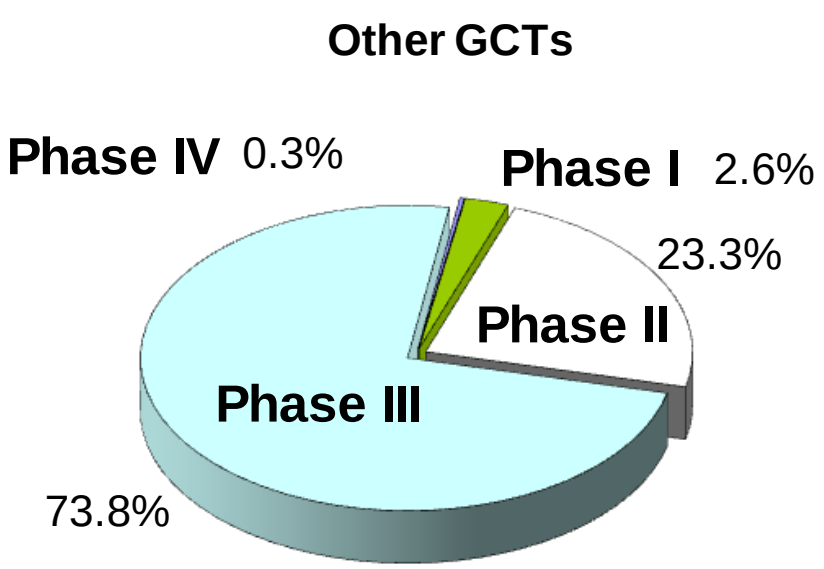
Regions of GCTs including Japan





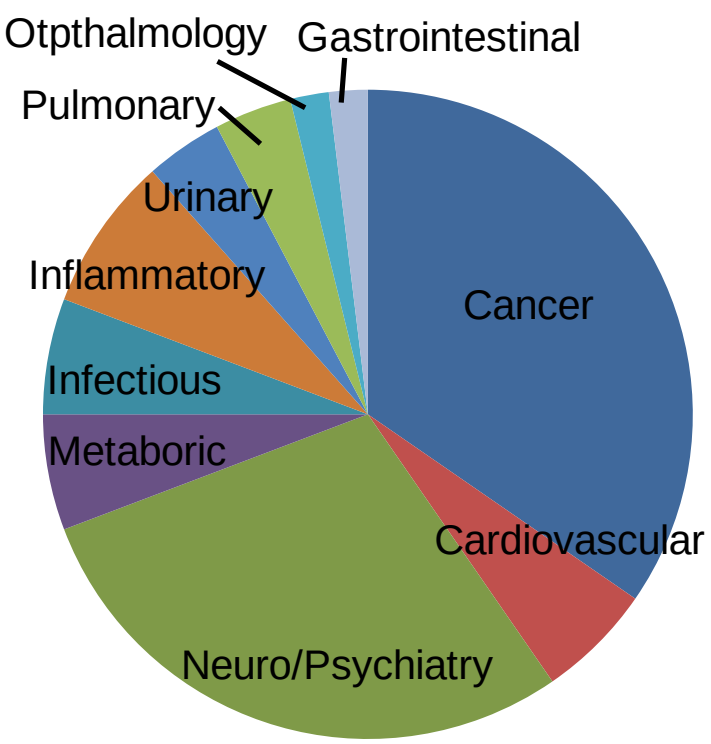
Development stage in GCTs including Japan



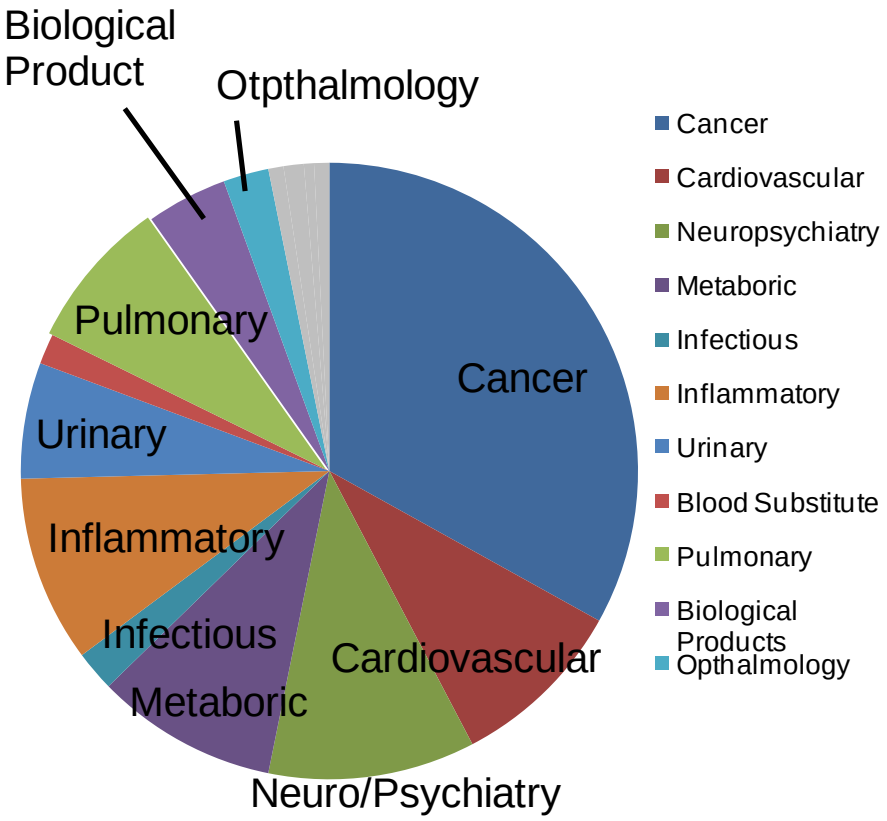


Target diseases in GCTs including Japan

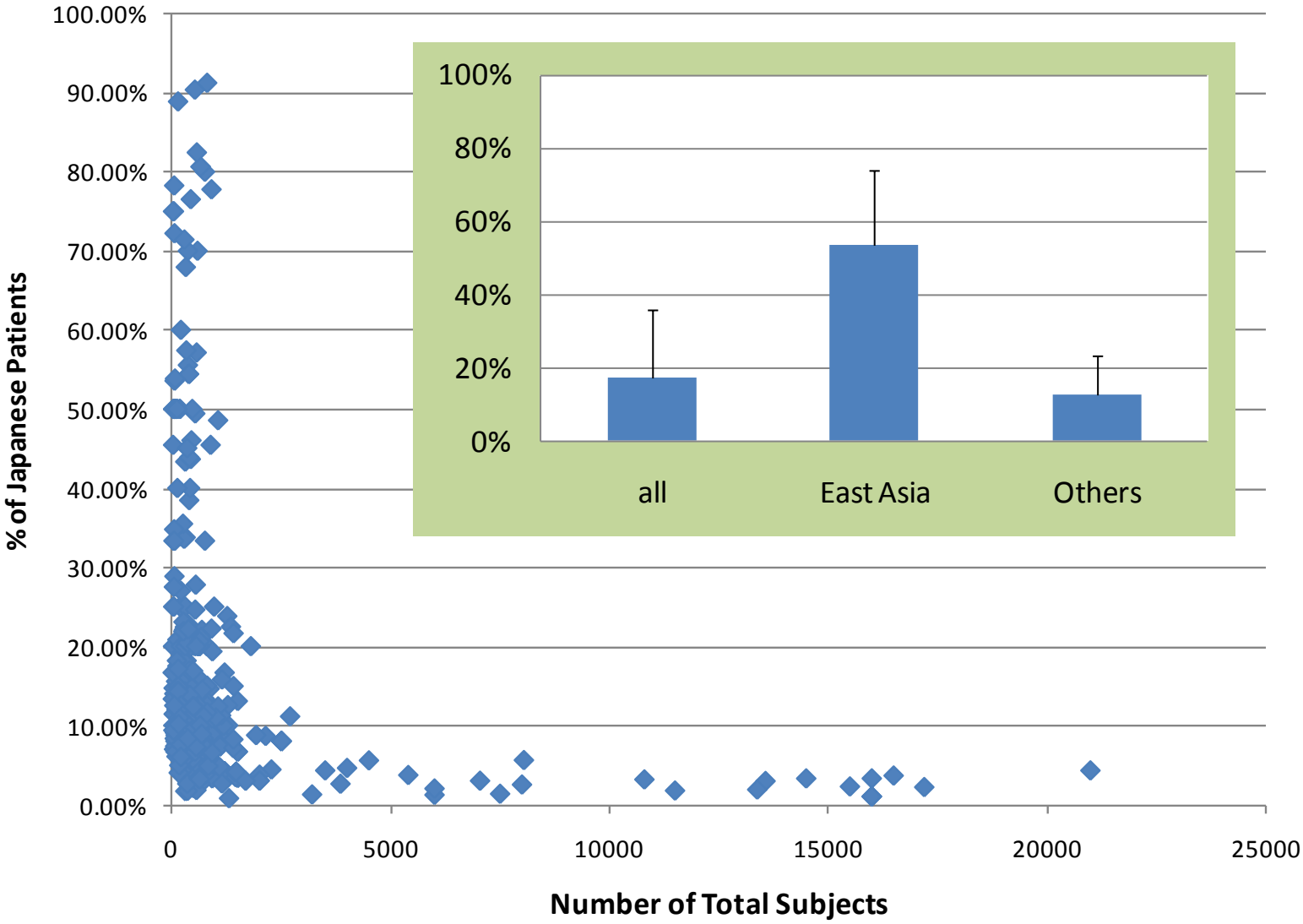
East-Asian GCTs



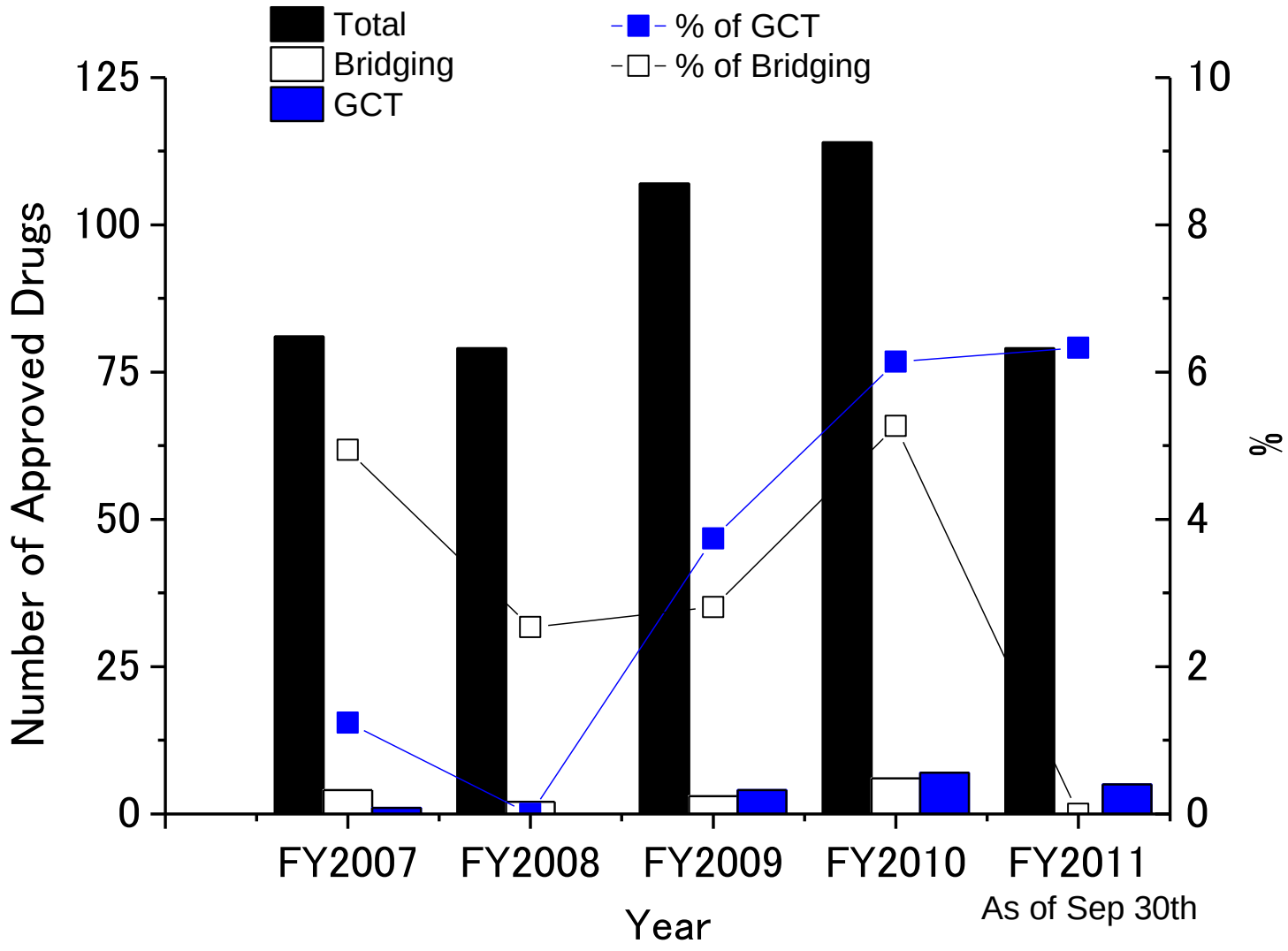
Other GCTs



Japanese population in GCTs

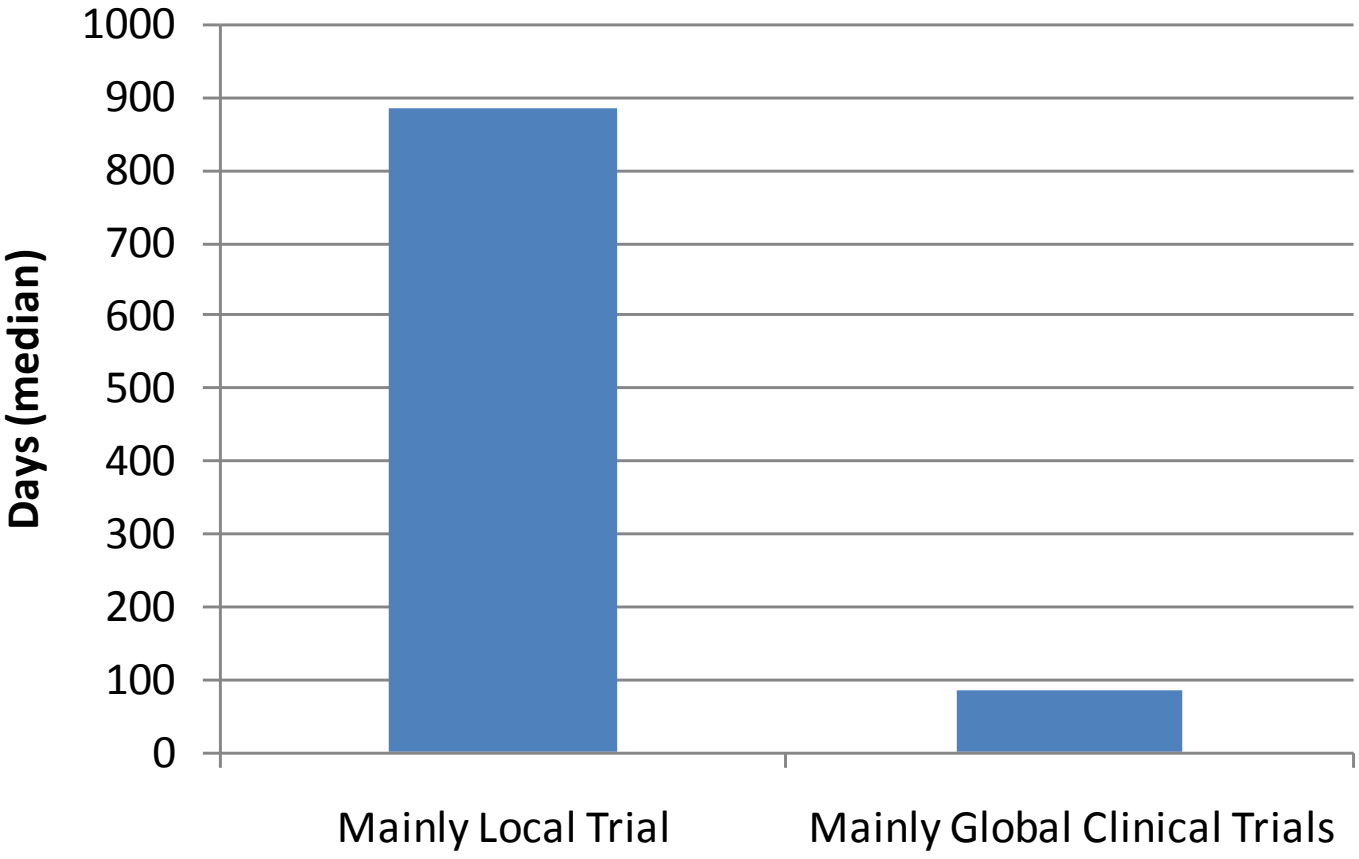


GCTs or Bridging-based drug approval



GCTs contribute to resolve Drug lag

Approved in FY2009-FY2011（as of Sep. 30th）



*: Difference of NDA application date between USA and Japan is calcualted.
The difference is asuumed 0, if a drug is not approved in USA.

Oncology drugs

GCTs-based approval

	Japan	US	Lag (month)	EU	Lag (month)
Gefitinib	2002.7	2003.5	-10	—	—
Trastuzumab (Adju, Breast cancer)	2008.1	2006.11	15	2006.5	21
Everolimus (RCC)	2010.1	2009.3	10	2009.8	5
Panitumumab (2nd line)	2010.4	—	—	—	—
Temsirolimus	2010.7	2007.5	39	2007.11	33
Nilotinib	2010.12	2010.6	6	2010.12	0
Trastuzumab (Gastric cancer)	2011.3	2010.10	5	2010.1	14
Dasatinib	2011.6	2010.10	8	2010.12	6
Gefitinib (EGFR mut+)	2011.11	—	—	2009.6	0*
Everolimus (pNET)	2011.12	2011.5	7	2011.8	4
Denosumab	2012.1	2010.11	15	2011.5	8

Sample size

Japanese population in GCTs

	Total	Japan	Japan / Total (%)
Gefitinib	210	102	48.6
Trastuzumab (Adju, Breast cancer)	5,090	138	2.7
Everolimus (RCC)	416	24	5.8
Panitumumab (2nd line)	1,186	20	1.7
Temsirolimus	82	20	24.4
Nilotinib	846	79	9.3
Trastuzumab (Gastric cancer)	584	101	17.3
Dasatinib	519	49	9.4
Gefitinib (EGFR mut+)	1,217 (233)	261 (56)	21.4 (24.0)
Everolimus (pNET)	410	40	9.8
Denosumab (Breast cancer)	2,046	136	6.6

“Basic principals on Global Clinical Trials”

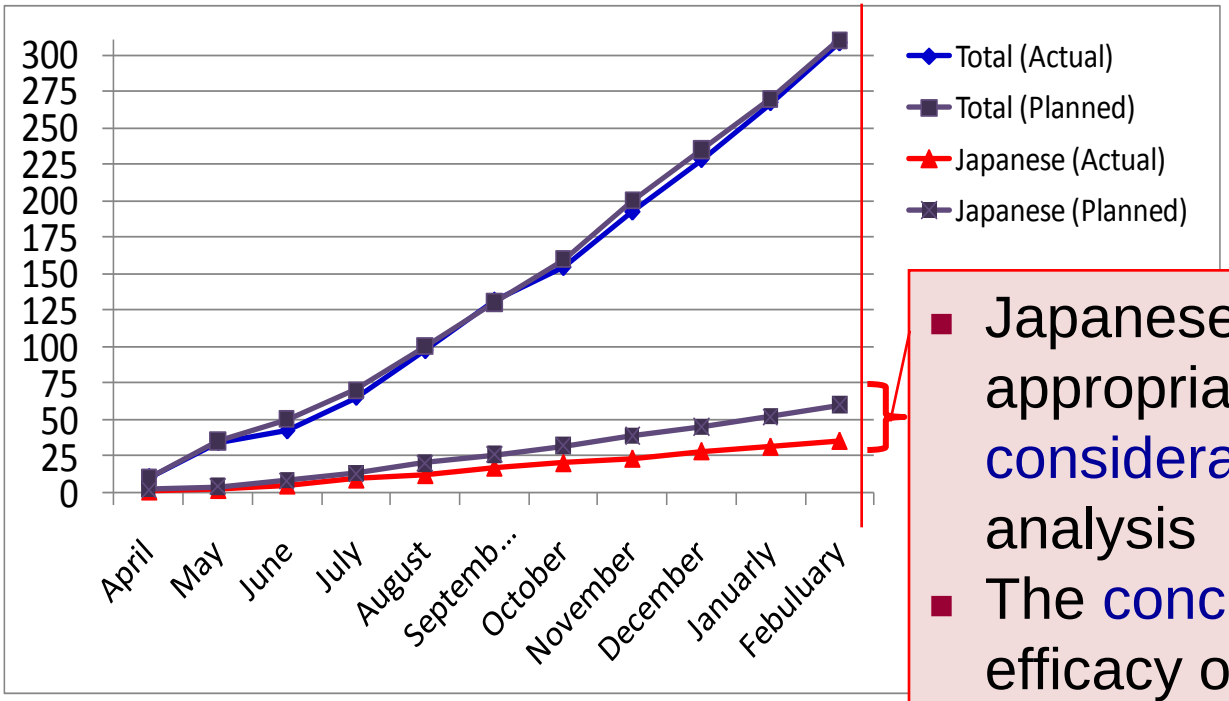
6. When conducting an exploratory trial like a dose-finding study or a confirmatory trail as a global clinical trial, how is it appropriate to determine a sample size and a proportion of Japanese subjects?

- A global trial should be designed so that consistency can be obtained between results from the entire population and the Japanese population, and by ensuring consistency of each region, it could be possible to appropriately extrapolate the result of full population to each region.

Regional data for interim analysis in GCTs

Example:
<Original Plan>

- Total subjects: 600 including 120 Japanese
- Interim analysis is conducted at the time which 50% of total subjects are enrolled



- Japanese data are not appropriately taken into consideration for the interim analysis
- The conclusion may not reflect efficacy or safety in Japanese correctly

Ethnic difference

Ethnic factors (ICH E5 Guideline)

Classification of intrinsic and extrinsic ethnic factors

INTRINSIC		EXTRINSIC
Genetic	**Physiological and pathological condition**	**Environmental**
Gender		**Climate**
Height		**Sunlight**
Body weight		**Pollution**
	Liver	**Culture**
	Kidney	**Socioeconomic status**
	Cardiovascular functions	**Educational status**
		Language
ADME		
Receptor sensitivity		**Medical practice**
		Disease definition/Diagnostic
Race		**Therapeutic approach**
		Drug compliance
		Smoking
		Alcohol
Genetic polymorphism of the drug metabolism		
		Food habit
		Stress
Genetic diseases	**Diseases**	**Regulatory practice/GCP**
		Methodology/Endpoints

Everolimus & Temsirolimus

Indication : Unresectable or metastatic renal cell carcinoma

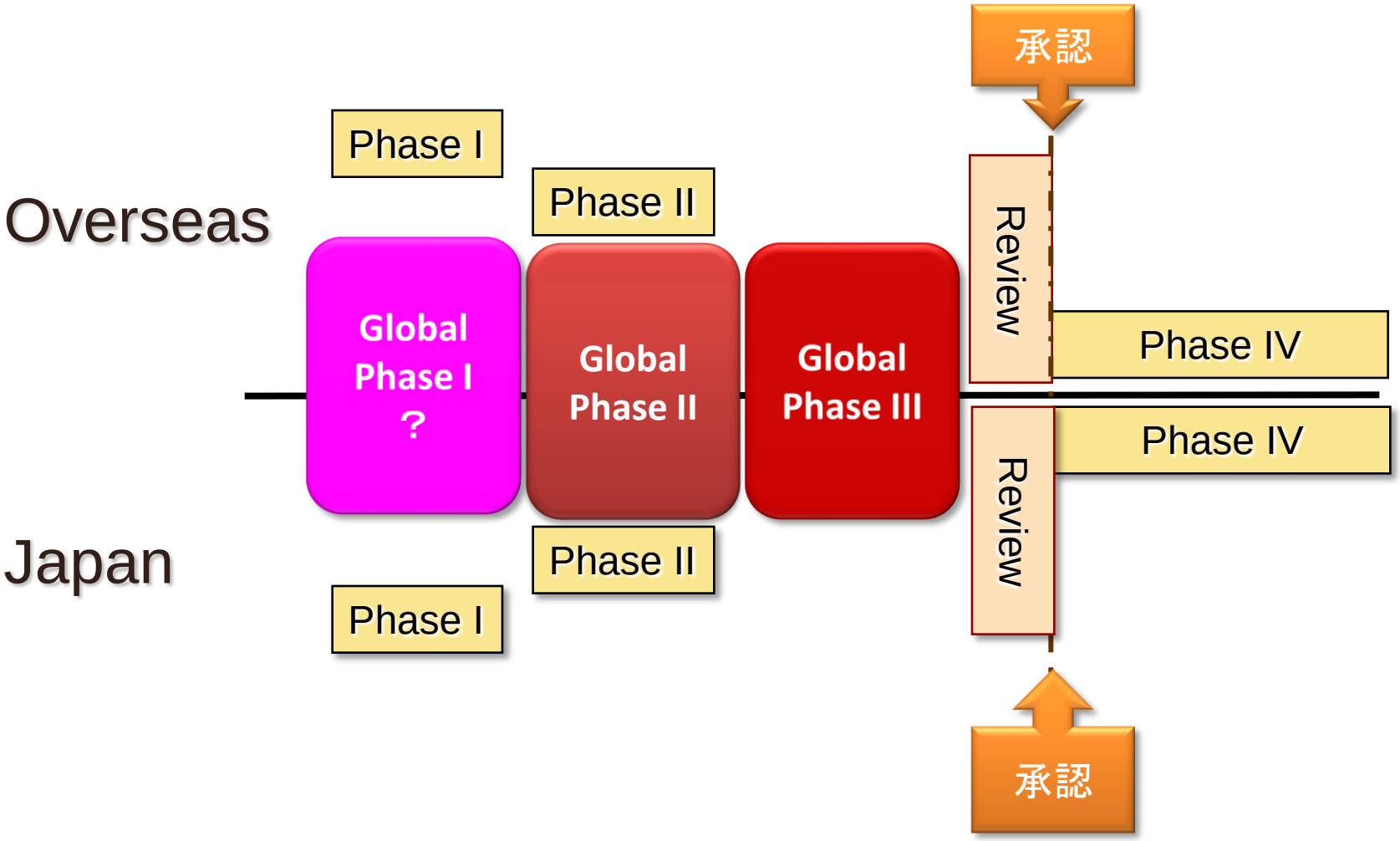
Drug safety:

Incidence rate of Interstitial lung disease (ILD)

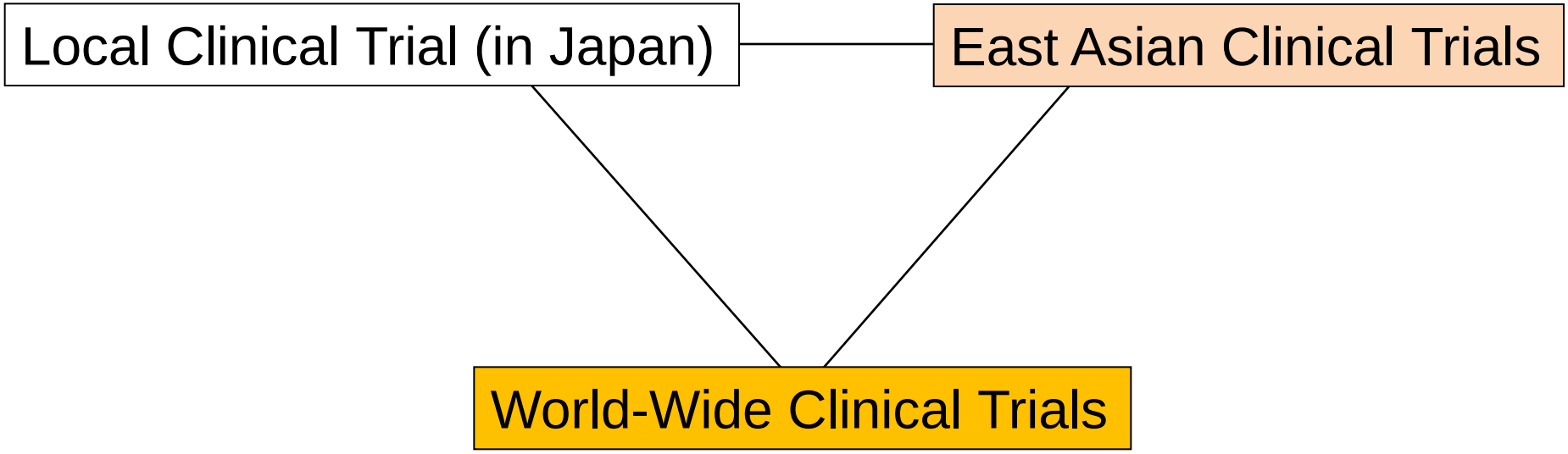
<table>
<tr><th></th><th>Everolimus</th><th></th><th colspan="2">Temsirolimus</th></tr>
<tr><td>Japan</td><td>26.7%
(4/15)</td><td>Japan</td><td>55.0%
(11/20)</td><td rowspan="3">58.4%
(45/77)</td></tr>
<tr><td rowspan="3">Overseas</td><td rowspan="3">12.7%
(33/259)</td><td>China</td><td>55.2%
(16/29)</td></tr>
<tr><td>Korea</td><td>64.3%
(18/28)</td></tr>
<tr><td>US & EU</td><td colspan="2">29.2%
(52/178)</td></tr>
</table>

Summary (1)

To promote global drug development



Summary (2)



Flexible drug development strategy !

- Many strategies are available.
- Establish a best trial plan based on all available data at that point.

Thank you for your attention !