Global Drug Development in consideration of Ethnic Factors -Regulatory Perspective-

Pharmaceuticals & Medical Devices Agency
(PMDA)
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Global Drug Development

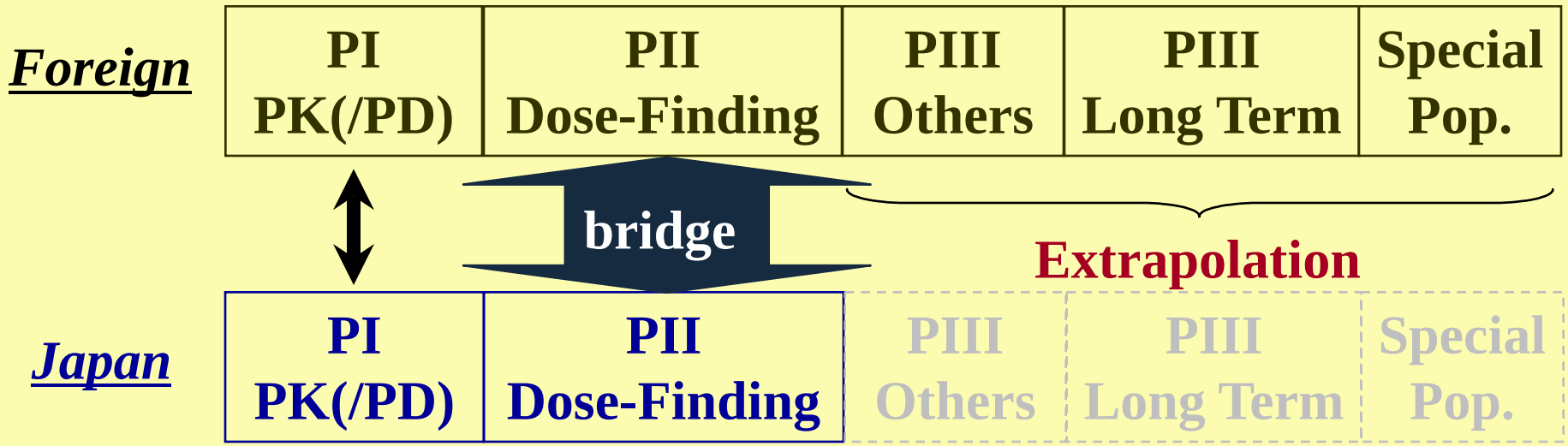
- Why it is increasing?
  - can prevent unnecessary duplication of clinical trials
  - can make drug development more efficient and cost-effective
  - can enable simultaneous drug submission and approval all over the world
  - can achieve faster access of effective and safe drug to patients

- Issues to be considered
  - What type of/how much data should we collect for an investigational drug?
  - When? Where? How?

History of evaluating ethnic factors in Japan (1)

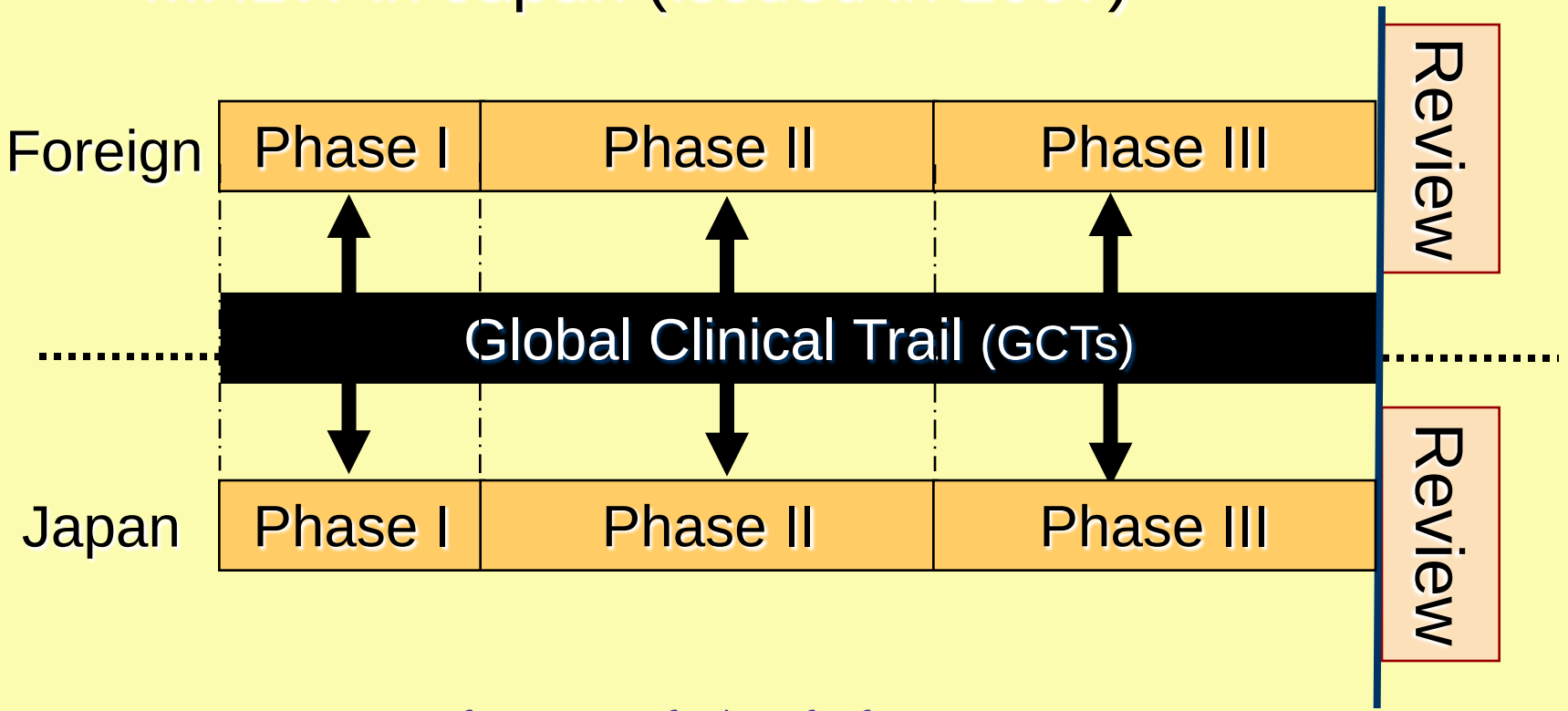
Uyama Y et al, *Clin Pharmacol Ther*, 78: 102-113, 2005

- Bridging Strategy
  - "Ethnic Factors in the Acceptability of Foreign Clinical Data"(ICH-E5, issued in 1998)
  - Extrapolating foreign data (mainly US, EU) to Japan

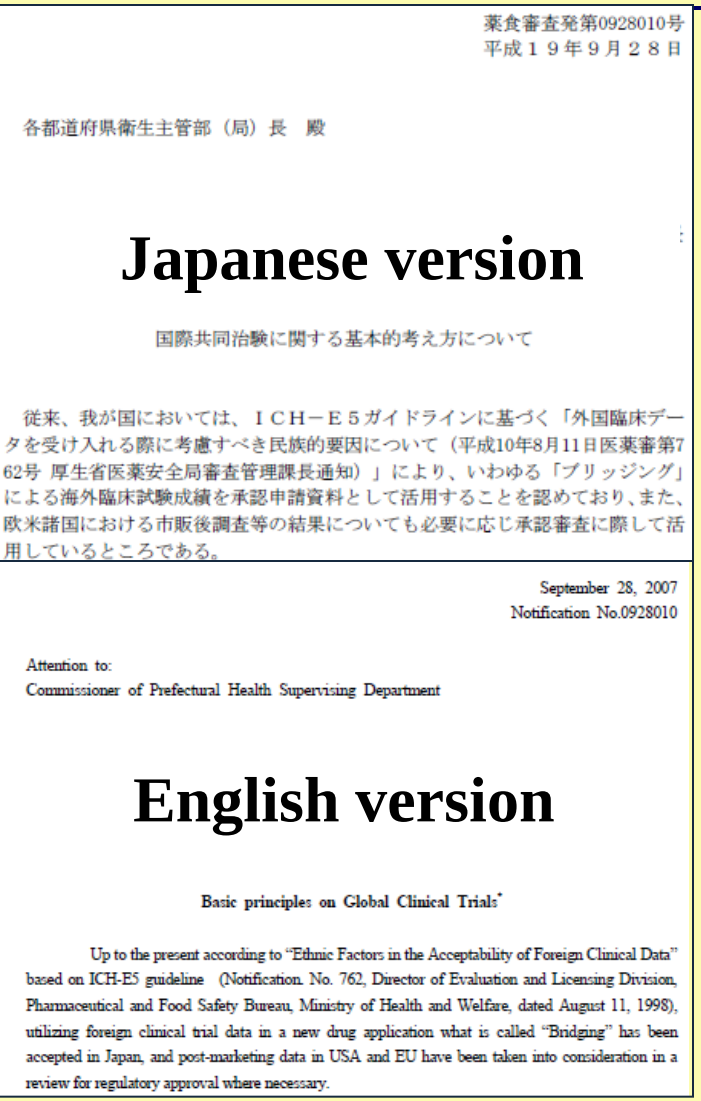


History of evaluating ethnic factors in Japan (2)

- Global Clinical Trials (GCTs)
  - ICH-E5 Q&A11 for GCTs (issued in 2006)
  - “Basic Principles on Global Clinical Trials” by MHLW in Japan (issued in 2007)



Basic Principles on Global Clinical Trials



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平成１９年９月２８日

各都道府県衛生主管部（局）長　殿

Japanese version

国際共同治験に関する基本的考え方について

従来、我が国においては、ＩＣＨ－Ｅ５ガイドラインに基づく「外国臨床データを受け入れる際に考慮すべき民族的要因について（平成10年8月11日医薬審第762号 厚生省医薬安全局審査管理課長通知）」により、いわゆる「ブリッジング」による海外臨床試験成績を承認申請資料として活用することを認めており、また、欧米諸国における市販後調査等の結果についても必要に応じ承認審査に際して活用しているところである。

September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

English version

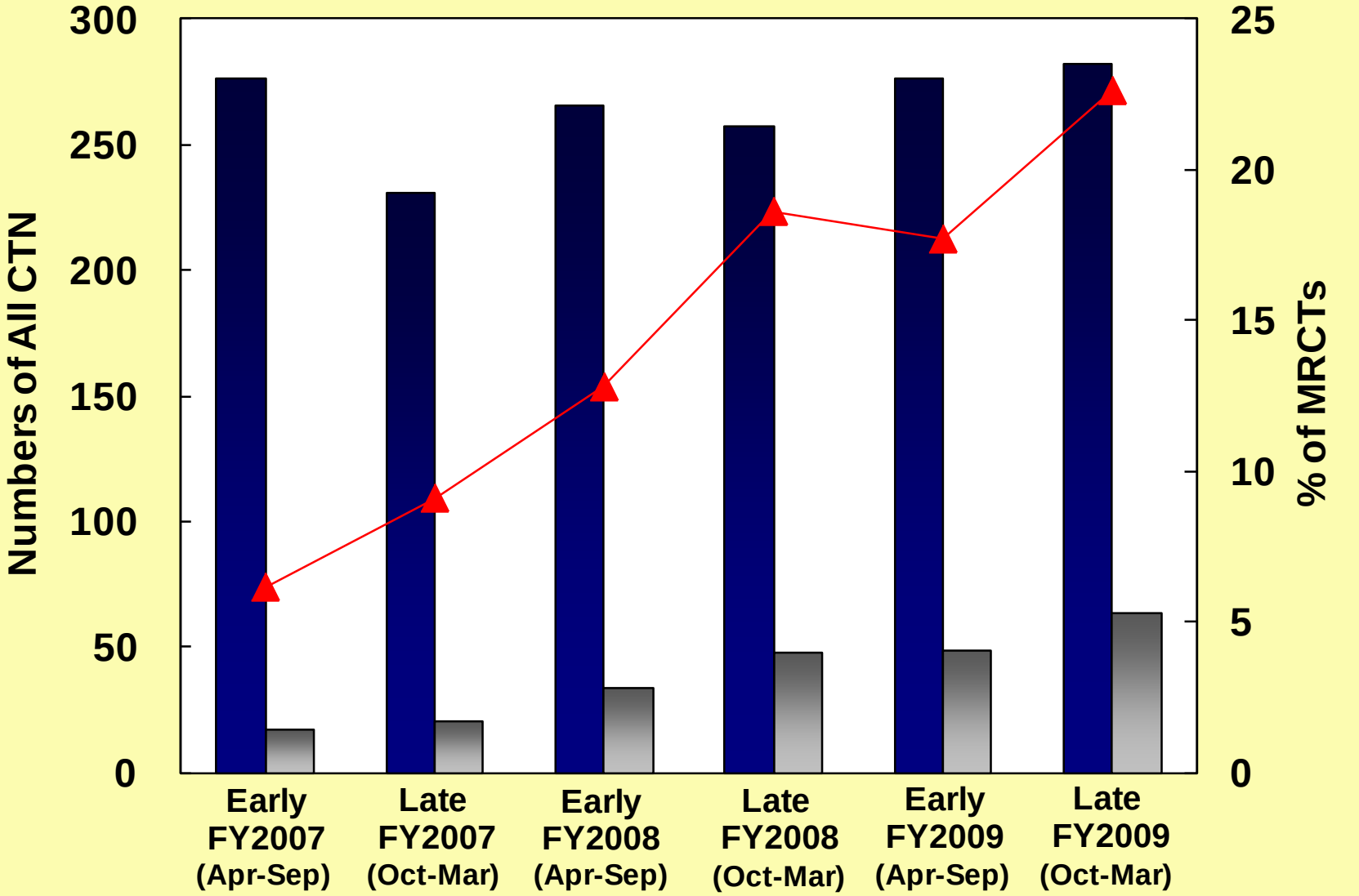
Basic principles on Global Clinical Trials*

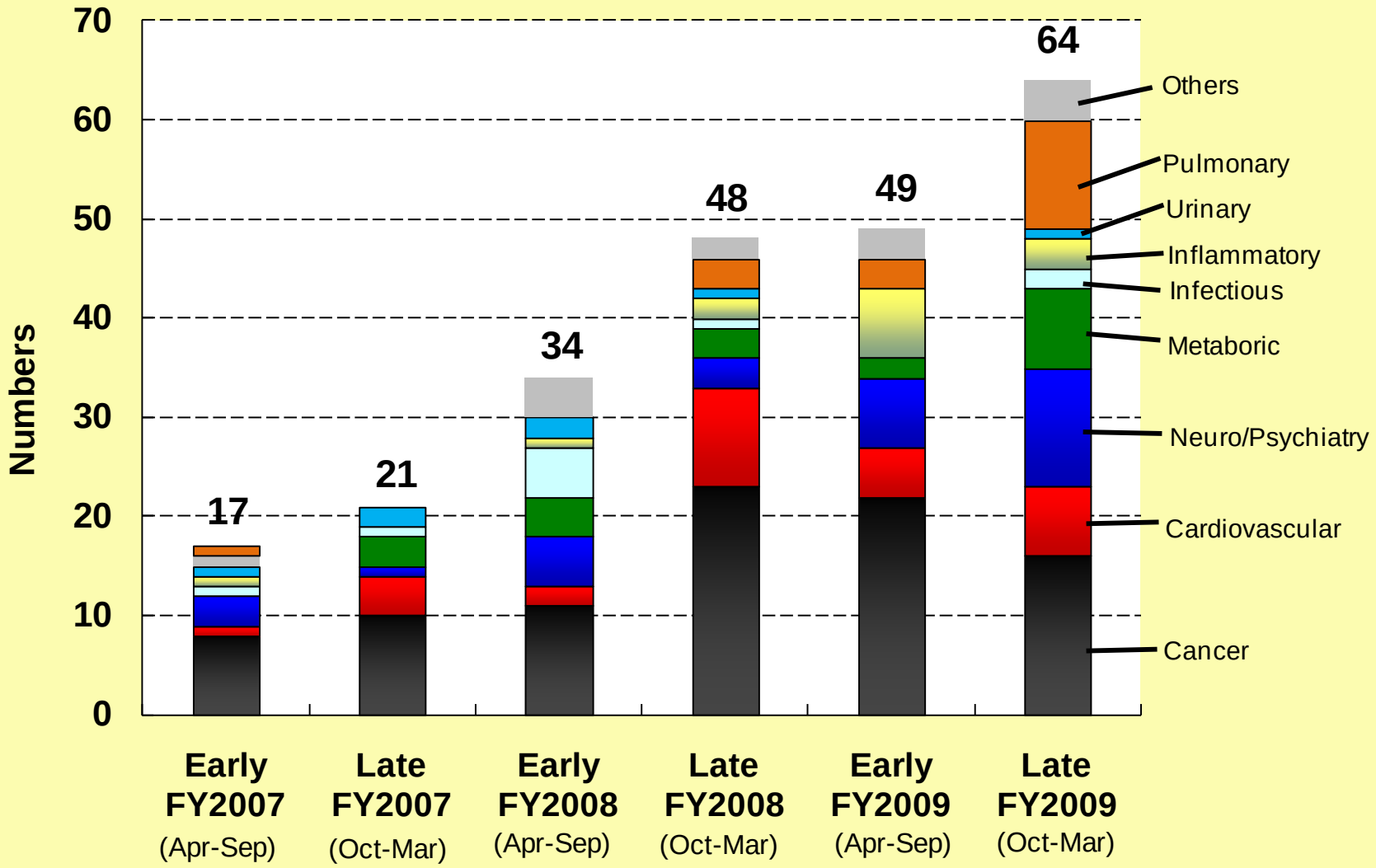
Up to the present according to "Ethnic Factors in the Acceptability of Foreign Clinical Data" based on ICH-E5 guideline (Notification No. 762, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign 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.

－Key Message－

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

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


Numbers of All CTN
% of MRCTs
300
250
200
150
100
50
0
25
20
15
10
5
0
Early FY2007 (Apr-Sep)
Late FY2007 (Oct-Mar)
Early FY2008 (Apr-Sep)
Late FY2008 (Oct-Mar)
Early FY2009 (Apr-Sep)
Late FY2009 (Oct-Mar)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60
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Numbers
17
21
34
48
49
64
Others
Pulmonary
Urinary
Inflammatory
Infectious
Metaboric
Neuro/Psychiatry
Cardiovascular
Cancer
Early FY2007 (Apr-Sep)
Late FY2007 (Oct-Mar)
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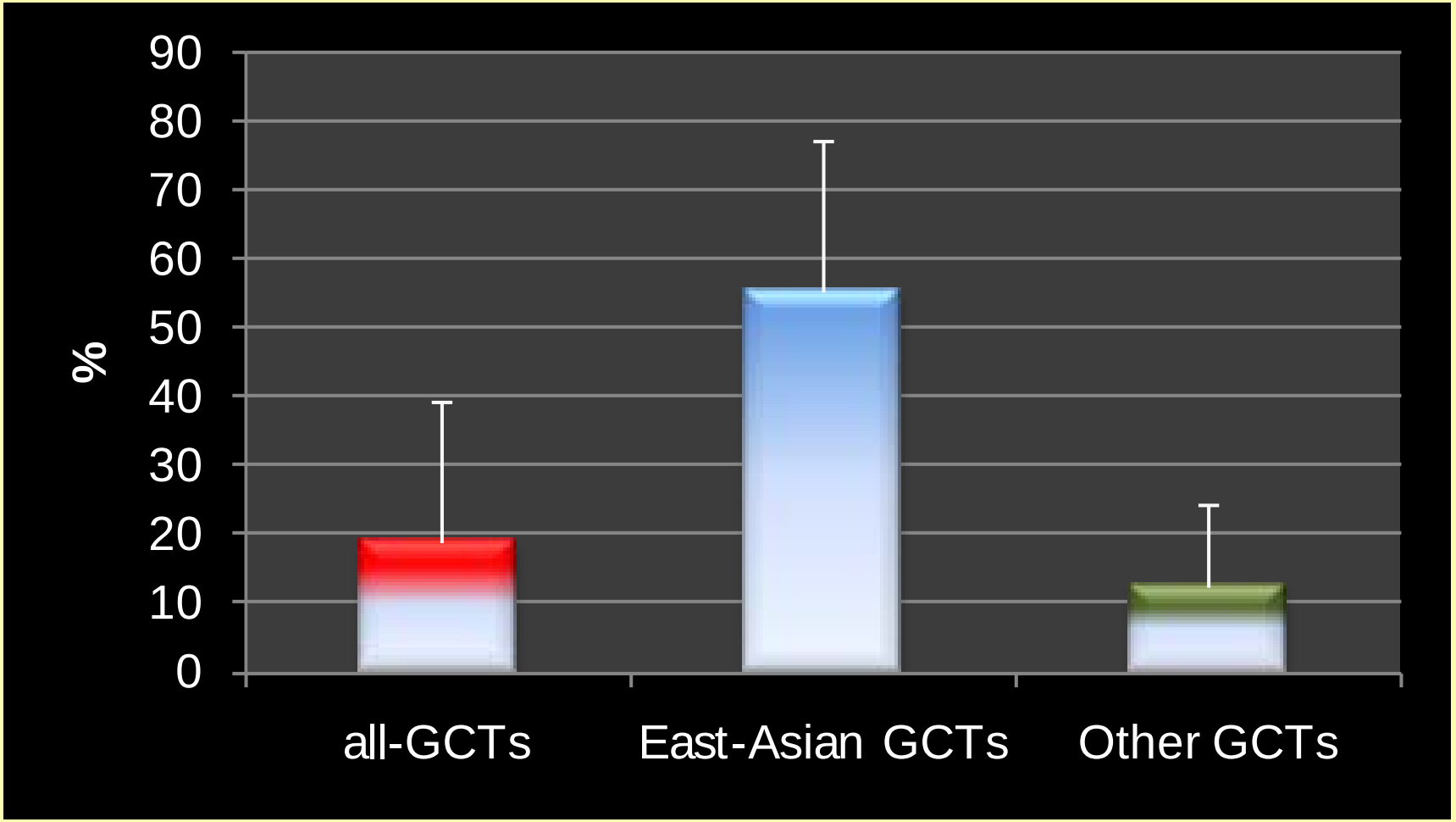
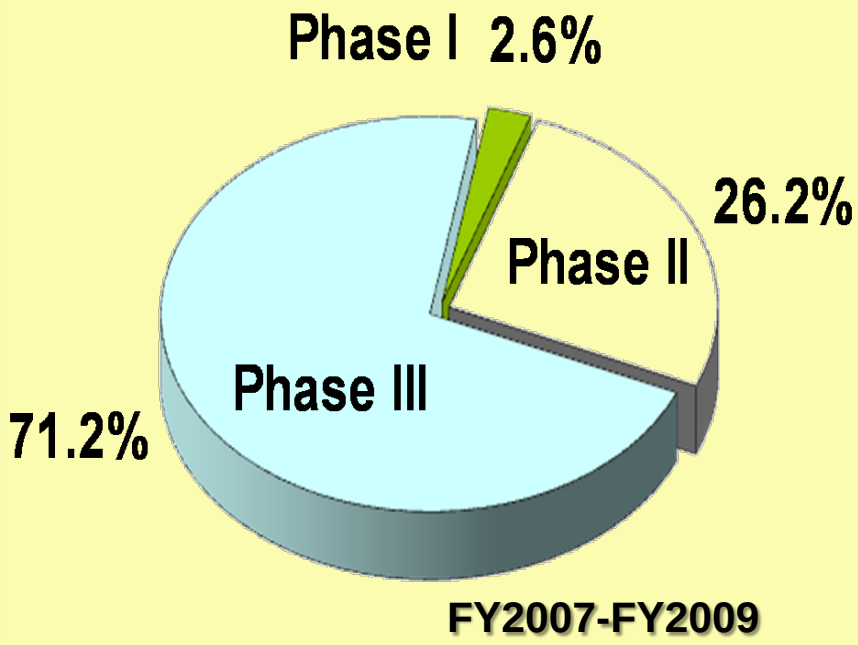
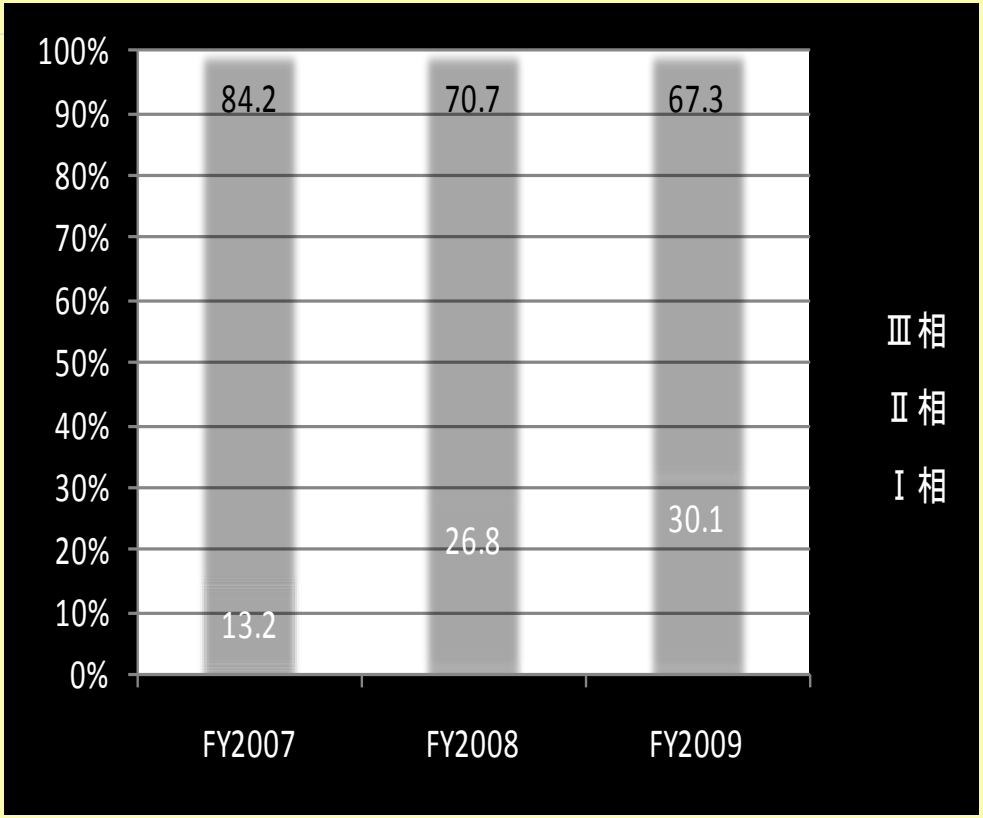
Late FY2008 (Oct-Mar)
Early FY2009 (Apr-Sep)
Late FY2009 (Oct-Mar)

FY2008-FY2009




Phase I 2.6%
26.2%
Phase II
Phase III
71.2%
FY2007-FY2009


100%
90%
80%
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50%
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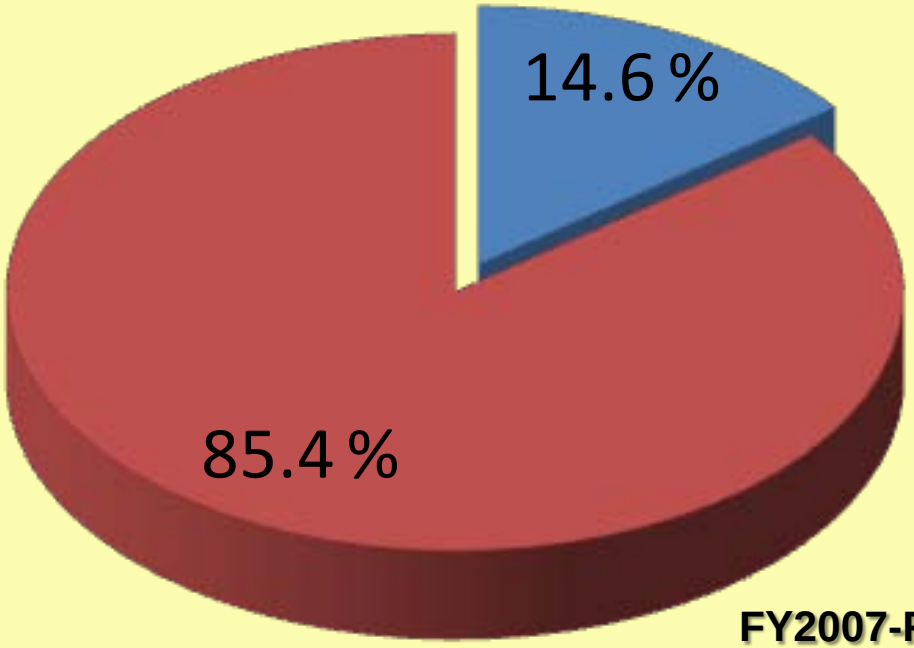
Japan based Company



FY2007-FY2009

US/EU based Company

Review Experiences of Global Clinical Trials

GCTs: Approved cases in Japan

	Indication	Date of Approval	Note
Tolterodine tartrate	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	April 2006	Korea-Japan
Losartan potassium	Diabetic nephropathy with proteinuria and hypertension in patients with type 2 diabetes	April 2006	Global (Asian data)
Trastuzumab	Adjuvant therapy for HER2-positive breast cancer	February 2008	Global Oncology
Insulin glulisine	Diabetes mellitus	April 2009	Korea-Japan
Tadalafil	Pulmonary arterial hypertension	October 2009	Global Dose-response
Peramivir	Type A and Type B Influenza virus infection	January 2010	Asian
Everolimus	Metastatic renal cell carcinoma	January 2010	Global Oncology

Recent Examples of Data in GCTs

Insulin glulisine

- Indication
  - Diabetes mellitus

- Global Clinical Trial
  - Conducted in Korea and Japan
  - Number of patient
    - Total: N=387
      - Korea: N=189
      - Japan: N=198
  - Objective: To demonstrate efficacy and safety of glulisine+OHA* and glulisine-only compared to OHA
  - Primary endpoint: change in HbA1c from baseline to trial endpoint (Week6)

*OHA: Oral hypoglycemic agents

- PK/PD study in Korean and Japanese healthy volunteers

Insulin glulisine

Result of primary endpoint: HbA1c

		Glulisine+OHA	Glulisine	OHA
All regions	Baseline	8.99	9.02	9.04
	Study endpoint	6.93	7.76	8.42
	Adjusted change	-2.07	-1.25	-0.61
	N	128	124	128
Korea	Baseline	9.02	9.14	9.07
	Study endpoint	7.13	7.92	8.31
	Adjusted change	-1.91	-1.2	-0.77
	N	61	59	63
Japan	Baseline	8.96	8.91	9.01
	Study endpoint	6.75	7.62	8.53
	Adjusted change	-2.21	-1.31	-0.45
	N	67	65	65

Insulin glulisine

- Primary result
  - Glulisine+OHA and glulisine-only show superiority in efficacy compared to placebo

- Review points
  - No major differences were observed in efficacy of Glulisine in both Korean and Japanese subgroup

- Conclusion
  - Efficacy of glulisine was demonstrated in this trial

Peramivir

- Indication
  - Type A and Type B Influenza virus infection

- Multiregional clinical trial
  - Conducted in Japan, Korea, Taiwan
  - Number of patient
    - Total: N=1099
      - Japan: N=743, Korea: N=106, Taiwan: N=250
  - Objective: To demonstrate non-inferiority of 300 mg and 600 mg of peramivir to oseltamivir phosphate
  - Primary endpoint: Time to alleviation of influenza symptoms
  - PK data

Peramivir

Result of primary endpoint:
Time to alleviation of symptoms (hr)

		300mg	600mg	Oseltamivir
All regions	Median (95%CI)	78.0 (68.4, 88.6)	81.0 (72.7, 91.5)	81.8 (73.2, 91.1)
	HR (97.5%CI)	0.946 (0.793, 1.129)	0.970 (0.814, 1.157)	-
	N	364	362	365
Japan	Median (95%CI)	78.0 (68.1, 88.6)	80.7 (71.1, 91.3)	80.6 (70.0, 92.3)
	HR (97.5%CI)	0.916 (0.740, 1.135)	0.946 (0.764, 1.171)	-
	N	247	249	246
Korea	Median (95%CI)	68.4 (43.5, 119.0)	49.7 (31.1, 103.0)	63.4 (37.6, 86.8)
	HR (97.5%CI)	1.349 (0.733, 2.482)	1.196 (0.635, 2.252)	-
	N	36	34	35
Taiwan	Median (95%CI)	80.0 (57.4, 107.8)	104.0 (72.2, 150.1)	103.4 (77.2, 137.2)
	HR (97.5%CI)	0.939 (0.628, 1.402)	0.969 (0.658, 1.426)	-
	N	81	79	84

Cox proportional hazard model

Peramivir

- Primary result
  - Non-inferiority of 300 mg and 600 mg of peramivir to oseltamivir phosphate was demonstrated
- Review points
  - Primary endpoint was subjective based on patient's diary
  - Shorter time to alleviation in Korea (possibly caused by difference of subtype of virus)
- Conclusion
  - There was no major differences in efficacy of peramivir among regions

Everolimus

- Indication
  - Metastatic renal cell carcinoma

- Multiregional clinical trial
  - Conducted in 10 countries including Japan
  - Number of patient (for interim analysis of efficacy)
    - Total: N=410
      - Japan: N=18
  - Objective: To demonstrate efficacy of everolimus compared to placebo
  - Primary endpoint: Progression Free Survival
  - Early terminated by interim analysis for efficacy

Everolimus

Result of primary endpoint: PFS

		everolimus	Placebo
All regions*	Median PFS (95%CI) N	4.01 (3.71, 5.52) 272	1.87 (1.81, 1.94) 138
Japan	Median PFS N	- 10	2.60 8

*: Hazard ratio (95%CI): 0.30 (0.22, 0.40), P<0.001 (Log-rank test)

- Primary result
  - Everolimus prolongs PFS relative to placebo
- Conclusion
  - Although sample size and follow-up period of Japanese patients were limited, Japanese result was not markedly different from the result of all regions

Lessons learned (continued)

- Difficulty of evaluating data from GCTs
  - Small number of patients for one region
    - Enough number of Japanese population is necessary to evaluate data appropriately
  - Comparing dose-response relationship among regions
    - Japanese patients should be included not only confirmatory trials but also exploratory POC/Dose-Finding Study

Lessons learned (Continued)

- Importance of data in Asia
  - Closer ethnicity among Asian population
  - Increasing experiences to review Asian data which provide an informative information
  - But, efficacy/safety of a drug may be different even among Asian populations
  - Need to accumulate more experiences and Asian data to understand similarities/differences in drug response(efficacy/safety) among Asian populations

Future Global Drug Development Strategies

Transition of Japan contribution to global drug developments in last several years

Watch

2005

Try

2006

Catch up

2007

Cooperation

2008

Collaboration

2009

Partner

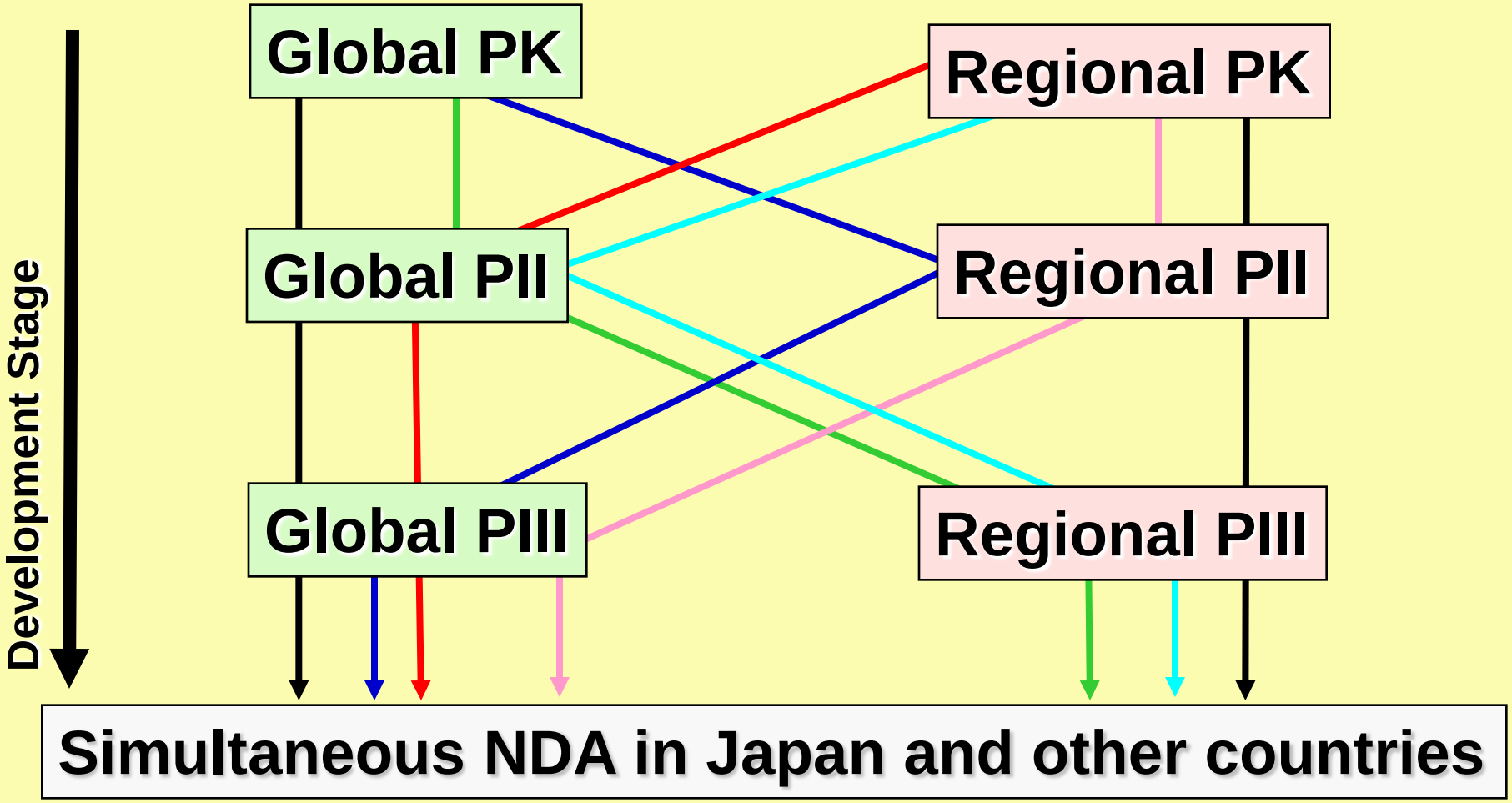
2010

The time for EVOLUTION

Flexible Global Drug Development Strategy

- Global communication including regulatory agency from an initial stage is a key to establish a best strategy

Ichimaru et al, *Clin Pharmacol Therapeut*, 87: 362-366, 2010



Information

- **PMDA HOMEPAGE**
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