

# 日本が変わるべき点・残すべき点 — Which way should we go?

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# Outline of Presentation

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- Latest trend of multi-regional clinical trials in which Japan participates
- Globalization of clinical trials worldwide
- For successful global clinical trials
- Which way should we go?

# ClinicalTrials.gov

**ClinicalTrials.gov**  
A service of the U.S. National Institutes of Health

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ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals. [Read more...](#)

## ▶ [Search for Clinical Trials](#)

Find trials for a specific medical condition or other criteria in the ClinicalTrials.gov registry. ClinicalTrials.gov currently has **80,834 trials** with locations in **170 countries**.

## ▶ [Investigator Instructions](#)

Get instructions for clinical trial investigators/sponsors about how to register trials in ClinicalTrials.gov. Learn about mandatory registration and results reporting requirements and US Public Law 110-85 (FDAAA).

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Learn about clinical trials and how to use ClinicalTrials.gov, or access other consumer health information from the US National Institutes of Health.

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## Study Topics:

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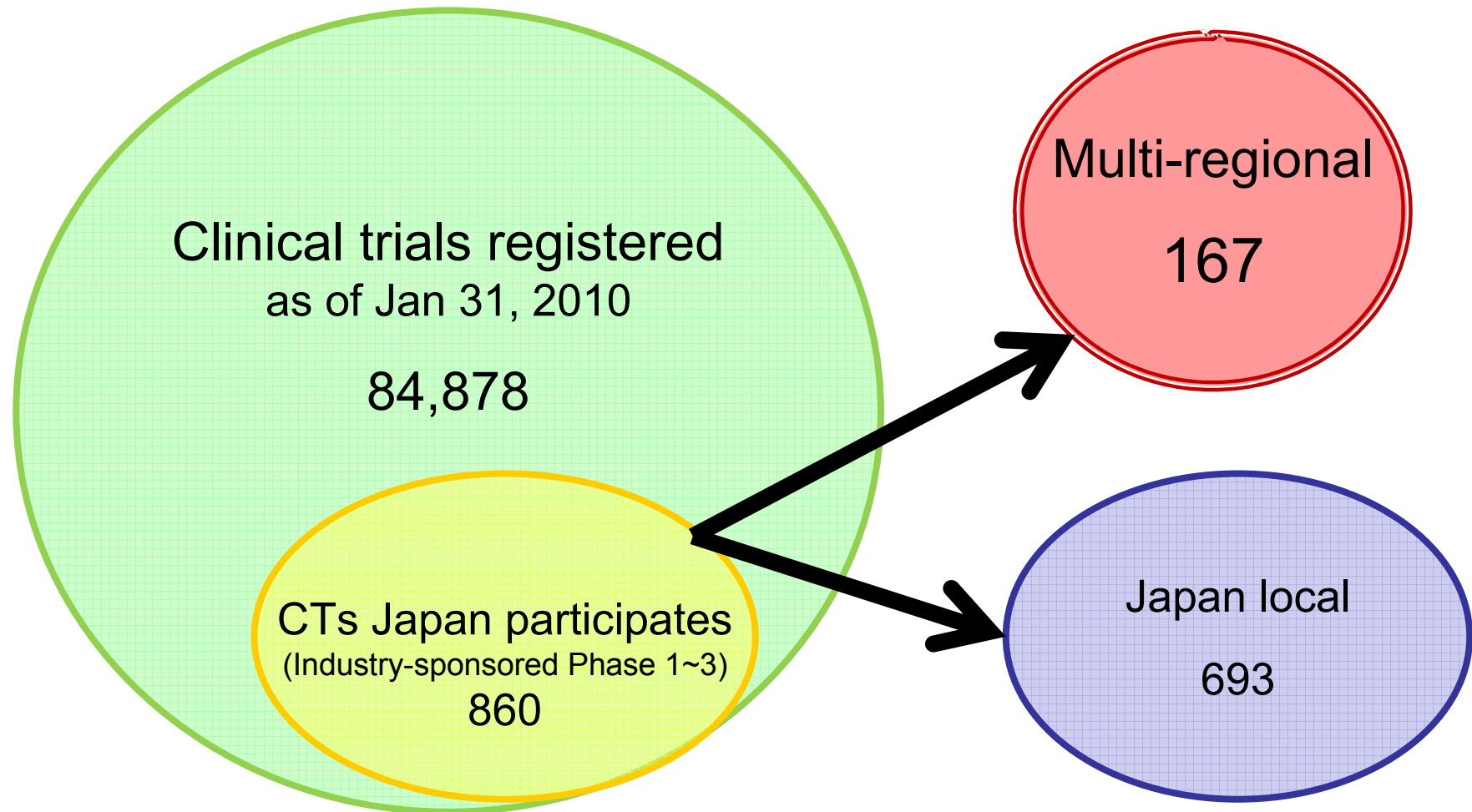
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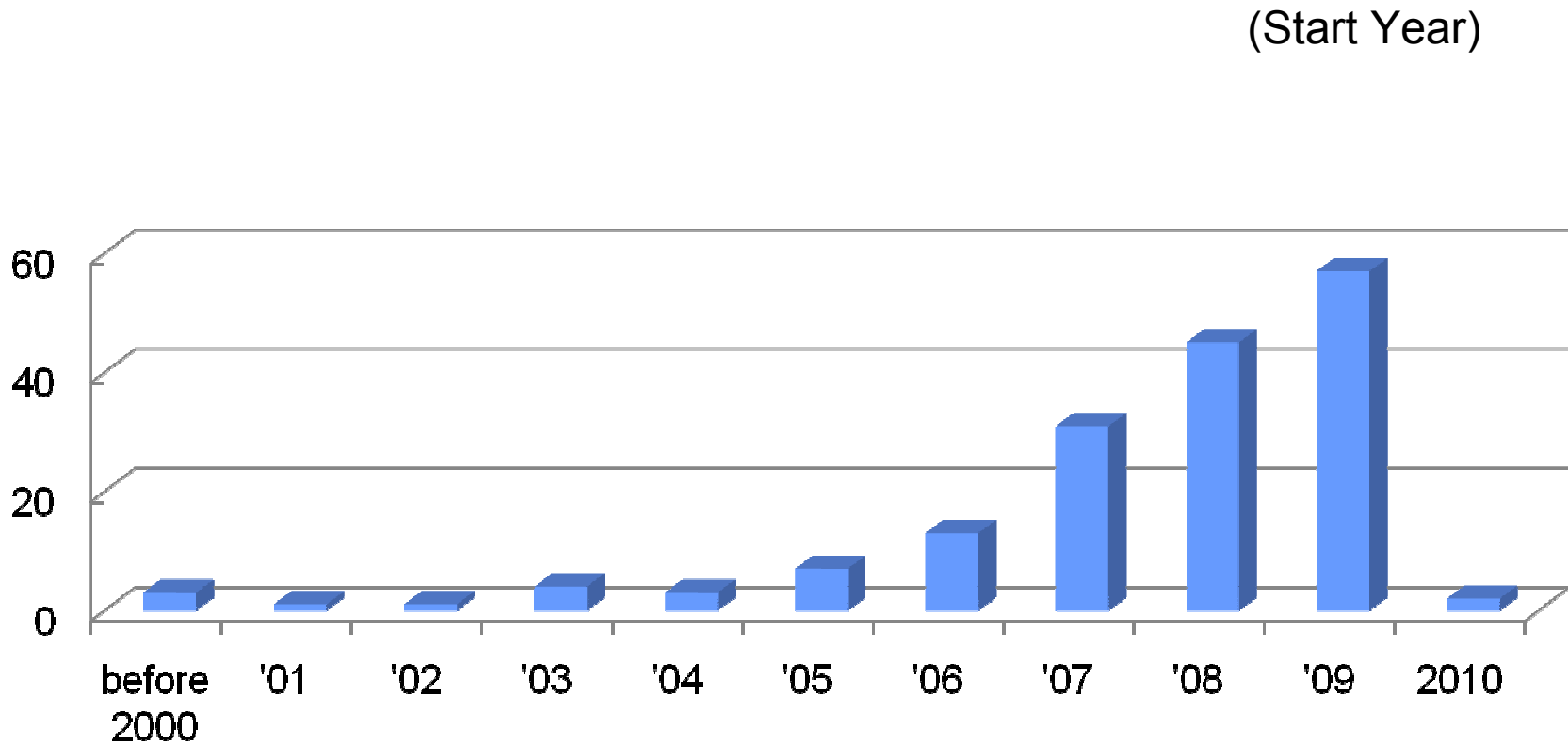


# Clinical Trials Analyzed

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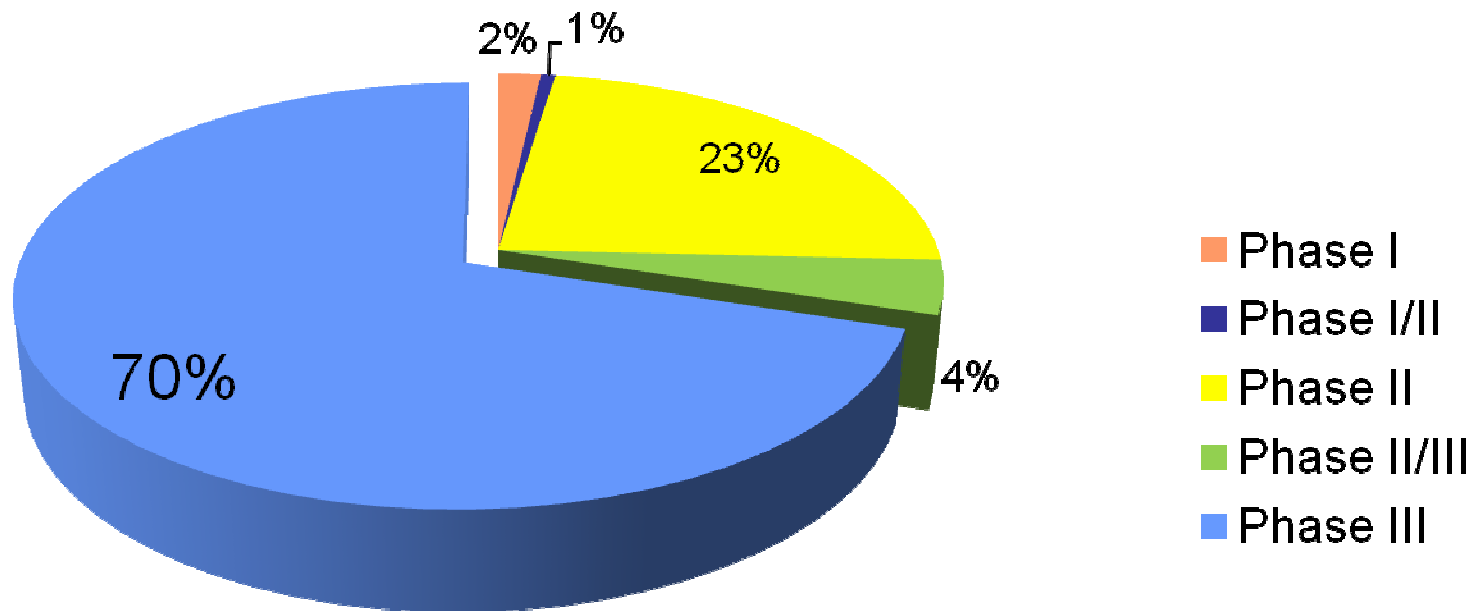


# Changes in the Number of Multi-regional Trials Japan participates



# Number of Trials by Study Phase

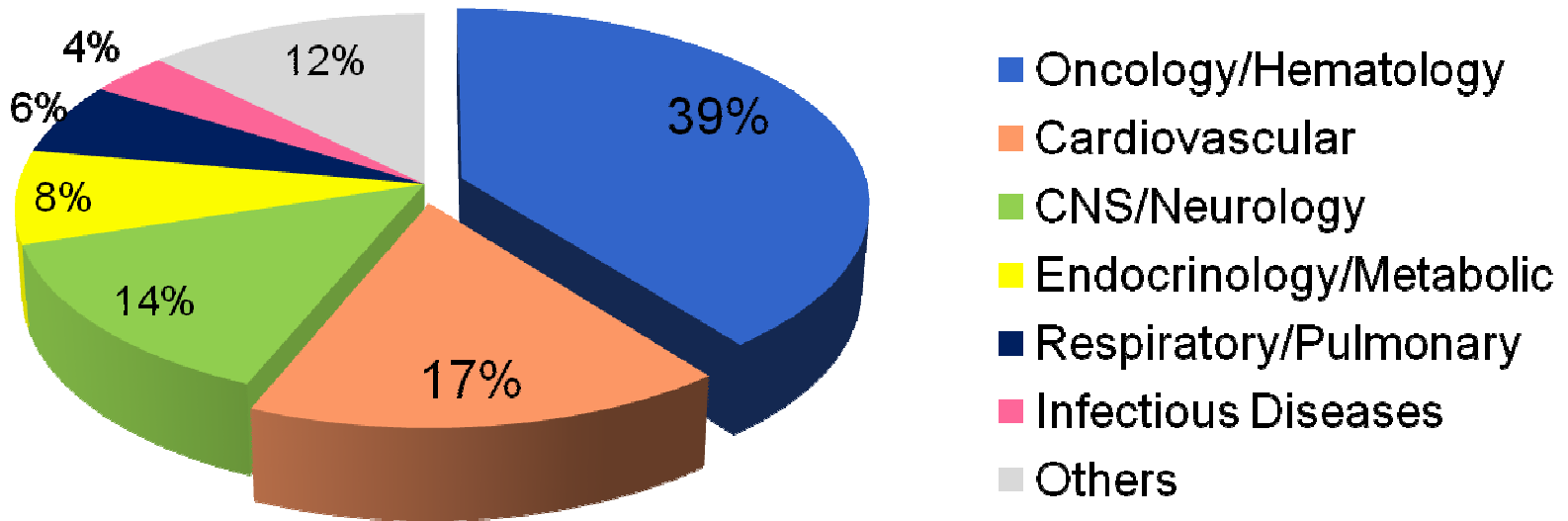
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N=167

# Number of Trials by Therapeutic Area

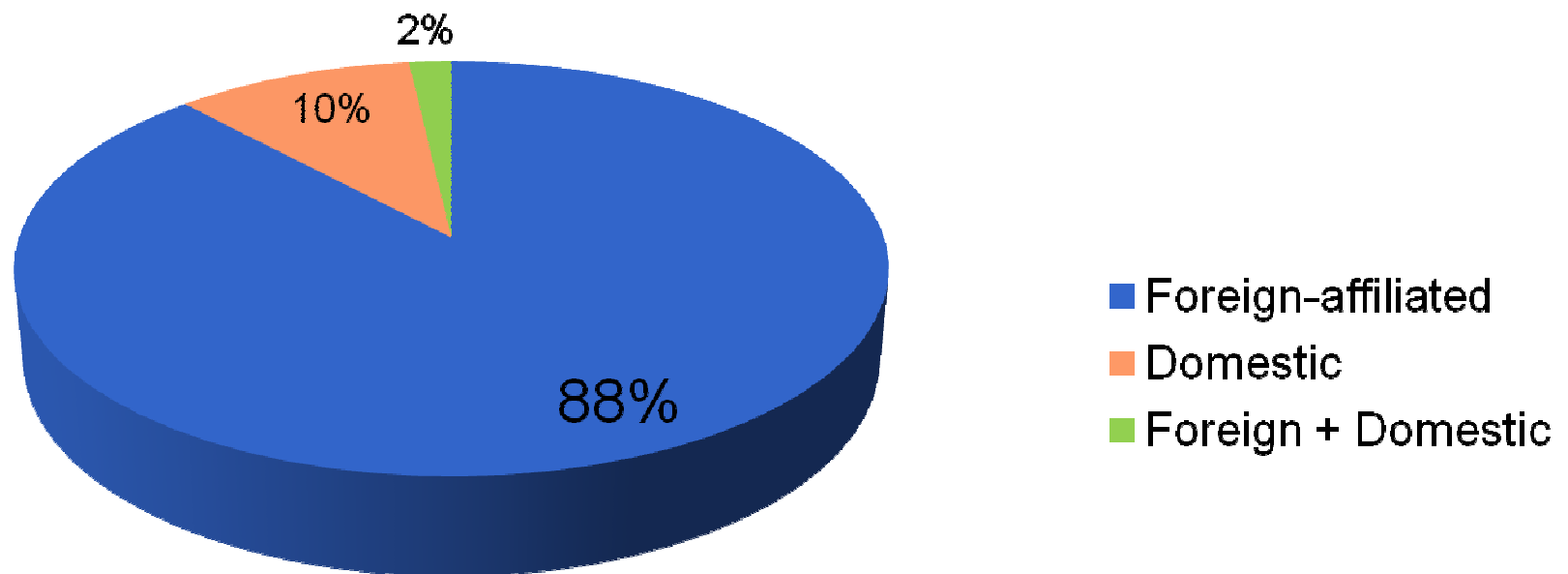
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N=167

# Number of Trials by Company Type

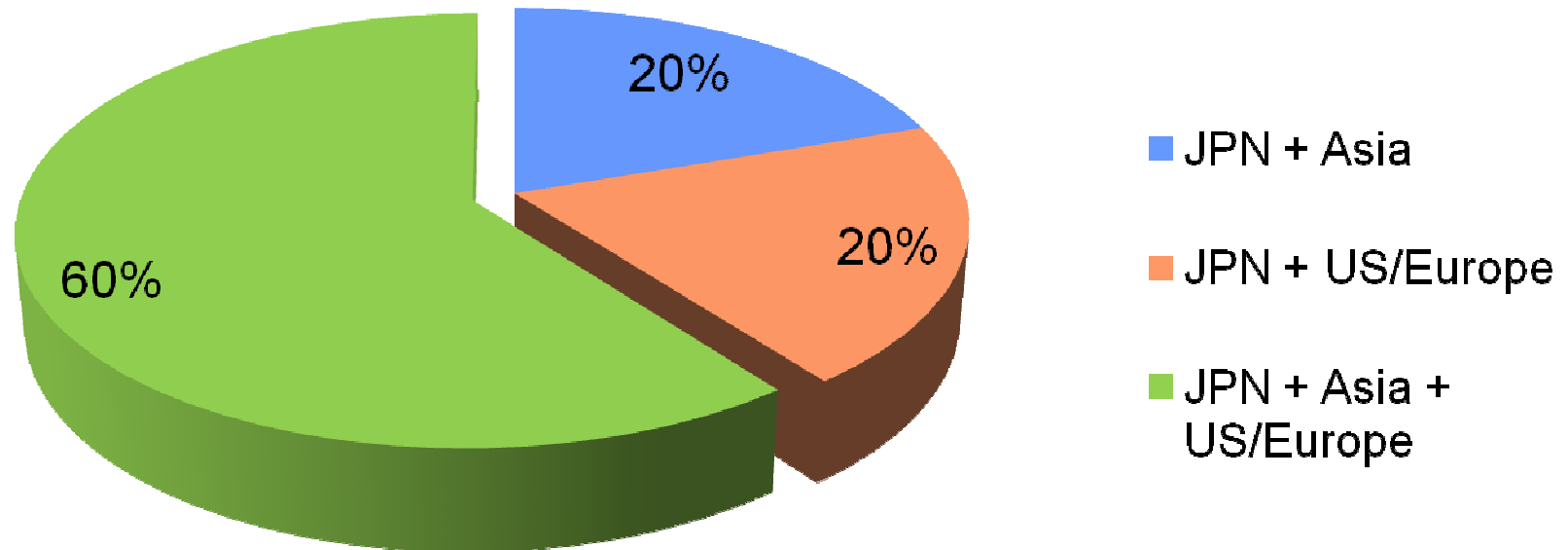
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# Number of Trials by Collaborating Countries/Regions

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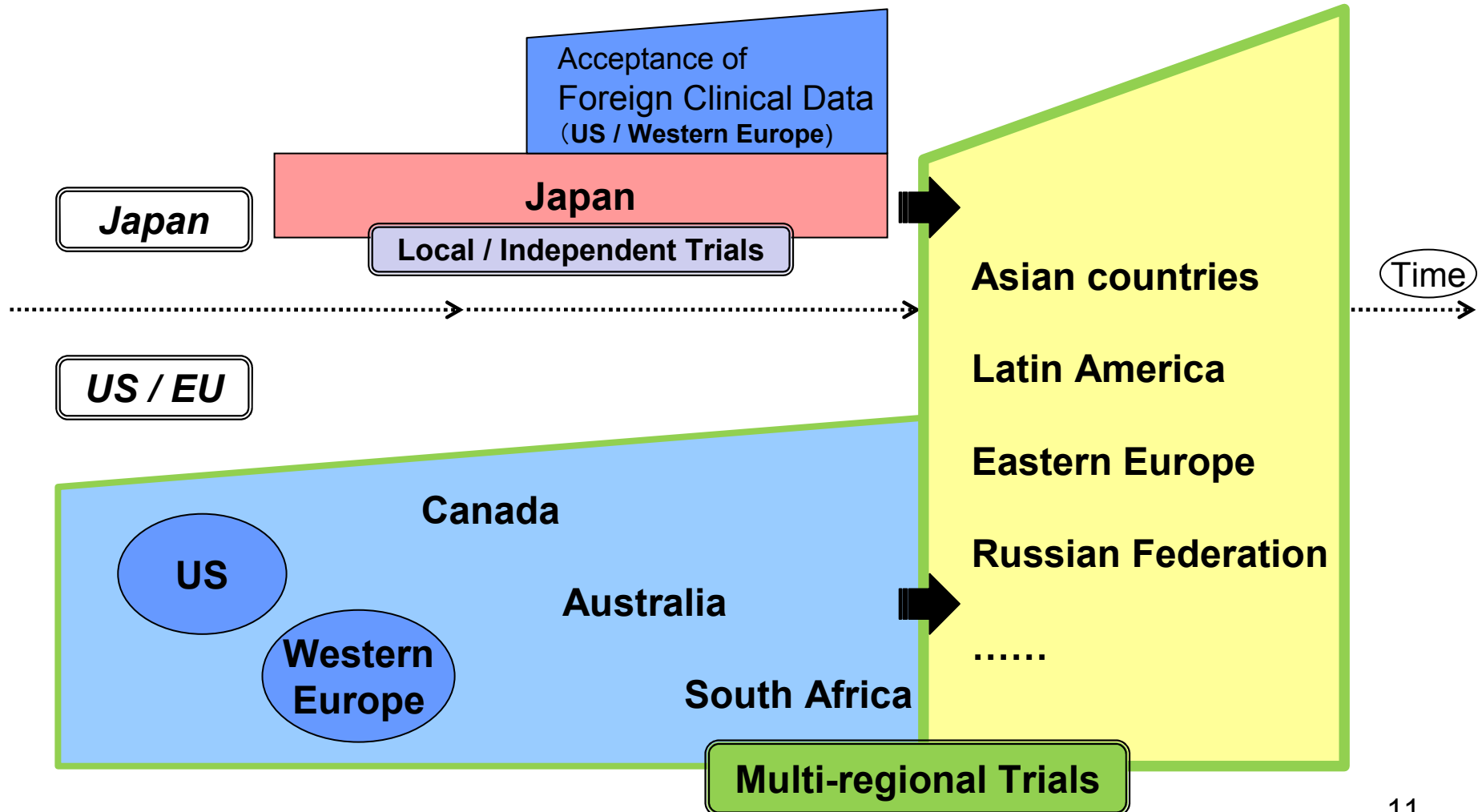
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# Tipping Points of Clinical Trials in Japan

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- '97/98~mid-2000's
  - Adaptation to the international norms
  - Floods of foreign clinical data
  
- Today
  - Globalization of clinical trials
  - Globalization of clinical development

# Globalization of Clinical Trials



# ICH E5 GL was Developed

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ICH E5 was developed to address a very specific issue:

- the conditions in which clinical data developed mainly in the heterogeneous markets of the United States and Europe, but also potentially in other parts of the world, might be acceptable for use in Japan,
- although it was envisaged that the principles of ICH E5 could be applied regardless of where the initial clinical data had been generated.

(Drug Information Journal 2009;43:339-347.)

# Ethical and Scientific Implications of the Globalization of Clinical Research

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- **Industry-sponsored Phase 3 Trials** for the 20 largest US-based companies, as of Nov 2007
  - One third of the clinical trials [157/509] are being conducted solely outside the US.
  - A majority of study sites [13,521/24,206] are outside the US.
  
- This phenomenon raises important questions about:
  - The economics and ethics of clinical research, and
  - The translation of trial results to clinical practice.

(N Eng J Med 2009;360:816-823)

# Reflection Paper by EMEA

## Reflection Paper on the Extrapolation of Results from Clinical Studies conducted outside the EU to the EU-population

(EMEA. Oct 22 2009)

- Drug development is increasingly global.
- An increasing percentage of pivotal studies submitted to the EMEA are conducted outside the EU.
- There is a need to understand the differences and concerns that may arise in the extrapolation of study results to the EU population.
- This paper shows that in particular extrinsic factors, such as ***medical practice, disease definition and study population***, may influence the applicability of foreign data to an EU setting.

## Case Study-1 (EU)

# Difference in Medical Practice

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- Antiplatelet (ST segment elevation acute myocardial infarction)

Study #1: US and European population (Caucasian), # PTs ~3,500  
placebo-controlled, surrogate endpoint

Study #2: China, # PTs ~46,000, placebo-controlled, hard endpoint

- The new drug superior to placebo in both studies
- In Study #2, low use of background beta-blockers and much higher mortality rate compared to Study #1

⇒ Difference in medical practice suggested

## Case Study-2 (Japan)

# Failure of a Bridging Strategy

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- Humanized IgG monoclonal antibody for severe persistent asthma
  
- A bridging study in Japanese prematurely terminated because of too slow subjects' enrolment.
  
- The reason:
  - The protocol was designed in reference to the US protocol.
  - Concomitant medication was too severely restricted in light of Japanese medical practice.

# Ethnic Factors (Intrinsic/Extrinsic)

INTRINSIC		EXTRINSIC
Genetic	Physiological and pathological conditions	Environmental
Gender	Age (children-elderly)	Climate Sunlight Pollution
	Height Bodyweight	<b>Culture</b> Socioeconomic factors Educational status Language
	Liver Kidney Cardiovascular functions	<b>Medical practice</b> Disease definition/Diagnostic Therapeutic approach Drug compliance
	ADME Receptor sensitivity	Smoking Alcohol Food habits Stress
Race		Regulatory practice/GCP Methodology/Endpoints
Genetic polymorphism of the drug metabolism		
Genetic diseases	Diseases	

(ICH E5 GL)

# Attractiveness of East Asian Trials

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- Geographical Closeness
- Large Population
- Low Cost
- Growing Market



- Racial Similarity

# For Successful Global Clinical Trials

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## Desirable Conditions:

- Internationalized Diagnostic Criteria
- Internationalized Therapeutic Approach
- Internationalized Trial Practice
  
- Controllability of the Influence of Ethnic Factors  
in Drug Development and Evaluation  
*(Not necessarily free from the influence of ethnic factors)*

# Clinical Evaluation by Global Development / Bridging Development

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## ■ Applicability / Acceptability of Foreign Clinical Data

- Pre-study Consideration: Study Design



- Post-study Consideration: Result Analysis

- Clinical Pharmacology

(Genetic Polymorphism, PK, Dose, ...)

- Medical Practice

(Disease Definition, Therapeutic Approach,  
Evaluation Methods, ...)

**Our Experience in Bridging Strategy must be of great help!**

# Why Are We Expanding Overseas?

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- Just because it is the growing trend?
- Because;
  - Pharmaceuticals are international commodities.
  - We need to aim at the “Global Market.”

# Ranking of Countries by Study Phase (1)

(Number of trials in each country)

Phase I			Phase II			Phase III			Phase IV		
Rank	Country		Rank	Country		Rank	Country		Rank	Country	
1	US	1406	1	US	2970	1	US	3161	1	US	988
2	UK	135	2	Germany	656	2	Germany	1190	2	Germany	334
3	Germany	95	3	Canada	616	3	Canada	1062	3	France	240
4	Canada	92	4	UK	516	4	France	898	4	UK	212
5	Japan	71	5	France	444	5	UK	838	5	Spain	192
6	Australia	68	6	Spain	366	6	Spain	785	6	Canada	186
7	Netherland	46	7	Italy	342	7	Italy	778	7	Italy	167
8	France	44	8	Belgium	318	8	Poland	672	8	Netherland	132
9	Sweden	39	9	Australia	275	9	Belgium	649	9	Belgium	124
10	Spain	36	10	Netherland	256	10	Australia	595	10	Korea	108
			14	Japan	166	26	Japan	310	30	Japan	40

All Industry-Sponsored Clinical Trials, As of July 20, 2008

(Provide by S. Muroyama at Kitasato)

# Ranking of Countries by Study Phase (2)

(Percentage of trials in each country)

Phase I			Phase II			Phase III			Phase IV		
Rank	Country	%	Rank	Country	%	Rank	Country	%	Rank	Country	%
1	US	15.1	1	US	32.0	1	Malaysia	77.7	1	Korea	20.0
2	Japan	11.9	2	Canada	29.9	2	South Africa	68.0	2	China	19.2
3	UK	7.6	3	UK	29.1	3	Hungary	67.5	3	Philippines	16.1
4	Australia	6.3	4	Japan	27.9	4	Thailand	67.4	4	Switzerland	15.8
5	Sweden	4.7	5	Belgium	27.3	5	Argentina	67.3	5	Puerto Rico	15.2
6	Canada	4.5	6	Germany	27.1	6	Hong Kong	67.1	6	Thailand	15.1
7	Netherland	4.3	7	France	26.2	7	Brazil	66.3	7	Taiwan	14.8
8	Switzerland	4.2	8	Spain	25.8	8	India	66.3	8	Brazil	14.4
9	Germany	3.9	9	Australia	25.5	9	Poland	65.2	9	France	14.2
10	Denmark	3.9	10	Romania	25.1	10	Philippines	65.0	10	Germany	13.8
						33	Japan	52.0	36	Japan	6.7

All Industry-Sponsored Clinical Trials, As of July 20, 2008

(Provide by S. Muroyama at Kitasato)

# Which way should we go?

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## Phases of Development

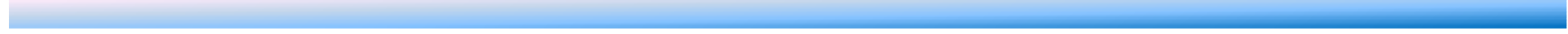


- More focused on exploratory phases
  - Sophisticated study design
  - Data of good quality
  
- Get involved in global development strategy as early as possible
  
- Reduce the burden of new drug development
  - Protocols and CRFs more efficient
  - Trial operations streamlined
  - Infrastructure of medical institutions improved
  - Regulatory thinking and behavior more flexible

# Summary

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- The number of multi-regional clinical trials in which Japan participates has been increasing steeply.
- The phenomenon of internationalization of clinical trials is not unique to Japan. The US and European people have been forced to worry about the influence of ethnic factors.
- For a successful global development, consideration in the study design, among others, is important.
- It is important to maintain the sustainability of new drug development in Japan, while going with the times.



Thank you for your kind attention.