Trend of Multi-Regional Clinical Trials (MRCTs) and Japan's approach

Yu KAGAMI, Ph.D.

Reviewer, Office of New Drug III, PMDA

Today's agenda

1. Current situation of Multi Regional Clinical Trial (MRCT)-related new drug development in Japan
2. Japan's approach for promoting MRCT

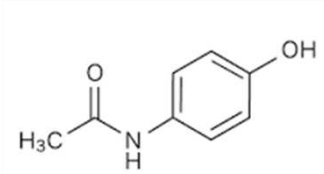
Environment changes of drug development

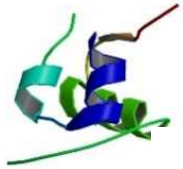
Target Diseases

Lifestyle-related Disease	Unmet Medical Needs	Rare Disease Oncology

Modality

Small Molecule	Bio Pharmaceuticals	Cellular, Genomics





MRCT - Pros & Cons

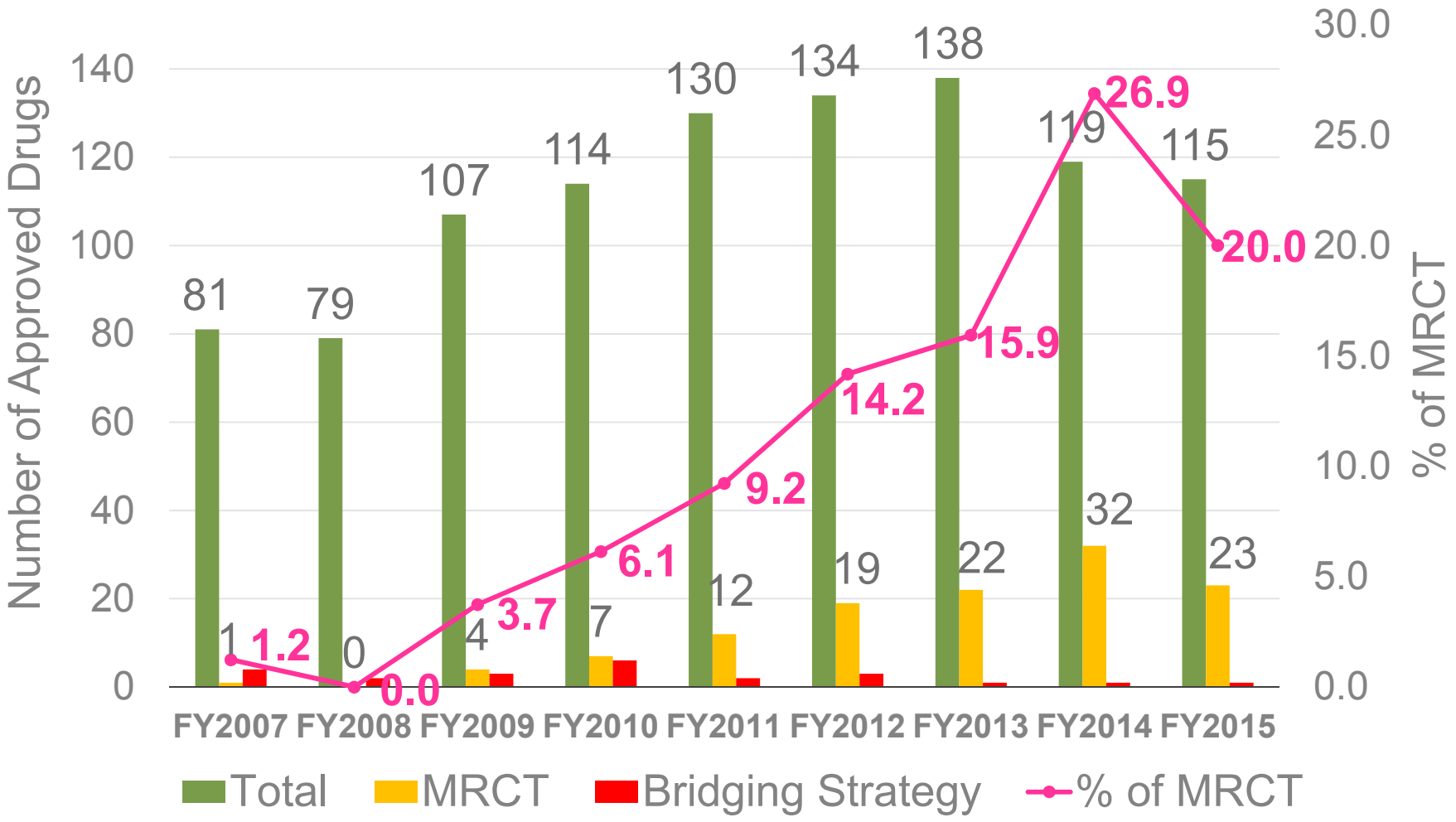
Pros

- Simultaneous application/approval in the world
- Shortening development period
- Understanding ethnic difference in efficacy/safety
- Evaluating rare AE based on larger patients enrollment
- Impossible to conduct a study in single country

Cons

- Similarity of dose response in each region
- Complicated global action for urgent issue
- Individual standard of care in each country

Trends of new drug application based on MRCTs in Japan



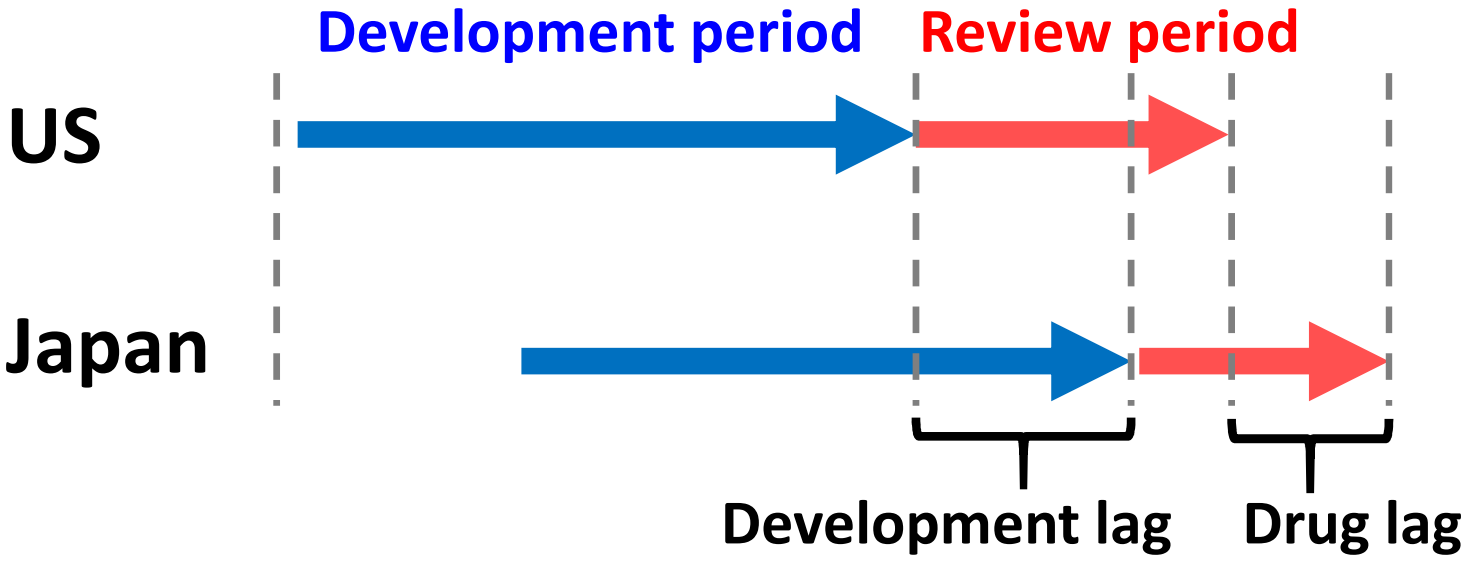
Lag in drug development between US and Japan

Drug lag

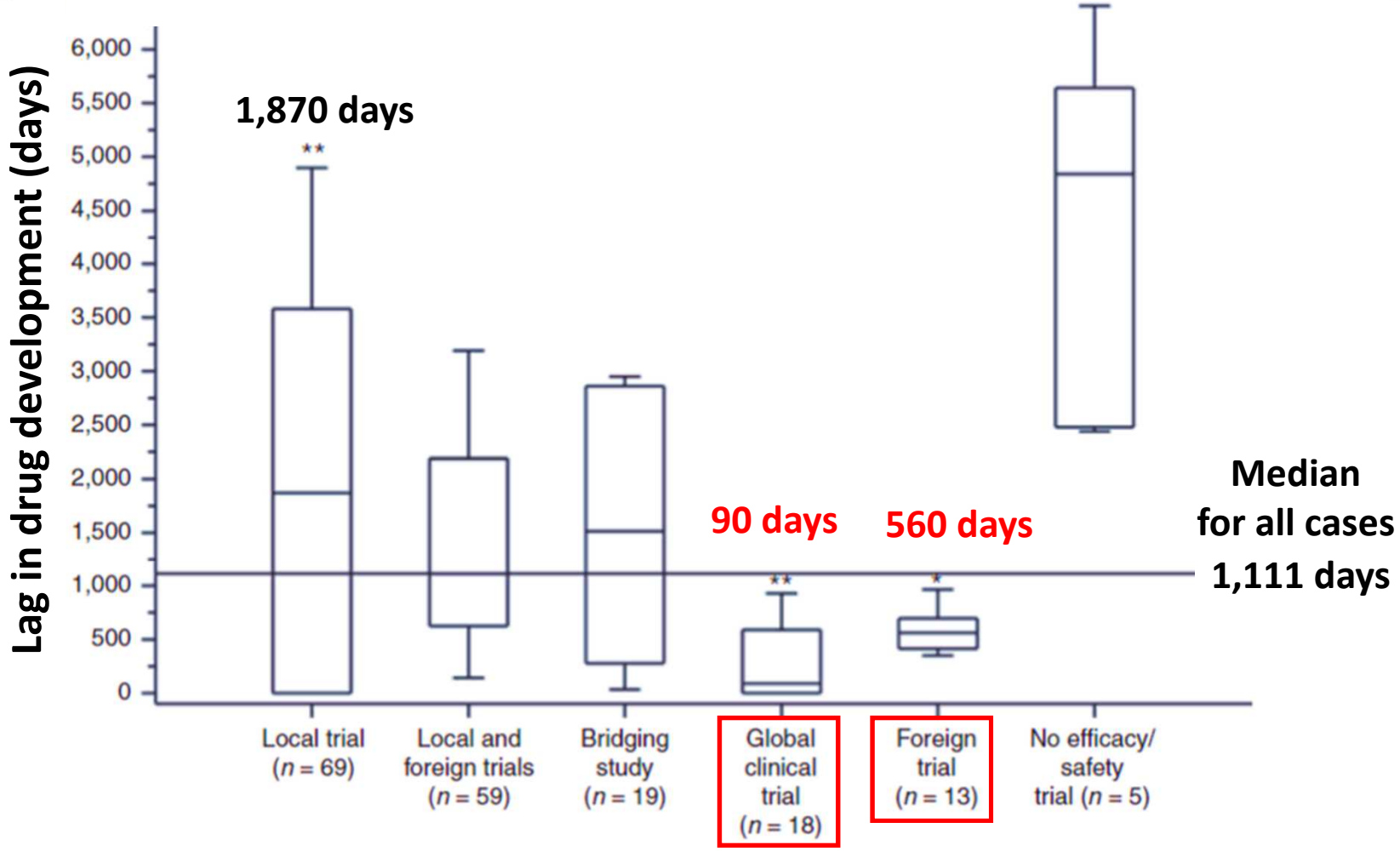
Drugs used in other country is not approved in Japan

Development lag

Delayed period of new drug application to Japan



Lag in drug development between US and Japan



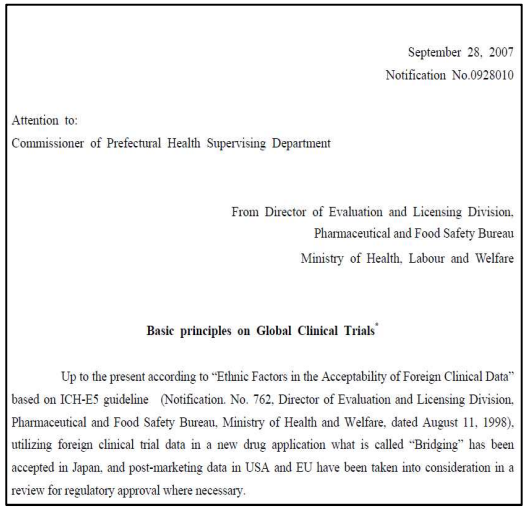
Ueno T et al, Clin Pharmacol Ther, 2014,95, 533-41

Today's agenda

1. Current situation of Multi Regional Clinical Trial (MRCT)-related new drug development in Japan
2. **Japan's approach for promoting MRCT**

Japanese guidance document for MRCT

2007 Guidance
Basic principles on Global Clinical Trials



September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

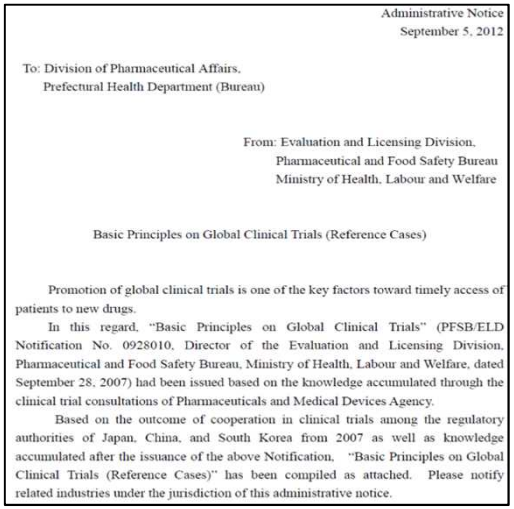
From Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

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.

English:
https://www.pmda.go.jp/files/000157900.pdf

2012 Addendum
Basic Principles on Global Clinical Trials (Reference Cases)



Administrative Notice
September 5, 2012

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Basic Principles on Global Clinical Trials (Reference Cases)

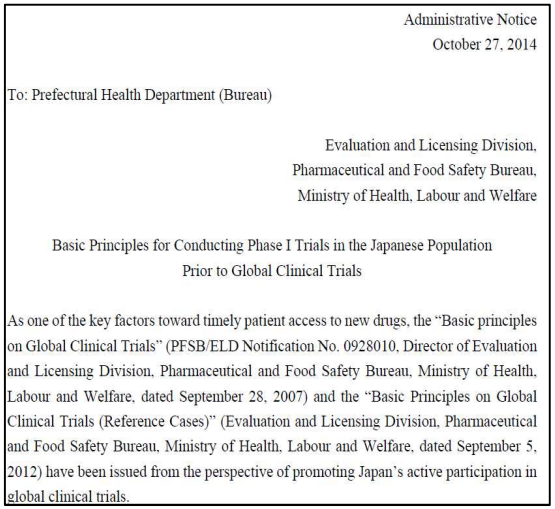
Promotion of global clinical trials is one of the key factors toward timely access of patients to new drugs.

In this regard, "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) had been issued based on the knowledge accumulated through the clinical trial consultations of Pharmaceuticals and Medical Devices Agency.

Based on the outcome of cooperation in clinical trials among the regulatory authorities of Japan, China, and South Korea from 2007 as well as knowledge accumulated after the issuance of the above Notification, "Basic Principles on Global Clinical Trials (Reference Cases)" has been compiled as attached. Please notify related industries under the jurisdiction of this administrative notice.

English:
https://www.pmda.go.jp/files/000157520.pdf

2014 Addendum
Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials



Administrative Notice
October 27, 2014

To: Prefectural Health Department (Bureau)

Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles for Conducting Phase I Trials in the Japanese Population
Prior to Global Clinical Trials

As one of the key factors toward timely patient access to new drugs, the "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) and the "Basic Principles on Global Clinical Trials (Reference Cases)" (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 5, 2012) have been issued from the perspective of promoting Japan's active participation in global clinical trials.

English:
https://www.pmda.go.jp/files/000157777.pdf

How to evaluate the MRCT data from PMDA's perspective ?

- **2007 Guidance mentioned the following Q&A.**

Q6. When conducting an exploratory trial like a dose-finding study or a confirmatory trial 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**

How to evaluate the MRCT data from PMDA's perspective ?

- **2007 Guidance mentioned the following Q&A.**

Q6. When conducting an exploratory trial like a dose-finding study or a confirmatory trial as a global clinical trial, how is it appropriate to determine a sample size and a proportion of Japanese subjects?

- **How to determine the number of Japanese subject**

  Method 1:

  D_{Japan}/ D_{all} > 0.5 will occur with a probability of 80 % or higher

  D : difference between placebo and study drug

  D_{all} : difference in the entire study population across regions

  D_{Japan} : difference within the Japanese sub-population

  Method 2:

  each of the D1, D2, and D3 show a similar tendency with a probability of 80 % or higher (e.g. D>0⇒ D1, D2, D3 >0)

  D_1, D_2, D_3 : differences between placebo and study drug groups in each region

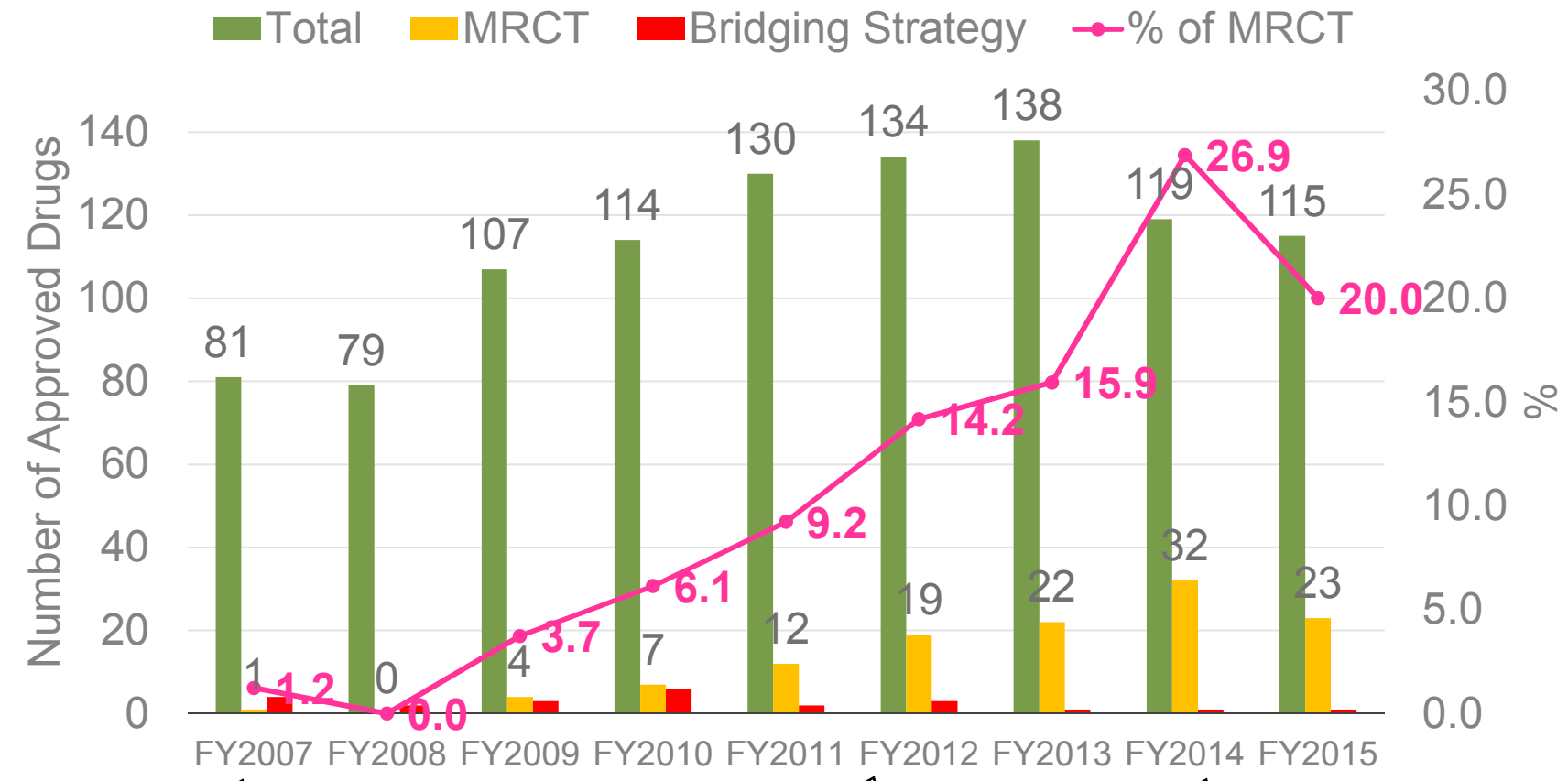
How to evaluate the MRCT data from PMDA's perspective ?

- **2007 Guidance mentioned the following Q&A.**

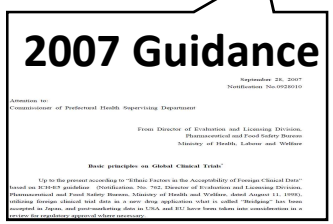
Q6. When conducting an exploratory trial like a dose-finding study or a confirmatory trial as a global clinical trial, how is it appropriate to determine a sample size and a proportion of Japanese subjects?

- **If results from a Japanese subgroup are markedly different from those in the entire study population, the reasons for it should be examined and in this case, because an additional clinical trial may be needed where necessary, it is recommended to utilize the clinical trial consultation with PMDA.**

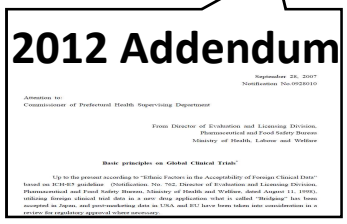
Trends of new drug application based on MRCTs in Japan



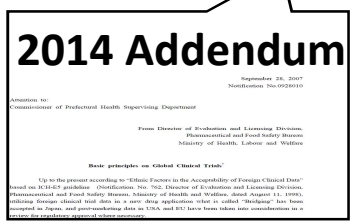
2007 Guidance



2012 Addendum



2014 Addendum



Summary

1. The number of MRCTs conducted in Japan is increasing from 2007
2. Japan's approach of issuing guidance for MRCT is thought to contribute to the increase of MRCTs involving Japan

Thank you for your attention!

PMDA-ATC MRCT Seminar 2017

- **Date：**23 January -26 January, 2017
- **Venue：**PMDA conference room　21-23
- **Number of participants: 32** in total from **14** countries/regions

（Brazil 2, China 1, Indonesia 3, Malaysia 5, Mexico 1, Myanmar 2, Nepal 1, Papua New Guinea 1, Peru 3, Philippines 4, Sri Lanka 2, Taiwan 3, Tanzania 2, Thailand 2)

- **Key Seminar Objectives:**

✓ To build skilled human capacity in regulatory science to promote and facilitate Multi-Regional Clinical Trials (MRCTs)

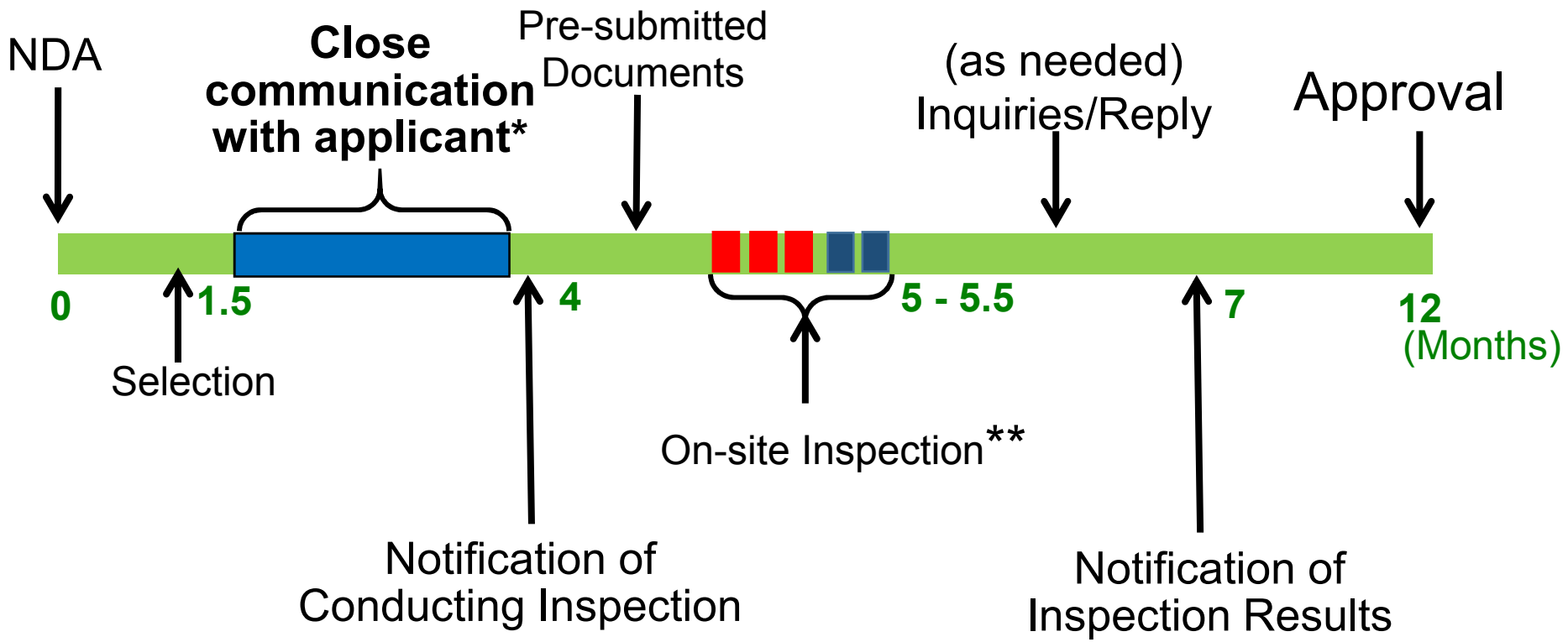
✓ To enhance regulatory cooperation in the APEC region on the evaluation and regulation of MRCTs

* Next MRCT Seminar is scheduled in January 2018
https://www.pmda.go.jp/english/int-activities/training-center/0001.html

How to perform GCP Inspection for MRCT

Office of Non-clinical and Clinical Compliance
Atsushi Kawashima

Typical Schedule of Oversea Inspection



* Arrangement of inspection schedule, F2F meeting

**Domestic sites → Foreign sites → Foreign sponsors → domestic sponsors

Selection of Clinical trials and Medical Institutions to be inspected (point to consider)

Clinical trials

- Priority in the clinical data package for J-NDA
  (e.g. pivotal trial, bridging trial)

Medical Institutions

- Sampling Number
  - The drugs with new active pharmaceutical ingredients
    (Excluding the drugs of quick/priority review, the orphan drugs)
    →Approximately 4 institutions
  - Others
    →Approximately 2 institutions
- The number of subjects
- Results of previous inspections

- Clinical trials and Medical Institutions to be inspected are decided on after discussing them with NDA reviewer.
- Additional institutions will be inspected if there are problems identified during review/inspection process.

Selection of Clinical trials and Medical Institutions in oversea inspection

Conduct Oversea Inspection?

- **Points to be considered**
  - ☐ (Pivotal trial in the package) was conducted in foreign countries?
  - ☐ (Product) already approved by foreign authorities?
  - ☐ (Trial/Institution) already inspected by foreign authorities?
  - ☐ Others (total ratio/number of subject in Japanese sites, etc.）

Selection of Clinical trials and Medical Institutions in oversea inspection (cont.)

Which country/medical institutions to be inspected ?

- **Points to be considered**
  - ☐ Conducted clinical trials at the site
  - ☐ The number of subjects
  - ☐ Results of previous inspections
  - ☐ Future inspection plan
  - ☐ Inspection of foreign authorities
  - ☐ Others (security situation, etc.)

↓

Usually 2 medical institutions in 1 country are selected.

Submitted Documents at the application from applicant

PMDA request applicant to submit the report contains the following :

1. Outline of Application (Product name, Product code, applicator name etc.)
2. Date of Application
3. Information of the Sponsor/ sponsor-investigator (including CROs)
4. The list of the medical institution (PI name, duration, number of subjects, number of discontinued subject, number of subjects occurred adverse reactions)
5. information of the prior inspection
6. others (result of the inspection by the foreign agency)

Based on this report and CTD, we select clinical trails and medical institutions to be inspected.

Main points in the Checklist of Medical institution

Outline of Clinical Trials

Requirement of Medical institute
Control of Clinical Trials

Investigator

Requirement, work
information transfer to the Staffs

Subjects

Selection of the Subjects
Informed consent

IRB

Organization, Management,
review process to result notification

Control of Clinical Trials

AE information, Investigational Drugs control,
Record keeping

Case Report

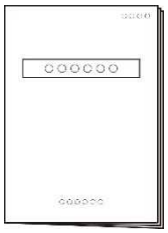
Consistency to the source documents
Investigator's confirmation

Sponsor's attendance at the medical institution is not permitted.

Checklist (Only Japanese) is available in the PMDA website
http://www.pmda.go.jp/files/000162584.doc

Main points in the Checklist of Sponsor

Clinical Trial Management



Protocol, Investigator's Brochure

Selection of Medical Institute, Principal Investigator

Contract of CT

Compensation

Preparing Clinical Trials

Control of IMPs

Safety information

Monitoring

Audit

Record Keeping

Confirm matters on the Medical Institute inspection at the Sponsor when it needed

Checklist (Only Japanese) is available in the PMDA website
http://www.pmda.go.jp/files/000162809.doc

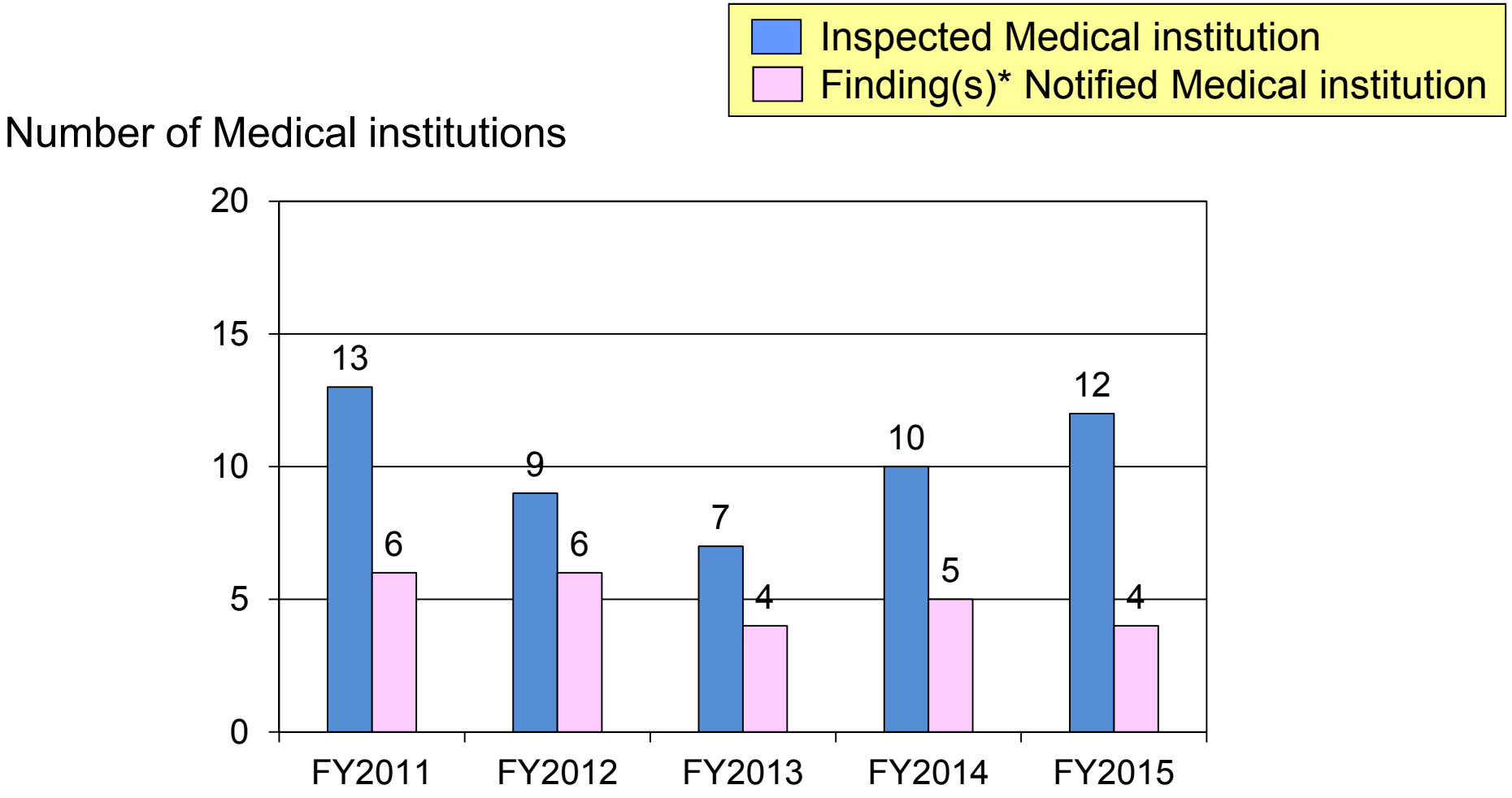
Experience of Oversea On-site Inspection [1)]

The number of IPs inspected[2)]	62	Breakdown by nations					
The number of sponsors inspected (including CROs)	63[3)]	USA	19	Swiss	2	Netherlands	1
		China	6	Poland	2	Philippines	1
		Korea	5	Belgium	2	France	1
		German	6	Spain	2	Czech Republic	1
		UK	4	Brazil	1	Italy	1
		Taiwan	4	Romania	1		
		Austria	3	India	1		
The number of medical institutions inspected	86	USA	19	Romania	4	France	2
		China	12	Czech Republic	2	Brazil	1
		Korea	8	India	2	Ukraine	1
		Taiwan	7	Canada	2	Netherlands	1
		UK	6	Hungary	2	Belgium	1
		German	6	Philippines	2	Australia	1
		Spain	4	Austria	2	Poland	1

1) Counted based on the notification published during Apr. 2008～Mar. 2016
2) Notification No. of inspection results in every calendar year (per applicant)
3) 9 cases are coincident inspection of on-site inspection and document-based inspection

Number of Medical institutions (Inspected and Finding(s) Notified)

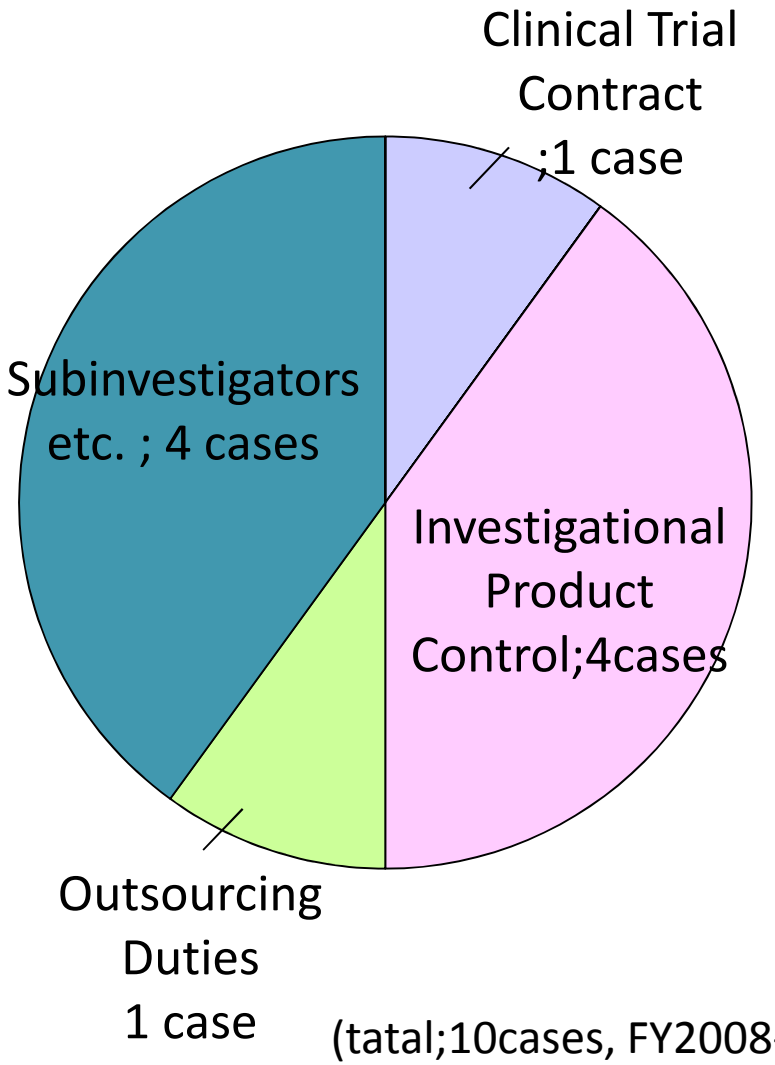
(Oversea inspection)



*including both General finding(s) and Finding(s) for individual subjects

Breakdown of General finding(s)

(Oversea inspection)



(tatal;10cases, FY2008-2012)

Clinical Trial Contract

- Incomplete Clinical Trial Contract (Article 13)

Investigational Product Control

- Incomplete Investigational Product Control/Accountability (Article 39)

Outsourcing Duties

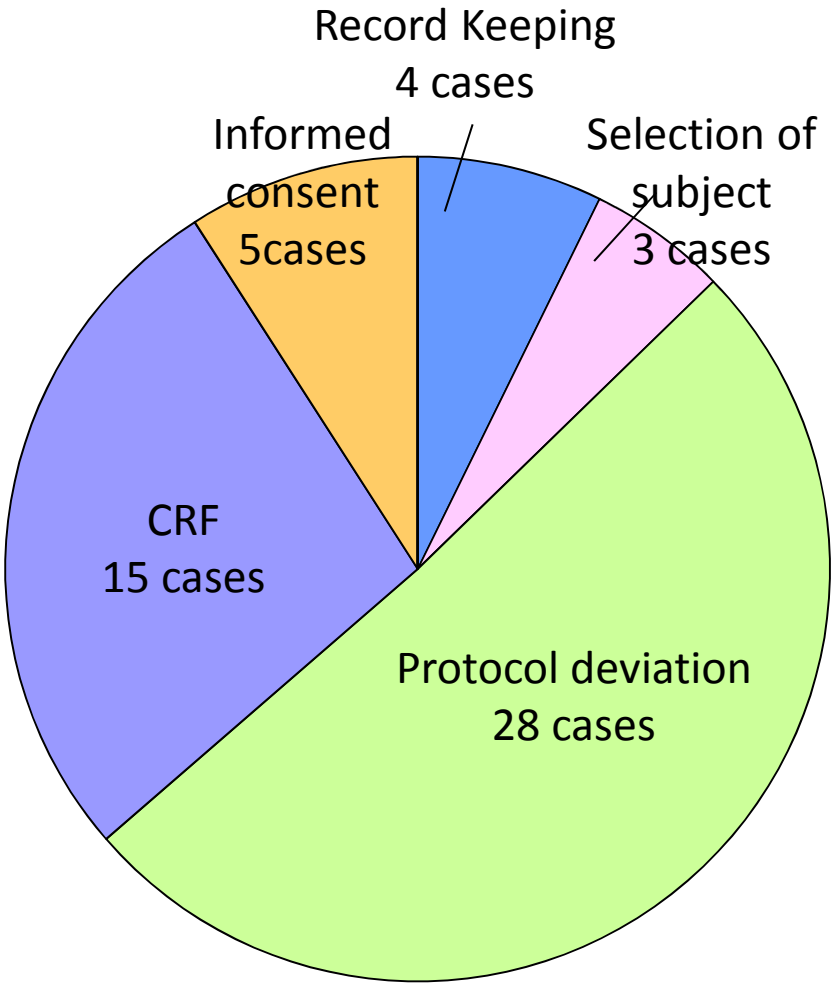
- Incomplete contract with Outsourcing Duties (Article 39-2)

Subinvestigators etc.

- Incomplete delegation of Subinvestigators etc. (Article 43)

Breakdown of Finding(s) for individual subjects

(Oversea inspection)



(Total：55 cases, FY 2008-2012)

- Record Keeping (Article 41-2)
  - ・Incomplete record keeping
    (Medical records, Examination report, etc.)
- Selection of Subjects(Article 44)
  - ・Noncompliance with inclusion/exclusion criteria
- Deviations from Protocol (Article 46-1)
  - ・Noncompliance with dosage/usage, use of prohibited concomitant medications
- Case Report Form (CRF) (Article47-1)
  - ・Inaccurate preparation of CRF
    (Examination results・AE・Concomitant medication)
- Informed Consent of Subjects
  (Article 50,51,52,53,54)
  - ・Incomplete Informed consent (Article 50)
  - ・Incomplete consent to continue (Article 54)etc.

Communication with foreign agency

- When foreign inspectors inspect Japanese site/sponsor, PMDA consider the participation of their inspection as a observer.
- When PMDA inspect foreign site/sponsor, foreign inspectors can participate our inspection as a observer, too.
- FDA and PMDA hold the meeting about inspection method using the data conformed CDISC standard.

Dr V. G. SOMANI
Joint Drugs Controller (India)
Central Drugs Standard Control Organization
DGHS, MOHFW,
New Delhi
v.g.somani30@cdsco.nic.in

2nd JAPAN-INDIA MEDICAL PRODUCTS REGULATION SYMPOSIUM

24th APRIL 2017

CLINICAL TRIAL SYSTEM & REVIEW IN INDIA

Clinical Trial Regulations

Overall Summary

- Clinical Trial on new drugs/ IND requires permission from Ethics Committee and DCG(I) in India
- Clinical Trials are required to follow Indian GCP guidelines which are equivalent to ICH guidelines
- The application format and data requirements are as per CTD document and are given on CDSCO website i.e. www.cdsco.nic.in
- For obtaining permission to conduct Clinical Trial
  - Complete CMC data
  - Preclinical study
    - Pharmacological data
    - Toxicological data

Clinical Trial Regulations

- Report of earlier phases of studies (Phase I, II & III)
- Protocol, IB, ICF, details of site, EC approval etc. need to be submitted

- These are evaluated by Regulators and Subject Expert Committee (SEC) comprising of pharmacologist, toxicologist, relevant clinical subject expert (3 to 7) (Professor or Head of the Department of relevant therapeutic category from Government Medical Colleges)
- which is then deliberated in Technical and / or Apex committees
- Approval of protocol for the development of drugs/ vaccines for the diseases of relevance to Indian Health scenario are given fast track treatment

Requirements of Data in

Animal Pharmacology

- Summary
- Specific pharmacological actions
- General pharmacological actions
- Follow-up and Supplemental Safety Pharmacology Studies
- Pharmacokinetics: Absorption, Distribution; Metabolism; Excretion

Requirements of Data in

Animal Toxicology

- General Aspects
- Systemic Toxicity Studies
- Male Fertility Study
- Female Reproduction and Developmental Toxicity Studies
- Local toxicity
- Allergenicity /Hypersensitivity
- Genotoxicity
- Carcinogenicity

Phase I (Non therapeutic safety evaluation trial)

- In Normal Healthy Volunteers for deciding Maximum tolerated dose (MTD) i.e safety (by SAD, MAD study), additionally pharmacokinetics, pharmacodynamics, drug-drug and drug-food interaction may also be studied.
- Animal pharmacology and toxicology data are very important.
- NOAEL level and
- starting dose selected for First-in-human(FIH)
- MTD studies need to be reviewed for appropriateness

Phase II (Exploratory therapeutic trial)

- To evaluate efficacy of drug and to find appropriate dose in homogenous selected small patient group and to find out short term safety of drug.
- Aim is to generate sufficient data on efficacy, safety, dosage to be used for going in Phase III

Phase III-(Therapeutic Confirmatory trials)

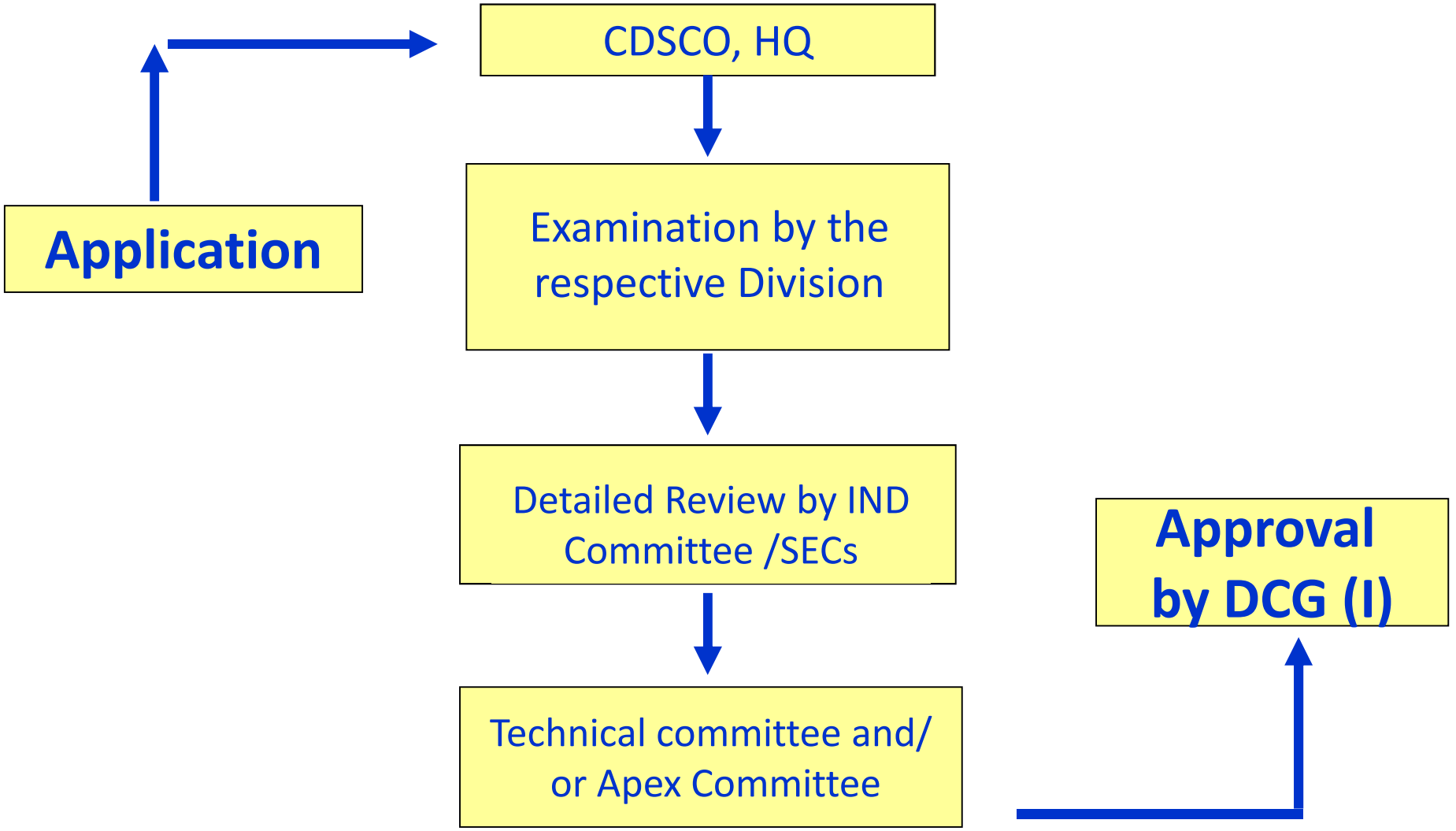
- To demonstrate safety and efficacy in large number of patients about stated indication
- Statistics (non inferiority, superiority , equivalence trial)
- Multicenter enrolment of all ethnic groups
- Choice of comparator , treatment duration
- Efficacy and safety assessment criteria (scoring etc) are important for review

Regulations for CT

Phase IV

- For optimization of drug utilization, for evaluating residual safety and various changes in the prescribing information

Evaluation of CT applications



Key areas of evaluation in an application

Risk Vs. Benefit

Innovation Vs. Existing Therapy

Unmet Medical Need

Ethical Aspects For Patient Safety

India Specific Concerns

Clinical Trial Regulations

Recent Changes

- Online submission and processing of Clinical trial applications is initiated by CDSCO.
- Expansion of Subject Expert Committee panels leading to reduction in the timeline.
- Training of Subject expert committee members and reviewers of CDSCO.
- Publication of “Handbook for Applicants and Reviewers of Clinical trials of New Drugs in India”.

Clinical Trial Regulations

Recent Changes

- Applicability of Audio Visual recording has been rationalized to match global and national requirements for conduct of good and quality clinical trial in India. It is now required for New Chemical Entities and in vulnerable populations only.
- Definitions of injury and compensation mechanism is rationalized.
- Timelines for SAE reporting by Investigator, Ethics Committee, Sponsor have been rationalized.
- Parallel submission of application of clinical trials of r-DNA based drugs /Vaccines to RCGM and CDSCO is now accepted.

Clinical Trial Regulations

Recent Changes

- Restriction of 3 trials per Investigators and requirement of 50 bedded hospital are removed with the condition that it shall be decided by Ethics Committee.
- Now Academic trials of approved drug formulation doesnot require DCG(I) permission in respect for any new claims including repurposing of drug & can be initiated on the basis of Ethics Committee approval.
- Import and export of biological Samples for testing etc does not require any permission (earlier it used to require HMSC and DCG(I) permission).

Clinical Trial Regulations

Recent Changes

- **Inspection** of clinical trial
- **Registration** of ethics committees
- Further regulation are under review and development in harmonisation with best practices

Thank You !

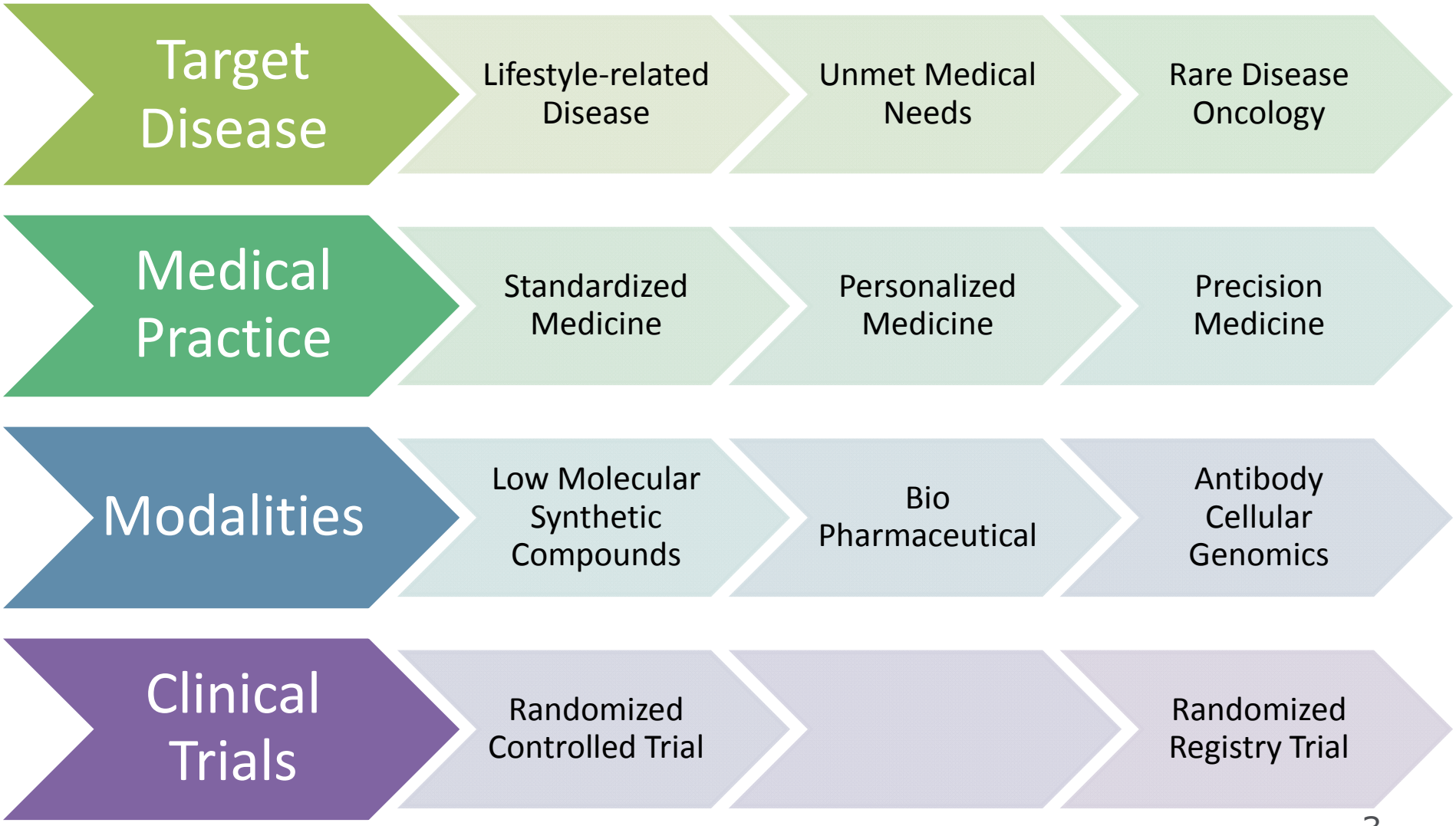
Strategies and challenges for drug development

April 24, 2017
SATOSHI KUNITADA, Ph.D.
Chairperson, Drug Evaluation Committee
Japan Pharmaceutical Manufacturers Association
Corporate Adviser, Daiichi Sankyo Co.,Ltd

Today's Agenda

- Surrounding Environment of Pharmaceutical Industries
  - ✓ Targets and Modalities
  - ✓ Drug Development
- Our forces
  - ✓ Multi Regional Clinical Trial
  - ✓ Alliance among industry, government and academy
  - ✓ An Example of MRCT
- Key success factors for MRCT
  - ✓ Everybody wins

Environmental Changes

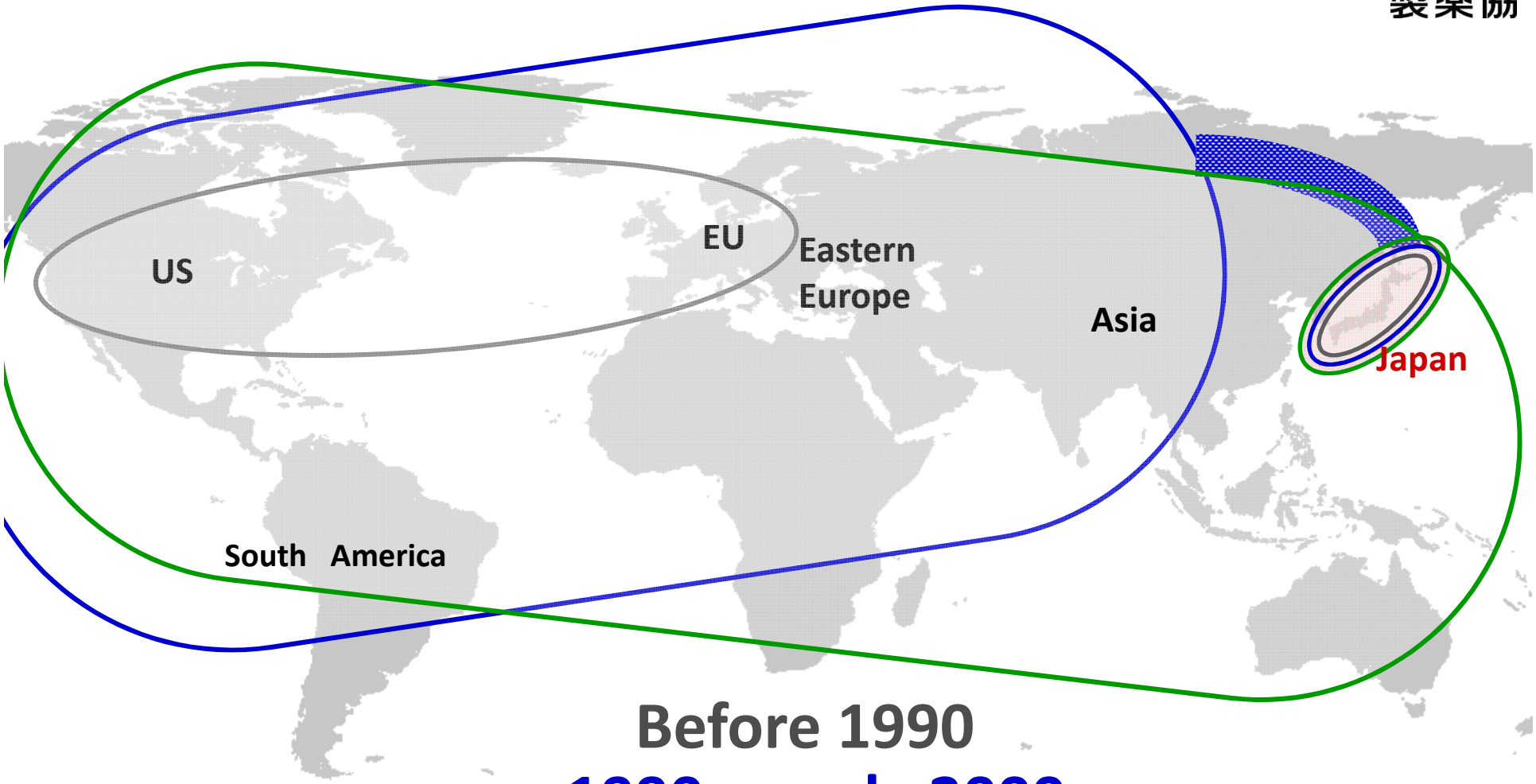


Our forces in drug development

製薬協

- Multi regional clinical trial
- Interaction among industry, academy and government
- Science & Network in Academia
- Highly predictable PoC study

Clinical Trials －Japan used to be isolated－



Before 1990

1990～early 2000

mid 2000～now

MRCT - Pros & Cons

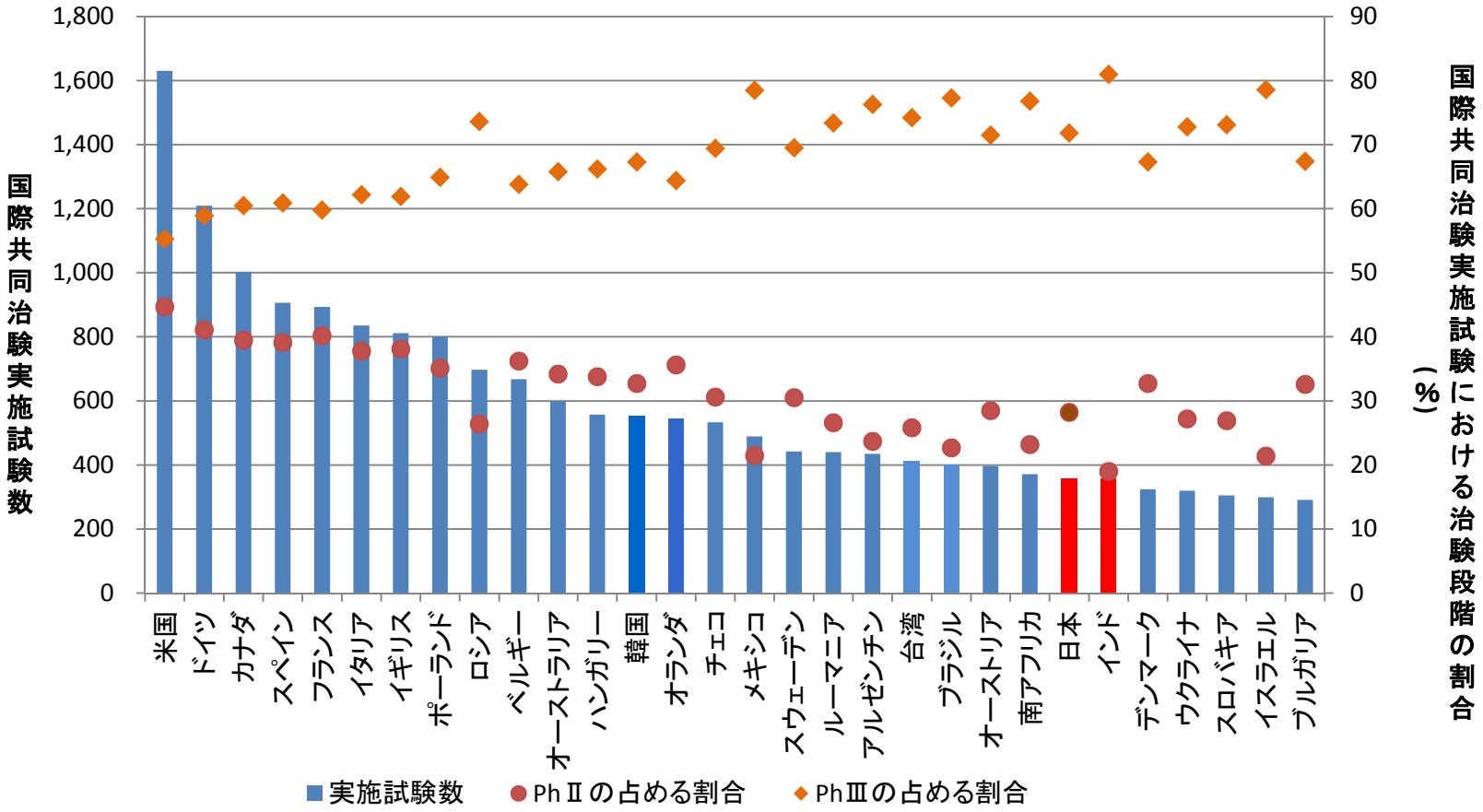
Pros

- Earlier launch possible
- Simultaneous Application/Approval in the world
- Shortening development – few Pts in each country
- Race difference in efficacy/safety understanding
- Rare AE based on larger patients enrolled
- Impossible to conduct a study in single country

Cons

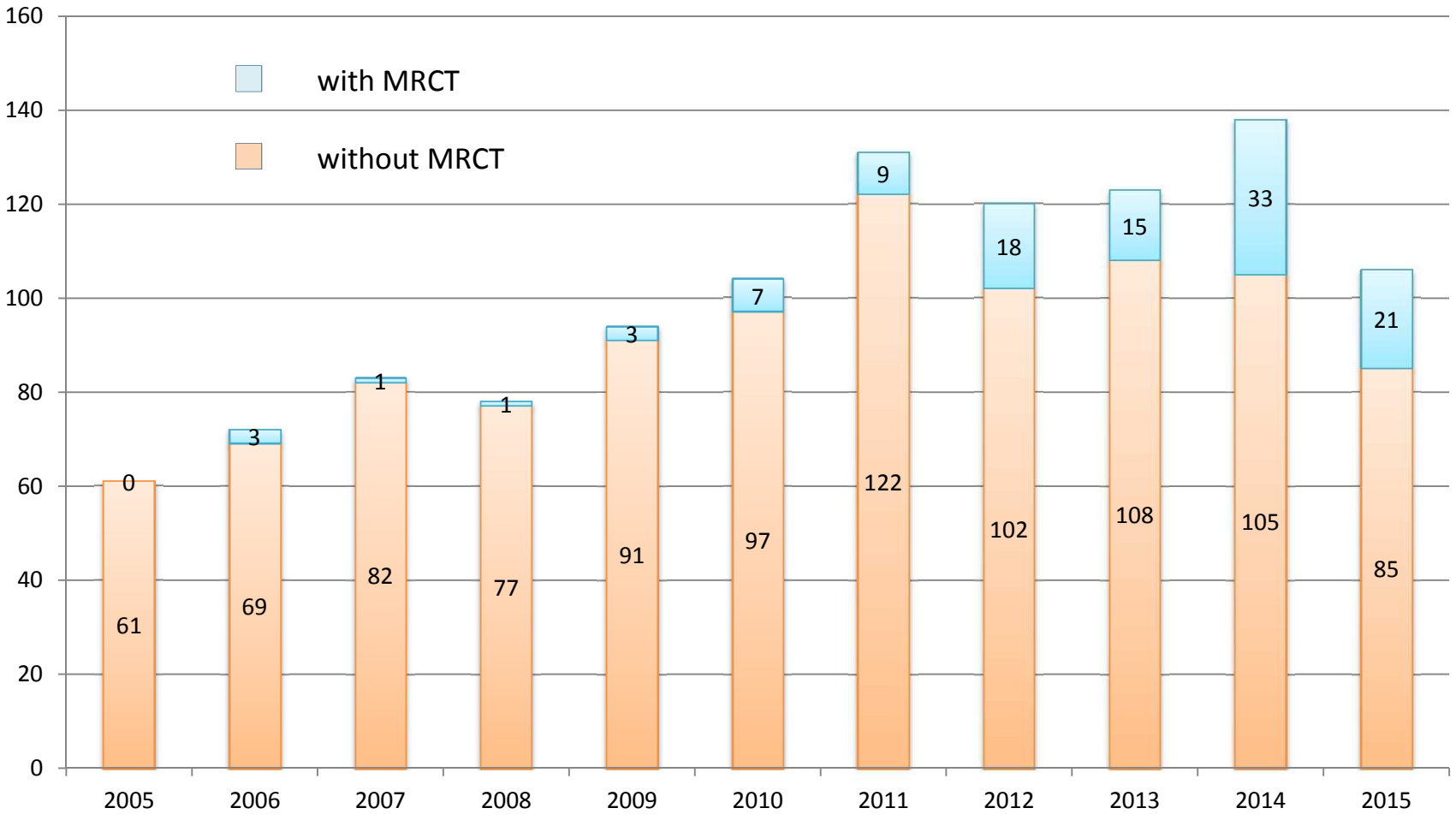
- Good dose rationale in each region necessary
- Complicated global action for urgent issue
- Individual SOC in each countries

Top 30 countries participated in MRCT (2008 – 2012)



注：調査対象は2008年～2012年に開始した試験の累積、2347試験
出所：Evaluate　Pharma　（2014年7月時点のClinical.Trial.govのデータを集計）
Report from Office of Pharmaceutical Industry Research　No.5 (Dec, 2014)

MRCTs for New approved drugs in Japan



News from Office of Pharmaceutical Industry Research. No.48, Jul. 2016

An Example of Multi Regional Clinical Trial

Clinical trials for Edoxaban
（AF, DVT/PE）

(年) 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

Atrial Fibrillation

- Phase 2a (Japan)
- Phase 2b (Japan)
- Engage AF TIMI 48
- Phase 2b (US/EU)
- Phase 3（MRCT）
- Phase 2b (Asia)

Dec, 2013 JP SNDA
→ Sep, 2014 Approved

Apr, 2014 US NDA
→ Jan, 2015 Approved

DVT/PE

- Hokusai VTE
- Phase 3（MRCT）

Jan, 2014 EU NDA
→ Jun, 2015 Approved

Hokusai-VTE: study design

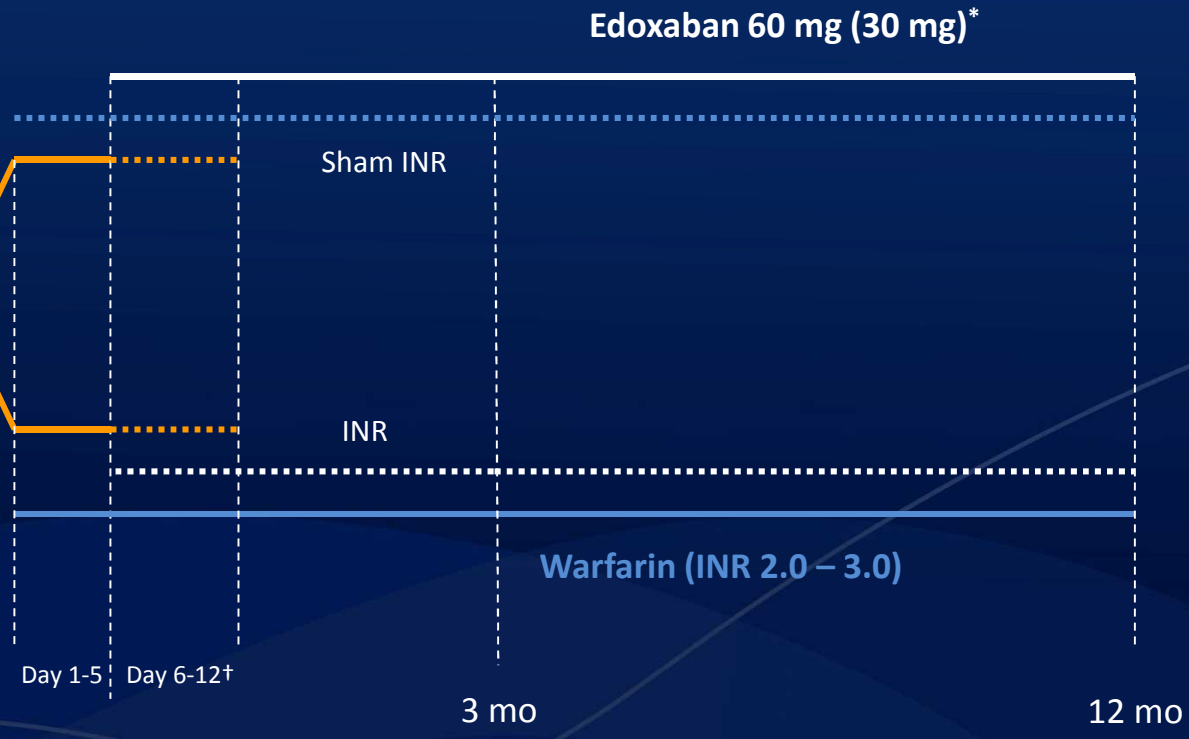
Randomized, double-blind, event-driven study

N=8,292
439 sites in 37 countries

Objectively confirmed VTE

Stratified randomization:
- DVT / PE
- Dose of edoxaban
- Risk factors

All patients followed for 12-months regardless of treatment duration



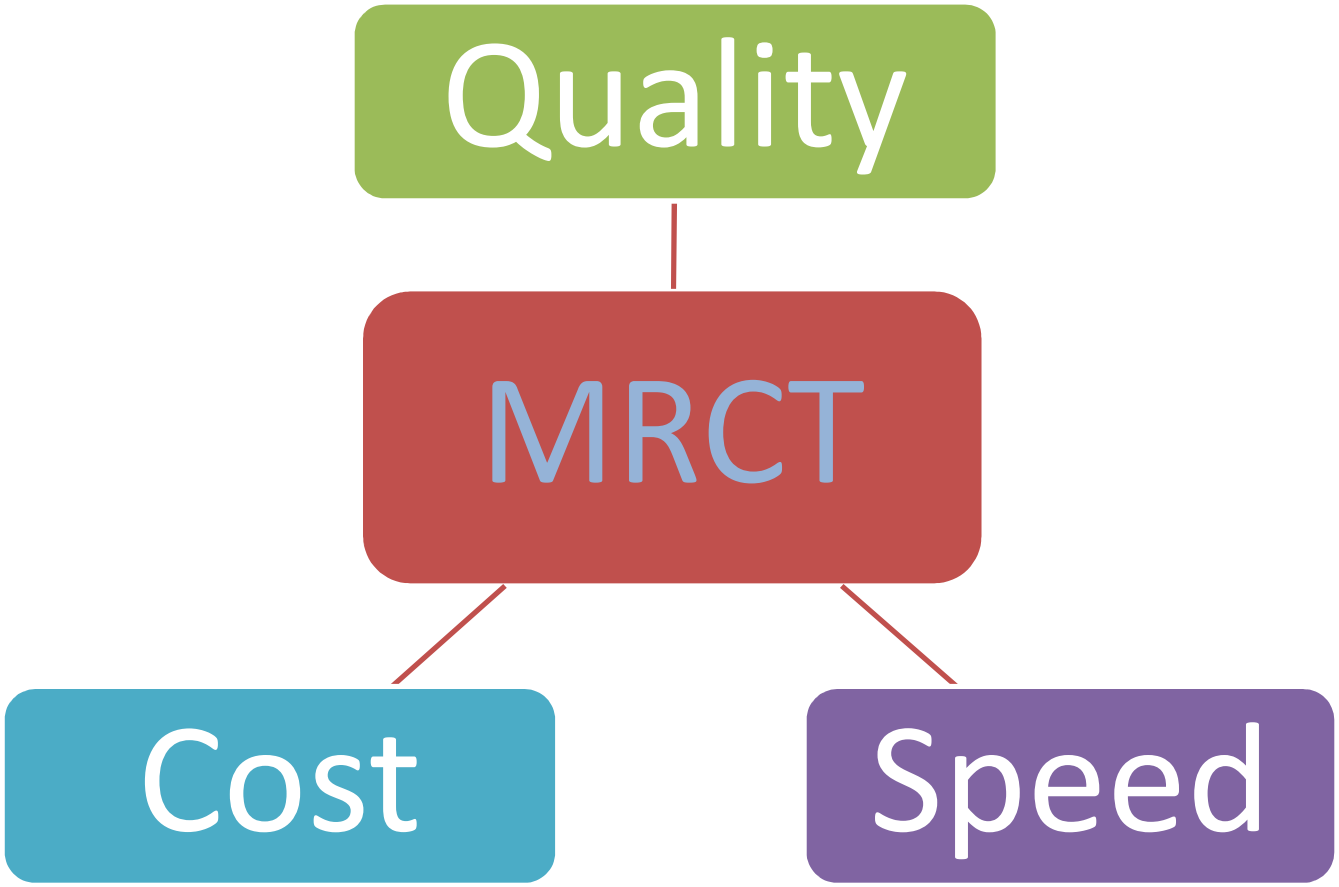
Edoxaban
Placebo Edoxaban
Warfarin
Placebo Warfarin
Low-molecular-weight heparin / UFH

*Dose was halved to 30 mg in patients perceived to be at higher risk for bleeding due to potential overanticoagulation by predefined criteria

†During days 6-12 edoxaban or placebo edoxaban was started once heparin was stopped

Raskob et al. J Thromb Haemost 2013;11:1287–1294
The Hokusai-VTE Investigators. N Engl J Med 2013; doi:10.1056/NEJMoa1306638

Basic Considerations for a Project

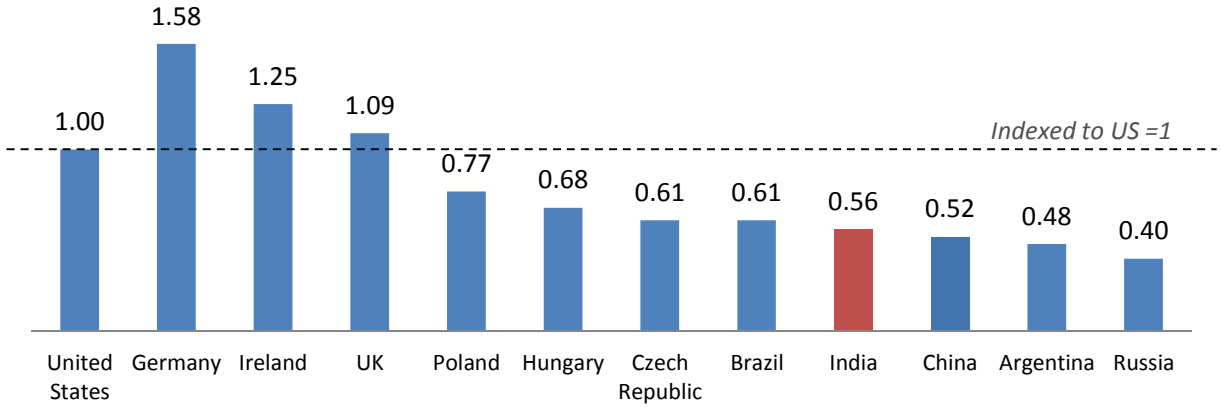


Rationale for Development activity in India : Comparison on Cost and Quality

FACTUAL EXTERNAL EXAMPLE

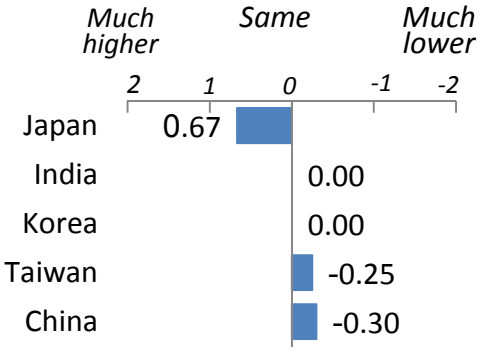
- **Cost of clinical trials in India is ~40% lower than in the US**
- Inspections by international agencies such as FDA and EMEA have revealed **limited quality issues**
- PwC's PRTM conducted the Asia clinical trials outsourcing survey in 2009-10 to assess the clinical trials industry on various parameters. Some of the key survey responses were:
  - Data quality in India is on par with that in the US
  - **Local empowerment can be very effective. Pharmaceutical companies that assign local leadership teams to manage local operations for global trials tended to score better in managing multiple vendor relationships**

Overall Indexed Clinical Trial Costs[1]



Performances of Clinical Trial Operation in Each Country - Level of Data Quality [2]

(Average score as compared with US) *



* Number of respondents = Japan: 3, China: 10, India: 5, Korea:8, Taiwan:8

Source: 1. AT Kearney Analysis; 2. Trends in Asia Clinical Outsourcing 2010 - insights from 2009–10 PwC's PRTM industry survey

Comparison of data queries

製薬協

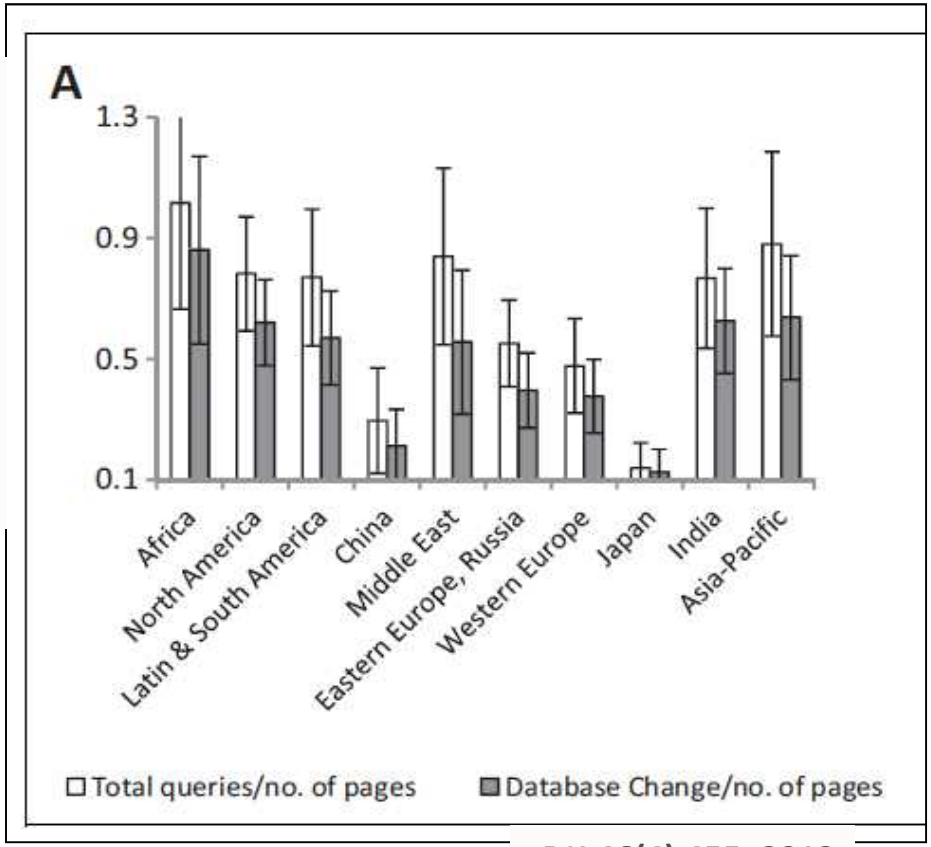
Quality

FACTUAL
EXTERNAL
EXAMPLE

Drug Information Journal

- 26 multinational studies
- 10 therapeutic areas
- 4,721 enrolling sites
- 63,871 patients
- 7 global CROs
- From 2005 to 2010

→ No statistically significant differences in the query rate



DIJ 46(4) 455, 2012

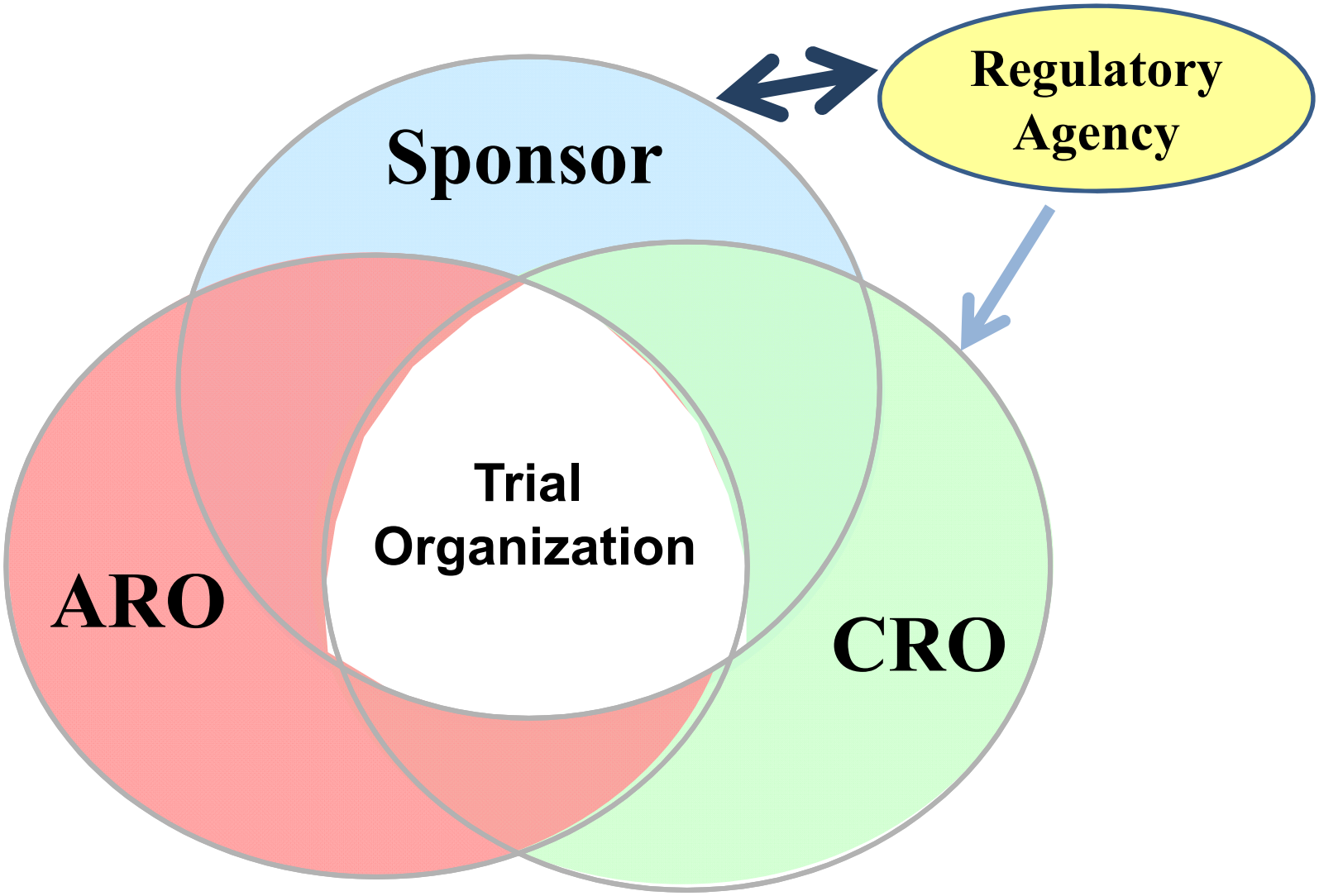
Key factors enabling global Phase III study

- Phase I studies in EU, JP, Asia
  - ✓ confirmed PK/PD and safety in any population
- Phase IIb studies in US/EU, JP and Asia
  - ✓ confirmed optimum safe dose regimens for patients in all regions
- Common standard of care or standard guideline including globally available comparator
- Endorsement of Phase III protocol by RA
  - ✓ FDA : EOP2 meeting, SPA
  - ✓ CHMP: Scientific Advise meeting, SPA
  - ✓ PMDA : EOP2 meeting

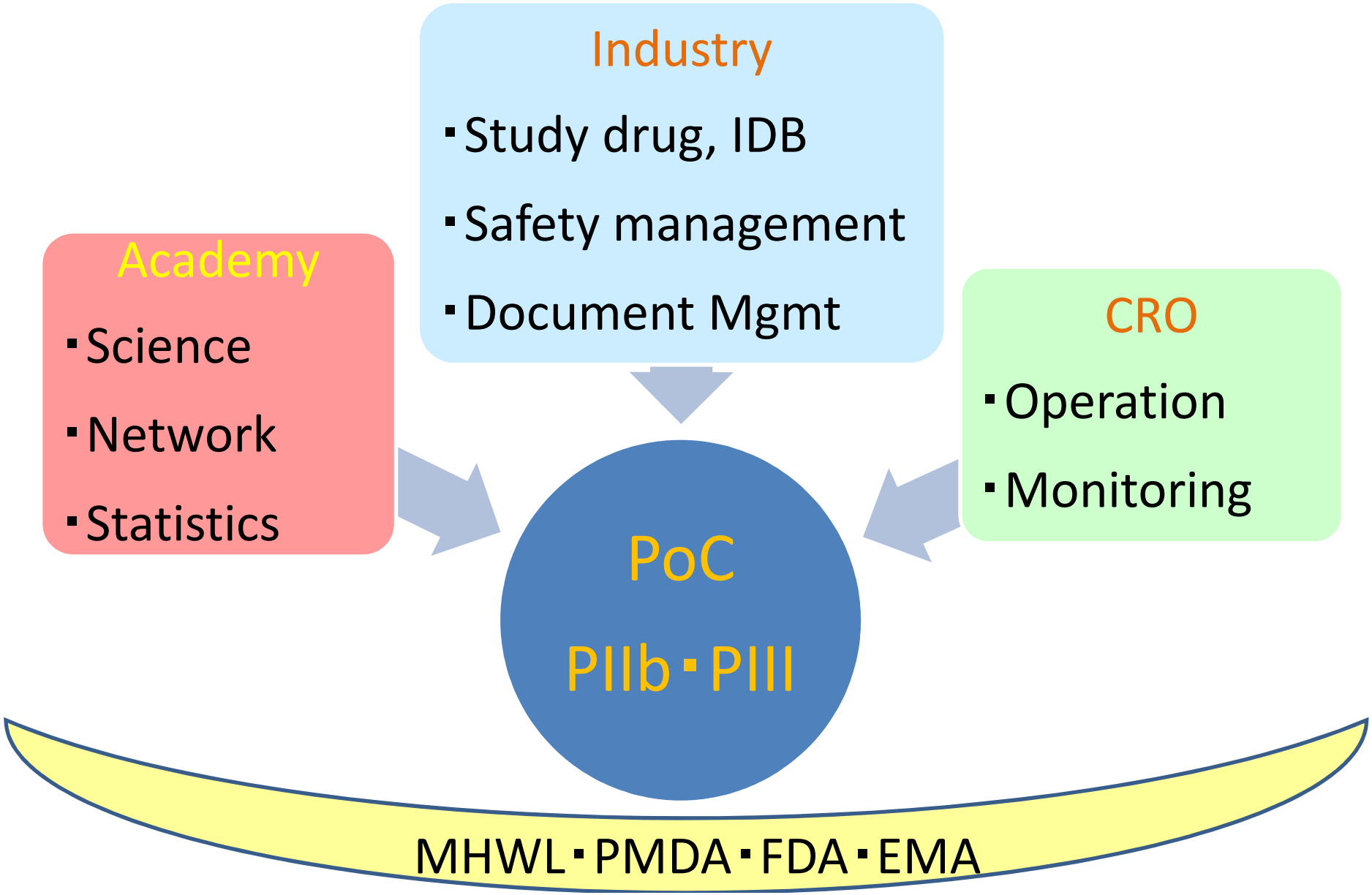
MRCT – Another Key Factors

- ARO / CRO collaboration
  - ✓ right ARO and right CRO
  - ✓ clarify role and responsibility for three parties
- Role of National Lead Investigator (NLI)
- CRO management
  - ✓ intensive oversight of CRO is required in JP/Asia due to inexperienced CRAs and insufficient number of CTLs
  - ✓ Management of CRAs is solely performed by CRO CTLs, not by sponsor in US/EU

Four Way Partnership



Multiple alliances for MRCT



MRCT must be essential

- Single confirmatory study in the world
- Simultaneous development
- High Probability Success based on
  - large patient volume
  - multiple consultation with PMDA/FDA/EMA