Clinical trials and regulatory supports for innovative drug development in Japan

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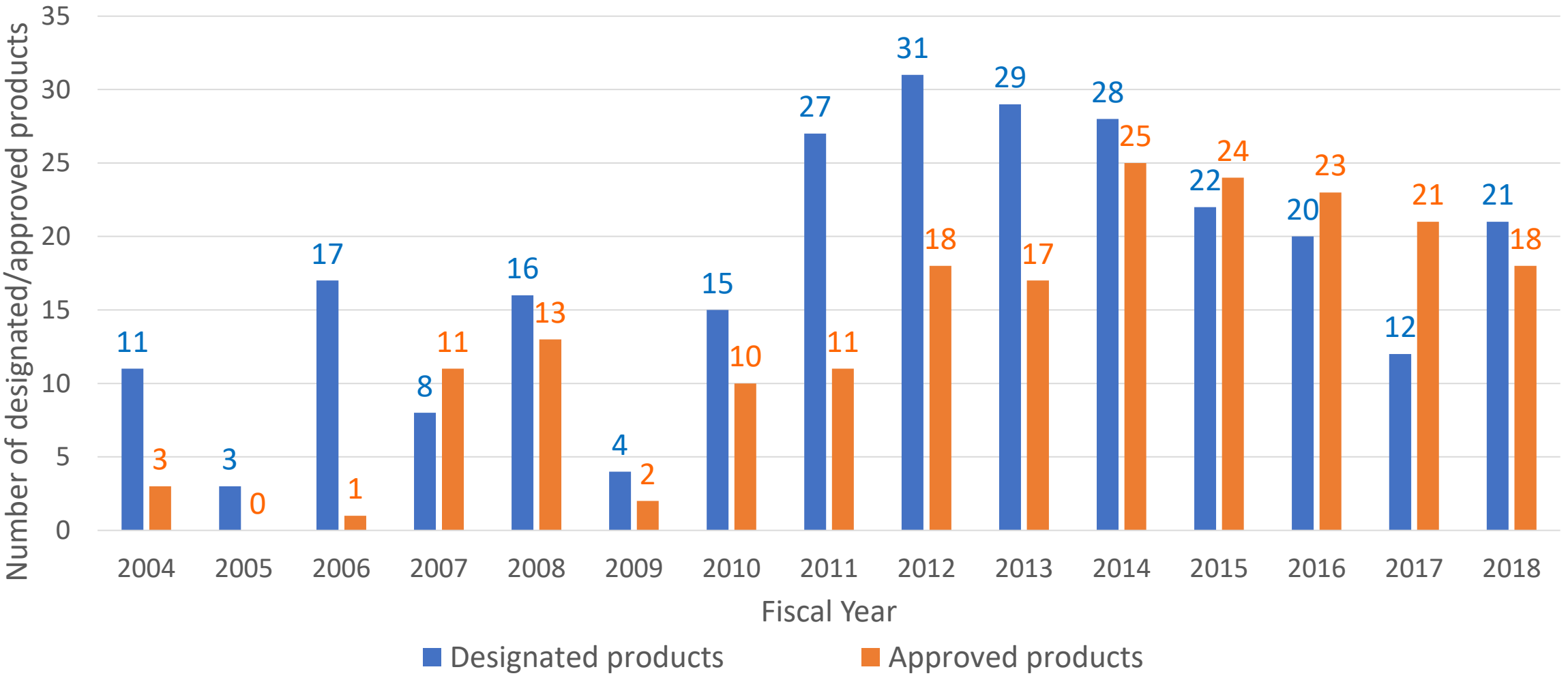
Today's topics

- Recent clinical trials for innovative drug development in Japan

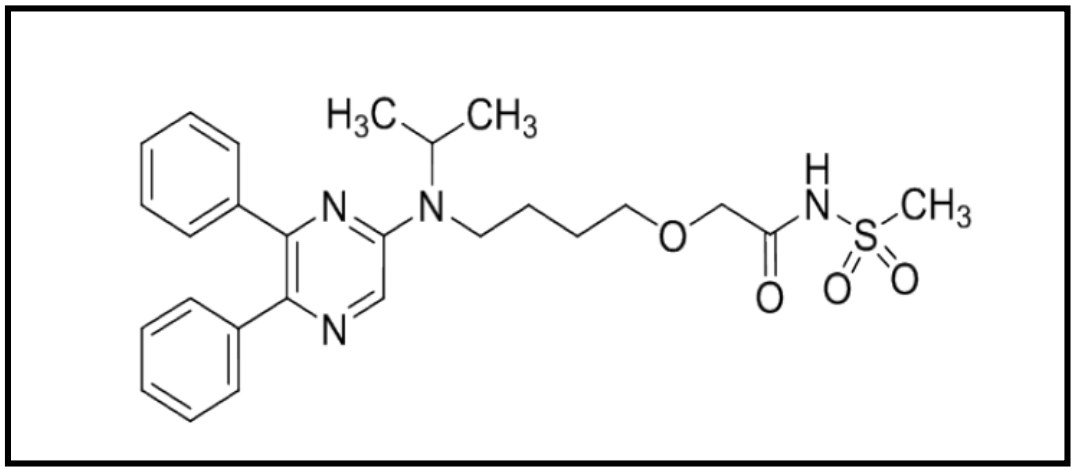
~ Two Cases of orphan drugs and related guidelines ~

- Regulatory supports (clinical trial consultations)

Number of Designated/Approved orphan drugs in Japan



Case 1 : Selexipag (Uptravi Tablets)



Selexipag is a non-prostanoid prostacyclin receptor (IP receptor) agonist

Indication

Pulmonary arterial hypertension (PAH)

(Selexipag Review Report)
http://www.pmda.go.jp/files/000222147.pdf

Case 1 : Selexipag (Uptravi Tablets)

Clinical Data Package

【Foreign Studies】
- Phase II study in PAH patients
- randomized, placebo-controlled, double-blind, parallel-group phase III study in PAH patients

The applicant submitted evaluation data from 13 clinical studies (1 each of Japanese phase I and II studies, 9 foreign phase I studies, and 1 each of foreign phase II and phase III studies)

【Japanese Studies】
- Phase I study in healthy adults
- Single-arm phase II study in PAH patients (37 patients)

(Selexipag Review Report)
http://www.pmda.go.jp/files/000222147.pdf

Case 1 : Selexipag (Uptravi Tablets)

Outline of the review conducted by PMDA

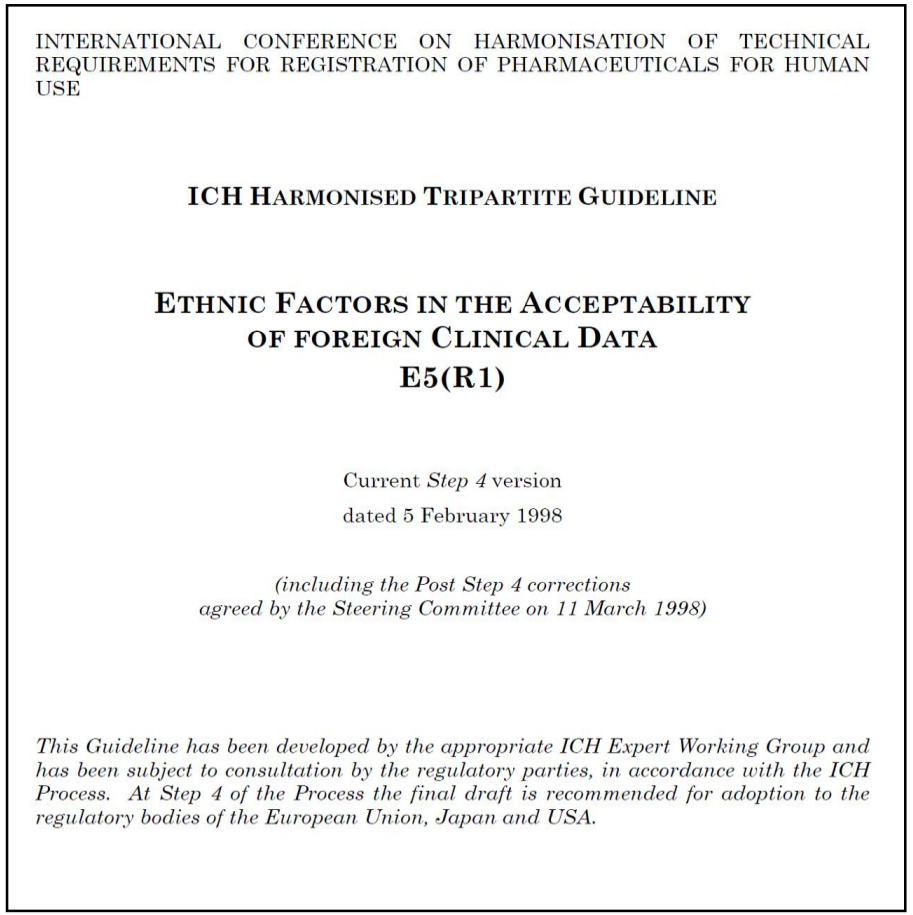
- Use of the results of foreign clinical studies
  - Comparison of intrinsic and extrinsic ethnic factors in PAH treatment between Japanese and non-Japanese patients
  - Appropriateness of using foreign clinical study data

PMDA has concluded that it is appropriate to evaluate the efficacy and safety of selexipag in Japanese patients with PAH based also on the foreign clinical study data, for the following reasons: (a) only a limited number of Japanese patients with PAH were available for enrollment in the Japanese clinical study; (b) no difference was observed in intrinsic or extrinsic ethnic factors [see "7.R.2.1 Comparison of intrinsic and extrinsic ethnic factors in PAH treatment between Japanese and foreign patients"] or in the efficacy or safety between Japanese and non-Japanese patients [see "7.R.3 Efficacy" and "7.R.4 Safety"].

(Selexipag Review Report)
http://www.pmda.go.jp/files/000222147.pdf

ICH Guideline

ICH E5



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA
E5(R1)

Current *Step 4* version
dated 5 February 1998

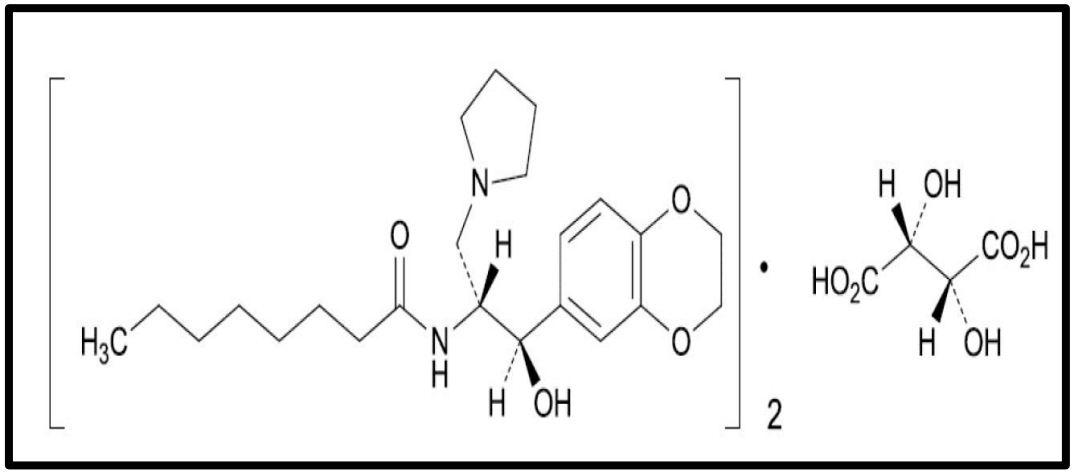
(including the Post Step 4 corrections agreed by the Steering Committee on 11 March 1998)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA

https://www.pmda.go.jp/files/000156836.pdf

Case 2：Eliglustat Tartrate (Cerdelga Capsules)



Eliglustat tartrate inhibits the synthesis of glucosylceramide by inhibiting glucosylceramide synthase.

Indication

Alleviation of symptoms of Gaucher disease (anemia, thrombocytopenia,hepatosplenomegaly, and skeletal pathology)

(Eliglustat Tartrate Review Report)

http://www.pmda.go.jp/files/000215814.pdf

Case 2：Eliglustat Tartrate (Cerdelga Capsules)

Clinical Data Package

(Eliglustat Tartrate Review Report)

http://www.pmda.go.jp/files/000215814.pdf

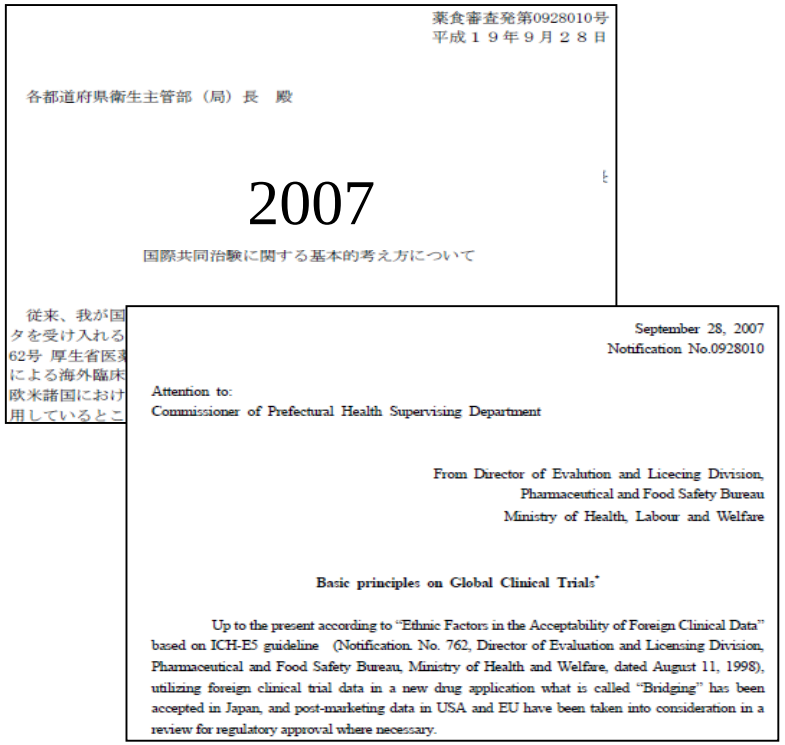
Global/ Foreign/ Domestic	Title	All subjects	Japanese subjects
MRCT	Global phase III study in Japanese and non-Japanese patients with Gaucher disease	170	10
Foreign	Phase II study in treatment-naïve patients with Gaucher disease type 1	26	0
Foreign	Phase III study in treatment-naïve patients with Gaucher disease type 1	40	0
Foreign	Phase III study in patients with a history of enzyme replacement therapies	159	0

Outline of the review conducted by PMDA

In light of the rare nature and seriousness of Gaucher disease, PMDA evaluated the efficacy of eliglustat with data including those from non-Japanese clinical studies. PMDA evaluated the efficacy also in the individual Japanese subjects because the number of Japanese patients were as small as 10 in the global phase III study (Study EDGE)111 in which Japanese subjects participated.

Japanese Point to consider for MRCT

Basic principles on Global Clinical Trials

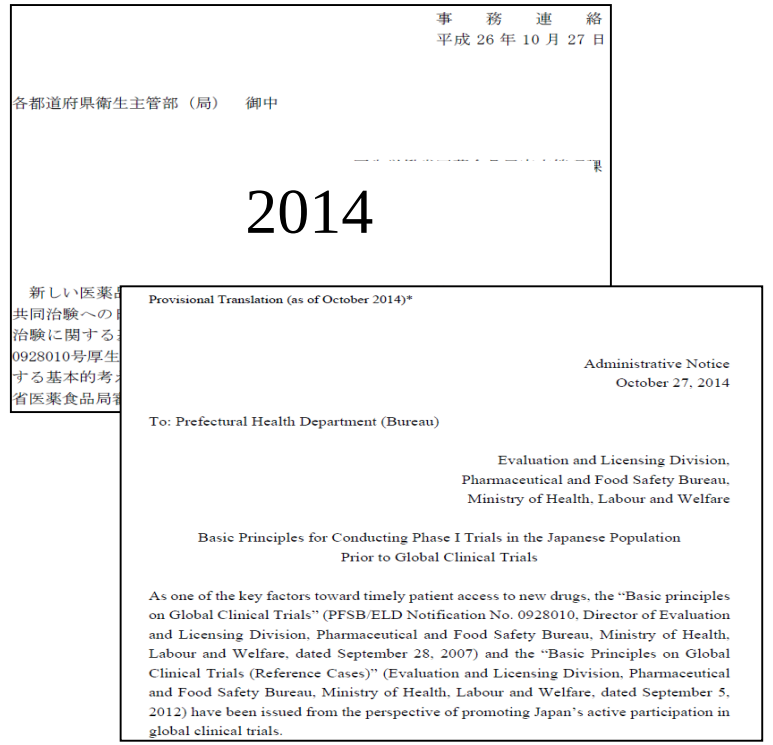


Japanese : http://www.pmda.go.jp/files/000157000.pdf
English : http://www.pmda.go.jp/files/000157900.pdf

Basic principles on Global Clinical Trials (Reference Case)

Japanese : http://www.pmda.go.jp/files/000157901.pdf
English : http://www.pmda.go.jp/files/000157520.pdf

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



Japanese: http://www.pmda.go.jp/files/000157480.pdf
English: http://www.pmda.go.jp/files/000157777.pdf

How to determine a sample size

The size of a trial is influenced by the disease to be investigated, the objective of the study and the study endpoints. Statistical assessments of sample size should be based on the expected magnitude of the treatment effect, the variability of the data, the specified (small) probability of error (see ICH E9) and the desire for information or subsets of the population or secondary endpoints. In some circumstances a larger database may be needed to establish the safety of a drug. ICH E1 and ICH E7 suggest a minimum experience to assess safety for a registrational database for a new indication.

These numbers should not be considered as absolute and may be insufficient in some cases (e.g. where long-term use in healthy individuals is expected).

(ICH E8 :General considerations for clinical trails)

https://www.pmda.go.jp/files/000156703.pdf

How to determine a sample size and proportion of Japanese subjects (MRCT)

Question 6: 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?

- In a global trial, sample size can be calculated assuming results from the entire study population across regions. In this case, a sufficient statistical power to detect statistically significant difference should not necessarily be secured within the Japanese subpopulation. However, when the entire study population across regions is defined as a primary analysis population in a confirmatory study, the justification should be explained as to why the entire population can be deemed as one population, while each regional population is not used.

(Basic principles on Global Clinical Trials)

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

How to determine a sample size and proportion of Japanese subjects (MRCT)

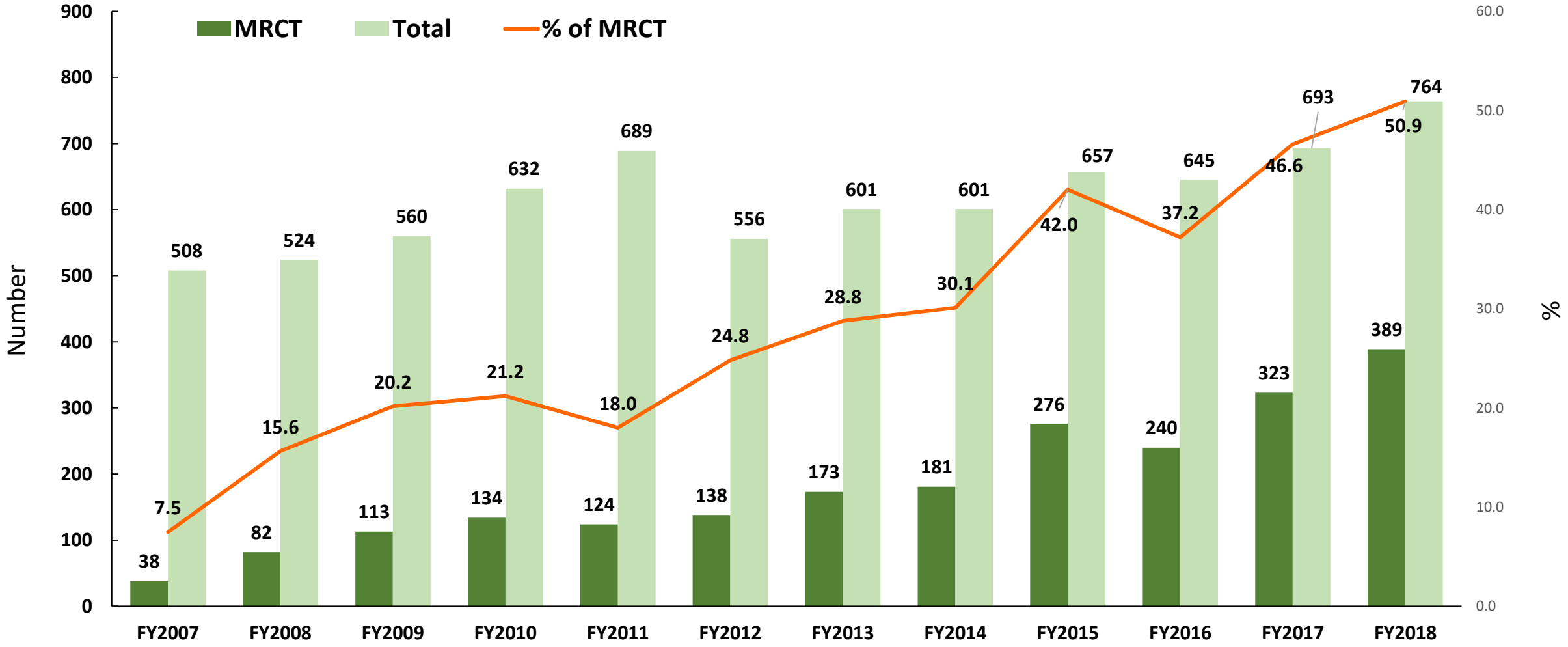
Question 6: When conducting an exploratory trial like a dose-finding study or a confirmatory trial as a global clinical trial, how is it appropriate to determine a sample size and a proportion of Japanese subjects?

- 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.

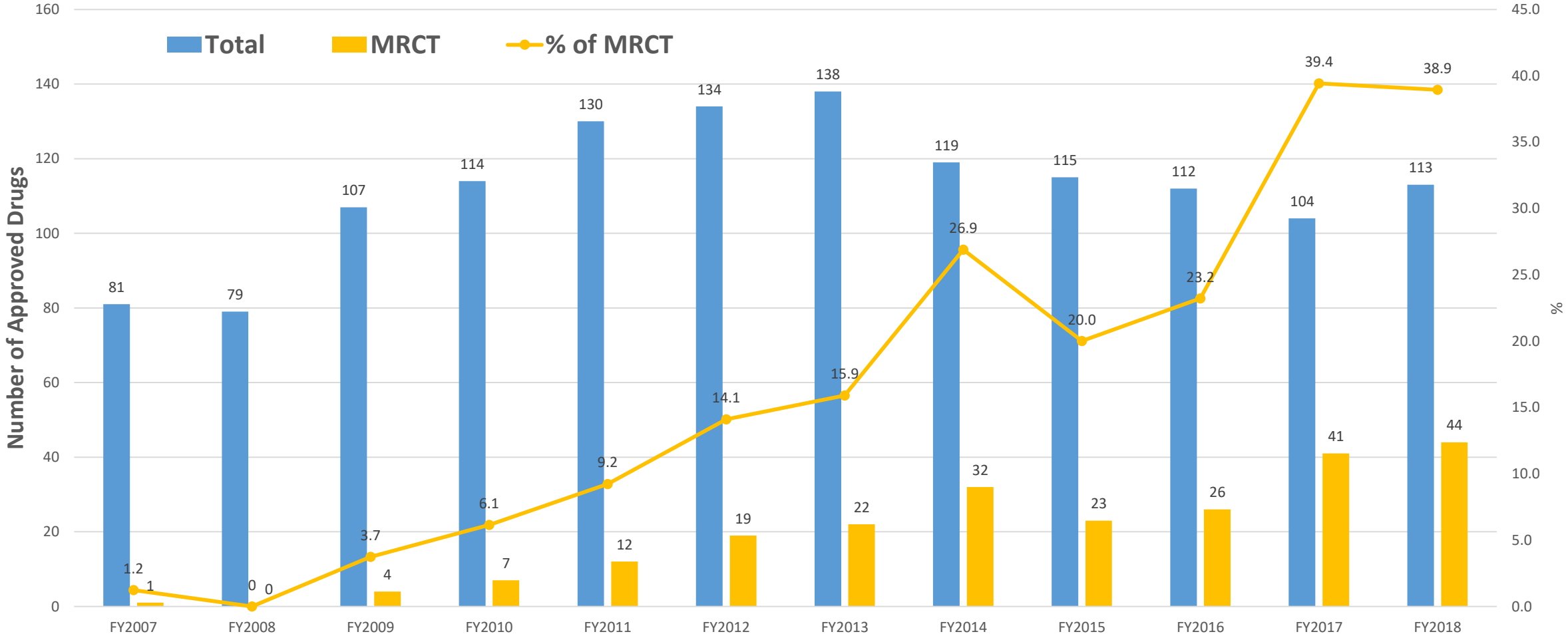
(Basic principles on Global Clinical Trials)

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

Number of Clinical Trial Notification in Japan

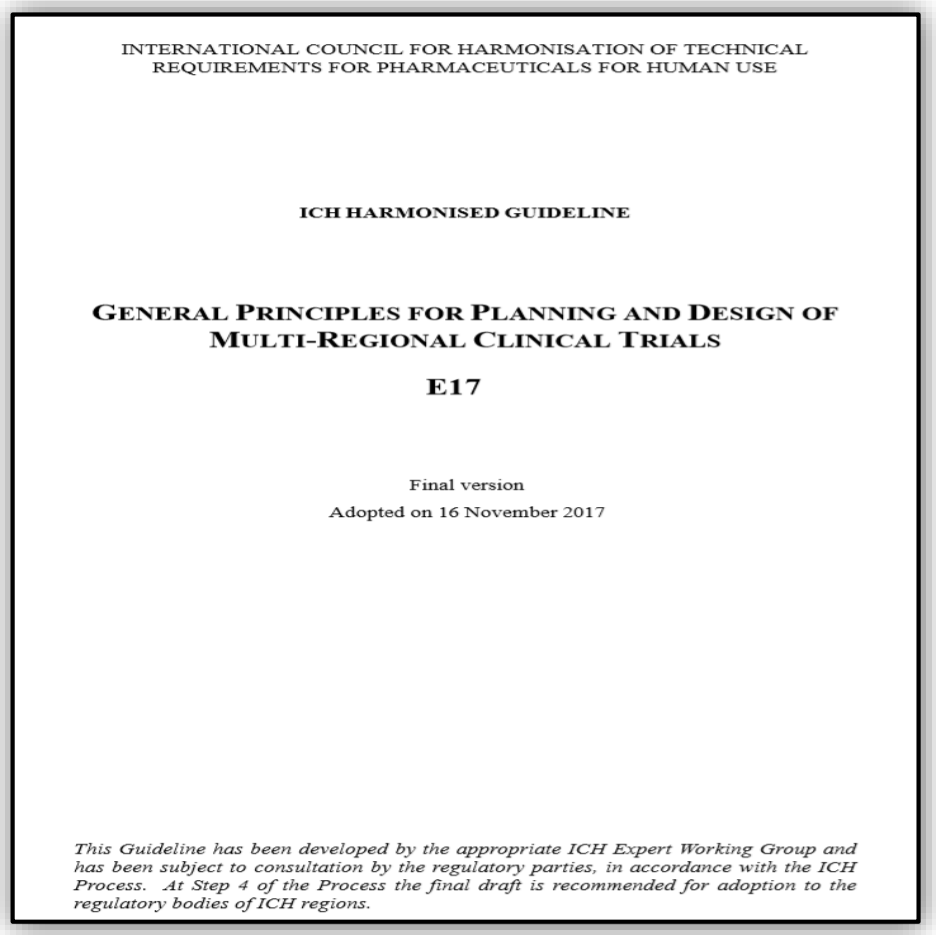


Number of Approved drugs in Japan



ICH Guideline

ICH E17



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR PLANNING AND DESIGN OF MULTI-REGIONAL CLINICAL TRIALS

E17

Final version

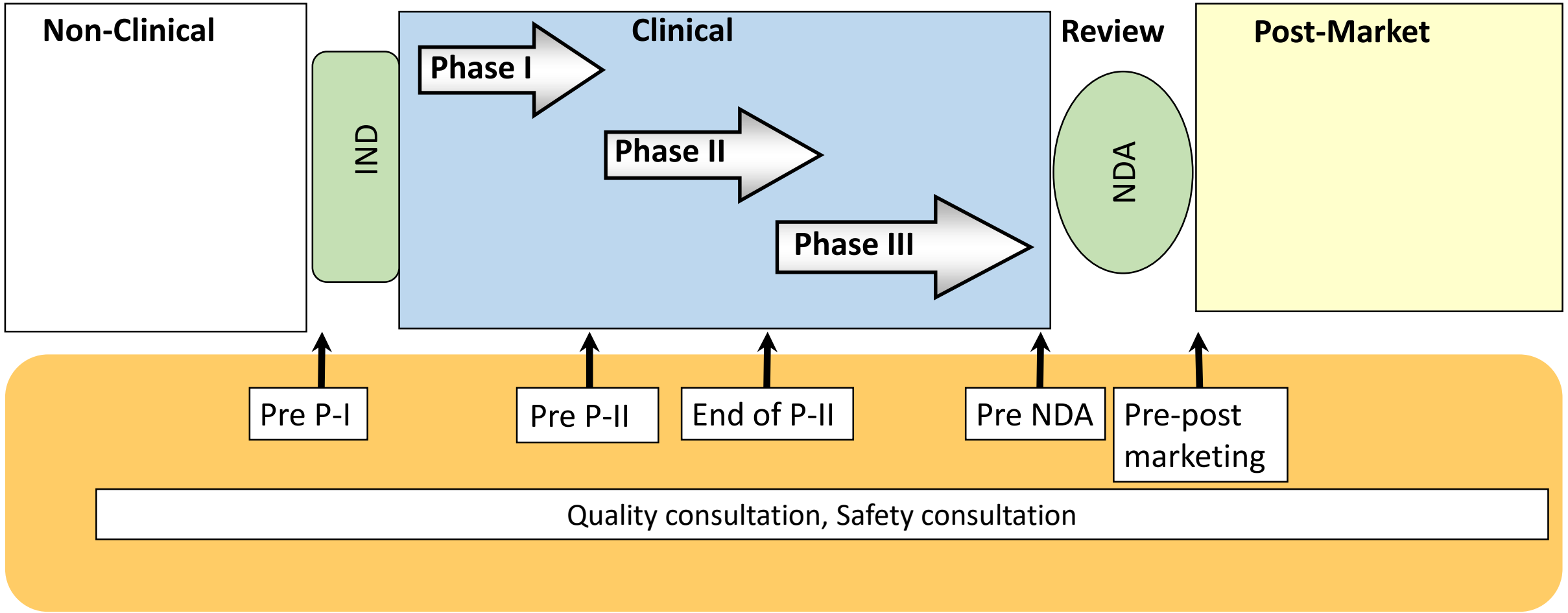
Adopted on 16 November 2017

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

GENERAL PRINCIPLES FOR PLANNING AND DESIGN OF MULTI-REGIONAL CLINICAL TRIALS

https://www.pmda.go.jp/files/000224562.pdf

Clinical trial consultations by PMDA



Example：Clinical trial consultations by PMDA

Question 1: Are the following plan in phase 3 study acceptable ?

1.1 Inclusion criteria and exclusion criteria

1.2 Dosage and administration

1.3 Open-label uncontrolled design

1.4 Endpoint (primary endpoint and secondary endpoint etc…)

1.5 Number of subjects (Japanese subjects)

Question 2: Is the clinical data package acceptable ?

Proper endpoint ?
Historical control ?

Very small Japanese subjects?

Example：Clinical trial consultations by PMDA

Question 1: Are the following plan in phase 3 study acceptable ?

1.1 To include Japanese patients in MRCT phase 3 study?

1.2 Inclusion criteria and exclusion criteria

1.3 Dosage and administration

1.4 Selection of control group

1.5 Endpoint (primary endpoint and secondary endpoint etc…)

1.6 Number of subjects (all subjects and Japanese subjects)

Question 2: Is the clinical data package acceptable ?

Example：Clinical trial consultations by PMDA

company

All subjects：300 subjects ?
Japanese subjects： 60 subjects ?

Acceptable?
【Clinical Data package】
- Phase I
- Phase III

Acceptable/ Not acceptable

Summary

- ICH guidelines and Japanese Point to consider are referred in orphan drug development. Therefore, to publish guidelines and Point to consider will promote drug development.

- It is important to discuss with the regulatory agencies how many Japanese subjects are needed and what clinical trials are required before application of approval. Therefore, clinical trial consultation by regulatory agencies plays a major role. Using clinical trial consultations will promote drug development appropriately.