# Clinical trial notifications and scientific consultation system in Japan

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**（PMDA）**

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# Contents

**① Outline of clinical trial notifications for drugs and consultation system**

**② Clinical trial notifications for drugs**

**③ Clinical trial consultation and prior assessment consultation**

# Background

**October, 1994**

**Increase in the number of drugs which have potent pharmacological effects.**

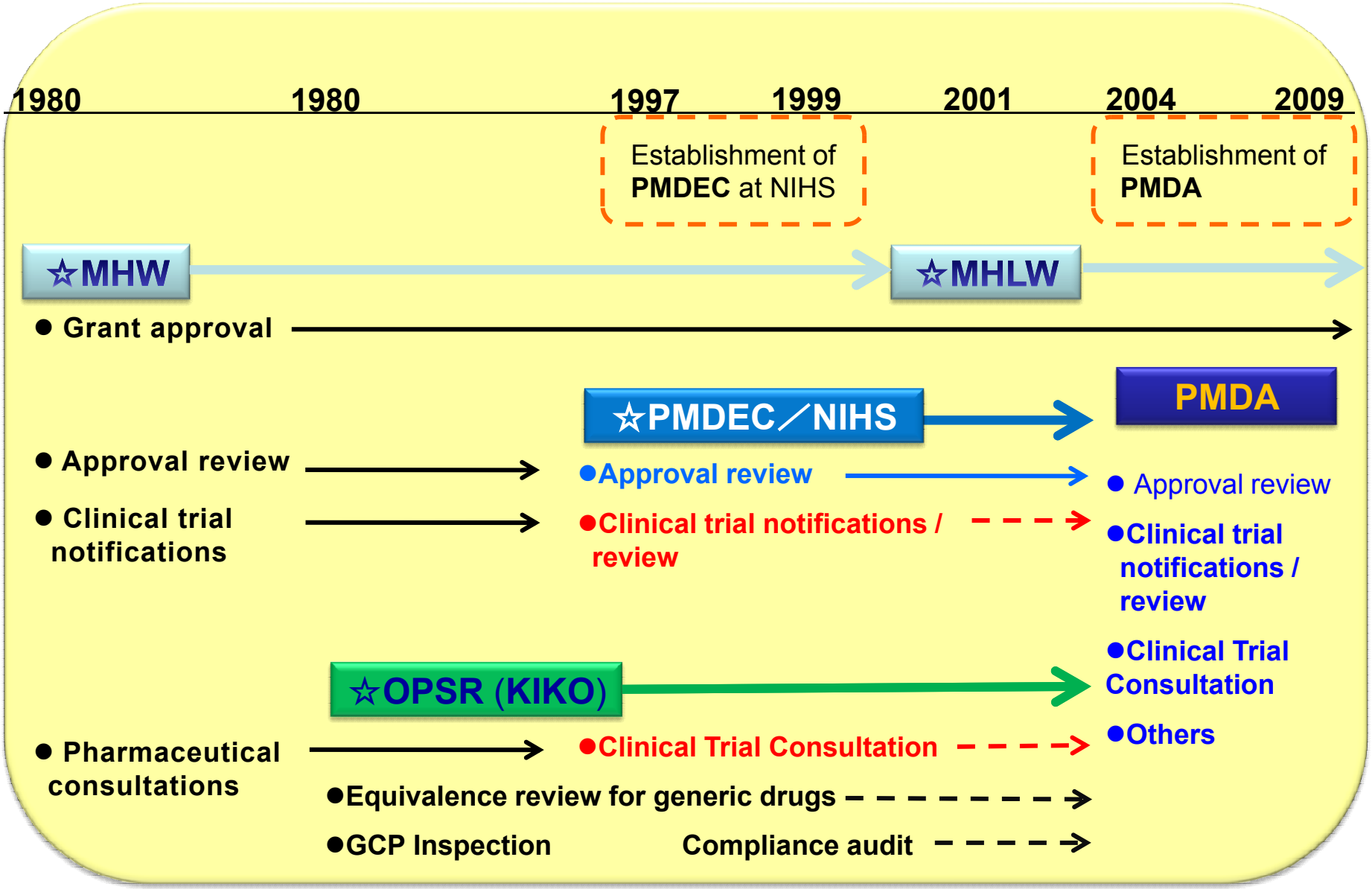
**→ Needs for improving drug safety**

**Strengthening of the role of pharmaceutical companies**
**Taking comprehensive measure for pharmaceuticals**

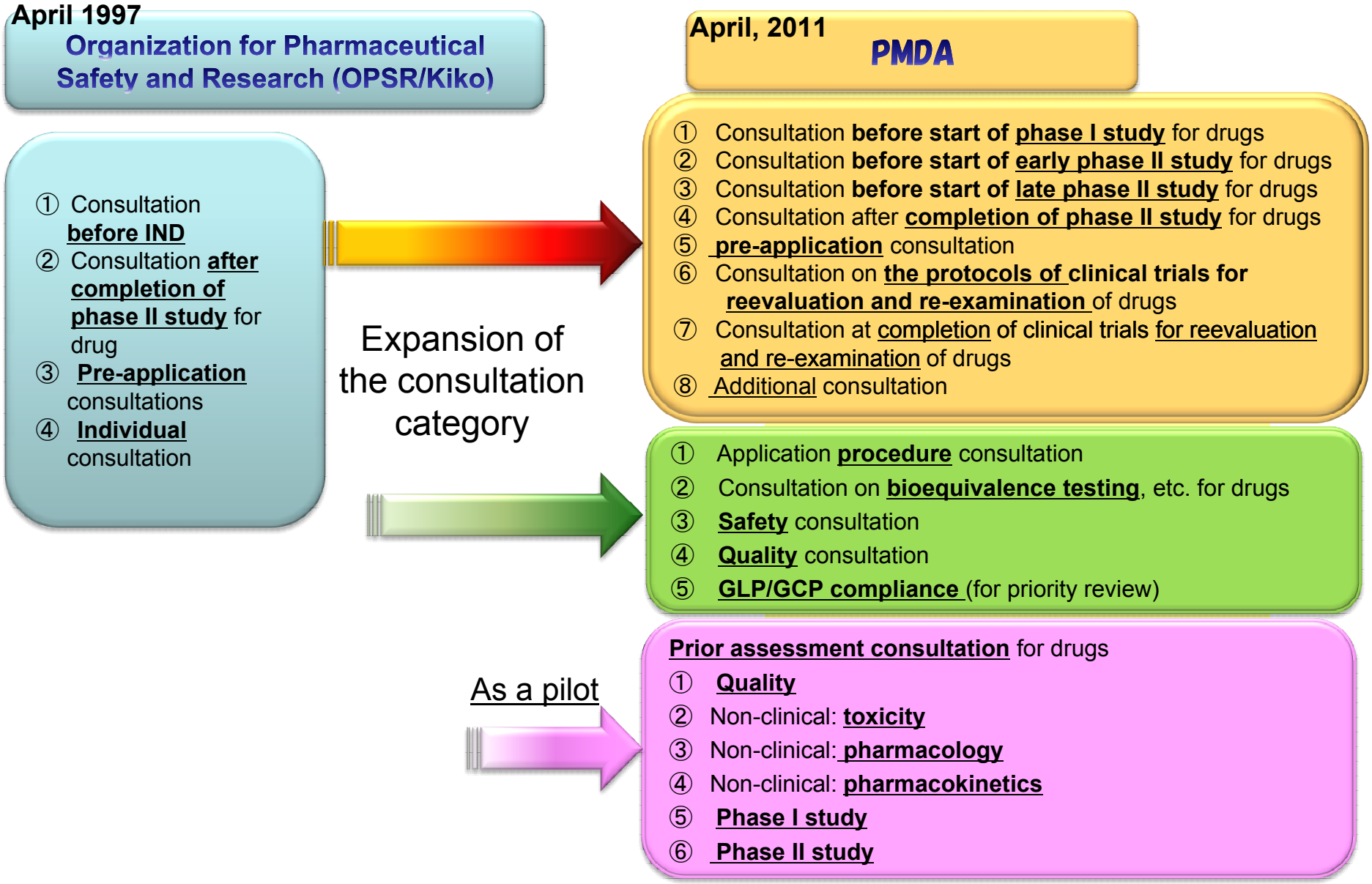
**June, 1996 Publication of the revised Pharmaceutical Affairs Law**
**April, 1997 Enforcement of the revised Pharmaceutical Affairs Law**

1. **Reinforcement of consultation/guidance for Clinical trials**
2. Reinforcement of approval review
3. **Strengthening of post-marketing measures**
4. **Others**

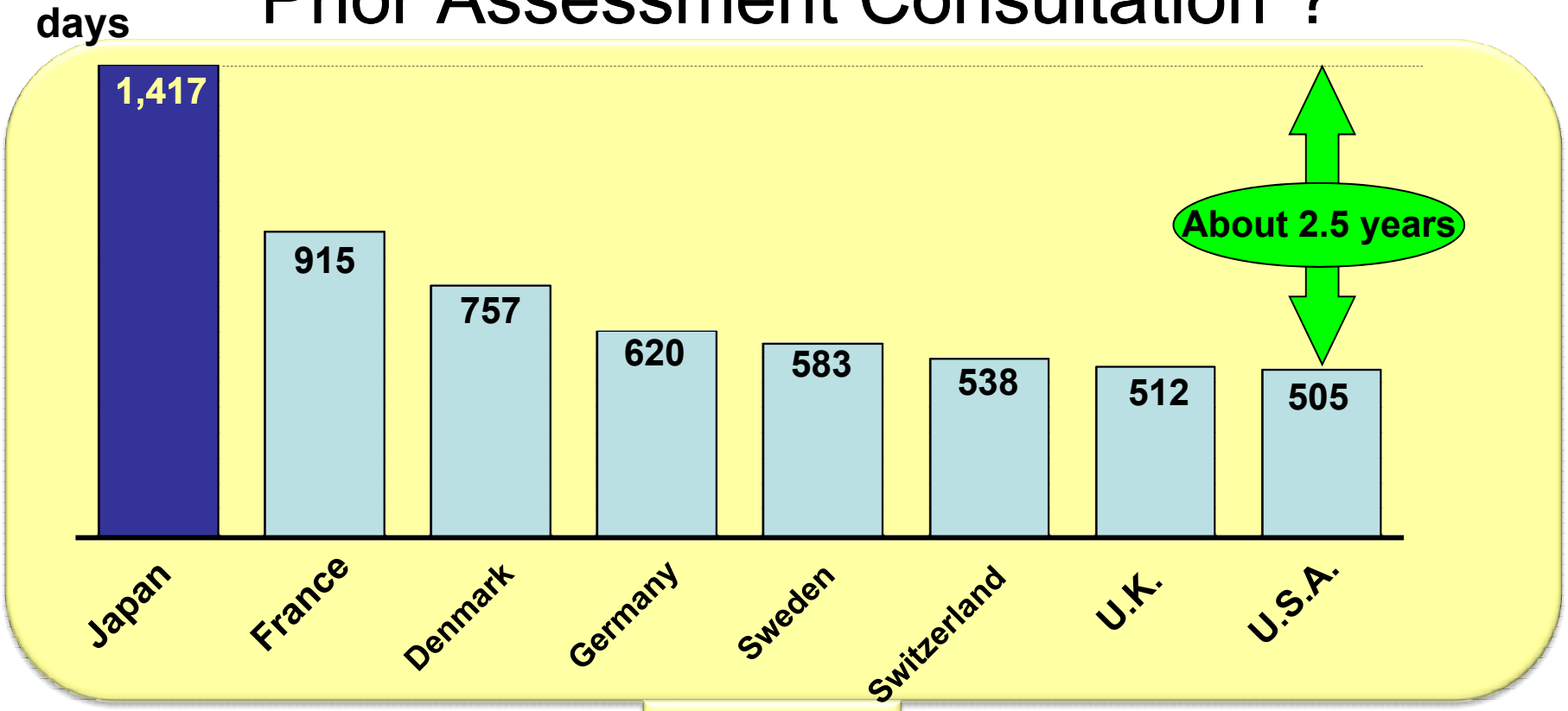
# The change of the enforcement system of IND and Consultation



# Consultations according to individual needs



# Why did we introduce "Prior Assessment Consultation"?




"Measure to eliminate drug lag ?"

The source：JPMA The Office of Pharmaceutical Industry Research
Research Paper No.31（May 2006）

# Measures by PMDA for eliminating drug lag

# Submission of the Clinical trial notification

## (Pharmaceutical Affairs Law)

(Handling of Clinical Trials )

**Article 80-2** Sponsors of clinical trials must conduct in accordance with standards specified in MHLW Ordinance.

② Sponsors of clinical trials must submit the clinical trial protocol to the Minister beforehand as specified in MHLW Ordinance.

③ Persons submitting protocols, shall not sponsor the clinical trial until after of 30 days has passed from the submission date . **In such cases, the Minister shall undertake a review of the clinical trial protocol** to prevent from jeopardizing public health and hygiene.

# Drugs requiring submission of CT notifications(1)

① Drugs with **active ingredients differing** from that of approved drugs .

② Drugs with active ingredients that are **same** but **the route of admission differing** from approved drugs.

③ Drugs **differing** from **combination ratio** of active ingredients, or **indications** or **dosage and administration** of approved drugs.

④ Drugs with active ingredients that are **same ingredient which had approved** as new molecular entity, but that **reexamination period has not expired**.

⑤ Drugs expected to be as **biological products**.

⑥ Drugs manufactured using **recombinant technology**.

The Pharmaceutical Affairs Law, Enforcement Regulations: Article 268
No. 0815001 of Director of Evaluation and Licensing Division dated August 15 2008.
No. 0815005 of Director of Evaluation and Licensing Division dated August 15 2008.

# Drugs requiring submission of CT notifications(2)

**The person** who has submitted a clinical trial notification **must inform** 【●●】 when the contents of **the notification were changed**.

●【*The Minister*】

- Notifications of **changes** in clinical trial **protocol** and **completion** or **discontinuation** of the clinical trial.

●【 *Director of Evaluation and Licensing Division*】

- Notifications of **discontinuation** of the development

*The Pharmaceutical Affairs Law, Enforcement Regulations: Article 270*
*No. 0815001 of Director of Evaluation and Licensing Division dated August 15 2008.*
*No. 0815005 of Director of Evaluation and Licensing Division dated August 15 2008.*

# Documents which is required to be attached to the clinical trial notifications

① Statement regarding the reason why the sponsoring of the proposed clinical trial is scientifically justified.

② A protocol of the proposed clinical trial

③ An explanation document used for informed consent and consent form

④ Sample of Case Report Form

⑤ Current investigator's brochure

The Pharmaceutical Affairs Law, Enforcement Regulations: Article 269
No. 0815001 of Director of Evaluation and Licensing Division dated August 15 2008.
No. 0815005 of Director of Evaluation and Licensing Division dated August 15 2008.

# Timing of submission of clinical trial notifications

① The first notifications of regarding trial drugs must be submitted **at least more than 31 days before** the day of planning on contract with the medical institutions.

② Notifications other than those specified in ① above shall be submitted **at least around 2weeks before** the day of planning on contract with the medical institutions.

The Pharmaceutical Affairs Law, Enforcement Regulations: Article 269
No. 0815001 of Director of Evaluation and Licensing Division dated August 15 2008.
No. 0815005 of Director of Evaluation and Licensing Division dated August 15 2008.

# What kind of drug is needed to submit the 1st notification before at least 31 days of the contract?

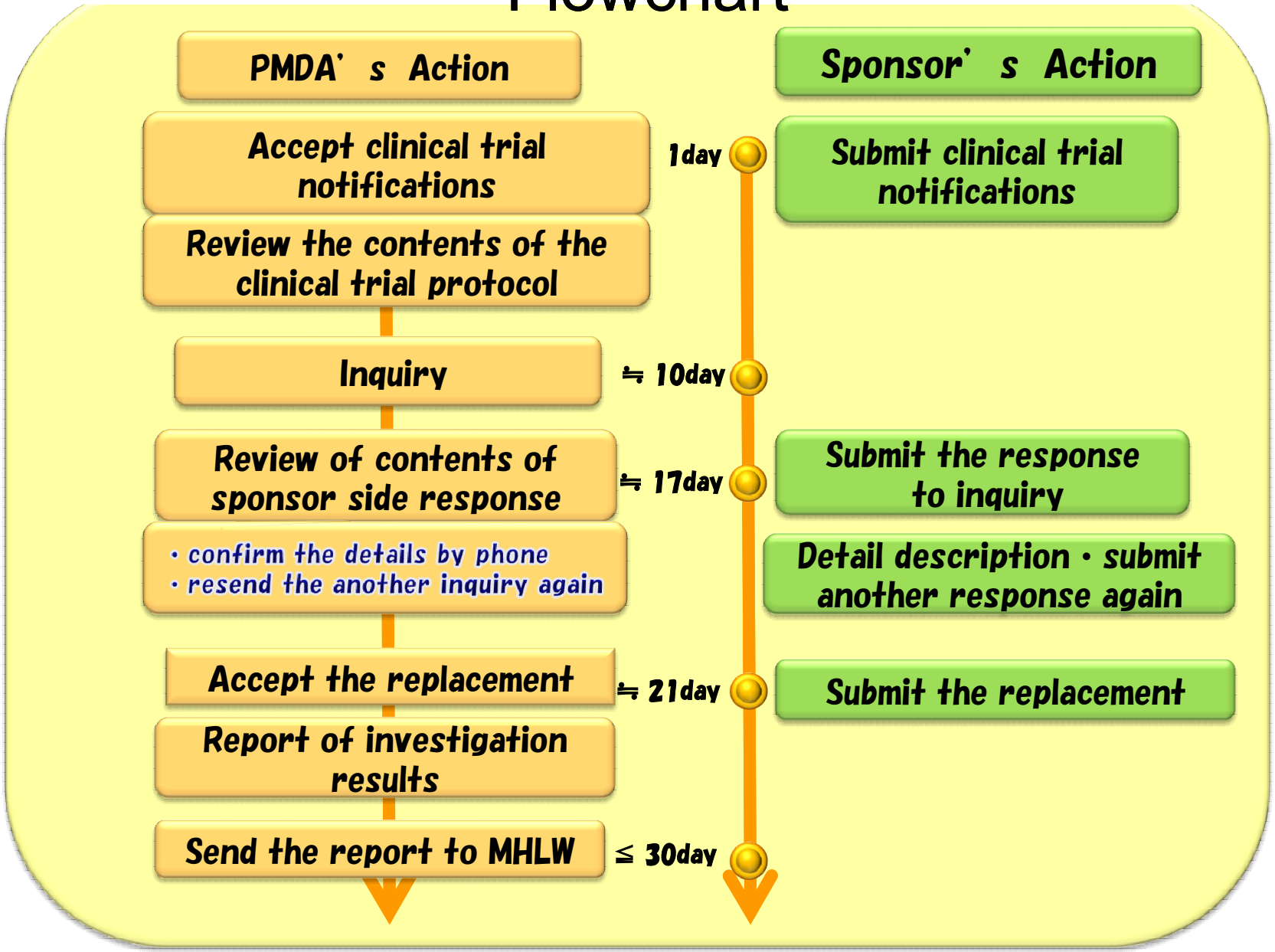
① Drugs with active ingredients differing from that ingredient of approved drugs.

② Drugs that are the same active ingredients but the route of administration differing from approved drugs.

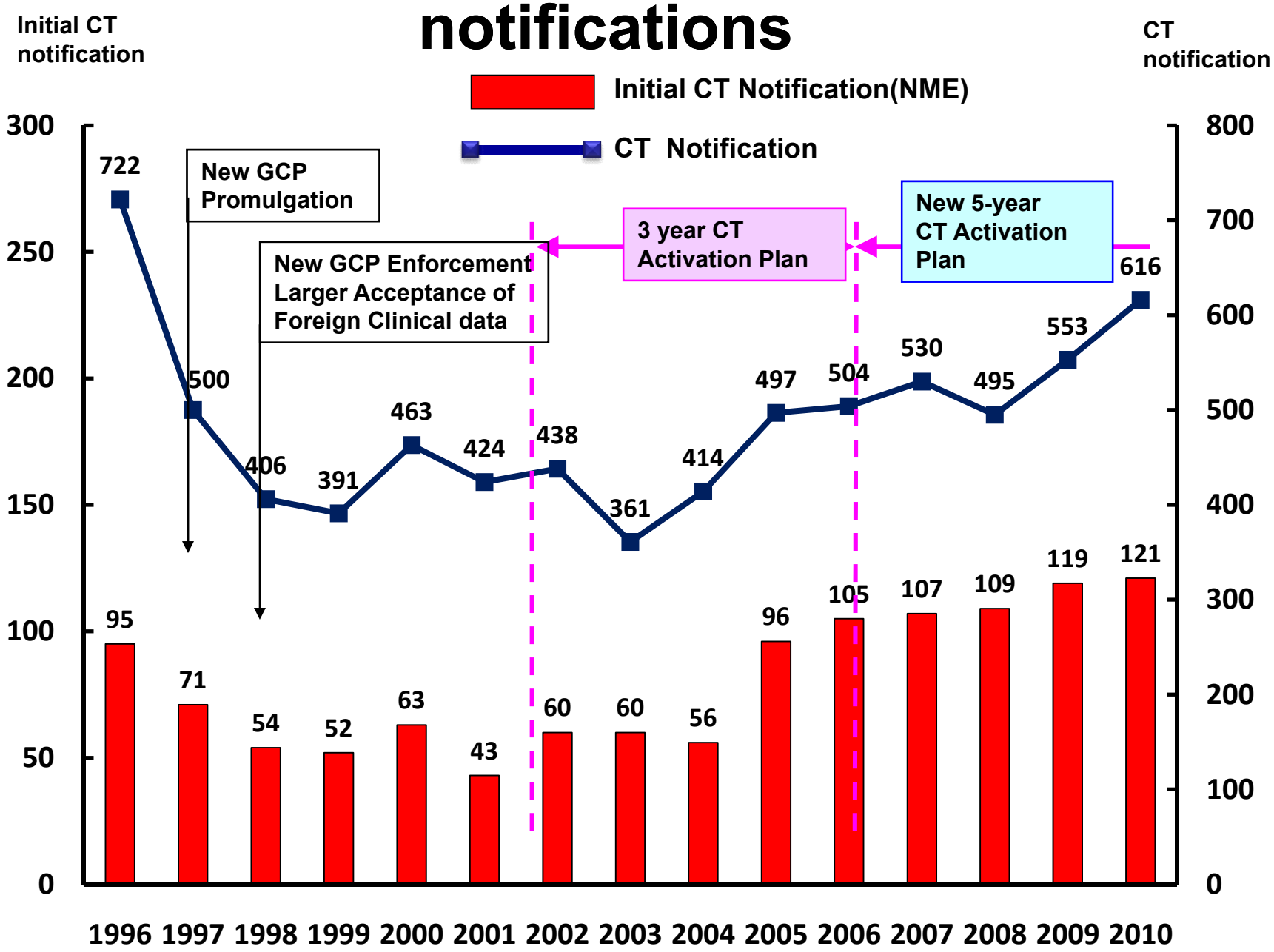
③ Medical combination drugs excluding similar medical combination agent .

# For review of the clinical trial protocol

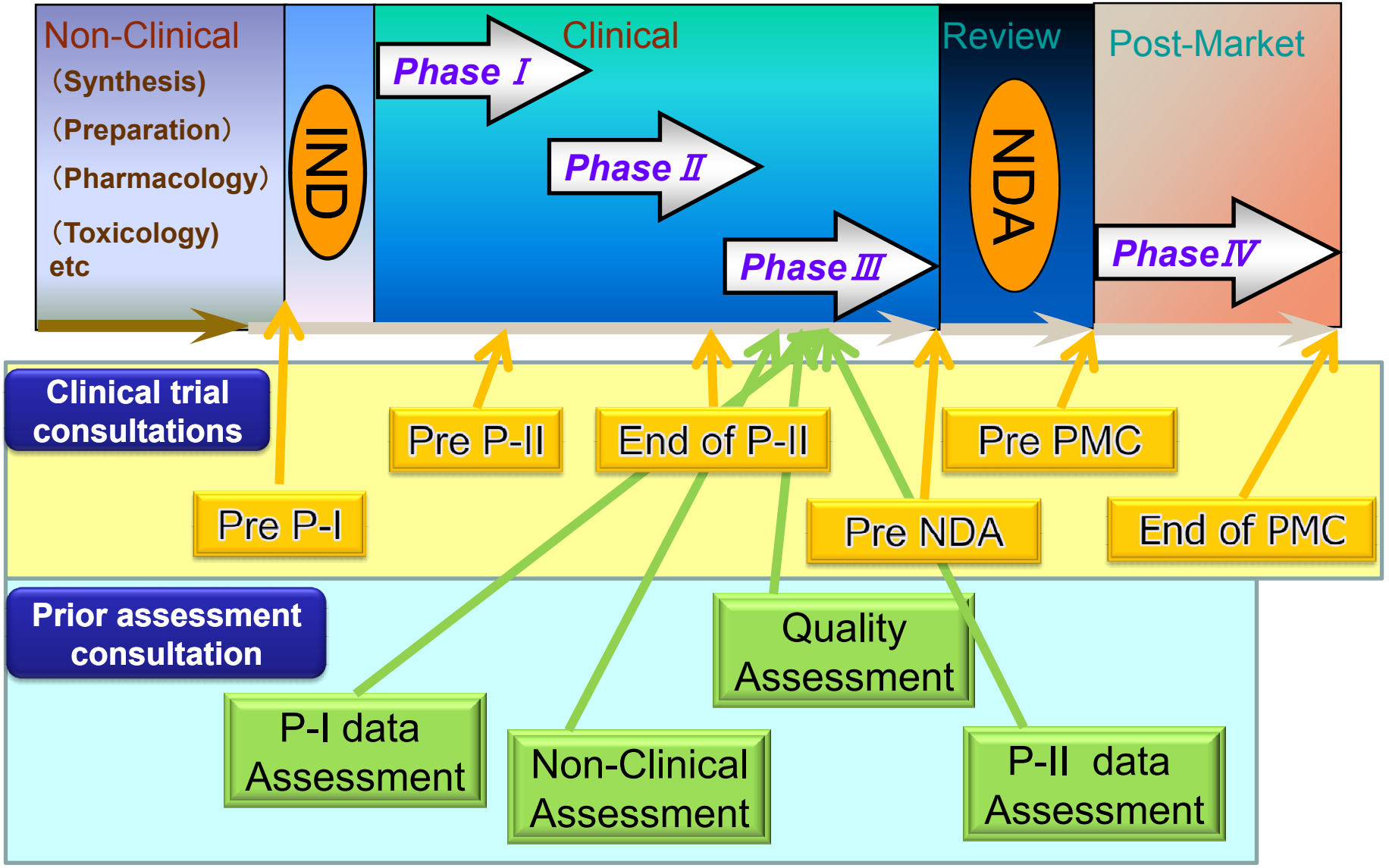
## Flowchart



# The change of number of clinical trial notifications



# PMDA's scientific consultation



# Purpose and contents of clinical trial consultations

## Purpose

**By implementation of consultation in development stage**

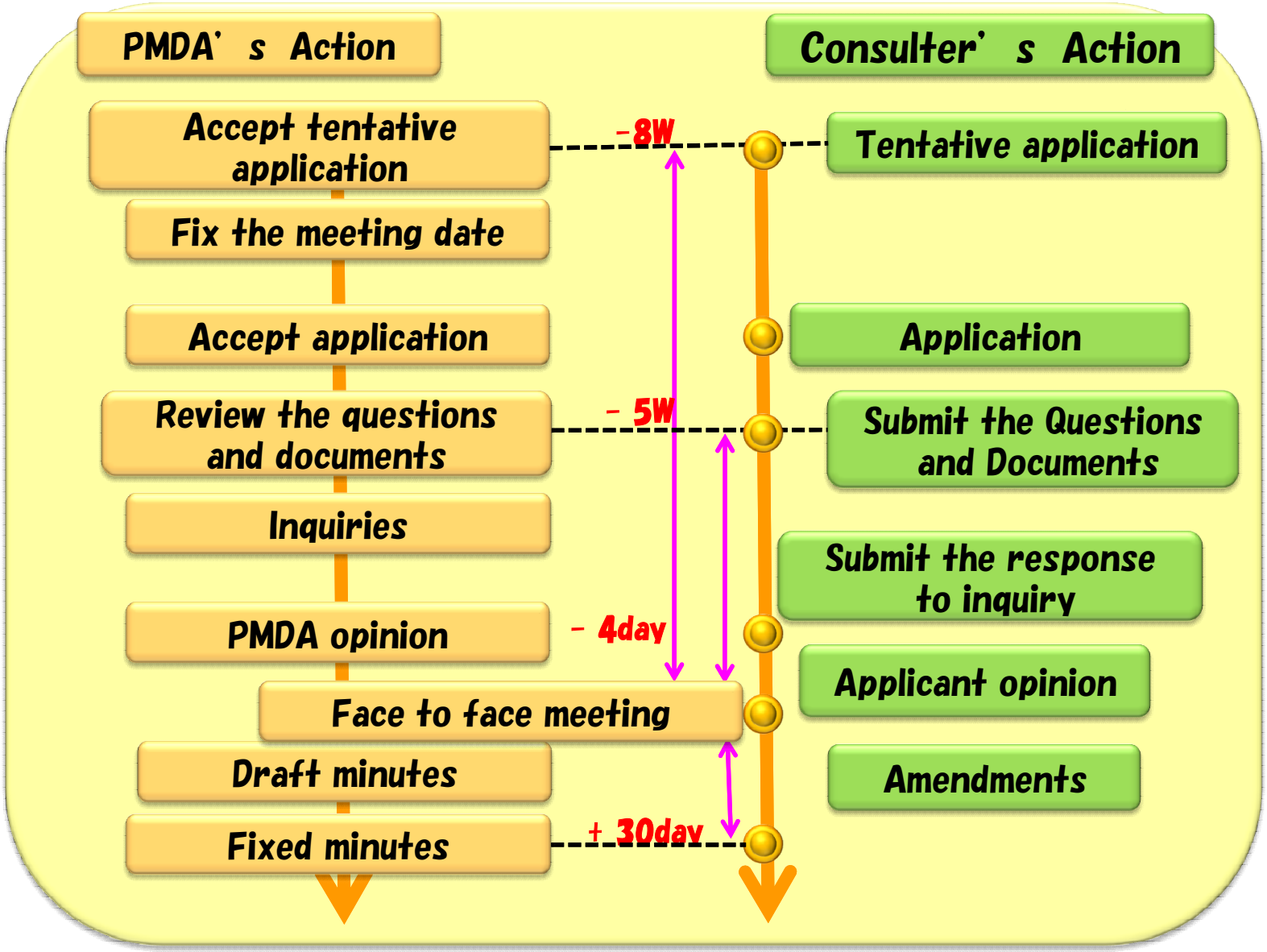
- **Solve the issues in clinical development →shortening of the time before the application / cost reduction**
- **Avoid finding any critical issues on NDA review**

## Consultation contents

- Consultation **before start of phase I study** for drugs
  - ***The validity of applying the drug to a person for the first time***
  - ***Clinical study design of Phase I etc.***
- Consultation **before start of phase II** or **after completion of phase II study** for drugs
  - ***Clinical study design of phase II or phase III etc.***
- **Pre-application** consultation
  - ***The way for compiling the application document***
  - ***Sufficiency of the application document***

# Clinical trial consultations

## Flowchart



# Implementation status of each consultation

***Total number of each IND scientific consultation about the new medical supplies*** (case)

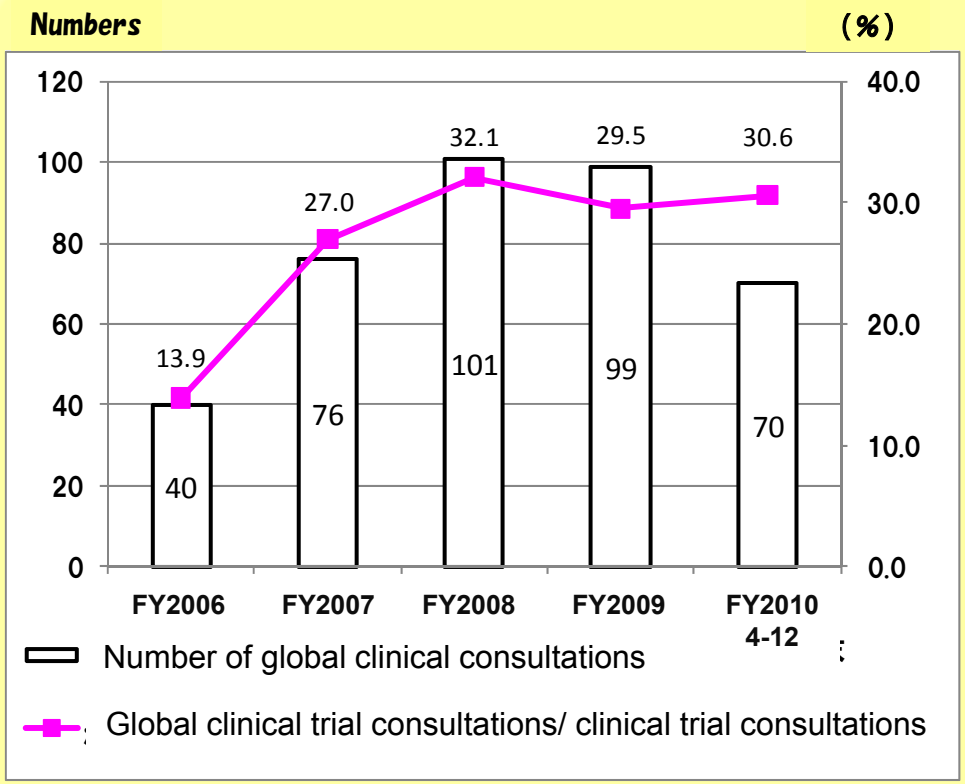
| Fiscal year | FY2005 | FY2006 | FY2007 | FY2008 | FY2009 |
|---|---|---|---|---|---|
| Total (Storing number) * | 215 | 327 | 303 | 337 | 332 |
| Consultation before start of phase I study for drugs | 42 | 73 | 65 | 48 | 47 |
| Consultation **before start of early phase II study** for drugs | 2 | 5 | 13 | 12 | 14 |
| Consultation before start of late phase II study for drugs | 47 | 67 | 67 | 62 | 40 |
| Consultation after completion of phase II study for drugs | 33 | 67 | 63 | 110 | 109 |
| Pre-application consultations | 41 | 42 | 24 | 38 | 34 |
| **Additional** consultation | 31 | 35 | 20 | 28 | 45 |
| Consultation on **the protocols of clinical trials for reevaluation and re-examination** of drugs | 2 | 3 | 2 | 2 | 2 |
| Consultation at **completion of clinical trials for reevaluation and re-examination** of drugs | 0 | 0 | 0 | 0 | 0 |
| Application **procedure** consultation | 2 | 17 | 16 | 7 | 7 |
| **Quality** consultation | 5 | 8 | 23 | 8 | 14 |
| **Safety** consultation | 5 | 6 | 5 | 7 | 13 |
| Consultation on **bioequivalence testing**, etc. for drugs | 3 | 4 | 5 | 10 | 6 |
| Consultation on **GLP/GCP compliance**(for priority reviews) | 2 | - | - | 1 | 1 |
| Consultation on document maintenance of ***Cell-and-tissue-based products*** | | | - | 4 | - |

* : **including a withdrawal**

# The change of the consultation and notification number of GCTs

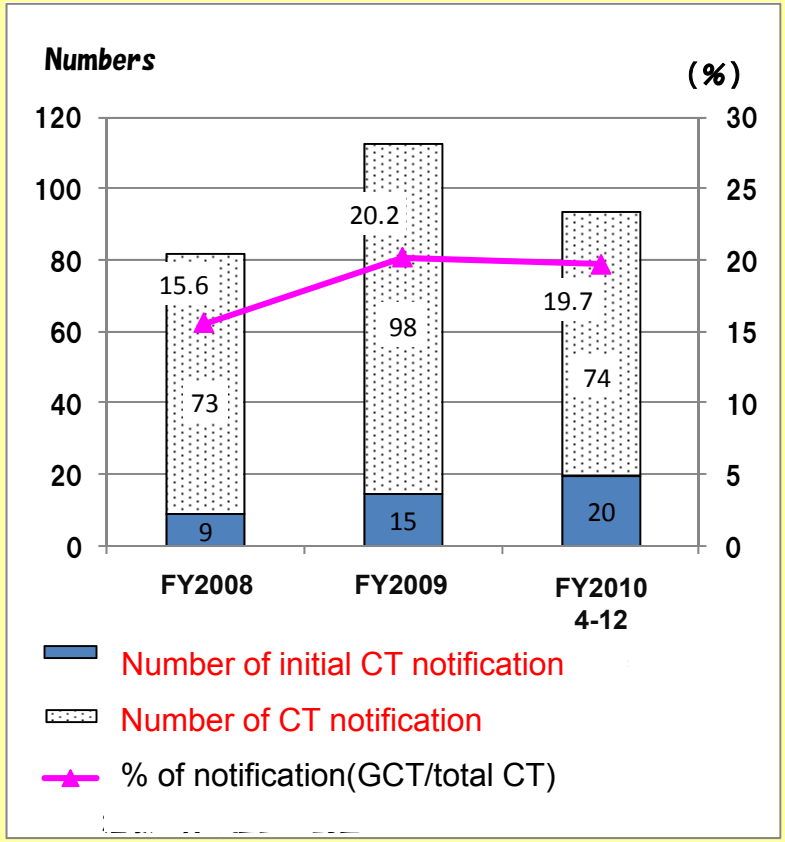
**Basic principles on global Clinical Trials** was published on September 28th, 2007 for helping to make a strategy and clinical trial designs for Global Drug Development

***Number of global clinical trial consultations ※***




***※ excluding consultation of prior assessment and pharmacogenomics/biomarkers***

***Number of global clinical trial notification***




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

# Purpose and contents of prior assessment consultation

## Purpose

**By implementation of consultation before formal NDA**

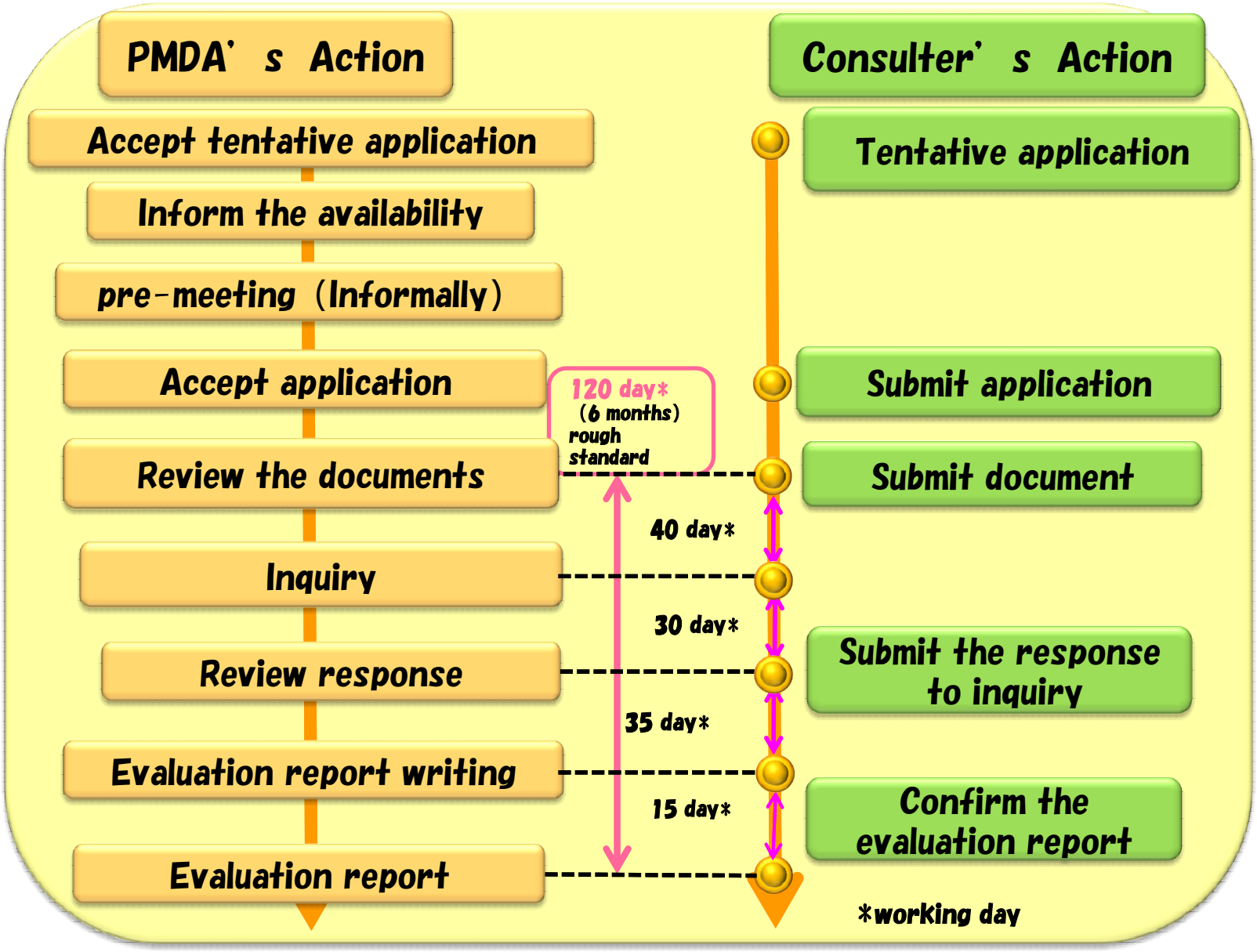
- **Shorten NDA review time**
  - **Identify major discussion points and tasks for NDA submission**
  - **Help applicant to prepare a good CTD with the inclusion of PMDA's view points**

## Consultation contents

- **Quality**、**Toxicity**（non-clinical）、**Pharmacology**(non-clinical)、**Pharmacokinetics**(non-clinical)、**Phase I study**、**Phase II study**
  - ***Data evaluation before a formal NDA submission***
  - ***PMDA provides a prior-assessment report for the submitted data/study***

# For Prior assessment consultation

# Flowchart



# Implementation status of prior- assessment consultation

| (FY) | Status of acceptance | | Status of consultation (Numbers of category) | | | Status of review (Number of the ingredient) |
|---|---|---|---|---|---|---|
| | Total of the ingredient | Total of the acceptance | Before consultation | on going | completion | Approval |
| 2009 | 7 | 33 | 0 | 0 | 33 | 4 |
| 2010 | 9 | 30 | 2 | 20 | 8 | 0 |

※Data: the end of January 2011

# Summary of survey for sponsor（1）

**Q: Consultation Items were resolved or cleared ?**

| | |
|---|---|
| **Resolved or Cleared** | **5** |
| **Relatively cleared** | **2** |
| Neither | 0 |
| Relatively Not cleared | 0 |
| Not resolved or Not cleared | 0 |

○ **Generally cleared**

**Q: How can you conclude a value of the consultations ?**

| | |
|---|---|
| **Very useful** | **3** |
| **Useful** | **4** |
| Neither | 0 |
| Not useful | 0 |

○ **Found the value in the all consultations**

# Summary of survey for sponsor（2）

**Q: How frequently should the application opportunity of consultations be available to apply?**

| | |
|---|---|
| 1 / year | 0 |
| 2 / year | 1 |
| 4 /year | 3 |
| 6 /year | 0 |
| Every Month | 3 |

**Q: Do you think a new category (prior consultation for Phase III data) is necessary ?**

| | |
|---|---|
| Yes | 4 |
| Probably Yes | 1 |
| Neither | 1 |
| Probably No | 0 |
| No | 1 |

○ Everybody hopes to increase opportunities of the consultation than the present (1/year)

○ Recognize a necessity of new category to cover clinical data assessment in later stage

# Next steps

Further improvement through the Communicative Process

In FY2011, Prior-assessment consultation will be implemented with following improvement.

- Increased an application opportunity
  - ☞ Once/year ➡ Twice/year（March & June）
- Established New Category
  - ☞ Phase Ⅱ/Ⅲ study consultation

# PMDA challenges

- Many projects in PMDA support and encourage drug development for regulatory approval
- PMDA would be happy to discuss what strategy/plan is the most appropriate for your drug development
- PMDA will continue challenges to improve processes and promote drug development for providing effective and safe drugs quickly to patients

# Thank you for your attention !

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