The PMDA's GCP Inspection Methods, the Current State of Overseas GCP on-site inspections by PMDA

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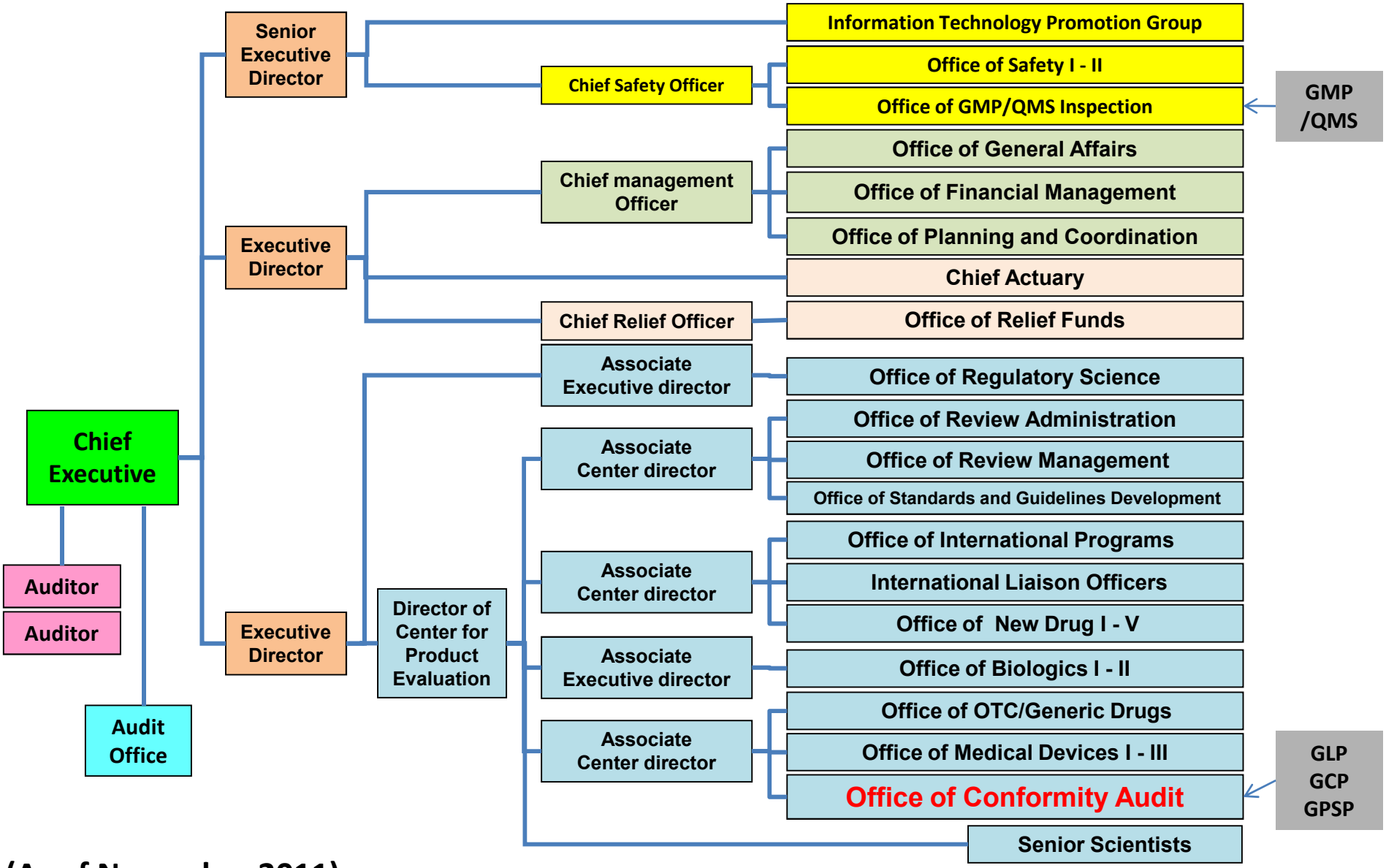
Introduction of PMDA

Pharmaceuticals and Medical Devices Agency

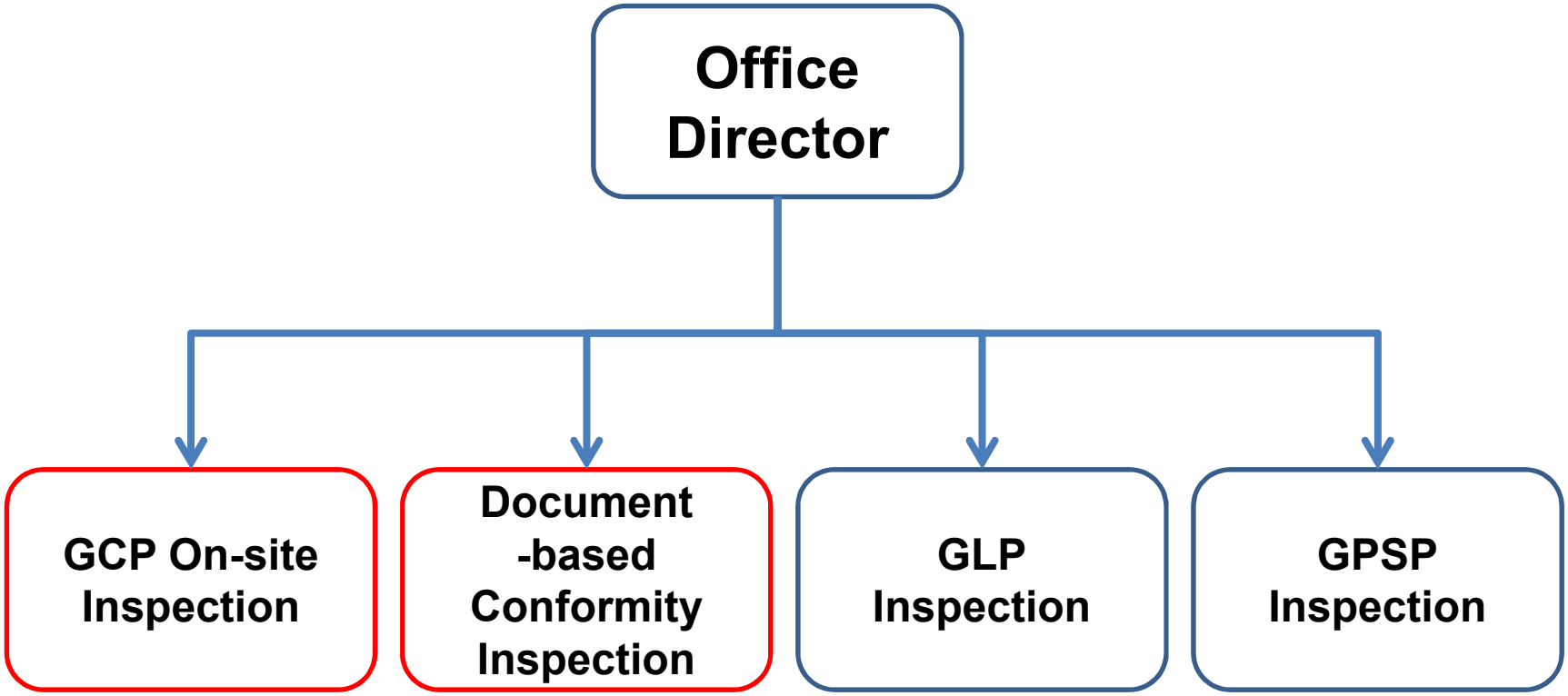
- Established in April 2004
- Number of permanent staff
  256 (Apr.'04)
  → 341 (Apr.'07)
  → 648 (Apr.'11)
  → 751 (by the end of FY 2013)
- PMDA submits performance report to MHLW annually.

Organization Chart of PMDA



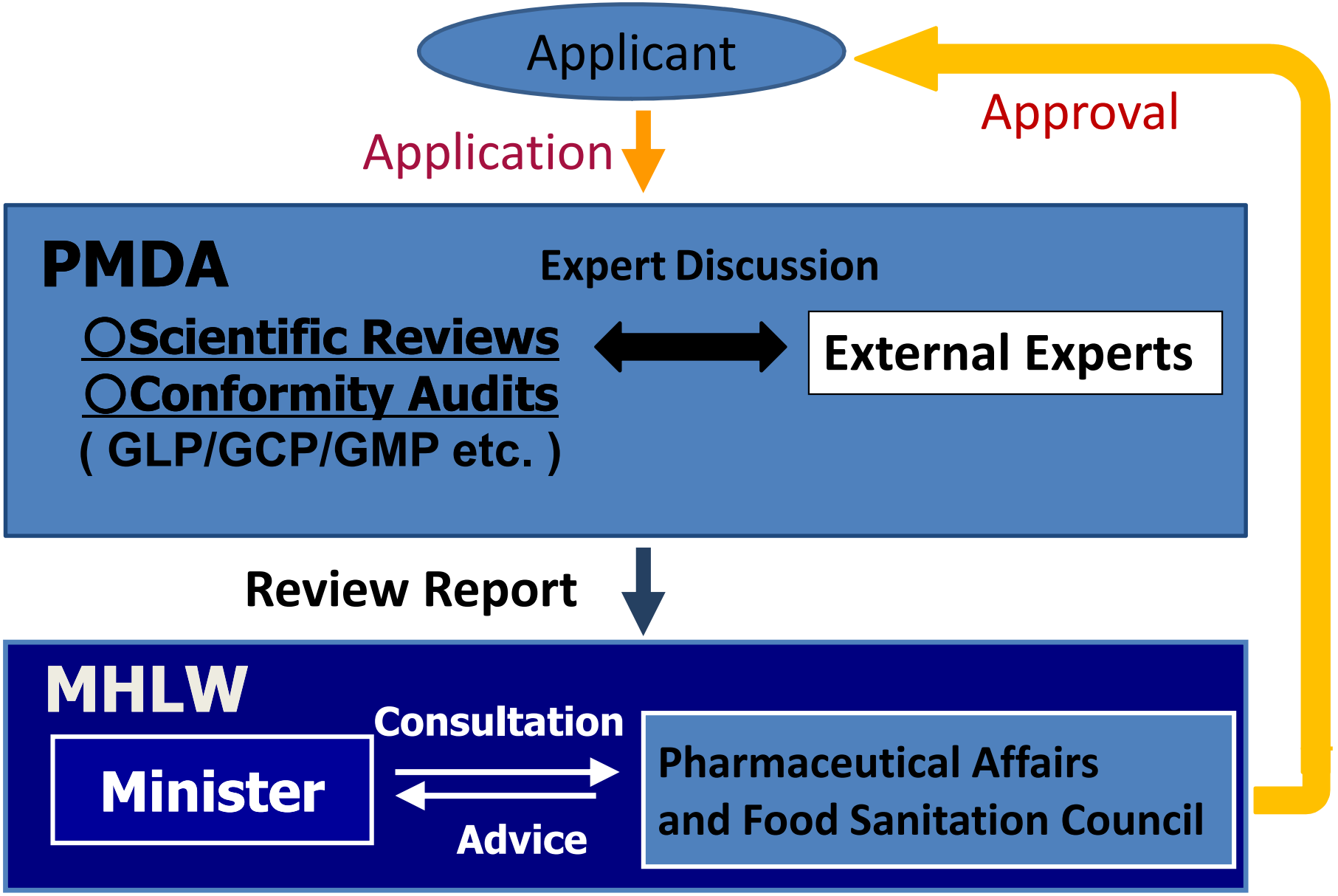
(As of November 2011)

Office of Conformity Audit, PMDA

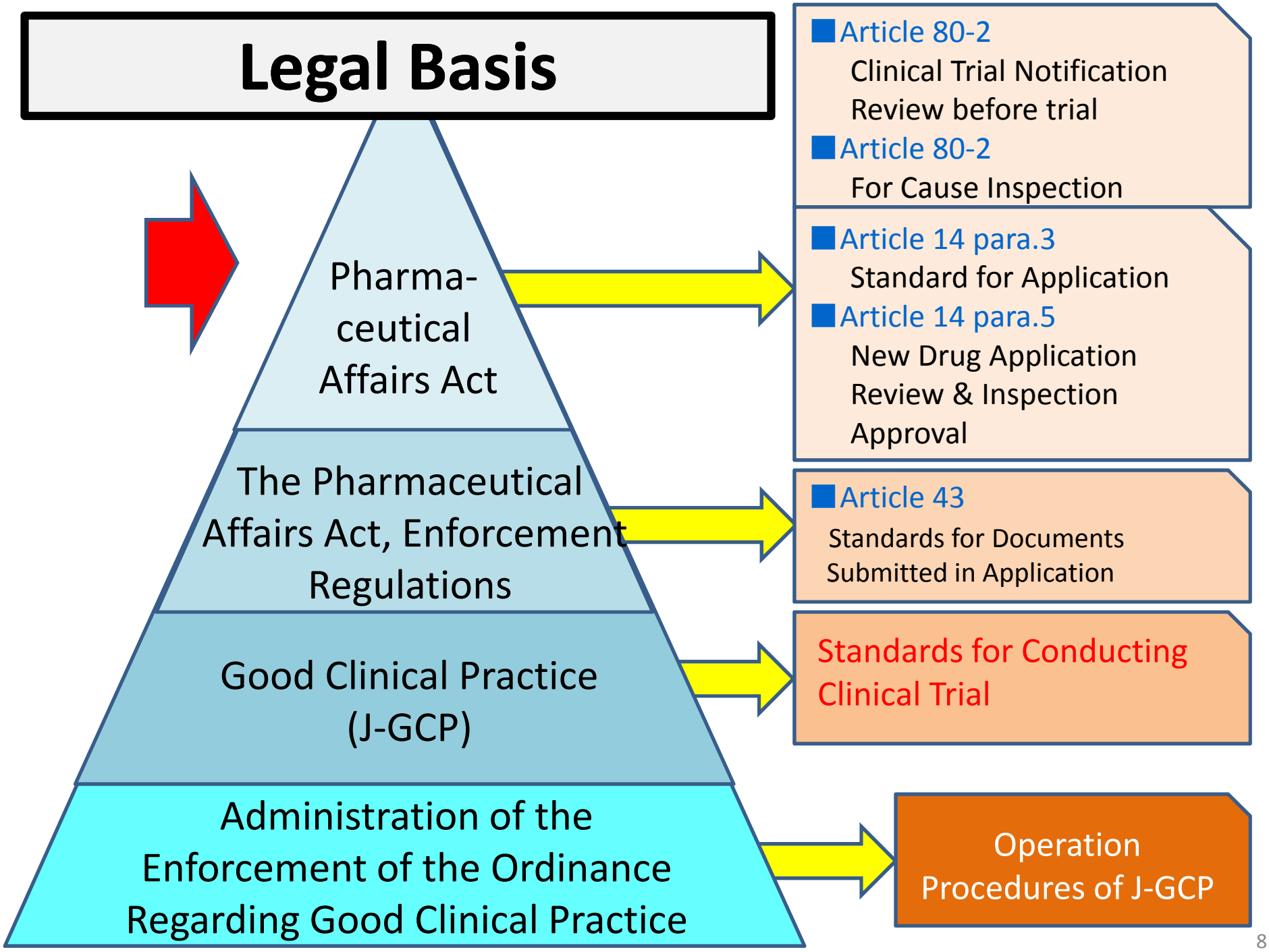


2. Conformity Audit Program and the PMDA's GCP Inspection Methods

Outline of Approval Review Process



Legal Basis


Pharma-
ceutical
Affairs Act
The Pharmaceutical
Affairs Act, Enforcement
Regulations
Good Clinical Practice
(J-GCP)
Administration of the
Enforcement of the Ordinance
Regarding Good Clinical Practice
Article 80-2
Clinical Trial Notification
Review before trial
Article 80-2
For Cause Inspection
Article 14 para.3
Standard for Application
Article 14 para.5
New Drug Application
Review & Inspection
Approval
Article 43
Standards for Documents
Submitted in Application
Standards for Conducting
Clinical Trial
Operation
Procedures of J-GCP

Legal Basis for “For Cause Inspection” in Japan

Article 80-2 of
The Pharmaceutical Affairs Act

If necessary, MHLW may

- Request “necessary reports” from sponsor, medical institute, etc.
- Inspect the related structure (the hospital, clinic or veterinary clinic, factory, office, etc)
- Question the employees or other personnel concerned.

Legal Basis for Standard of Clinical Trials for Application in Japan(1)

Article 14, Paragraph 3, of
The Pharmaceutical Affairs Act

- If a clinical trial is conducted for application submitted to MHLW, the sponsor must conduct a clinical trial in compliance with the standards provided in the MHLW Ordinance.

Article 43 of The Pharmaceutical
Affairs Act, Enforcement Regulations

- Reliability Criteria of Application Data are below.
  GCP, GLP, GPSP/GPMSP
  Accuracy/ Completeness, Comprehensiveness/ Retention

Legal Basis for Standard of Clinical Trials for Application in Japan(2)

Article 14, Paragraph 5
(& Article 19, Paragraph 2), of
The Pharmaceutical Affairs Act

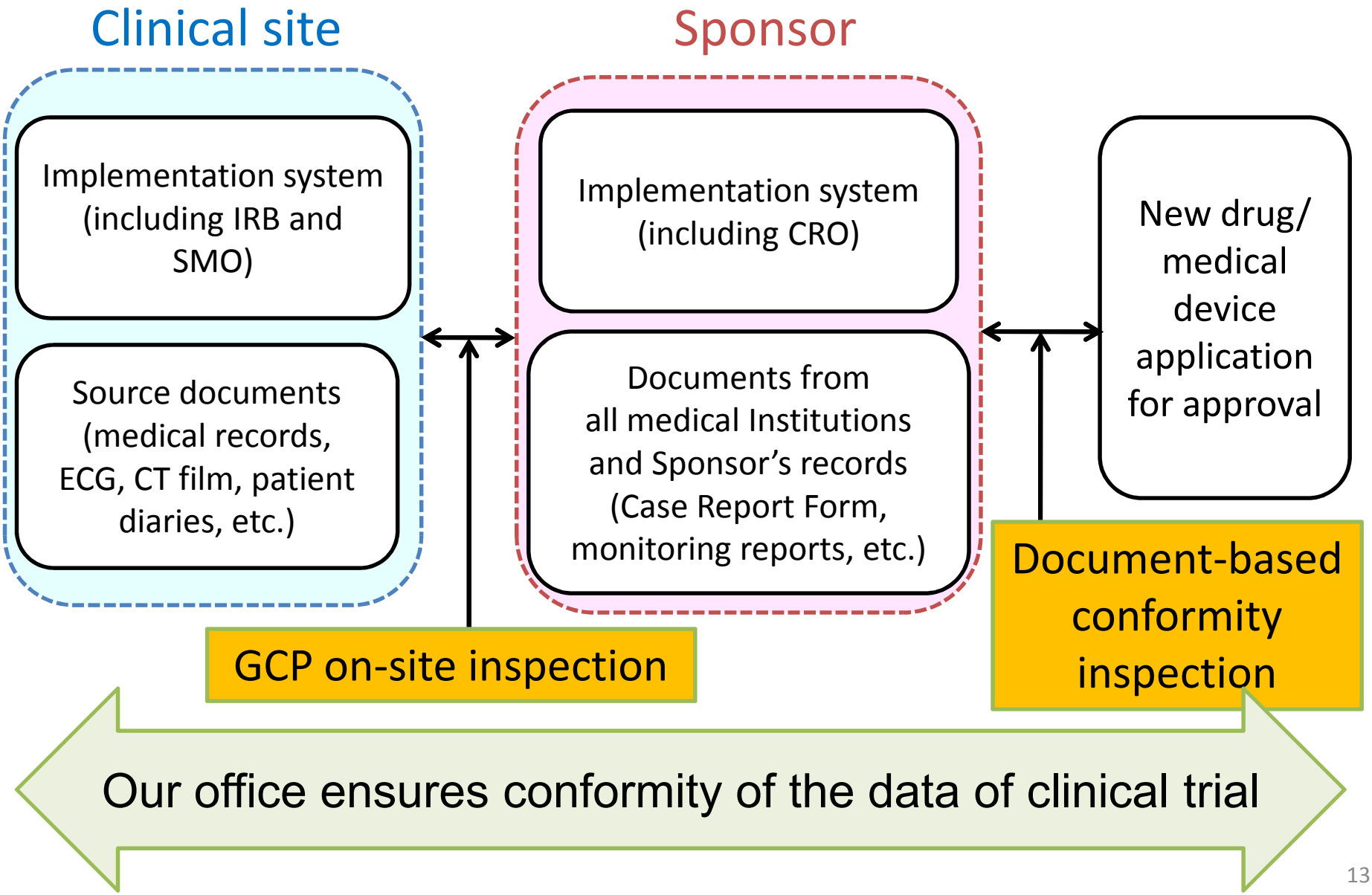
The quality, efficacy and safety of the product (drug or medical device) shall be reviewed based on documents that are submitted with marketing approval applications of medicinal products.

A document-based inspection or an on-site inspection shall be performed to determine whether or not documents were created in compliance with the standards provided in the MHLW Ordinance.

Our office conducts two types of inspection for documents for application.

- Document-based conformity inspection
- GCP on-site inspection

What is “GCP on-site inspection”?
What is “Document-based conformity inspection”?



Model Schedule of Inspection

NDA

Submit the Preliminary Documents

Document-based conformity inspection

(as needed) Inquiries/Reply

Approval

Selection for CT and CS

GCP-Inspection (Clinical Site)

GCP-Inspection (Sponsor)

Notification of Inspection Results

4.5months

5.7months

6.9months

※Performance of Document-based conformity inspection in 2010 (average)
New Pharmaceutical Drug, classification No. 1 to 9, conducted on the same day inspection (excluding additional Inspection)

Selection of Study, Clinical Site and Subject (1)

- Study Selection (Document-based, GCP on-site)
  - Extract pivotal studies in application for approval
- Clinical Site Selection (GCP on-site)
  - New active pharmaceutical ingredients : Approximately 4 institutions (except in case of priority/prompt review)
  - Orphan drugs and other application categories: Approximately 2 institutions
  - Number of subjects, result of previous inspection and etc. will be considered

Consultation for decision between Office of Conformity Audit and Office of Drug Evaluation

Selection of Study, Clinical Site and Subject (2)

- Subject selection
  - (Document-based) Sampling rate is dependent on importance of study
    (Sampling rate: up to 20% per 1 site)
  - (GCP on-site) All subjects in the site

Inspection for Foreign Site

- At any situation do we conduct inspection for foreign site?
  - If the case of pivotal clinical trials are conducted in overseas
    (global clinical trials including Japan, bridging study)
  - Approval in overseas and experience of Inspection(s) by Foreign Authorities will be considered
- Selection of Clinical Site
  - Same rule as inspection of clinical site in Japan

Consultation for decision between Office of Conformity Audit and Office of Drug Evaluation

Conclusion of Document-based conformity inspection

- **Warning/Critical findings**

- **No warning letter**

✓Need inquiry response and improvements are indicated
✓Need inquiry response but improvements are not indicated
✓No Inquiries

Conclusion of GCP on-site Inspection

Compliance :

accepted as application dossier
(Voluntary, improvements are indicated)

Compliance with condition :

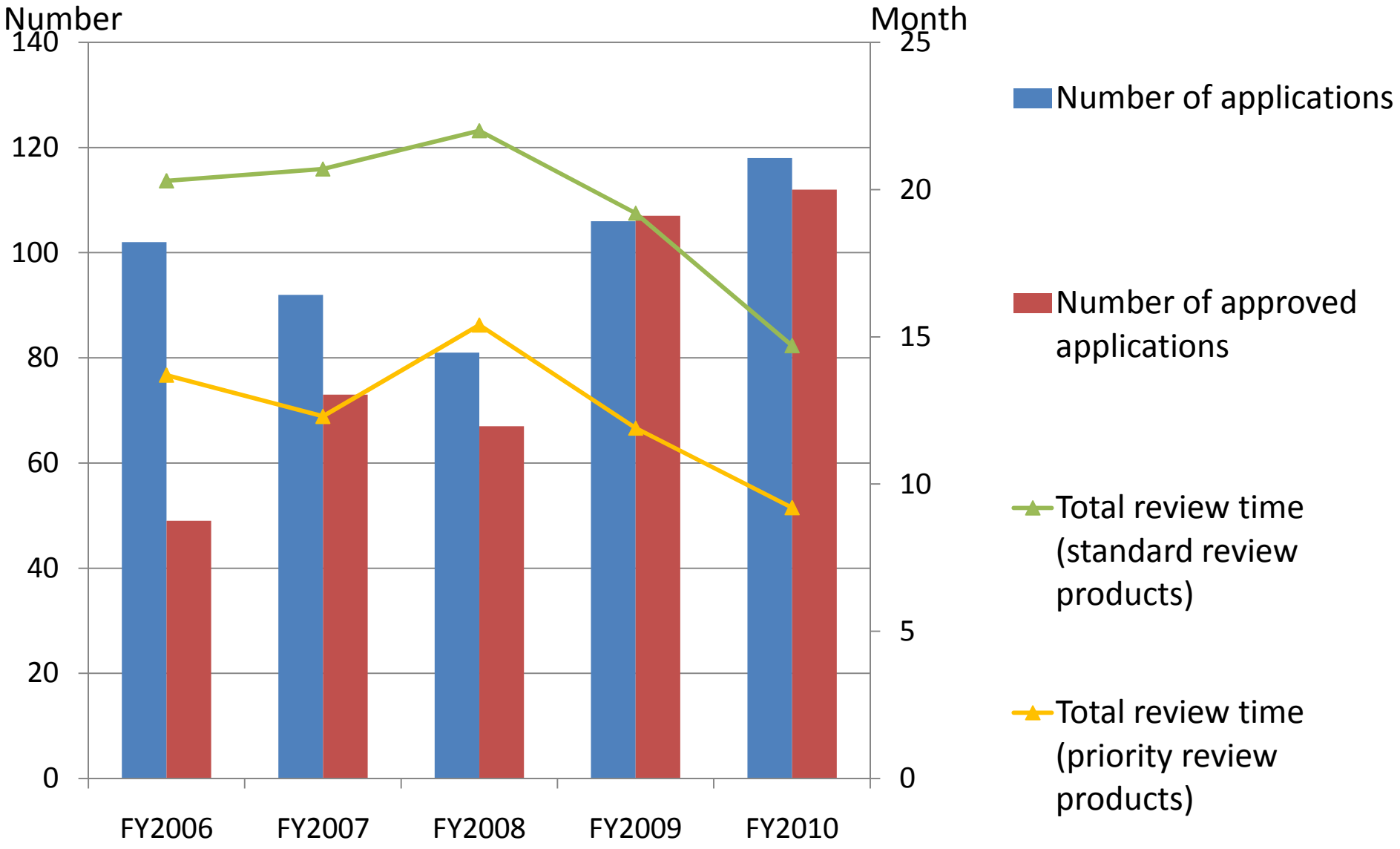
the violation of GCP was confirmed for a part of the subjects
→ accepted as application dossier after deleting the data from NDA package.

Non-compliance :

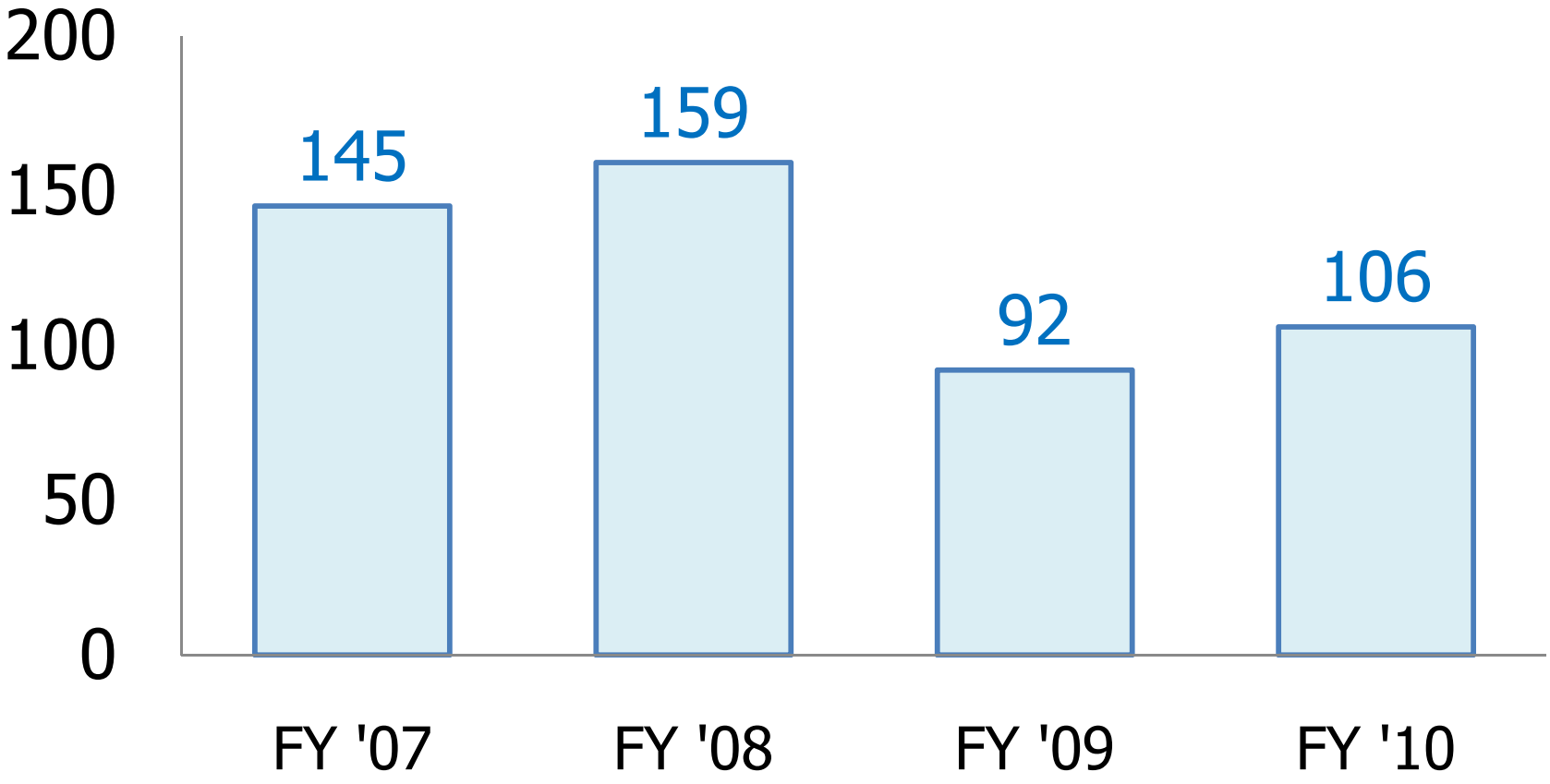
the violation of GCP was found generally and systematically
→ no reliability
→ whole clinical trial data should be deleted

3. Document-based Conformity Inspection and GCP on-site Inspection

Reviews of new Drugs



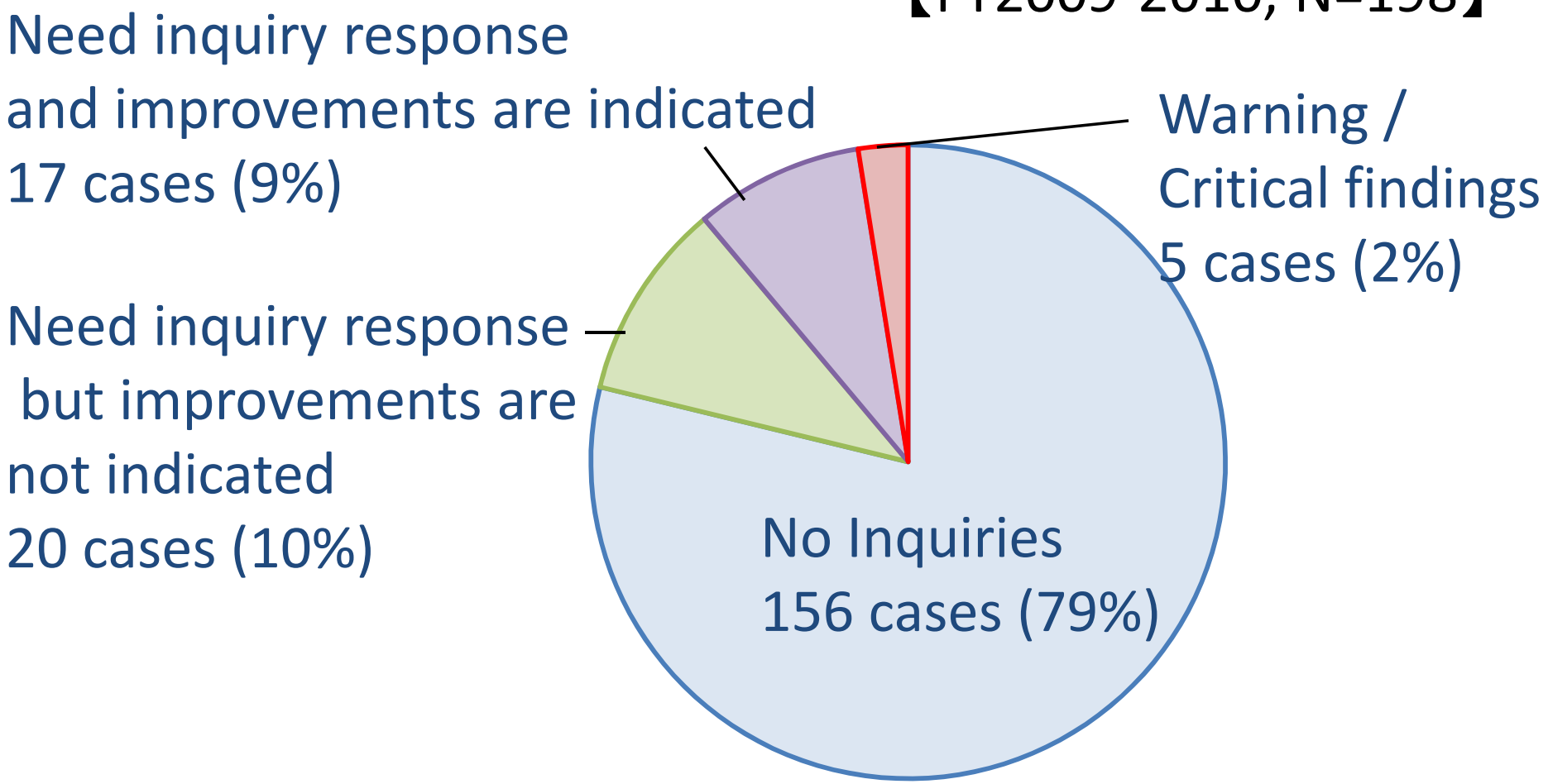
Number of Document-based conformity inspection for New Drug



1) New Pharmaceutical Drug, classification No.1 to 9
2) Number of issued completion notice of inspection per year (applicant unit)

Conclusion of Inspection for New Drug Document-based conformity inspection

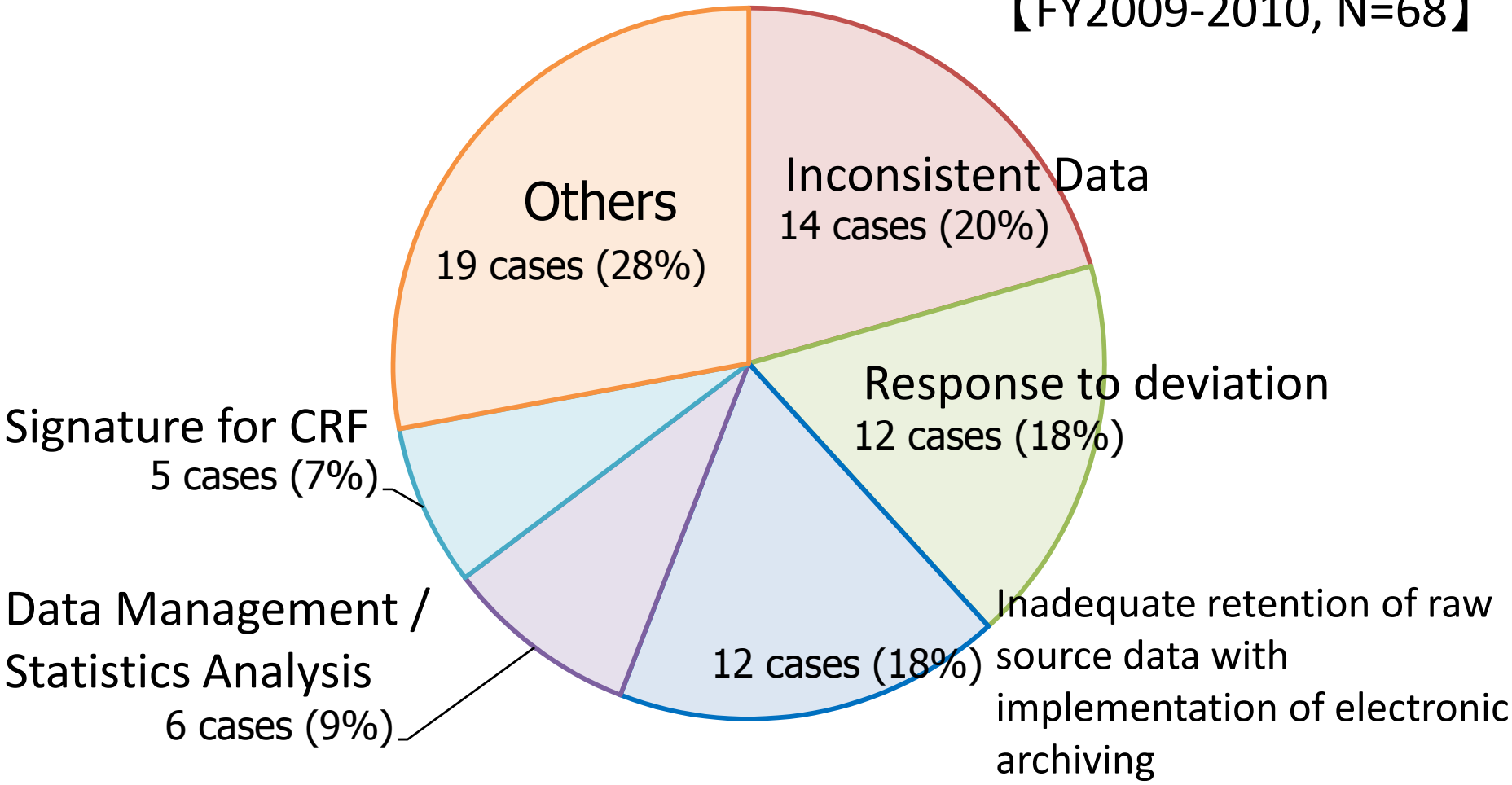
【FY2009-2010, N=198】



Note: In case of “No inquiries”, there are examples of application dossiers modification occurs.

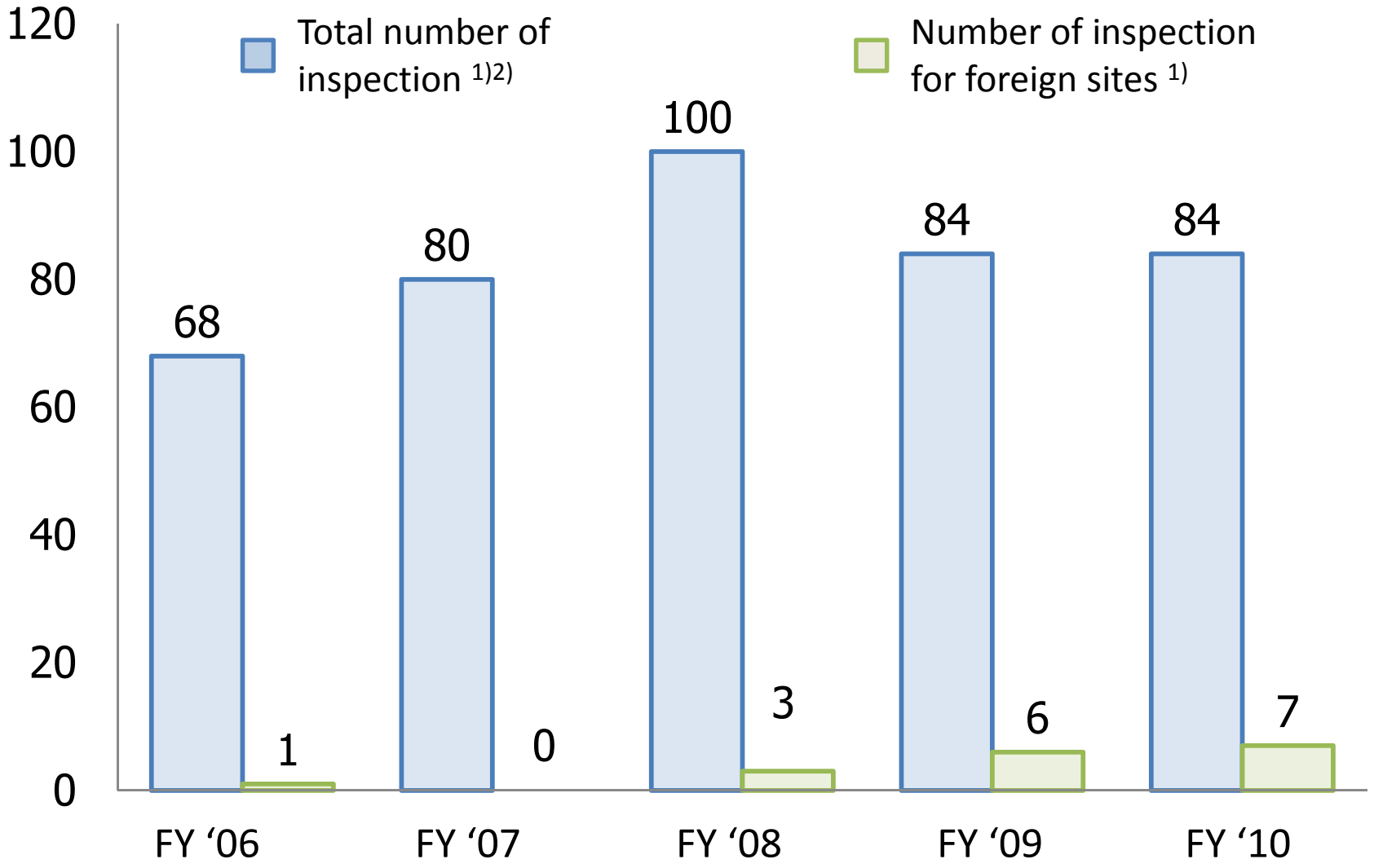
Issued inquiries of Inspection for New Drug
Document-based conformity inspection

【FY2009-2010, N=68】



*Number of issued inquiries of inspection (Total number), release to 41 application (applicant unit)

Number of GCP On-site inspection for New Drug

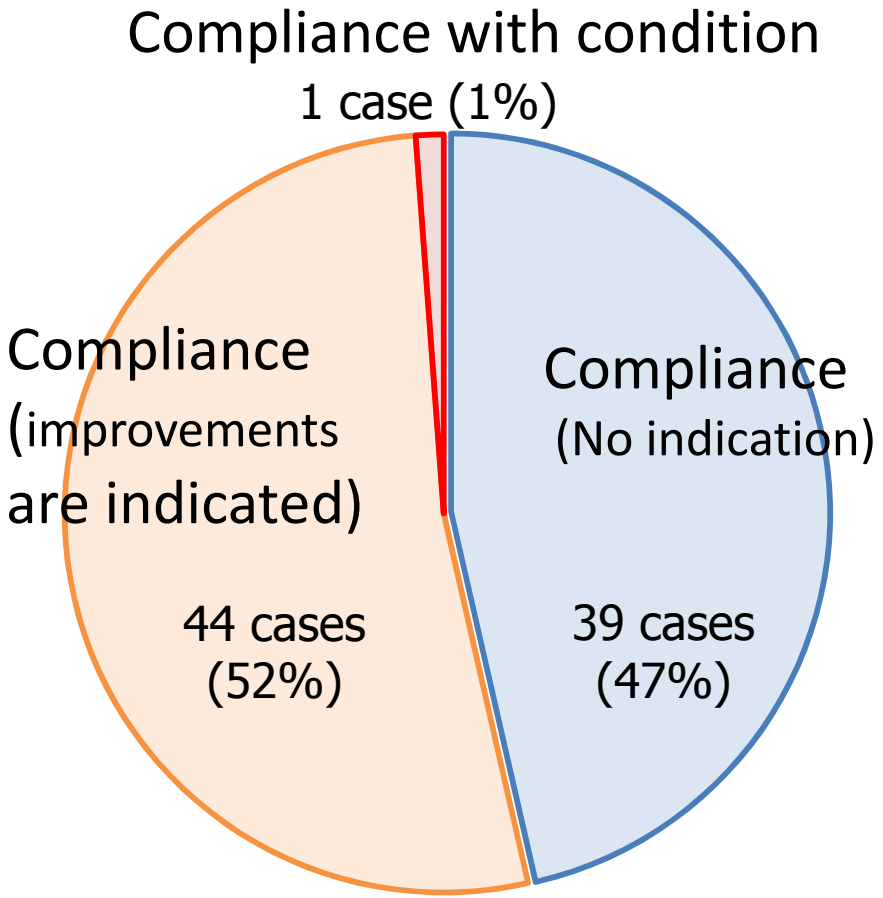


1) Number of issued completion notice of inspection per year (applicant unit)
2) Including inspection for Foreign Sites

Conclusion of GCP On-site Inspection for New Drug

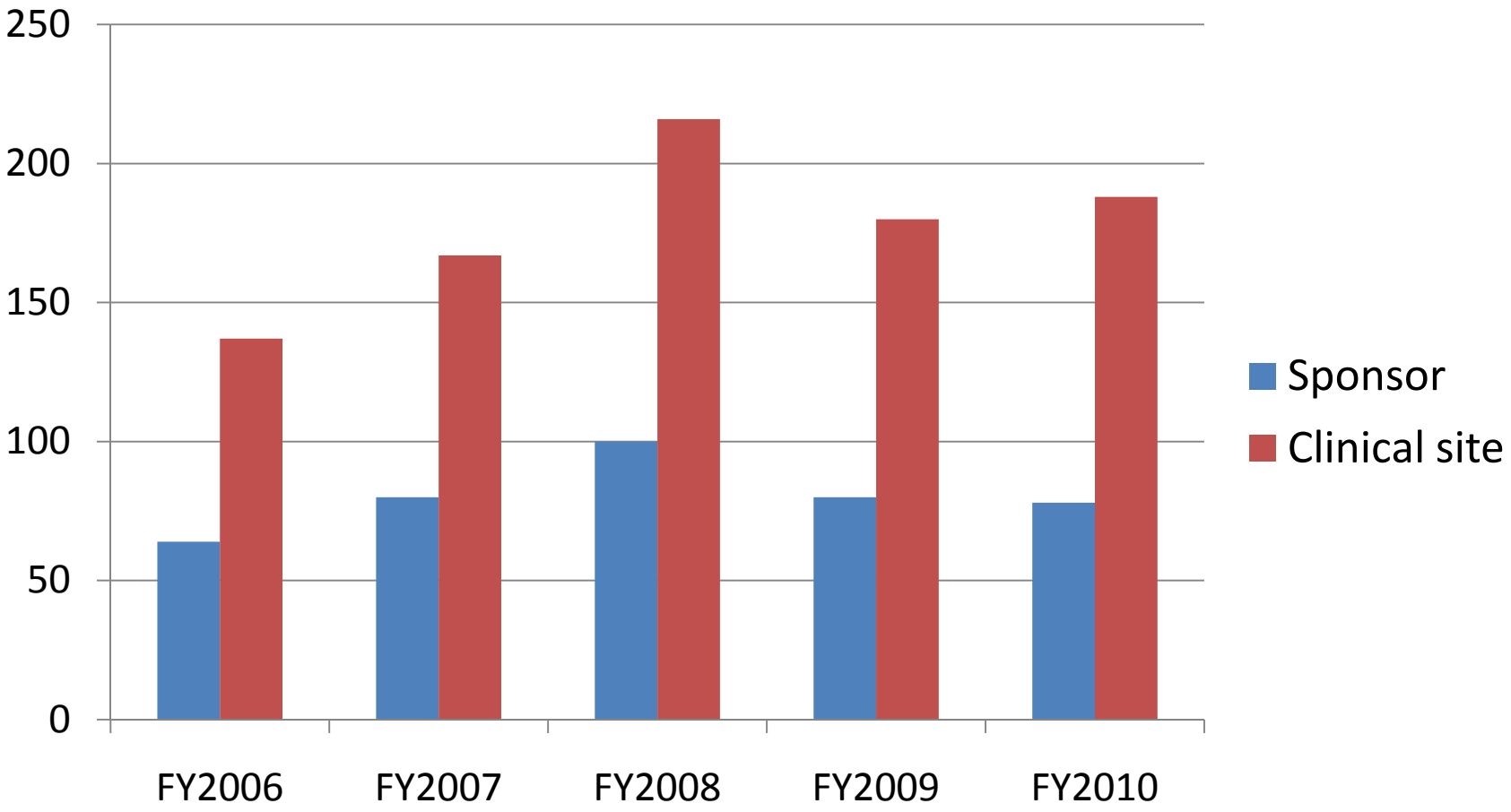
【FY2010, N=84】

- **Compliance**
  - Voluntary, improvements are indicated
  - No indication
- **Compliance with condition**
- **Non-compliance**

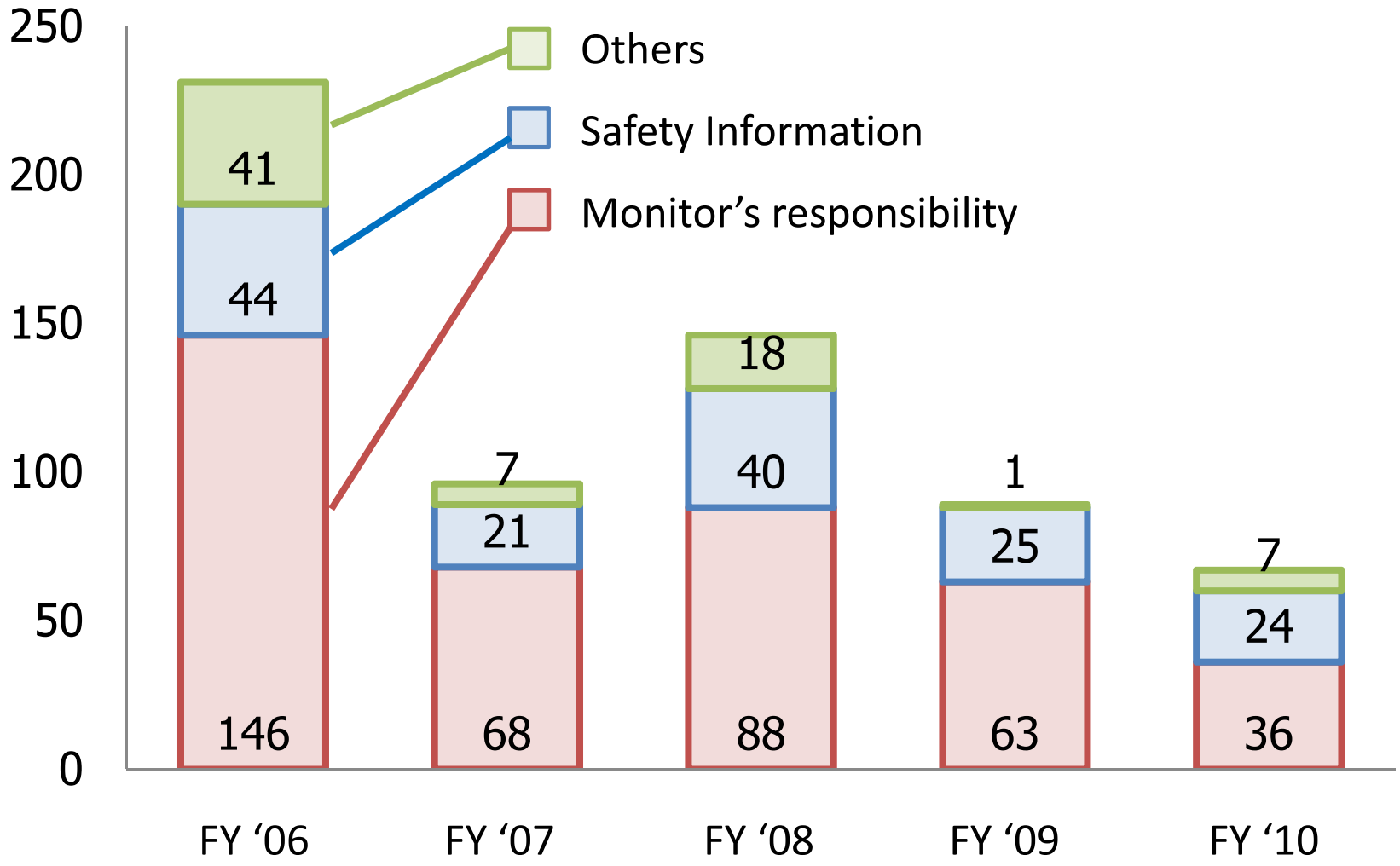


No non-compliance

Number of GCP On-site inspection for New Drug



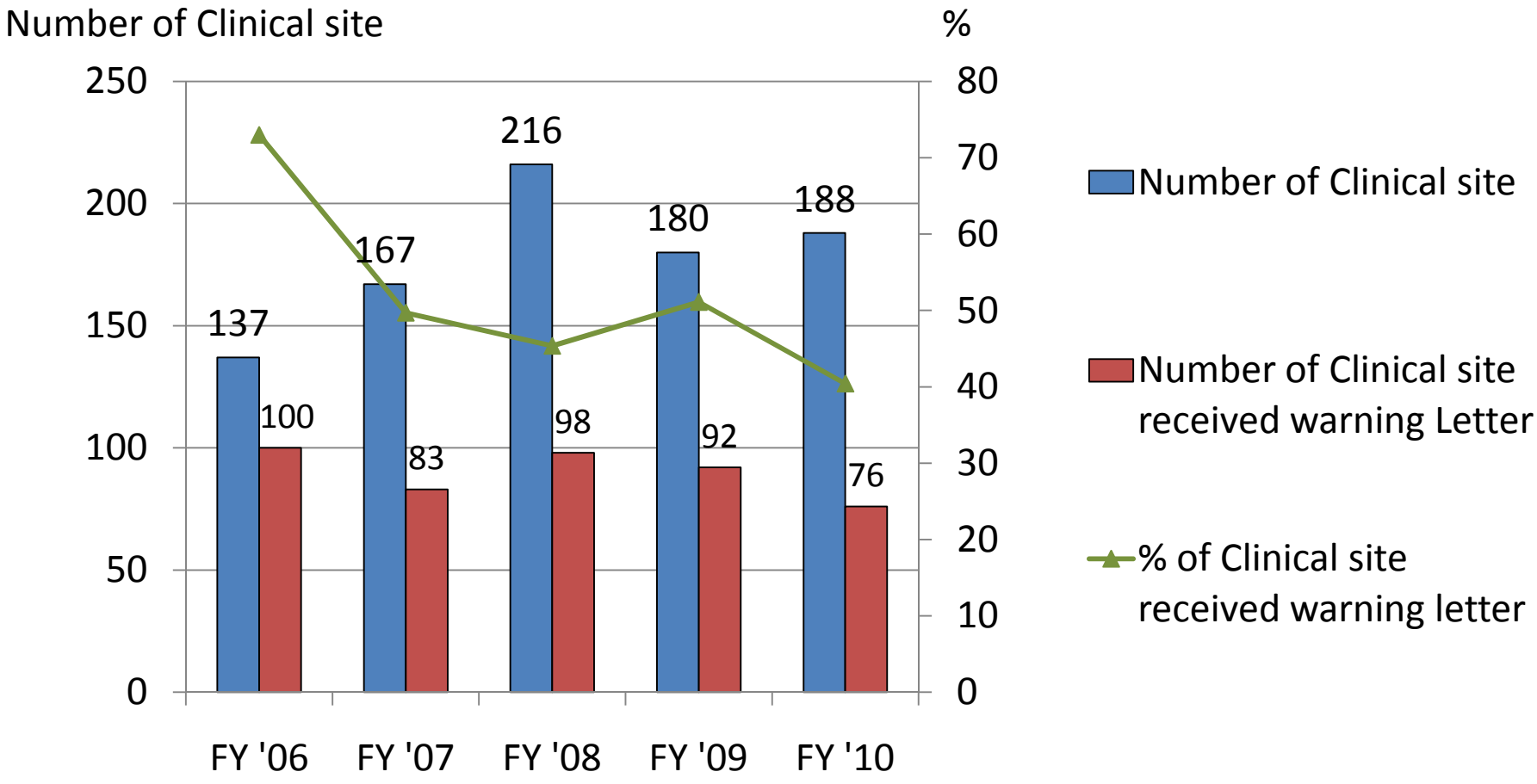
Trend in Number of Findings at Sponsors (GCP on-site Inspection)[1)]



1) Excluding inspections for Foreign Site

Changes in number of GCP on-site inspection for Clinical site

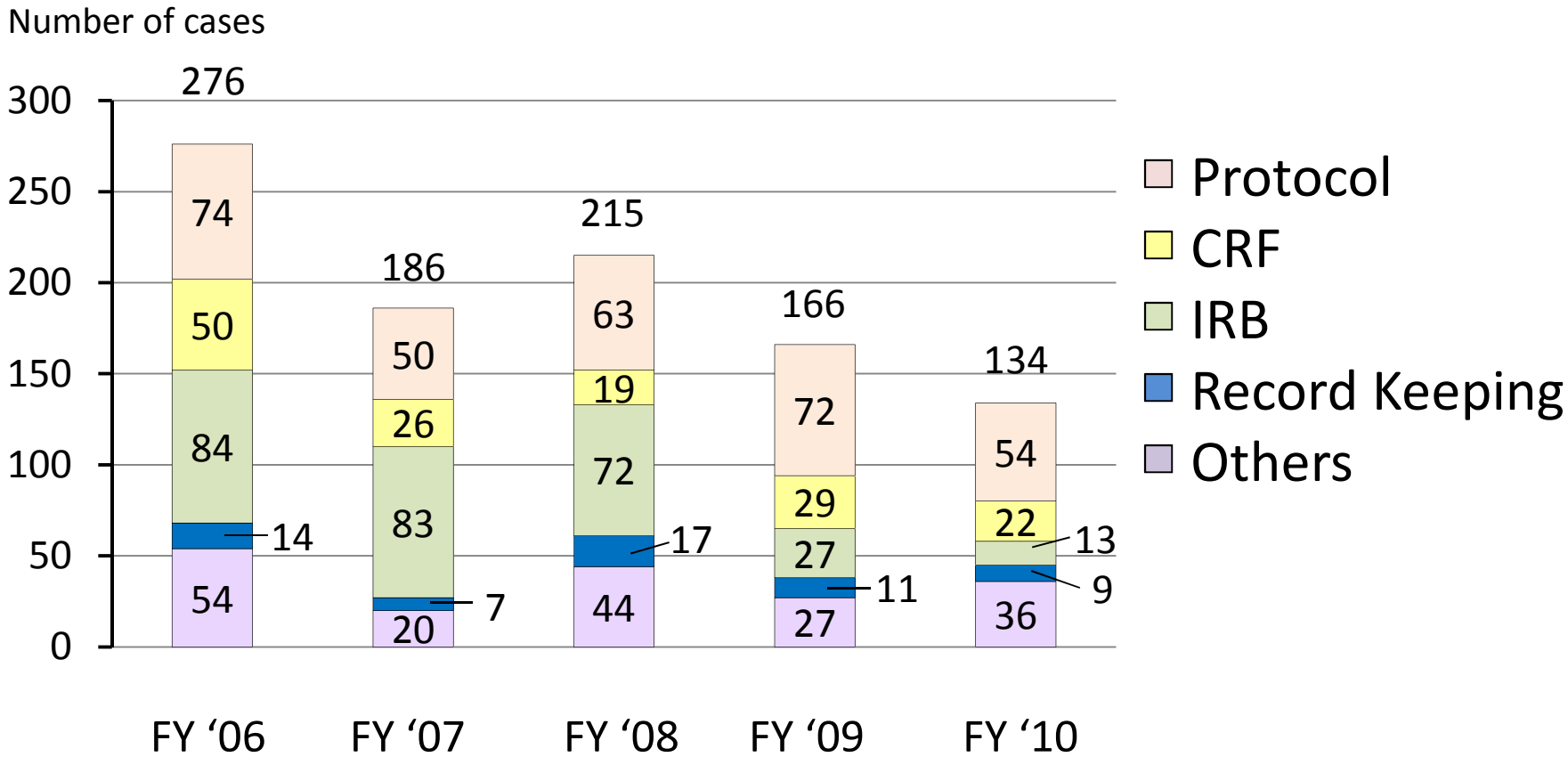
(excluding inspections for foreign sites, clinical trials applied for New GCP only)



*Data from notice of results issued each year (total number)

Changes in number of Findings to be improved - Inspection for Clinical sites - 1 of 2

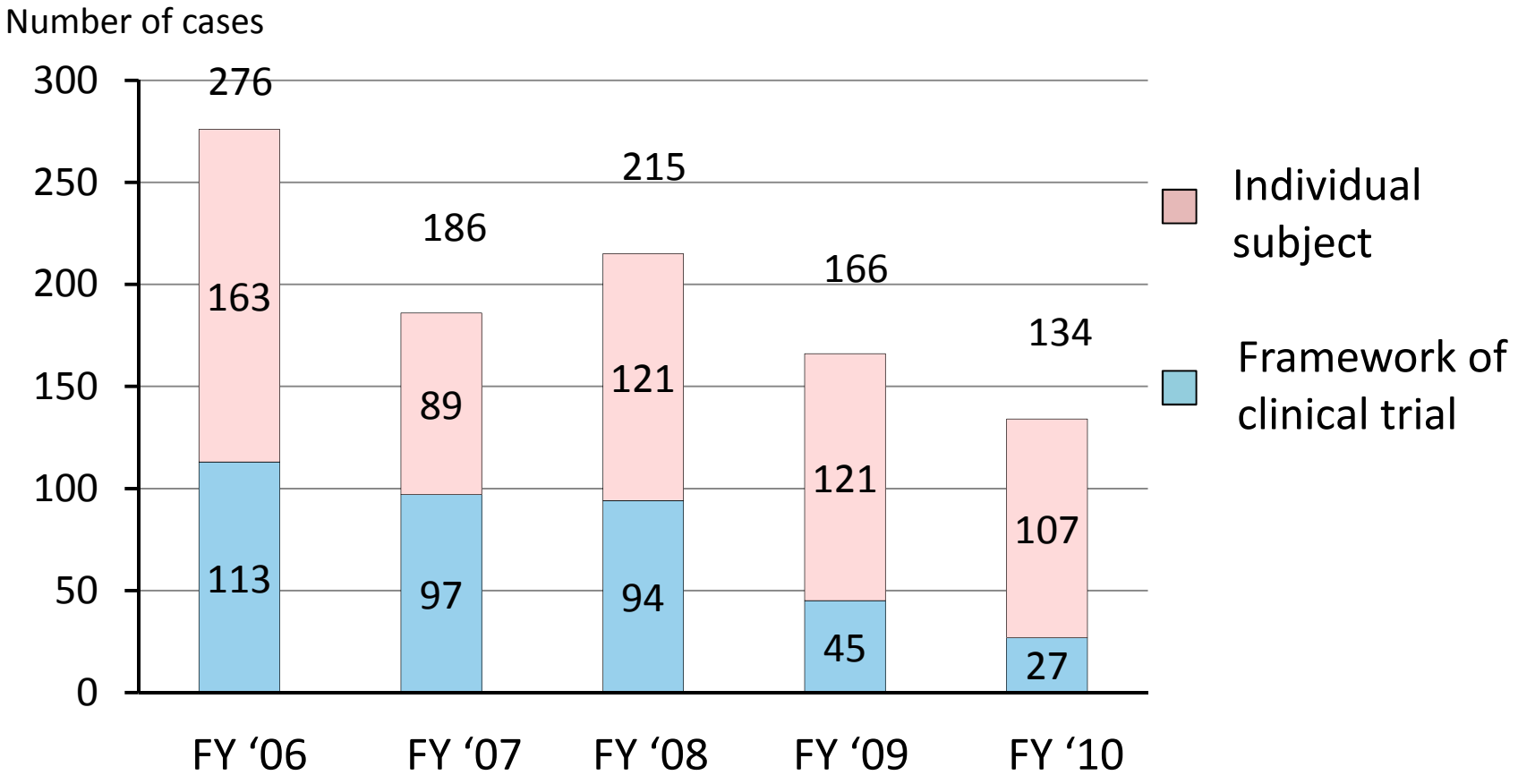
(excluding inspections for foreign sites, clinical trials applied for New GCP only)



*Data from notice of results issued each year (total number)

Changes in number of Findings to be improved - Inspection for Clinical sites - 2 of 2

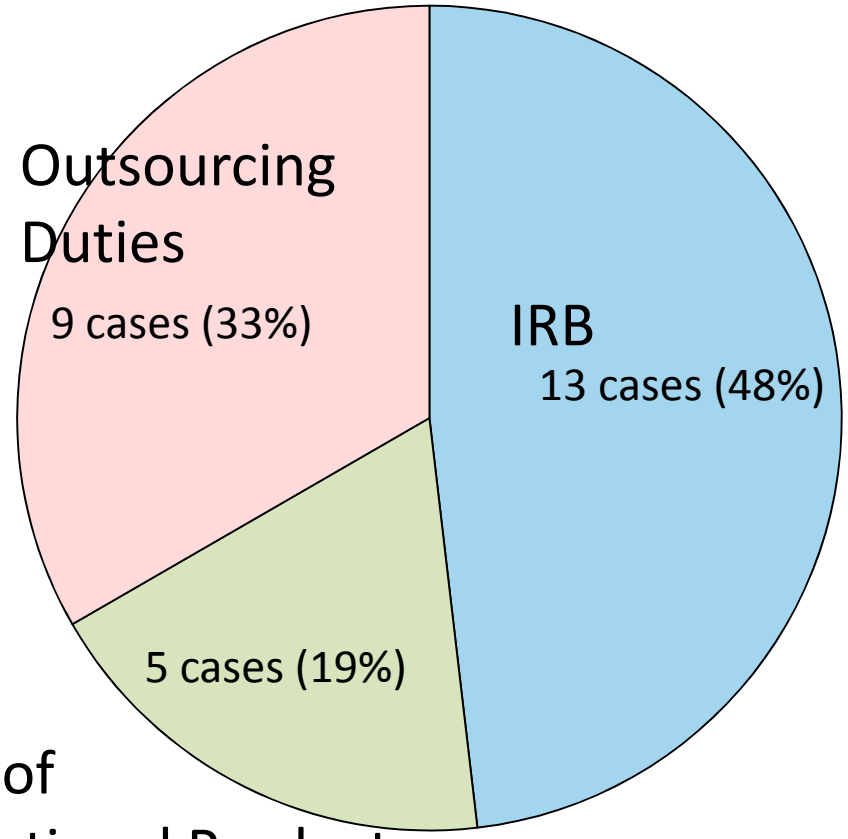
(excluding inspections for foreign sites, clinical trials applied for New GCP only)



*Data from notice of results issued each year (total number)

Details of Findings to be improved in Clinical Site's framework

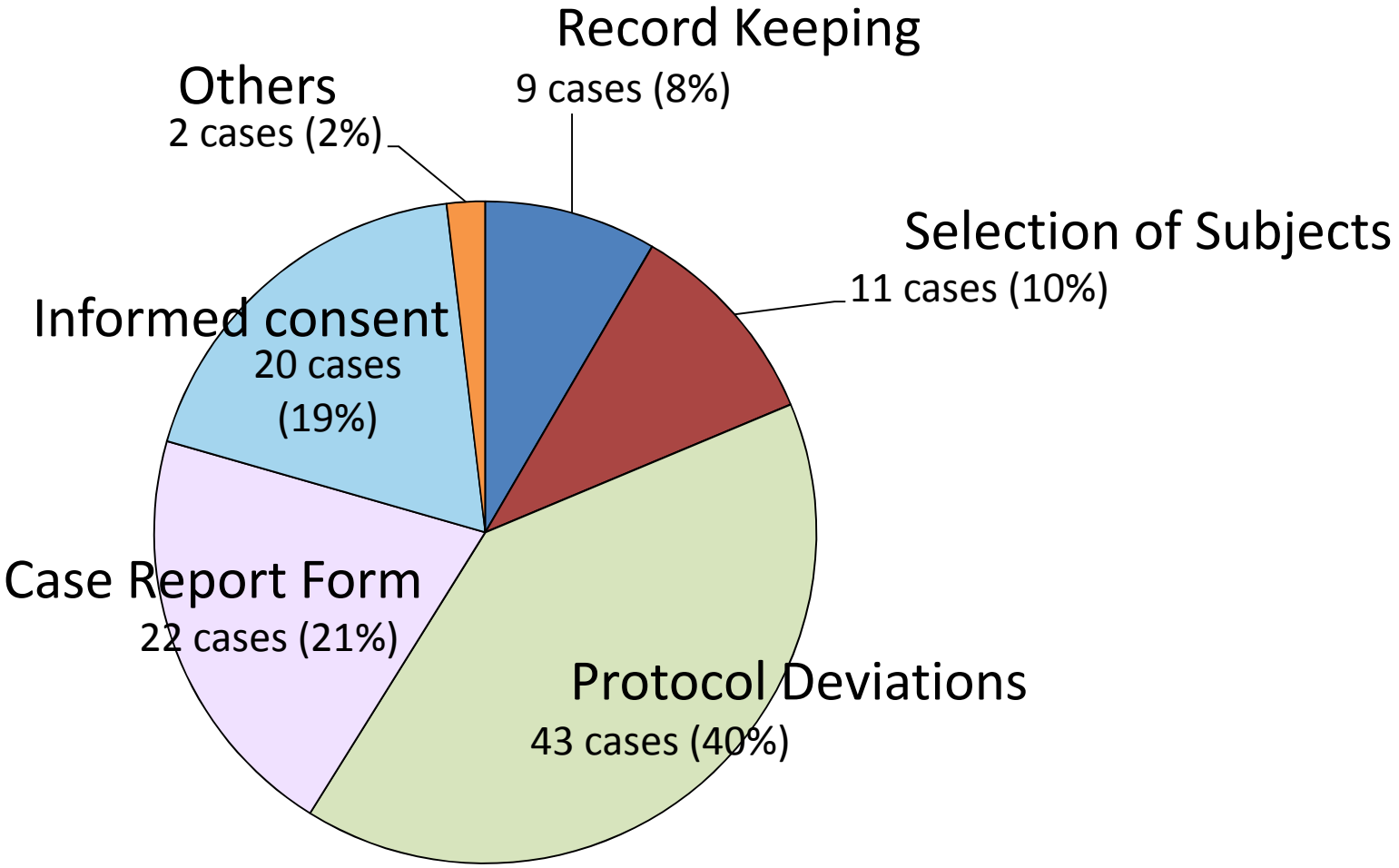
【FY2010, N=27】



(Total 27 cases)

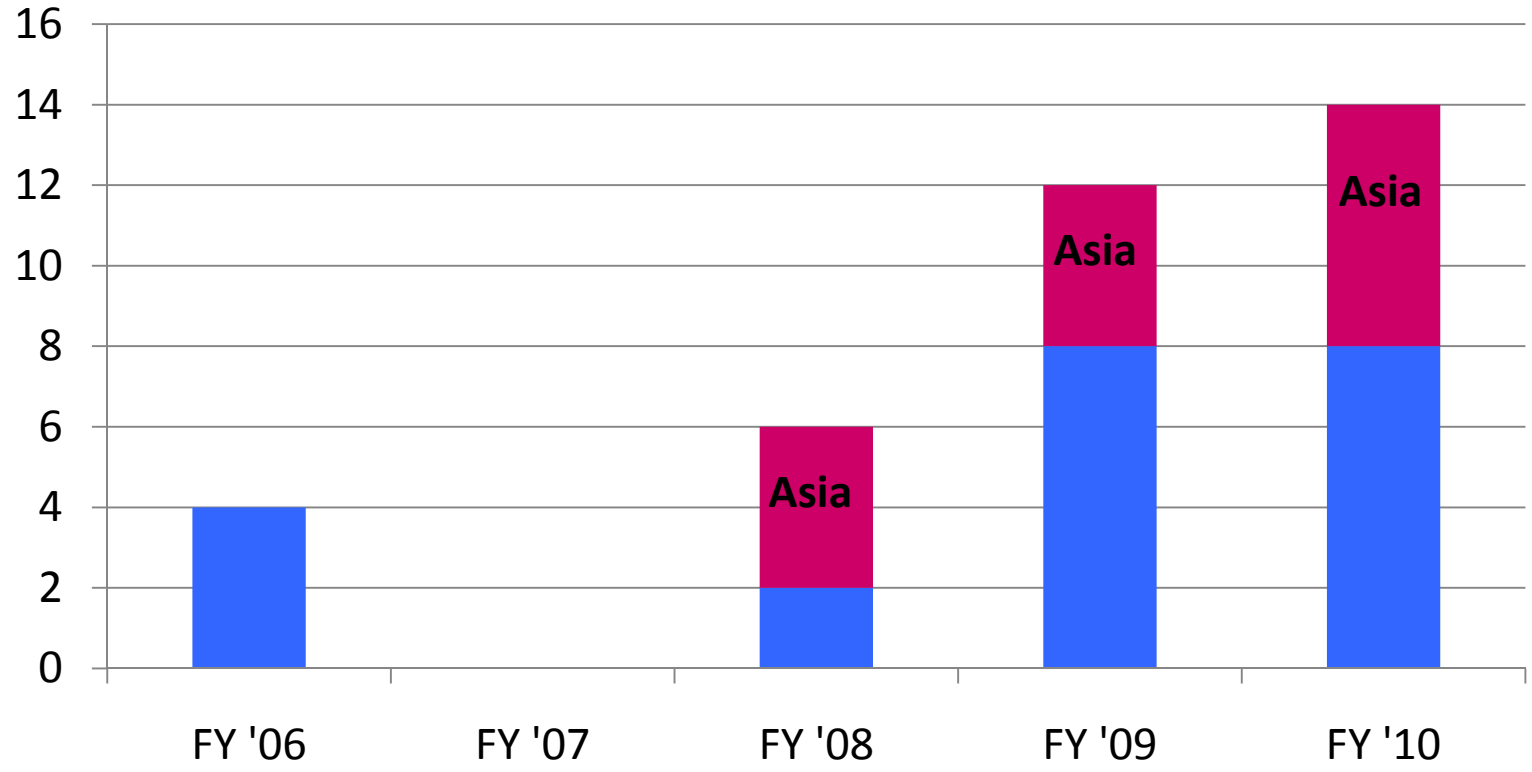
Details of Findings to be improved in Clinical Site (Individual subject)

【FY2010, N=107】



4. Current State of Overseas GCP on-site inspections

Number of GCP on-site inspections (Institutions, Foreign countries)



※The total number of drugs and medical devices

Global Clinical Trials and GCP inspections

Basic Requirements

- In compliance with the ICH-GCP in all participating countries and clinical trial sites.
- All clinical trials sites accept GCP inspection from Japan.

Basic Principles on Global Clinical Trials,
28 Sep. 2007, MHLW Notification (No.0928010)

J-GCP

- MHW Ministerial Ordinance No.28 (Mar. 27, 1997)
- MHLW Ministerial Ordinance No.106(Jun. 12, 2003)
- MHLW Ministerial Ordinance No.72 (Mar. 31,2006)
- MHLW Ministerial Ordinance No.24 (Feb. 29,2008)

[Basic concept]

- Harmonized with ICH-GCP

Points to be verified by Document-based Conformity Inspection and GCP on-site Inspection

- Ethics quality

  - Protect the rights, safety and well-being of trial subjects

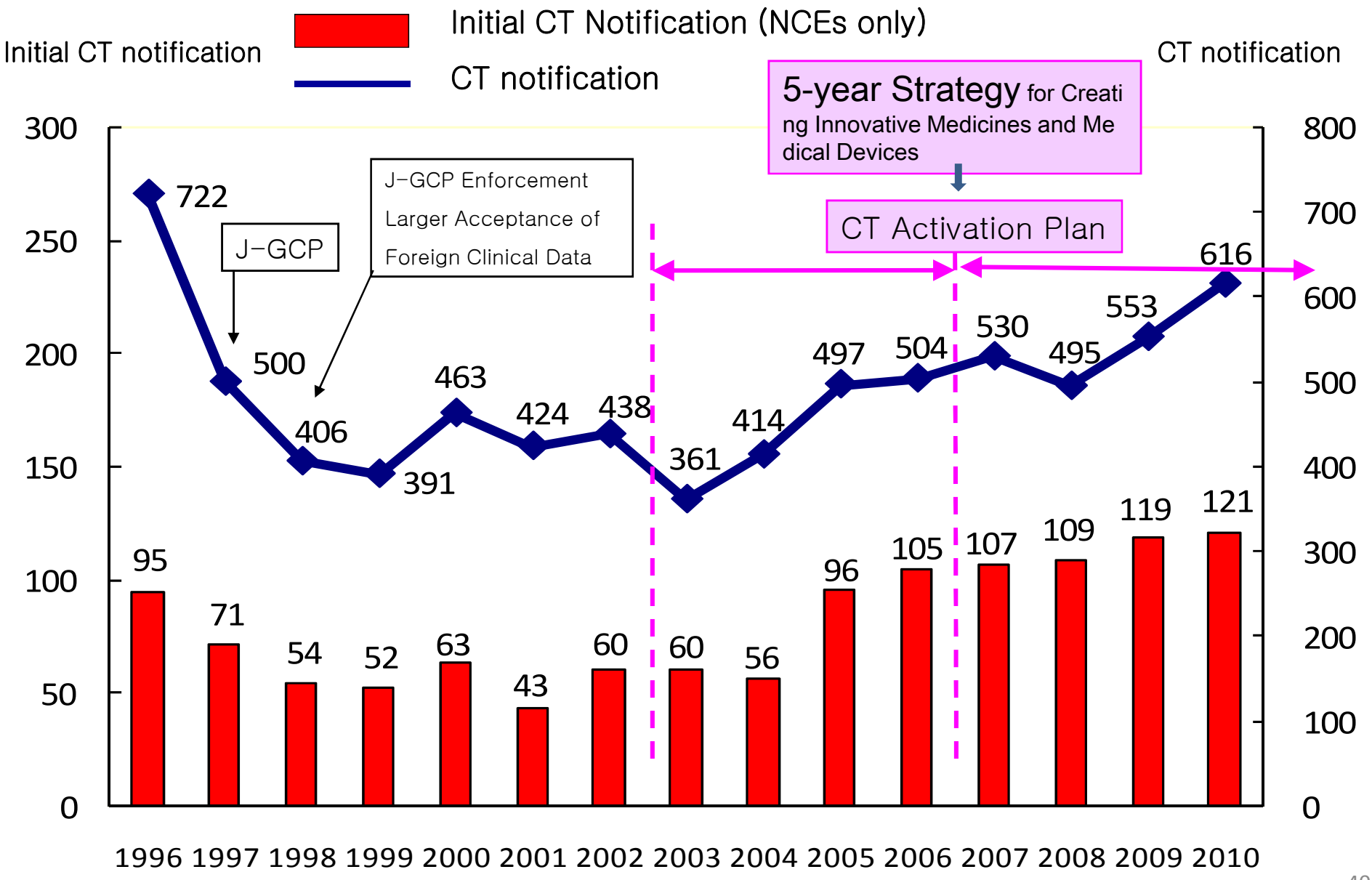
- Science quality

  - Accuracy and reliability of clinical trial data

  - Accuracy and adequacy of evaluation

5. From Recent Topics

Trends in Notified CT in Japan



- New 5-Year Clinical Trial Activation Plan (2007-2011)

New Activation Plan will be published soon

Clinical Trials in Japan

(Review Results of Working Group for the Streamlining of Clinical Trials, etc. 2010)

1.Cost
- ✓ Costs are decreasing
- ✓ Overall costs are still high compare to US and Europe

2.Speed
- ✓ Overall, Japan's level is comparable to US and Europe

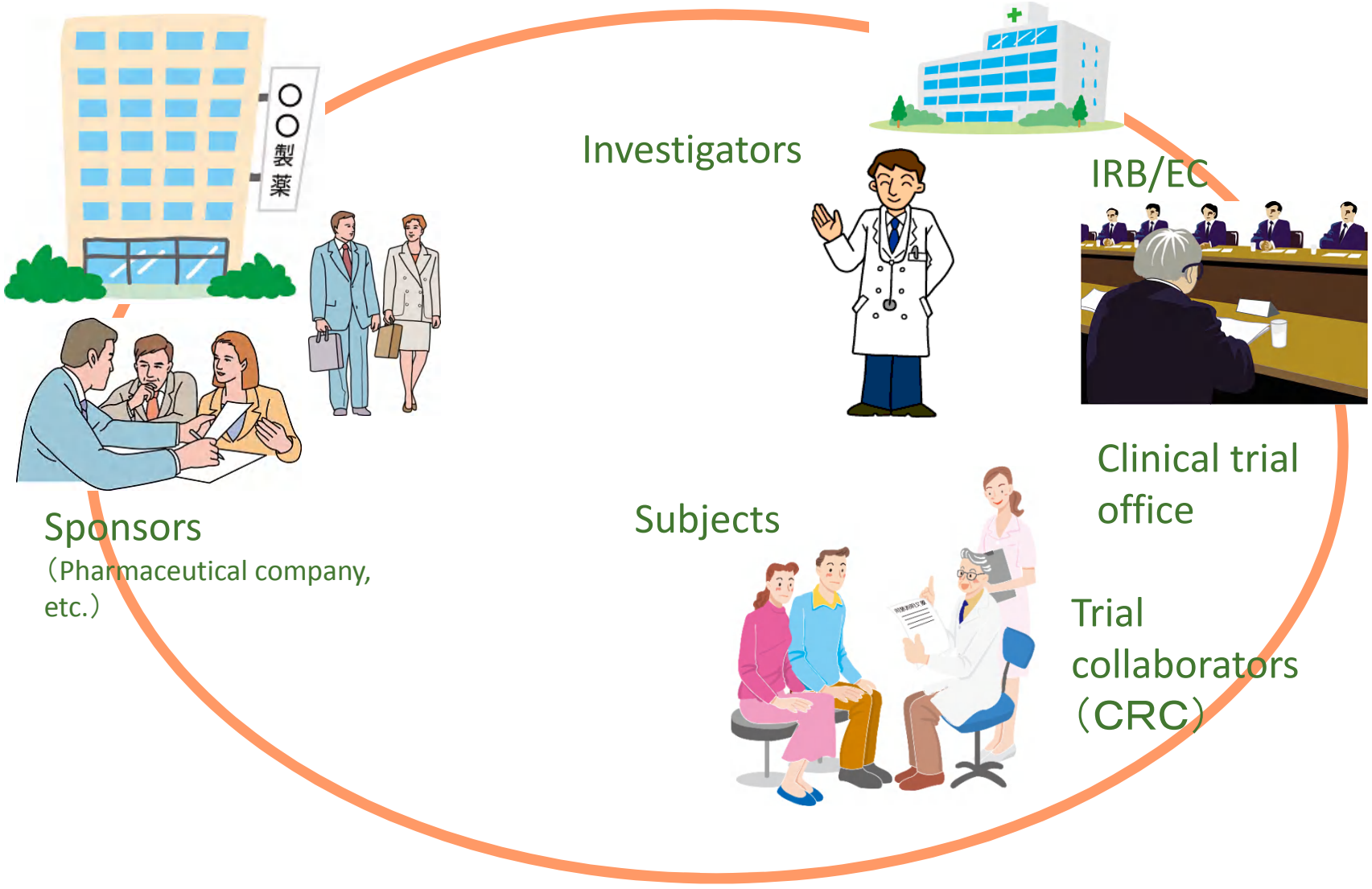
3.Quality
- ✓ No significant issues were seen in the quality
- ✓ In general, the current level is sufficient
- ✓ It is important to maintain a certain level of quality, but it is necessary for relevant parties to keep in mind not to go overboard in terms of quality

Revision of Notification on 24th October 2011

"Administration of the Enforcement of the Ordinance Regarding Good Clinical Practice Ministerial Ordinance on GCP for Drug"

- ✓ To ensure the reliability of the data more
- ✓ To promote more harmonization of J-GCP and ICH-GCP
- ✓ To streamline clinical trial procedures
- ✓ To activate clinical trial by a person conducting his or her own clinical trial

Smooth implementation of Clinical trials



Cooperation is indispensable.

For patients' prompt access
to new and better drugs,

Thank you for your attention!