

2012 EU GCP Inspectors Working Group Workshop

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Practical Experience in GCP inspections, non EU/EEA countries



# GCP Inspection by PMDA

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# 1. Introduction of PMDA

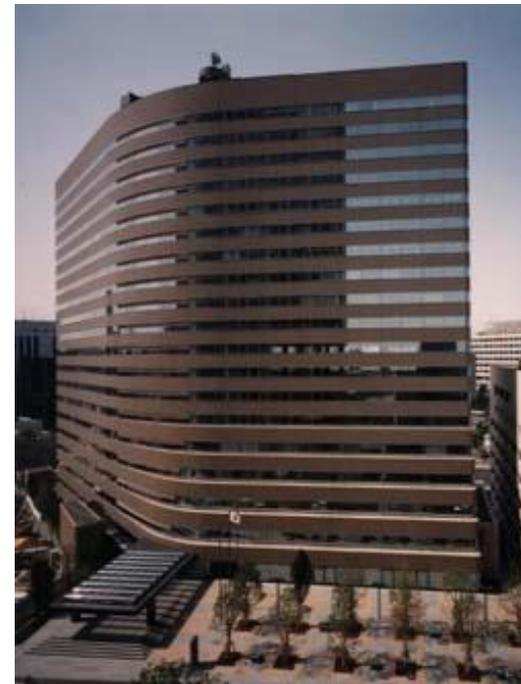
# Outline of PMDA

## PMDA

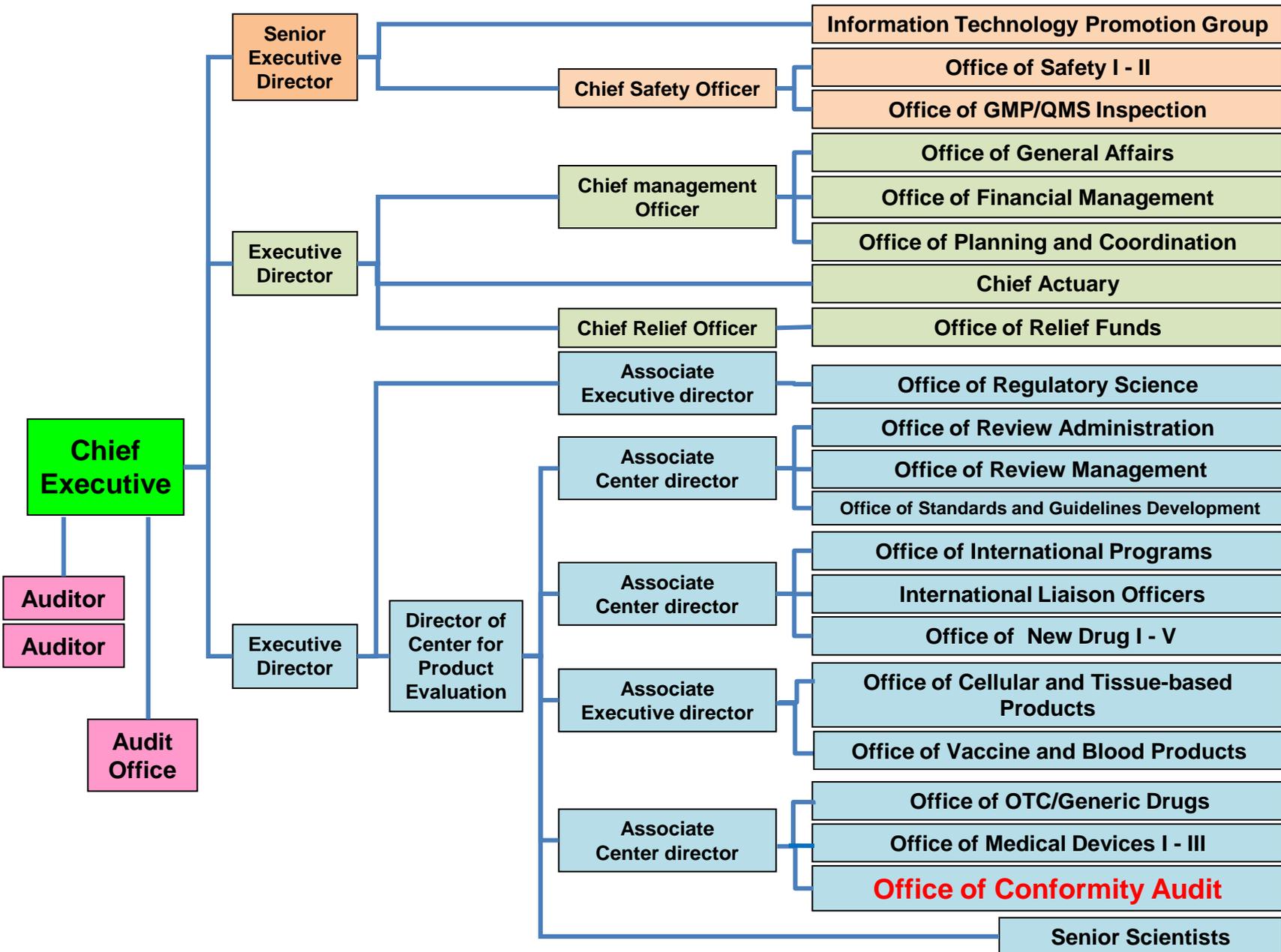


**Pharmaceuticals and Medical Devices Agency**

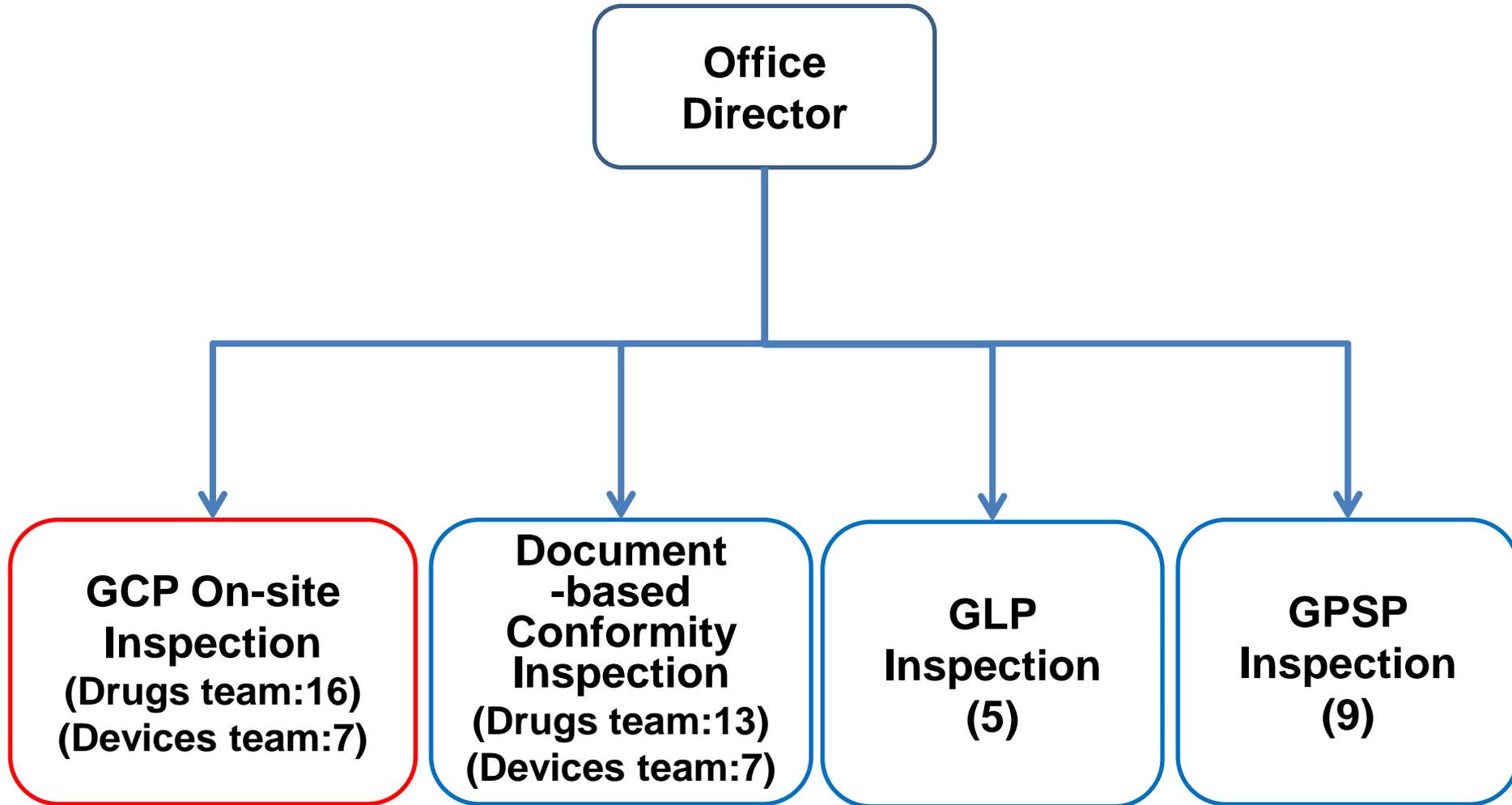
- **Was established in April 2004 as an independent administrative agency**
- **Has about 680 permanent staffs at April 1, 2012**
- **Has three major functions including scientific review and inspection for new drug approval**
- **Submits performance report to Ministry of Health, Labour and Welfare (MHLW) annually**



# Organization Chart of PMDA (As of Oct 1, 2012)



# Office of Conformity Audit, PMDA



( ): The number of inspectors

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## **2. “Good Clinical Practice” in Japan (J-GCP)**

# History of J-GCP

**J-GCP was harmonized with ICH-GCP  
in March 1997**

- **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)**

(\*URL of the ordinance:<http://www.pmda.go.jp/english/service/ministerial.html>)

# Contents of J-GCP

## **【MHLW Ministerial Ordinance No.24 (Feb. 29,2008)】**

- Chapter I. General Provisions (Articles 1~3)
- Chapter II. Standards for Preparing Clinical Trials
  - Section 1. Standards for Preparing Clinical Trials by Persons Who Intend to Sponsor Clinical Trials (Articles 4~15)
  - Section 2. Standards for Preparing Clinical Trials by Persons Who Intend to be a Sponsor-investigator (Articles 15-2~15-9)
- Chapter III. Standards for Clinical Trial Management
  - Section 1. Standards for Clinical Trial Management by Sponsor (Articles 16~26)
  - Section 2. Standards for Clinical Trial Management by Sponsor-investigator (Articles 26-2~26-12)
- Chapter IV. Standards for Conducting Clinical Trials
  - Section 1. Institutional Review Board (Articles 27~34)
  - Section 2. Medical Institution (Articles 35~41)
  - Section 3. Investigator (Articles 42~49)
  - Section 4. Informed Consent of Subjects (Articles 50~55)
- Chapter V. Standards for Documents Submitted in Reexamination etc. (Article 56)
- Chapter VI. Standards for Sponsoring Clinical Trials etc. (Articles 57~59)
- Supplementary Provisions

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## **3. GCP Inspection Procedure in Japan**

# The Pharmaceutical Affairs Act

## (Approval to Marketing of Drugs, etc.)

### Article 14 (3)

**A person who intends to obtain an approval under paragraph (1) shall attach data related to the results of the clinical study or any other material to the application, as provided for by Ordinance of the Ministry of Health, Labour and Welfare. In such cases, when the drug or medical device pertaining to the application is any of those drugs or medical devices specified by Ordinance of the Ministry of Health, Labour and Welfare, the data or materials shall be those collected and prepared in accordance with the standards specified by the Minister of Health, Labour and Welfare.**

# Ordinance for Enforcement of the Pharmaceutical Affairs Act

## (Data Reliability Standards for Applications)

### Article 43

The materials prescribed in the last sentence of paragraph (3) of Article 14 of the Act (including a case with application mutatis mutandis in paragraph (9) of Article 14) must be collected and prepared pursuant to the following items in addition to those specified in the Ordinance of Implementation Standards for Non-Clinical Studies on Safety of Drugs (Ordinance of Ministry of Welfare No.21 of 1997), **the Ordinance of Implementation Standards for Clinical Studies on Drugs (Ordinance of Ministry of Welfare No.28 of 1997)**, the Ordinance of Implementation Standards for Nonclinical Studies Related to Safety of Medical Devices (Ordinance of Ministry of Health, Labour and Welfare No. 37 of 2005), and the Ordinance of Implementation Standards for Clinical Studies of Medical Devices (Ordinance of Ministry of Health, Labour and Welfare No. 36 of 2005).

# The Pharmaceutical Affairs Act

## (Approval to Marketing of Drugs, etc.)

### Article 14 (5)

In the review pursuant to the provision of paragraph (2), item (iii), examinations of the quality, efficacy and safety of the relevant product item (including examinations of the equivalence of ingredients, quantities, structure, dosage and administration, direction of use, indications, effects, performance, etc., to those of product items which have already been approved for manufacturing and sales) shall be conducted on the basis of the contents of the application for the item concerned as well as the data and materials provided for in the first sentence of paragraph (3). **In such cases, when the product item concerned is any of those drugs or medical device specified by Ordinance of the Ministry of Health, Labour and Welfare as provided for in the second sentence of said paragraph, prior written or on-site examinations shall be conducted on whether the data and/or materials on the relevant product item comply with the provision of the second sentence of said paragraph.**

# The Pharmaceutical Affairs Act

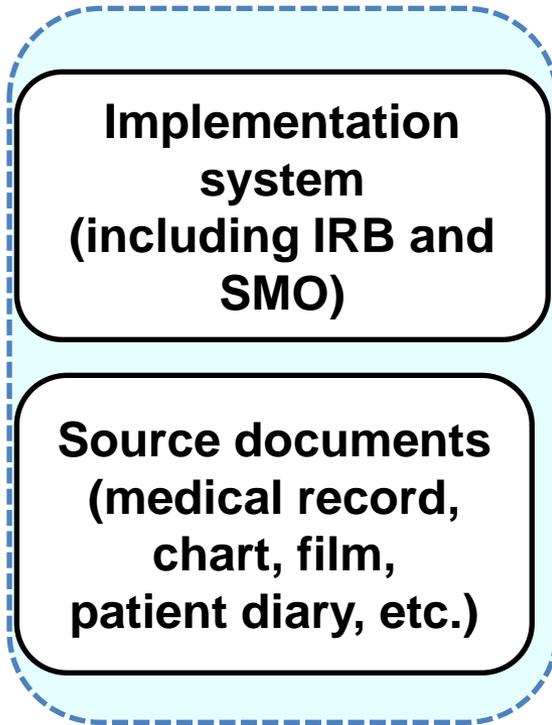
(Reviews, etc. Performed by the PMDA)

## Article 14-2 (1)

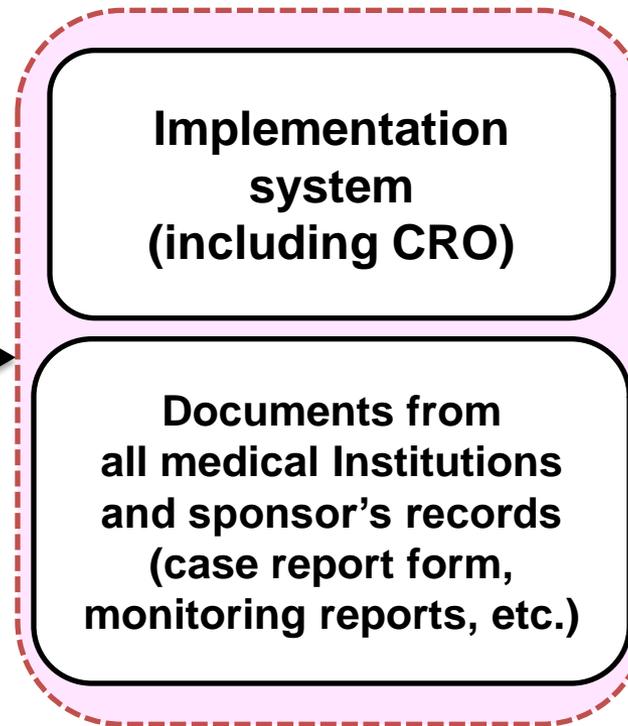
**The Minister of Health, Labour and Welfare may have the PMDA perform the review for approval pursuant to the provision of paragraph (1) or (9) of the preceding paragraph as well as the examinations or inspections pursuant to the provision of paragraph (5) of said Article or the examinations or inspections pursuant to the provision of paragraph (6) of said Article (including the cases where applied mutatis mutandis pursuant to paragraph (9) of said Article), with respect to those drugs (excluding those intended exclusively for use in animals; hereinafter the same shall apply in this Article), quasi-drugs (excluding those intended exclusively for use in animals; hereinafter the same shall apply in this Article), cosmetics or medical devices (excluding those intended exclusively for use in animals; hereinafter the same shall apply in this Article) which are specified by Cabinet Order.**

# GCP On-site Inspection and Document-based Conformity Inspection in Japan

## 【Medical Institution】



## 【Sponsor】



## 【PMDA】



**GCP On-site Inspection**

**Document-based Conformity Inspection**

**We verify conformity of the data of clinical trial in the application dossier**

# Selection of Medical Institutions

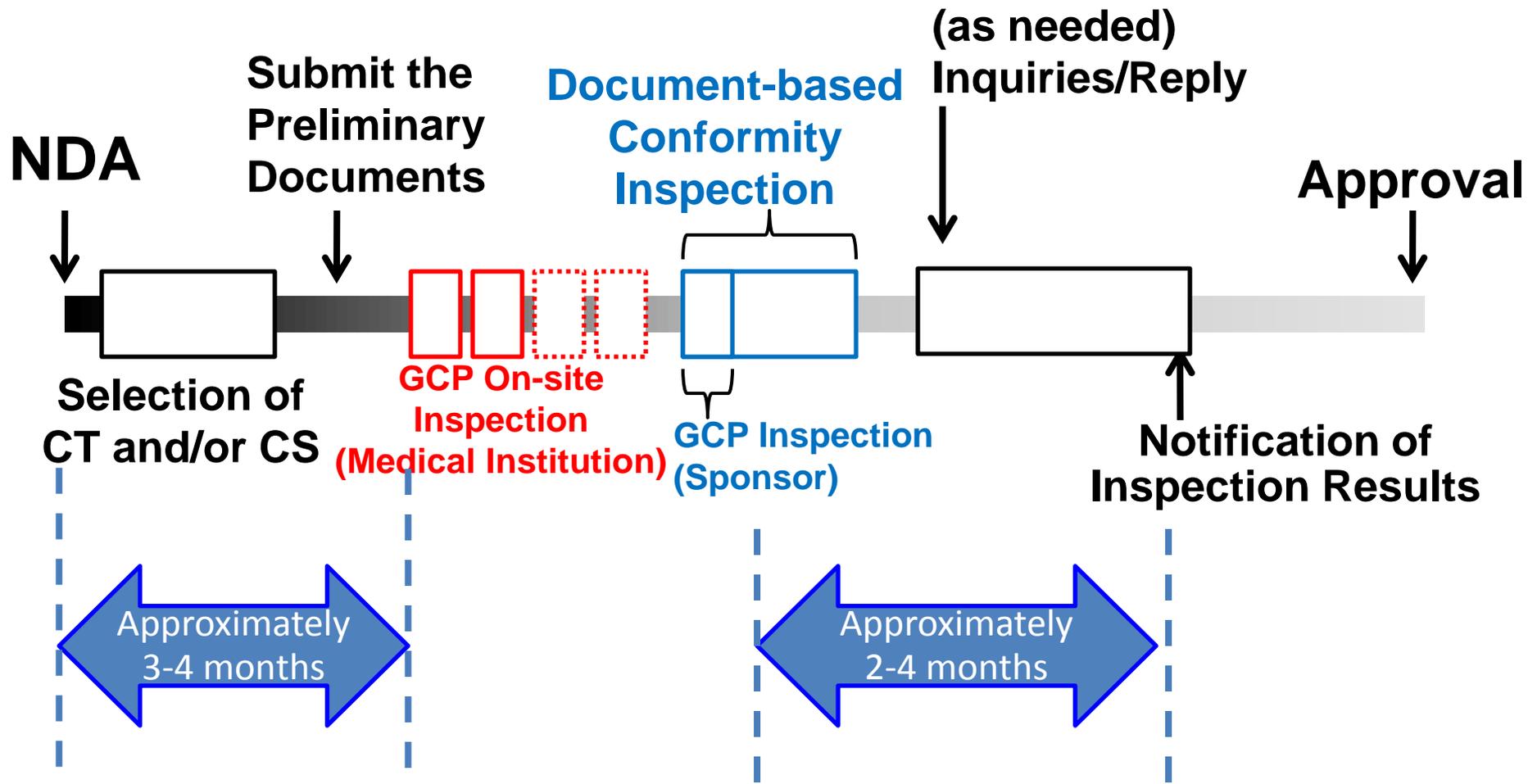
- **The drugs with new active pharmaceutical ingredients**  
(Excluding the drugs of quick/priority review, the orphan drugs)  
→ **Approximately 4 institutions**
- **Others**  
→ **Approximately 2 institutions**

## Points to be considered

- **Priority of clinical trials included in the application**  
(ex; pivotal clinical trial)
- **The number of subjects**
- **Results of previous inspections**
- ...

**\*Additional institutions will be inspected if there are problems identified during review/inspection process.**

# Typical Schedule of Inspection



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## **4. Details of GCP Inspection in Japan and Overseas**

# Conducting GCP Inspection in Overseas

## ➤ Points to be considered

- Pivotal clinical trials conducted in overseas?
- How many Japanese subjects included?
- Already approved product in overseas?
- Already inspected trial/institution by foreign authorities?

...

## ➤ Selection of medical institutions

- By the same way as in Japan

# Trend in GCP On-site Inspection

	FY '07	FY '08	FY '09	FY '10	FY '11
Number of drugs (NMEs)	80 (0)	100 (3)	84 (6)	84 (7)	83 (7)
Number of sponsors	80 (0)	100 (4)	80 (6)	78 (7)	87 (7)
Number of medical institutions	167 (0)	216 (6)	180 (13)	188 (14)	181 (13)

( ): The number of inspections in overseas

# Detail of GCP On-site Inspection in Overseas<sup>1)</sup>

	Countries	Number of GCP Inspection	Countries	Number of GCP Inspection
<b>Sponsors<sup>2,3)</sup></b>	<b>USA</b>	<b>7</b>	<b>Netherlands</b>	<b>1</b>
	<b>UK</b>	<b>3</b>	<b>China</b>	<b>3</b>
	<b>Germany</b>	<b>3</b>	<b>Korea</b>	<b>4</b>
	<b>France</b>	<b>1</b>	<b>Taiwan</b>	<b>3</b>
	<b>Switzerland</b>	<b>1</b>	<b>Philippines</b>	<b>1</b>
	<b>Belgium</b>	<b>1</b>		
<b>Medical institutions</b>	<b>USA</b>	<b>11</b>	<b>Belgium</b>	<b>1</b>
	<b>Canada</b>	<b>2</b>	<b>Netherlands</b>	<b>1</b>
	<b>UK</b>	<b>4</b>	<b>China</b>	<b>6</b>
	<b>Germany</b>	<b>2</b>	<b>Korea</b>	<b>7</b>
	<b>France</b>	<b>2</b>	<b>Taiwan</b>	<b>6</b>
	<b>Hungary</b>	<b>2</b>	<b>Philippines</b>	<b>2</b>

1) April, 2007~March, 2012

2) Including the number of CRO

3) 4 cases are GCP on-site inspection and document-based conformity inspection

# Conclusion of GCP On-site Inspection

## Compliance:

**Acceptable as application dossier  
(indicate voluntary action, if necessary)**

## Compliance with condition:

**Violation of GCP was found in a part of  
subjects**

→ **Acceptable as application dossier**

**after excluding the data from NDA package**

## Non-compliance:

**Violation of GCP was found generally and systematically**

→ **No reliability**

→ **Not acceptable as application dossier**

*(tentative translation)*  
*This English document has been prepared for reference purpose only. In the event of inconsistency between the Japanese original and the English translation, the former shall prevail.*

PMDA No. XXXXXX  
Month Day, Year

Notification of the Result of GCP Inspection

To Investigator at XXXX Hospital

From: Chief Executive  
Pharmaceuticals and Medical Devices Agency

This is to inform you of the result of the inspection for compliance with the GCP for drugs ("GCP"), which was conducted on MMMM DD, YYYY, in relation to the following investigational product. The critical findings of GCP non-compliance that form the basis for the overall result of the inspection and findings requiring corrective actions will be shown in the attachment.

1. Investigational Product

○○○  
(Active ingredients: XXXXX, Product code: XXXXXX  
Date of submission: MMMM DD, YYYY

2. Clinical Trial(s) Inspected

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ABC Tablets in Patients with ○○ disease

# The Results of GCP On-site Inspection

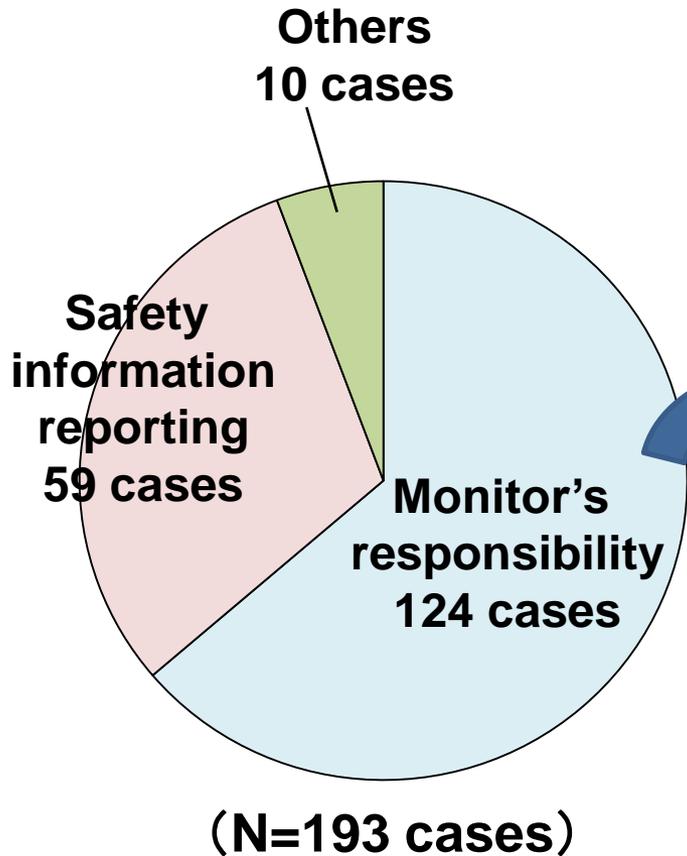
## To sponsors

- Finding(s) for preparation of clinical trials  
(preparation of protocol, investigator's brochure, etc.)
- Finding(s) for control of clinical trials  
(monitor's responsibility, provision of safety information, etc.)

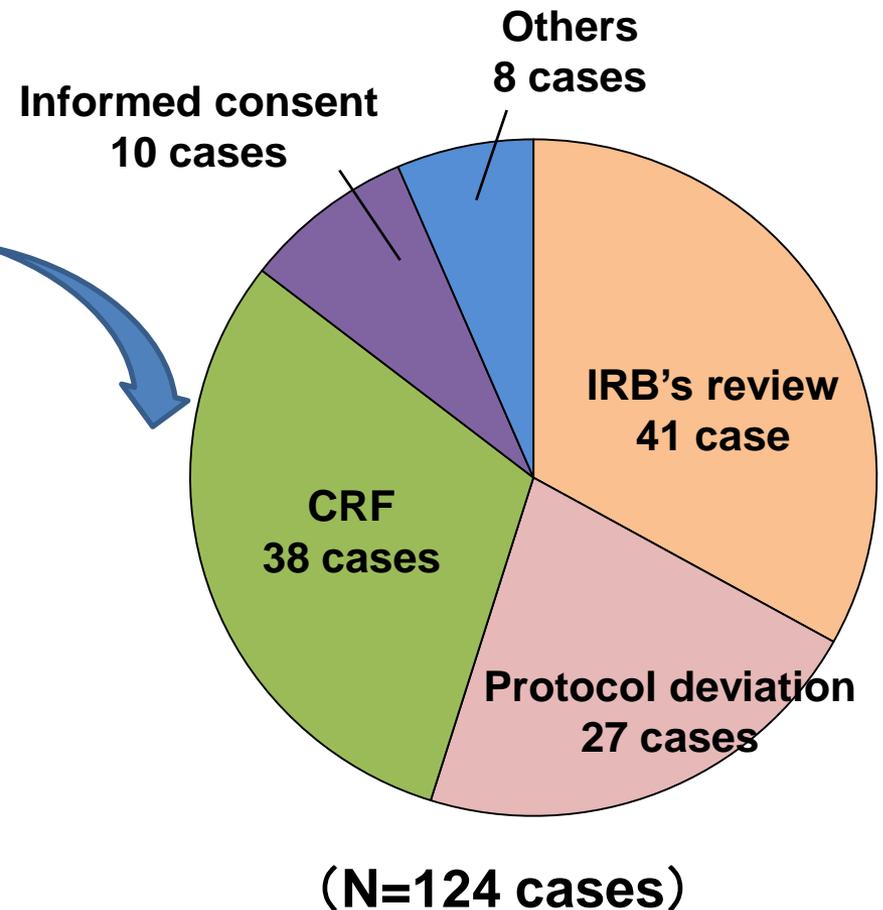
## To medical institutions

- General finding(s)  
(control of investigational products, IRB, etc. )
- Finding(s) for individual subjects  
(informed consent, protocol deviations, etc.)

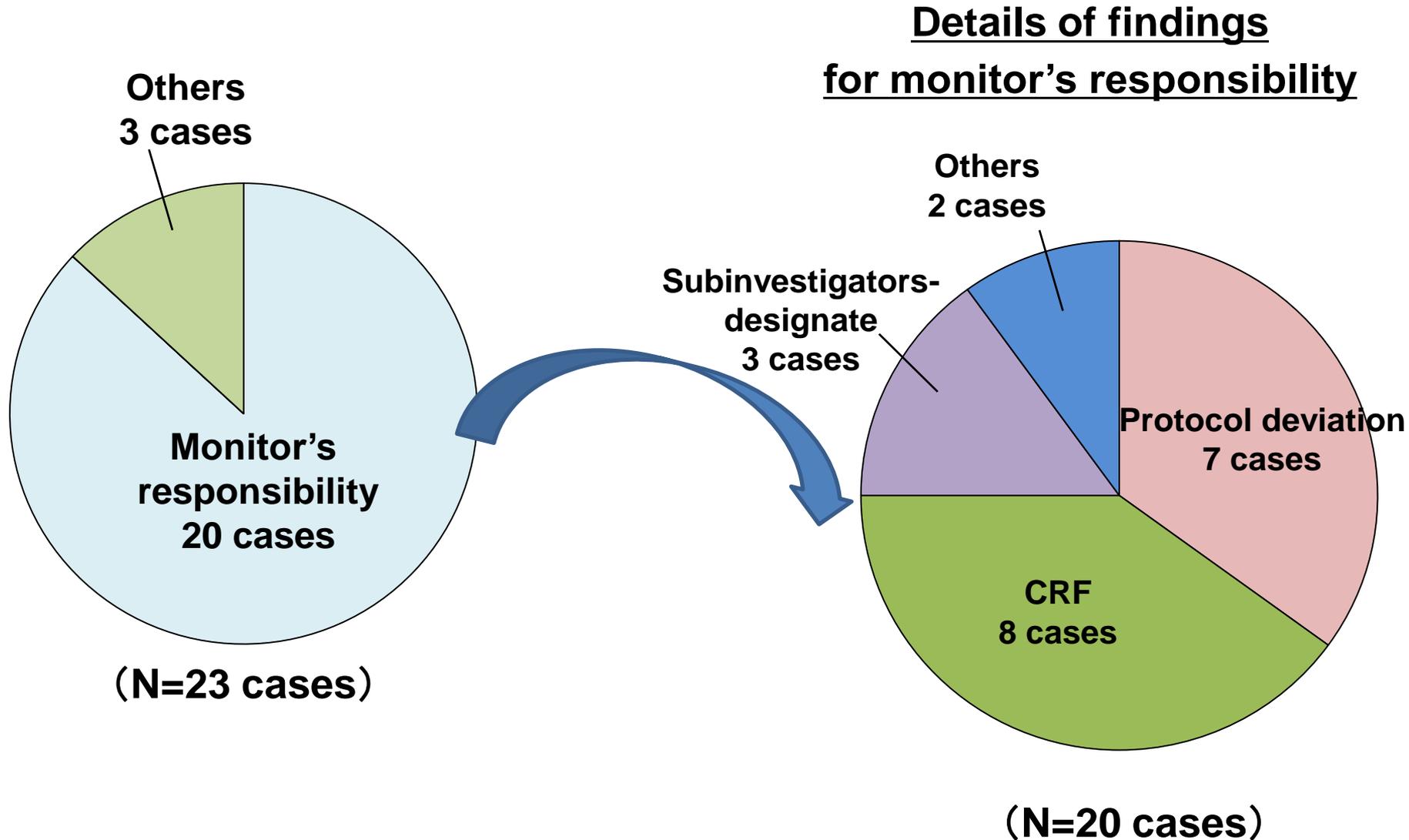
# Findings for Sponsors in JAPAN (2009 - 2011)



## Details of findings for monitor's responsibility

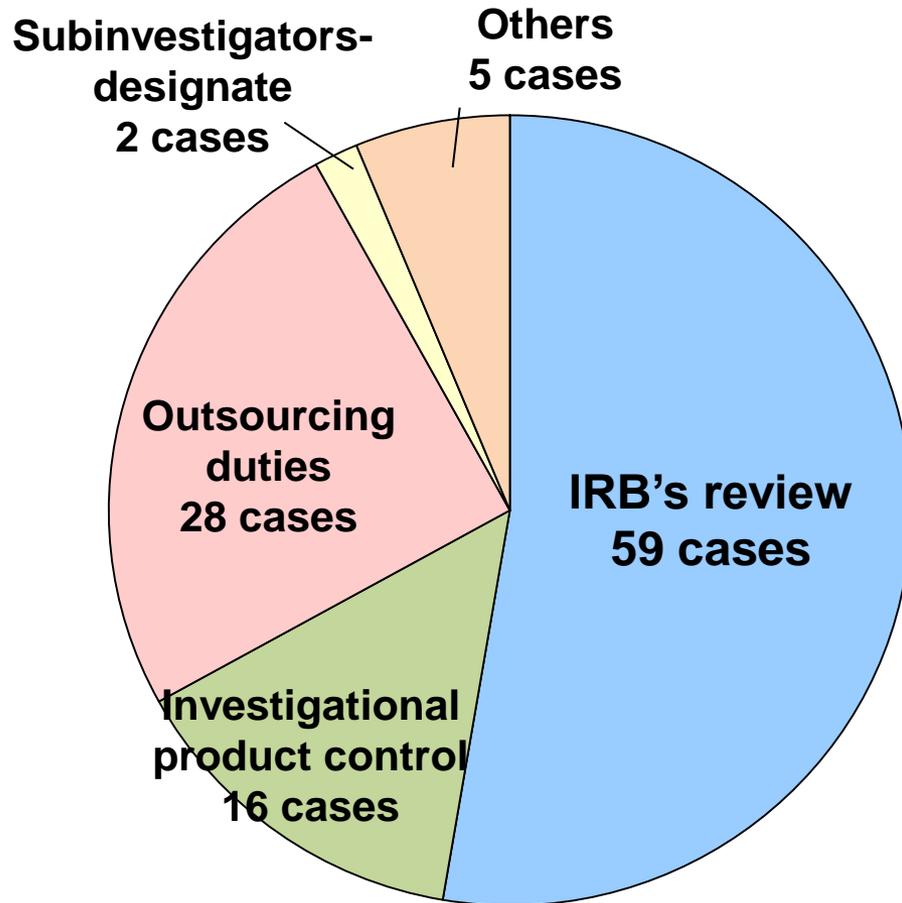


# Findings for Sponsors in Overseas (2009 - 2011)



# General Findings for Medical Institutions (2009 - 2011)

## JAPAN



(N=110 cases)

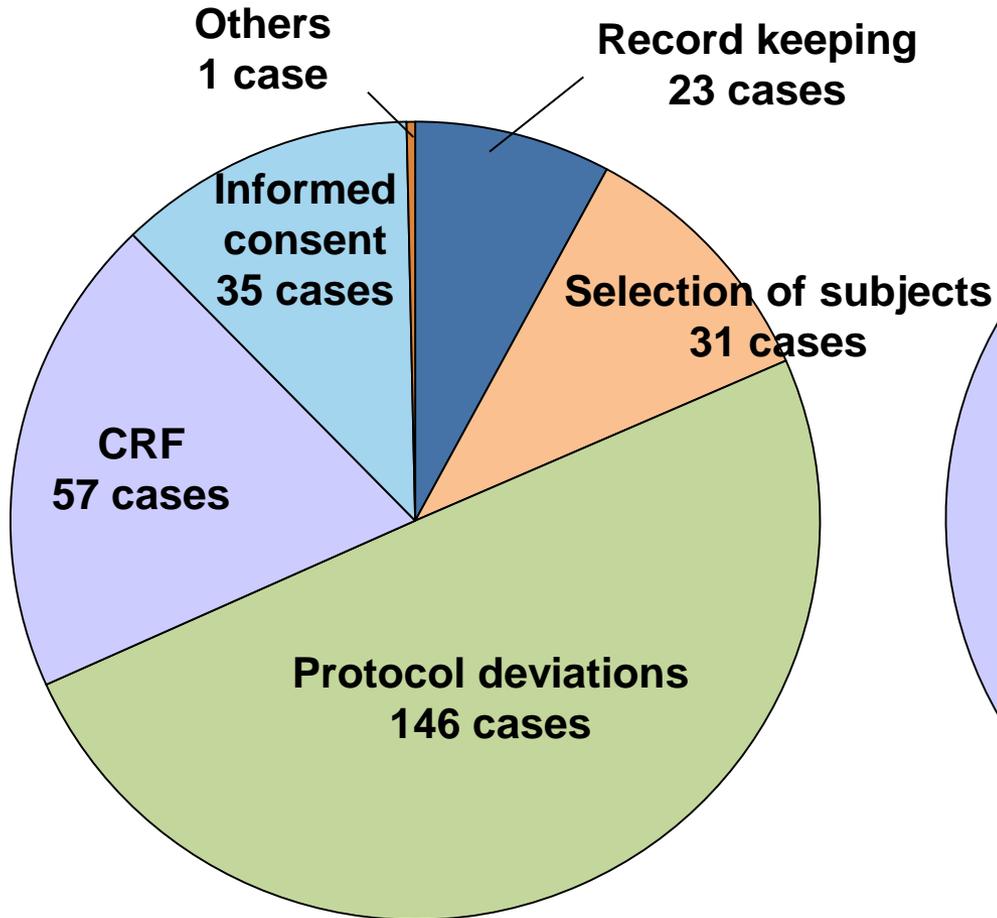
## Overseas



(N=7 cases)

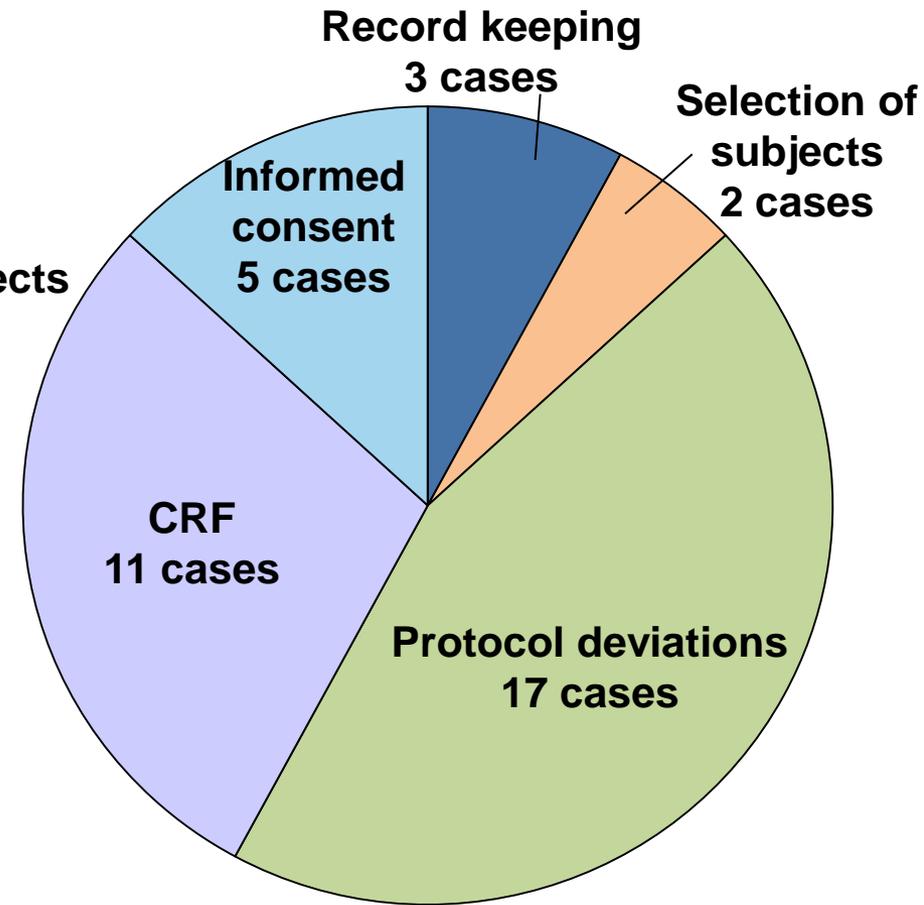
# Findings for Individual Subjects (Medical Institutions) (2009 - 2011)

## JAPAN



(N=293 cases)

## Overseas



(N=38 cases)

# Future Plan of GCP Inspection

- **Share information related to conducting clinical trials (local GCPs, legal basis of drug regulation, etc.)**
- **Exchange information on inspection with the overseas authorities (inspection schedule, inspection results, etc.)**
- **Inspect the organization relevant to the clinical trials as well as sponsors and medical institutions (SMO, clinical laboratories, etc.)**

