GCP/Clinical Investigation in Japan

27-28 August, 2018

Shinwa Shibata
Office of Non-clinical and Clinical Compliance
Pharmaceuticals and Medical Devices Agency

Today's Agenda

1. Japanese-GCP (J-GCP) for Medical Devices

* Requirement in using foreign clinical data for market approval application of medical devices in Japan

* Points to consider in judging necessity to include clinical data in market approval application

2. Inspection for Clinical Data

a. Document-based inspection

b. On-site inspection

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Good Clinical Practice

An international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects

Public assurance that the rights, safety, and well-being of trial subjects are protected

- Consistent with the Declaration of Helsinki
- Results in credible data

A Brief History of J-GCP

1964 Declaration of Helsinki
1977 FDA implements “several Proposals” for clinical trials.
⇒These are thought of as the first GCP guidelines
1989 J-GCP for Drugs (MHLW PAB Notification)
1991 GCP for Trials on Medical Products in the EC

1992 J-GCP for Medical Devices (MHLW PAB Notification)

1995 Guidelines for GCP for trials on pharmaceutical products (WHO-GCP)
1995 ICH-E6 GCP Guideline
1997 New J-GCP for Drugs (MHLW Ministerial Ordinance)
2003 ISO14155 Clinical investigation of medical devices for human subjects

2005 New J-GCP for Medical Devices (MHLW Ministerial Ordinance)

Content of J-GCP

Harmonization with ICH-GCP

MHLW Ministerial Ordinance No.36
(Mar.23,2005, latest revision on Jul.21, 2016)

- Chapter I. General Provisions (Articles 1 through 3)
- Chapter II. Standards for Preparing Clinical Trials (Articles 4 through 23)
- Chapter III. Standards for Clinical Trial Management (Articles 24 through 45)
- Chapter IV. Standards for Conducting Clinical Trials (Articles 46 through 75)
- Chapter V. Standards for Documents Submitted in Reexamination etc. (Article 76)
- Chapter VI. Standards for Sponsoring Clinical Trials etc. (Articles 77 through 79)
- Supplementary Provisions

http://www.pmda.go.jp/files/000153732.pdf

PMD Act

Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

Article 23-2-5, paragraph 3

Approval to Marketing

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,……, the data or materials shall be those collected and prepared in accordance with **the standards** specified by the Minister of Health, Labour and Welfare.

GCP standards
GLP standards
Data integrity standards

Data Integrity Standards for Product Applications

-Article114-22 of Ordinance for Enforcement of the PMD Act-

- Accuracy

  Accurate preparation of dossier based on the results of analyses and studies

- Completeness

  Description of results which cast doubt on quality, efficacy or safety

- Retention

  Retention of the original data

How to deal with Foreign Clinical Data

PFSB/MDE Notification No. 0331006 (Mar.31,2006)

Points to consider for applications, when using clinical data from studies conducted in foreign countries

- The clinical trial was conducted in the country or region where the GCP is equivalent to or better than J-GCP.
- The prepared documents have to be the equivalent to or better than the essential documents of the J-GCP.
- Sponsors, medical institutions and other parties involved in the clinical trial have to be ready for necessary cooperation in the inspection.
- Applicants have to ensure the reliability of the entire clinical trial by audit or other means.

http://www.pmda.go.jp/files/000153073.pdf

Necessity of Clinical Data in Market Approval Application

PFSB/ELD/OMDE Notification No. 0804001 (Aug.4, 2008)

Examples in which clinical data are required in market approval application

- Clinical efficacy and safety of the medical device cannot be evaluated by non-clinical studies, such as performance tests and animal studies, or already existing articles.
- Brand-new medical devices whose performance or structure, etc. is clearly different from already approved medical devices.
- MHLW notification, etc. request clinical data in market approval application of particular medical devices.

Necessity of clinical data is comprehensively judged considering the characteristics of individual medical devices, similarity to already approved devices, and non-clinical study data, etc.

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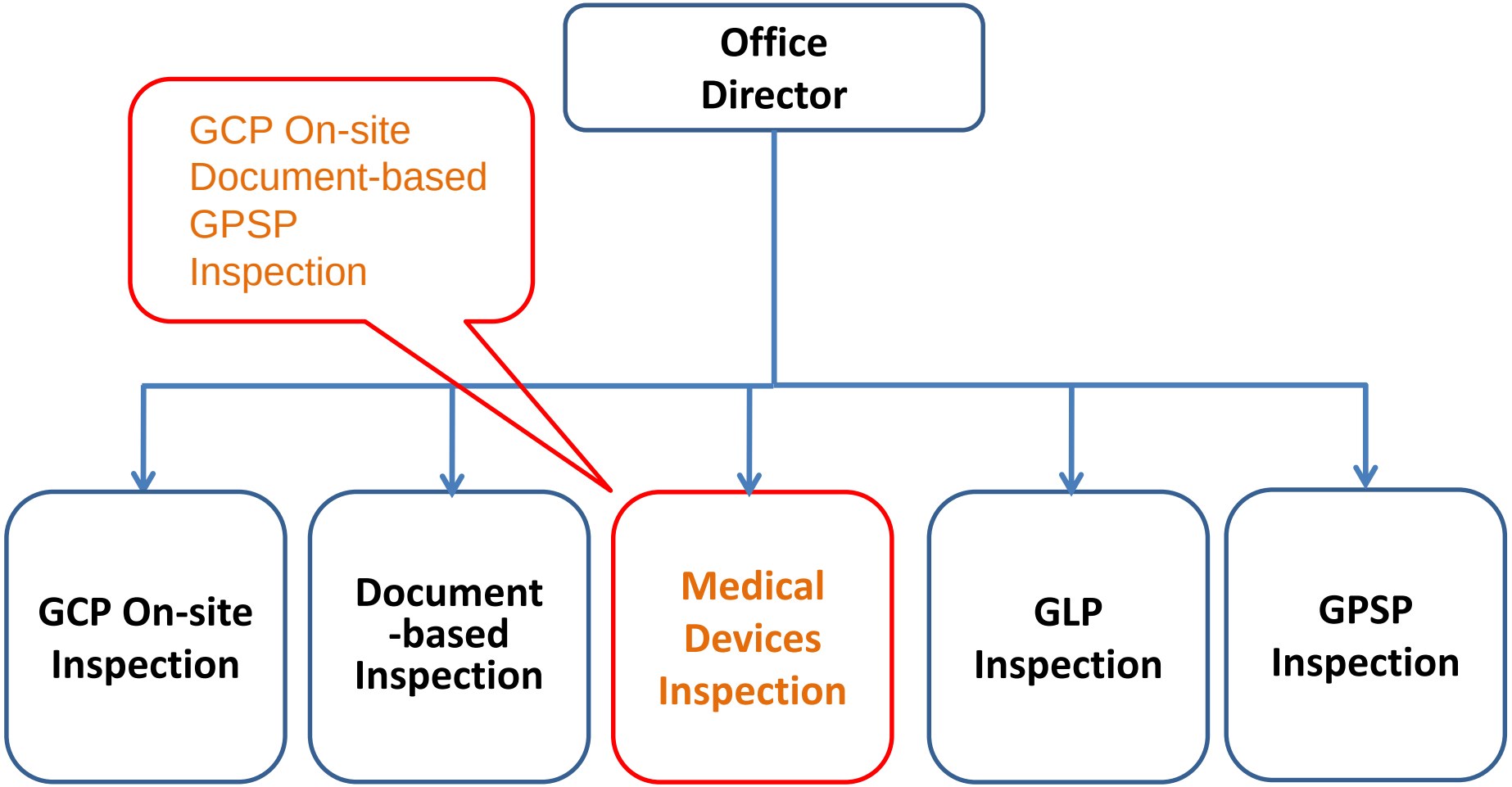
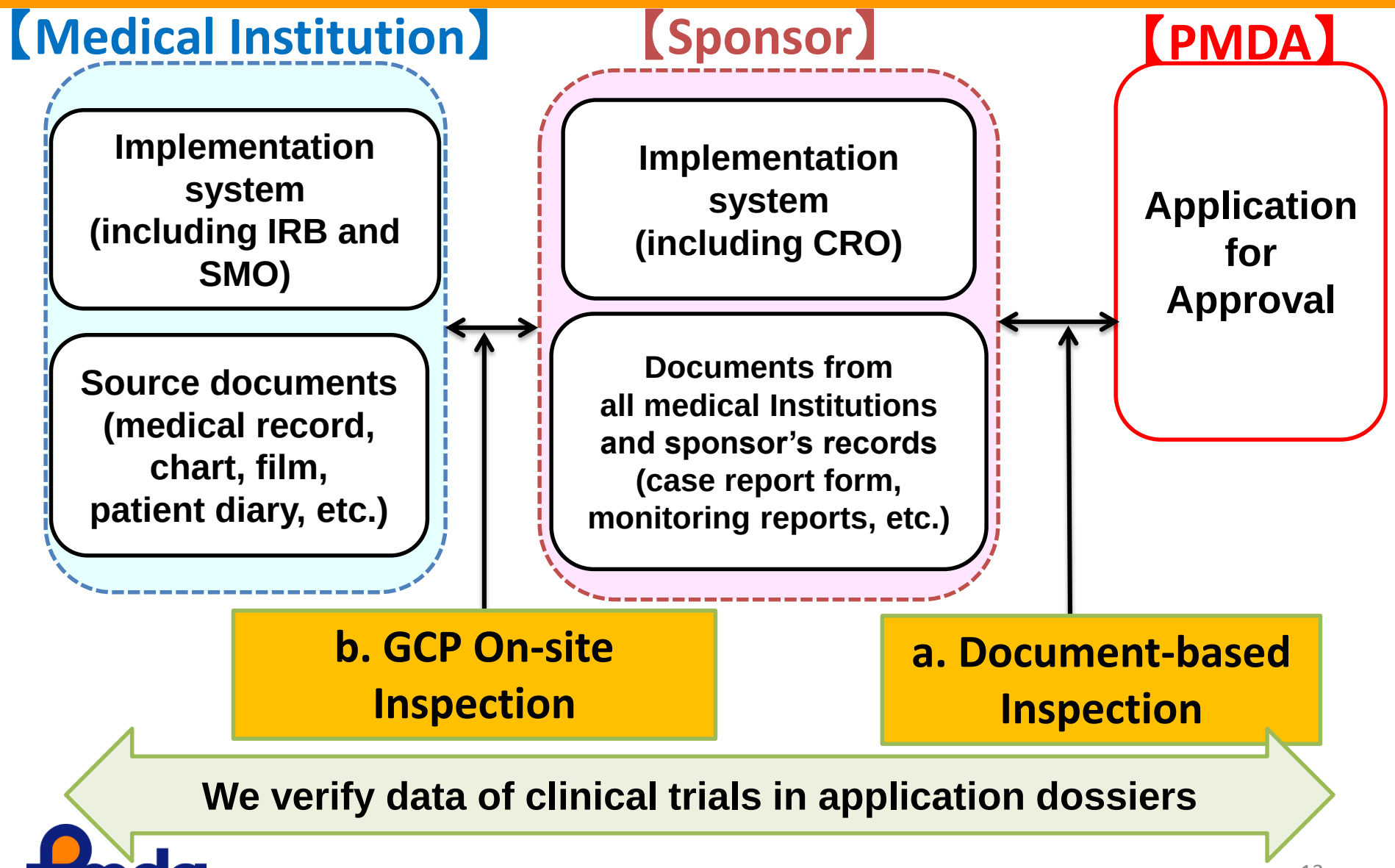
Office of Non-Clinical and Clinical Compliance



Inspection for Clinical Data



Process and Responsibilities in a Clinical Trial

Responsibility of the sponsor

・Preparing a SOP, a protocol, an investigational brochure.
・ Selection of the medical institution, the principal investigator. etc.

Responsibility of the head of the medical institution

Responsibility of the Institutional Review Board (IRB)

Request

Submit for review

Approval

contract

Conduct of clinical trial

CRF

Responsibility of the principal investigator, the medical device storage manager, the record keeping manager

- Selection of subjects, acquisition of informed consent
- Conducting trial in accordance with the protocol
- Appropriate control of the medical devices/accountability
- Reporting the serious adverse events
- Retain the source documents ……etc.

Example of items to be reviewed in Document-based Inspection

- SOPs
- Preparation of protocol and Investigator's Brochure
- IDE
- Investigator/Institution Selection
- Contract documents
- Notification of IRB
- Monitoring/Audit
- Safety information/SAE reporting
- CRFs (including EDC)
- Data management/statistical analyses
- Medical device control/accountability (including manufacturing records)
- Compensation
- Clinical study reports ・・・etc.

Key points to be considered:

1. The safety and rights of human subjects are guaranteed.

2. Data integrity of the study is maintained.

Overview of Document-based Inspection

Applicant brings documents in PMDA

Example of inspection schedule

10:00～ Opening meeting, morning session
12:00～ Lunch break
13:30～ Afternoon session
16:30～ Inspector meeting
17:00 ～ Feedback
…Inquiries are sent to the applicant if it is necessary

Inspection members

1～2 inspector(s) check SOP, DM, Stat, device accountability, contract docs, etc
3～4 inspectors check CRF, monitoring reports and other docs related to the subjects

Examples of Triggers for Inquiries

✓ Data management, statistical analysis :

- Since quality control of data was not adequately carried out, amendment of application dossier was required

✓ Discrepancy:

- The data described in the clinical study report were different from those in CRF and so on

✓ Record keeping in medical institution:

- Medical records had been discarded

➡ When there are no such issues, or issues are resolved by applicant's response, document-based inspection ends and on-site inspection is not conducted.

Conclusion of Document-based Inspection

- No Warning/Minor finding
  - ✓ Voluntary action is indicated after responding to the inquiry.
  - ✓ No action is indicated after responding to the inquiry (including the cases which need some modifications to application dossiers).
  - ✓ No action is indicated. (No inquiry)
- Warning/Critical finding
  - ✓ There is a finding which affects on the reliability of the clinical trial or evaluation of efficacy and safety of the devices.

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Examples of Problems which may cause On-site Inspection

On-site inspection is conducted when it is necessary, for examples in cases such as …

(1) Inappropriate informed consent (IC)

* Written IC forms cannot be found at the investigational site
* Clinical trial procedure might have been conducted before obtaining IC

(2) Problems on Data accuracy

* Inconsistency (CRF - CSR, CRF – Query forms / DCF)
* Lack of Principle Investigator's approval on CRF

(3) Monitoring is not reliable

* Monitor's ability is assumed to be insufficient

Overview of On-site Inspection

Process

- Opening meeting
- Review documents and interview with Staffs / Investigators
- Tour of the facility
- Feedback

Review items (Sponsor)

- Contract documents
- Sponsor's SOPs
- Preparation of protocol and Investigator's Brochure
- Investigator/Institution Selection
- SAE reporting
- Compensation

  etc.

Review items (Medical institutions)

- Institution's SOPs
- IRB's SOPs and Minutes
- Medical records
- Signed IC form
- Handling of the Investigational products
- Records of SAE and deviations

  etc.

Conclusion of On-site Inspection

Compliance

Submitted clinical trial data are acceptable as application dossier

(Sometimes, improvements may be suggested)

Compliance with condition

Certain deviation from GCP was confirmed in some data.

→ acceptable as application dossier after deleting data which is not GCP-compliant.

Non-compliance

The deviations from GCP were found generally and systematically

→ no reliability of data

→ whole clinical trial data should not be considered.

Trend in Number of Inspections

Fiscal Year	2013		2014		2015		2016		2017	
Category	Brand-new /Improved MD	Improved /Generic MD	Brand-new /Improved MD	Improved /Generic MD	Brand-new /Improved MD	Improved /Generic MD	Brand-new /Improved MD	Improved /Generic MD	Brand-new /Improved MD	Improved /Generic MD
	With Clinical Data	No Clinical data	With Clinical Data	No Clinical data	With Clinical Data	No Clinical data	With Clinical Data	No Clinical data	With Clinical Data	No Clinical data
Document-based inspection	94	847	69	762	70	793	56	743	66	767
GCP on-site inspection	6		5		1		1		6	

Noted: Based on the dates when notifications for inspection completion were published.

Thank you for your attention !