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)
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

Harmonization with ICH-GCP

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

- Article 114-22 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
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.

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

- GCP On-site Inspection
- Document-based Inspection
- Medical Devices Inspection
- GLP Inspection
- GPSP Inspection

Office Director
Inspection for Clinical Data

- **Medical Institution**
  - Implementation system (including IRB and SMO)
  - Source documents (medical record, chart, film, patient diary, etc.)

- **Sponsor**
  - Implementation system (including CRO)
  - Documents from all medical institutions and sponsor’s records (case report form, monitoring reports, etc.)

- **PMDA**
  - Application for Approval

We verify data of clinical trials in application dossiers.

3rd India - Japan Medical Products Regulation Symposium 2018
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)**

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.

Request → Submit for review → Approval → Contract → Conduct of clinical trial
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

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**Document-based inspection**

**GCP on-site inspection**

**Noted:** Based on the dates when notifications for inspection completion were published.
Thank you for your attention!