

(Tentative translation)

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Office of Non-clinical and Clinical Compliance, Pharmaceutical and Medical Devices Agency
Prepared on January 26, 2017 Version 1.0

Points to consider for implementation of document-based conformity inspection for medical devices (non-clinical studies)

Documents for approval application related to non-clinical studies of a medical device are required to be collected and prepared in accordance with the "Standard of Reliability of Application Data" under ordinances related to the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices. During the review of a medical device, a document-based conformity inspection is conducted to ensure that documents for approval application related to non-clinical studies of a medical device are compliant with the above standards. In the inspection, the primary data (supporting data and documents) that have served as the base of documents for approval application such as study protocol and testing records are inspected directly.

The matters listed in this document consist of important points in the supporting data and documents (hereinafter referred to as documents) subjected to a document-based conformity inspection to ensure smooth implementation of the concerned inspection on non-clinical studies after approval application. Please pay attention to these matters even at the stage of preparation for approval application. Because the matters listed in this document have been prepared for non-clinical studies of various medical devices, all the matters may not be uniformly applicable to a non-clinical study. Please select the matters according to characteristics of each non-clinical study, and apply the selected ones. Please note that an actual inspection may require information or explanation other than the matters listed in this document depending on the characteristics of the study inspected and implementation method.

PMDA plans to review the matters listed in this document as appropriate to improve their usefulness continuously. Please refer to the latest version when applying these matters. If there is anything unclear in the matters listed, or if you want to consult us, PMDA, about results of the preliminary check performed according to the matters, please use our consultation services (please refer to PMDA website: <https://www.pmda.go.jp/english/index.html>).

1. Control of supporting documents

- 1-1 Have you confirmed that the following supporting documents are maintained (for all the studies to be inspected)?
- A) Records related to the study plan (documents that demonstrate that an appropriate study plan has been established before implementation of the study, such as study protocol, testing procedures, and analysis procedures)
 - B) Records related to a study (documents in which study results generated during the study are recorded correctly, such as experiment notebooks, worksheets, charts, and checklists; primary records)
 - C) Records related to control and inspection of equipment used to obtain the study results and/or control precision of the testing conditions.
 - D) Records related to study reports
- 1-2 Have you confirmed that supporting documents can be submitted within approximately 4 weeks after receipt of request for their submission?
- 1-3 Have you confirmed that original copies of supporting documents owned by a party other than the applicant can be obtained immediately (if only duplicate copies are available, information about the place where the original copies are retained)?

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2. Contents in each piece of supporting documents

A. Records related to the study plan

- [1] Does a record such as study protocol clearly state the date of preparation (date of revision)? And is the concerned date before implementation of the study?
- [2] Does a record such as study protocol clearly state purpose of the study, specific test methods, testing conditions, analysis method, etc.?

B. Records related to a study (primary records)

- [1] Does a record clearly state date of testing and testing operators?
- [2] Does a corrected part have information about date of correction, person in charge of the correction, and reason for the correction? For a part corrected long after implementation of the study, is a clear rationale for the correction available?
- [3] Does a record have information for identification of test specimens (Lot No., serial No. or other unique identification)?
- [4] Are all the primary records that support results in study reports, etc. (including non-numerical results such as findings and observation records) available?
- [5] Are records stored electronically in which data can be modified after study, under quality control to prevent damage or unauthorized access to or amendment of these records.
- [6] In a case where study records are directly entered in a study report, etc., is a flow chart in place to explain procedures for implementation of the study, record keeping during the study, and preparation of the study report, including QC/QA system (see Reference 3)?
- [7] Has software used in measurement, analysis, etc. been suitably validated as being adequate for use?
- [8] Can the primary records demonstrate that the study has been conducted according to the testing conditions specified in the study protocol, etc.?
- [9] In a case where a specimen was pre-treated (sterilized, accelerated aging, acclimated to simulated use condition, etc.), can the primary records demonstrate such pre-treatment?
- [10] In a case where study results are presented as photographs, is information for identification of the test specimens available in the photograph?
- [11] Is information about identification of equipment used to obtain study results (product name, manufacturing No., serial No., etc.) available?
- [12] Is information about identification of equipment necessary for precision control of the testing conditions (product name, manufacturing No., serial No., etc.) available?
- [13] In a case where a study deviated from the study protocol, are the content and reason of the deviation documented?

<Studies using animals>

- [14] Are records on purchase (procurement) and rearing of animals, etc. available?
- [15] Are surgery records with individual animals, surgery site, details of the surgery, and implant and implantation site in a case of implantation procedure clearly described available?
- [16] In a case where a test device is implanted for a certain period, are records demonstrating the implantation for the planned period available?

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C. Records related to control and inspection of equipment

- [1] Are records on control and inspection of equipment used to obtain study results available?
- [2] Are records on control and inspection of equipment necessary for precision control of the testing conditions available?
- [3] Are these records linked with "information about identification of equipment" in the above B. Records related to a study?
- [4] Do the records demonstrate that the equipment was appropriately controlled and inspected during the study, which means that the records include the date when last calibrated and the date or expiration criteria when recalibrations due (whether calibration expired or not)?
- [5] Is traceability to the national or international standard ensured for applicable equipment?

3. Preparation of a study report

D. Records related to a study report

- [1] Do records on a study report clearly state the date of preparation (date of revision)? And is the concerned date at the same time as implementation of the study or after that?
- [2] Does a study report reflect information presented in the primary records in a correct and comprehensive manner?
- [3] Does a study report reflect results from an analysis performed using the primary records by a specified method?
- [4] Does a study report reflect results on all the specimens specified in the study protocol, etc.?
- [5] In a case where the study was conducted using a condition or method different from that in the study protocol, etc., is such a matter documented in the study report as a deviation, etc.?

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Reference: Concept of Standard of Reliability of Application Data

Standard of Reliability of Application Data

Data prescribed by the second sentence of paragraph 3 of Article 23.2.5 (including where (paragraph 11 of the same Article applies mutatis mutandis) shall be collected and prepared using the following methods as well as the ones set forth in the Ordinance on Standards for Non clinical Studies concerning Safety of Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 37 of 2005) and the Ordinance on Standards for Clinical Studies of Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 36 of 2005).

(i) The data shall be correctly prepared based on results of the investigation or the test conducted for the purpose of preparing the data.

(ii) In case where results of the investigation or the test in the preceding item cast a doubt on whether medical devices concerning an application have sufficient quality, efficacy, or safety pertaining to said application, results of the investigation and the test shall be reviewed and evaluated and the results shall be described in the data.

(iii) Data on which the data is based shall be preserved until the date of disposition when the approval stipulated in paragraph 1 or 11 of Article 23.2.5 of the Law is provided or not provided. However, this shall not apply to the case where it is recognized that the nature of the data makes it extremely difficult to preserve.

(see Article 114-22 of the Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices)

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References

1. Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices
2. Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices
3. PMDA Notification No. 0410024, by the Chief Executive of Pharmaceuticals and Medical Devices Agency, dated April 10, 2015: Partial revision of "Procedure for implementation of document-based conformity inspection on documents for approval application related to non-clinical studies of medical devices."
4. PMDA/CPE Notification No. 0410025, by the Director of Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency, dated April 10, 2015: Partial revision of "Questions & Answers for procedure for implementation of document-based conformity inspection on documents for approval application related to non-clinical studies of medical devices"
5. PMDA Notification No. 1121009, by the Chief Executive of Pharmaceuticals and Medical Devices Agency, dated November 21, 2014: Procedure for implementation of document-based conformity inspection on documents for approval application related to non-clinical studies of medical devices
6. PFSB/MDRMPED Notification No. 1121-27, by the Director of Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 21, 2014: Partial revision of "Procedure, etc. for implementation of document-based conformity inspection on documents for approval application related to non-clinical studies of medical devices"
7. PFSB/ELD/OMDE Notification No. 1112-1, by Director of Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 12, 2014: Partial revision of "Guidance for implementation of medical device standard document-based conformity inspection and on-site GCP conformity inspection" and "Procedure for implementation of document-based conformity inspection on documents for approval application related to non-clinical studies of medical devices"
8. Joint PFSB/ELD Notification No. 1121-9 and PFSB/MDRMPED Notification No. 1121-13, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau and by the Director of Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 21, 2014: Handling of documents and data related to non-clinical studies for the safety of drugs, medical devices, and regenerative medicine products to be attached in the marketing approval application of drugs, medical devices, and regenerative medicine products
9. Ministerial Ordinance on Standards for Manufacturing and Quality Controls for Medical Devices and In-vitro Diagnostics (QMS Ordinance)
10. PFSB/CND Notification No. 0827-4, by the Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 27, 2014: "Revision of the Ministerial Ordinance on Standards for Manufacturing and Quality Controls for Medical Devices and In-vitro Diagnostics in association with enforcement of the law of partial revision of the Pharmaceutical Affairs Law"
11. PFSB/MDRMPED Notification No. 0120-9, by the Director of Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated January 20, 2015: "Points to consider for preparation of data and documents to be attached to the marketing approval application form of medical devices"
12. ISO 13485
13. ISO 17025
14. JIS Q 17025