

Tentative translation (as of October 7, 2008)

Documents to be submitted for GMP Compliance Inspection

After applying for a GMP Compliance Inspection, an onsite inspection or document inspection will be conducted. The list below gives examples of documents that will be required by PMDA for the implementation of the inspection. As for items I.1 and II.1, please refer to the Office Memorandum from the Office of Compliance and Standards, dated July 29, 2008, and submit them at the time of application.

I. In the case of GMP Compliance Inspection conducted for marketing approval or approval of partial changes (Pre-approval Inspection)

1. Outline of drug manufacturing site^{*1}
2. Layout of the manufacturing site^{*2}
3. Plan of structures and facilities of the manufacturing site^{*3}
4. GMP organization chart and quality assurance system^{*4}
5. List of GMP documents^{*5}
6. Documents concerning the manufacturing process^{*6}
 - (1) Documents concerning the manufacturing process flowchart and detailed manufacturing methods pertaining to the relevant product(s)^{*7}
 - (2) Documents concerning the in-process control pertaining to the relevant product(s)
 - (3) Documents concerning the specifications and testing methods for intermediates and products pertaining to the relevant product(s)^{*8}
 - (4) Documents concerning the specifications and test methods of raw materials^{*9}
7. Summary of Process Validation^{*10}
8. Summary of cleaning validation^{*11}
9. List of lots of the product manufactured the in the past few years or planned annual lots
10. Documents concerning the system for product release from the manufacturing site
11. Documents concerning deviation control procedures and records^{*12}
12. Documents concerning change control procedures and records^{*13}
13. Documents concerning the status of compliance to *the Standard for Biological Ingredients*^{*14}

14. (Site Master File)

II. In the case of GMP Compliance Inspection conducted every five years following marketing approval (Periodical Inspection)

1. Outline of drug manufacturing site^{*1}
2. Layout of the manufacturing site^{*2}
3. Plan of structures and facilities of the manufacturing site^{*3}
4. GMP organization chart and quality assurance system^{*4}
5. List of GMP documents^{*5}
6. Documents concerning the manufacturing process^{*6}
 - (1) Documents concerning the manufacturing process flowchart and detailed manufacturing methods pertaining to the representative product(s)^{*7}
 - (2) Documents concerning the in-process control pertaining to the representative product(s)
 - (3) Documents concerning the specifications and testing methods for intermediates and products pertaining to the representative product(s)^{*8}
 - (4) Documents concerning the specifications and test methods of raw materials^{*9}
7. Documents that indicate the status of validation^{*15}
8. List of lots of the product manufactured the in the past few years or planned annual lots
9. Documents concerning the system for product release from the manufacturing site
10. Documents concerning deviation control procedures and records^{*12}
11. Documents concerning change control procedures and records^{*13}
12. Documents concerning the status of compliance to *the Standard for Biological Ingredients*^{*14}
13. (Site Master File)

Description for numbers with asterisk (*) :

- *1 Submit as the attached document in application for GMP Compliance Inspection in accordance with the Office Memorandum specified by the Office of Compliance and Standards.

- *2 Submit documents that indicate the environment of the location of the manufacturing site, and the layout of all facilities of the manufacturing site.
- *3 Prepare plans that indicate necessary information on facilities that are applied for the inspection. Also include related facilities such as laboratories and animal facilities.

Indicate clearly the personal and material flow, environmental control classifications in facilities, and pressure differentials between rooms. In addition to those indicate the diagram of HVAC systems as well..
- *4 Indicate the responsibility and name of person in charge. If a quality assurance department outside the manufacturing site is involved, indicate its relationship clearly.
- *5 Classify documents related to GMP by title, document number etc., and indicate their system clearly using a chart, list etc.
- *6 Submit the relevant parts etc. of copies of standard codes and/or procedures concerning the relevant product(s) (for example, copies of master production instructions, manufacturing records, test records, manufacturing and testing procedures etc. that are used actually at the manufacturing site).
- *7 If re-processing or re-working are designated, indicate them as well.
- *8 Indicate the classifications of regulatory specifications and in-house specifications.
- *9 Submit documents concerning raw materials for which specifications are fixed in the drug master file (MF), or those indicated in the “Qualitative and Quantitative Composition” column of the approval application.
- *10 Submit Process Validation documents concerning confirmation at an actual production scale. If confirmation at an actual production scale is below three (3) lots under some unavoidable reasons, submit the plan for confirmation at an actual production scale, such as a concurrent validation protocol. Subsequently, the results shall be reported to the Office of Compliance and Standards of PMDA as soon as they become available.
- *11 Submit the cleaning validation record in case of multipurpose manufacturing equipment.
- *12 As for “documents concerning history”, please submit records concerning deviation control relating to the product(s) during the past two years.
- *13 As for “documents concerning history”, please submit records concerning change control relating to the product(s) during the past two years.
- *14 Submit a statement, even if no raw material is used regulated by *the Standard for Biological Ingredients*.
- *15 Please refer to Attachment 3-4-2, Validation Standards, No.4 of Chapter 3, PFSB/CND Notification No. 0330001, March 30, 2005.(Summary of revalidation, if there is a major change in the manufacture and control of the product, summary of trend analysis of process control, and periodical revalidation).

III. **Other points to be considered**

- The provided above is only typical documents to be submitted for GMP Compliance Inspections. Actual required documents may vary by product(s), manufacturing process(es), and contents of partial change. Please follow the inquiries from inspectors.
- If major changes are made to the submitted information in the course of NDA review, contact the Office of Compliance and Standards of the PMDA immediately.
- In principal, the submitted document should be in Japanese. If the major part of documents written by foreign language, at least overview must be submitted in Japanese.
- In principal, documents should be submitted by marketing authorization holder. However, documents may be submitted directly from the manufacturer to the PMDA depend on the relationship between marketing authorization holder and manufacturer.
- In the case of document inspection, if a inspection was conducted by the PMDA over the past two years, and if similar documents were submitted in the past inspection, it is acceptable to submit only changes from the previous submission. In that case, please indicate the date of previous submission.
- If a GMP Compliance Certificate (original only) ,issued by the authorities covered by the MRA or MOU, is attached, the submission of 2 through 5 and 9 through 12 (2 through 11 in case of periodical inspection) of the above listed documents are not required.
“MRA” stands for “Mutual Recognition Agreement”. The MRA countries are as follows (Only referring to processes for pharmaceuticals as preparations excluding sterile drugs and biopharmaceuticals).
Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxemburg, Netherlands, Austria, Portugal, Finland, Sweden, and UK
“MOU” here stands for “Memorandum of Understanding”. The MOU countries are as follows.
Germany, Sweden, Switzerland, and Australia
- If a Site Master File (Japanese translation of overview shall be attached) according to the form specified in PIC/S is submitted, that include the information on 2 through 5 and 9 through 12 (2 through 5, and 8 through 11 in case of periodical inspection) , the submission of these documents are not required. “PIC/S” stands for “Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme”. For details, please refer to <http://www.picscheme.org>.