

Tentative translation (as of Oct. 30, 2020)

**GMP Compliance Inspection concerning Drugs and Quasi-drugs of Foreign
Manufacturers
(Overview Guidance for Foreign Drugs Manufacturers)**

Oct. 30, 2020

Office of Manufacturing Quality for Drugs
Pharmaceuticals and Medical Devices Agency

**GMP Compliance Inspection concerning Drugs and Quasi-drugs (hereinafter “Drugs”) of
Foreign Manufacturers
(Overview Guidance for Foreign Drugs Manufacturers)**

(1) Introduction

GMP Compliance Inspection concerning Drugs of Foreign Manufacturers is an inspection on the compliance of manufacturing control and quality control methods at the relevant manufacturing sites with Japanese GMP (“Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs”, Ordinance of Ministry of Health, Labour and Welfare, No. 179, 2004), conducted by the Pharmaceuticals and Medical Devices Agency (hereinafter “PMDA”). GMP compliance is a requirement for marketing approval.

(2) Types of GMP Compliance Inspection

There are two types of GMP Compliance Inspection :

- Inspections that are conducted upon the application for new marketing approval or the application for partial changes of approved information
- Inspections that are conducted every five years following the obtainment of marketing approval

(3) Manufacturing sites subject to the Inspection

1. In the cases of ‘Inspections that are conducted upon the application for new marketing approval or the application for partial changes of approved information’

Manufacturing sites and external testing laboratories listed in the application for new marketing approval or partial change approval, and whose GMP Compliance Inspection was determined to be required in the review are subject to the inspection.

Note that the following manufacturing sites do not need GMP Compliance Inspection:

- a. Manufacturing sites that meet requirements, that is, in the case where GMP compliance has already been confirmed for the same product based on the application of GMP compliance inspection, and the applicant submits “a copy of the GMP compliance notification” and “a copy of a document by which identity of the product can be confirmed” to the responsible authority of approval for GMP compliance application.
- b. Manufacturing sites for APIs of over-the-counter drugs (excluding products containing new drug substance)

2. In the cases of ‘Inspections that are conducted every five years following the obtainment of marketing approval’

All manufacturing sites, including manufacturing sites for formulation, APIs, intermediate API, and packaging/ labeling/ Storage, described in the application of marketing approval are

subject to the GMP compliance inspection.

Note that the following manufactures do not need GMP Compliance Inspection:

- a. Manufacturing sites that meet requirements, that is, in the case where GMP compliance has already been confirmed for the same product based on the application of GMP compliance inspection, and the applicant submits “a copy of the GMP compliance notification” and “a copy of a document by which identity of the product can be confirmed” to the responsible authority of approval for GMP compliance application.
- b. Manufacturing sites for APIs of over-the-counter drugs (containing products containing new drug substance).
- c. External testing laboratories

(4) Flow of GMP Compliance Inspection for the foreign manufactures

1. Application for GMP Compliance inspection by foreign manufacturers shall be applied by the marketing authorization holder who apply for the application of marketing authorization, those who have obtained exceptional approval for foreign manufacturers, or those who intend to obtain exceptional approval for foreign manufacturers. Manufactures who apply for exceptional approval for foreign manufacturers must appoint marketing authorization holders.

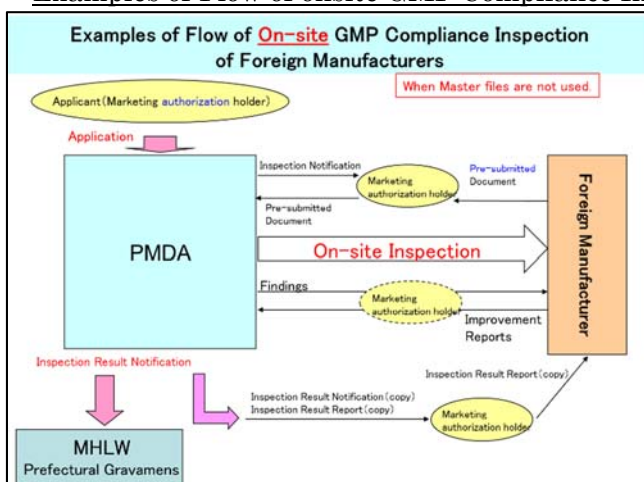
2. In principle, GMP Compliance Inspection shall be conducted by onsite inspection by the PMDA. However, PMDA may make a decision to conduct inspection on documents only (hereinafter desk-top inspection), considering products risk, corresponding country's GMP standard and its operation, and status of GMP conformity based on the pre-submitted documents.

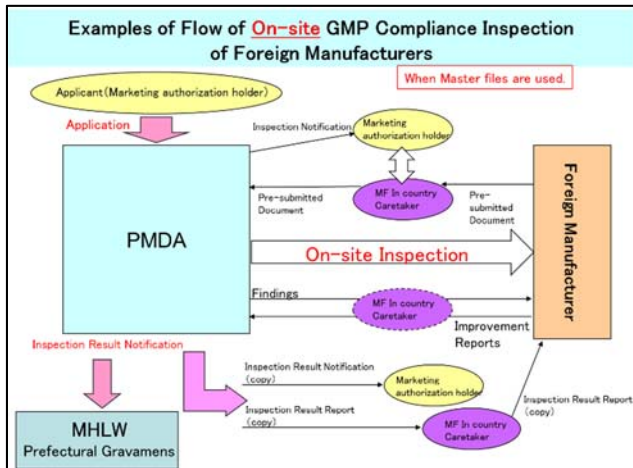
3. The PMDA shall report the inspection results to the Ministry of Health, Labour and Welfare, using the form of “GMP Compliance Inspection Result Notification”. The PMDA shall issue a copy of the GMP Compliance Inspection Result Notification to the marketing approval holder that applied for the inspection, and a copy of the “GMP Compliance Inspection Result Report to the foreign manufacturer on which the onsite inspection was conducted. In the case of desk-top inspection, a copy of the GMP Compliance Inspection Result Report is not issued.

4. Examples of Flow of GMP Compliance Inspection are shown below:

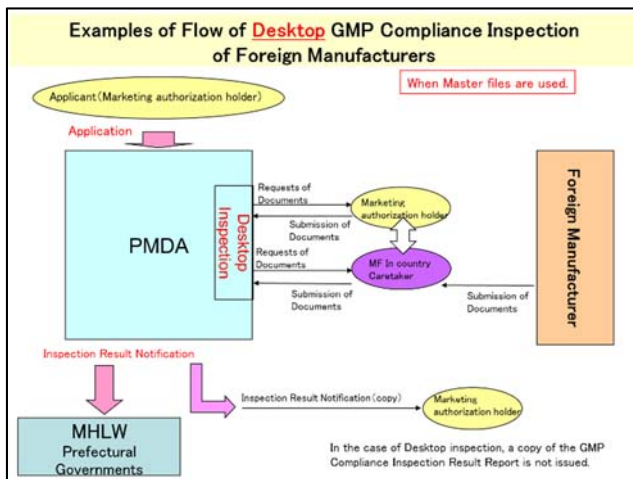
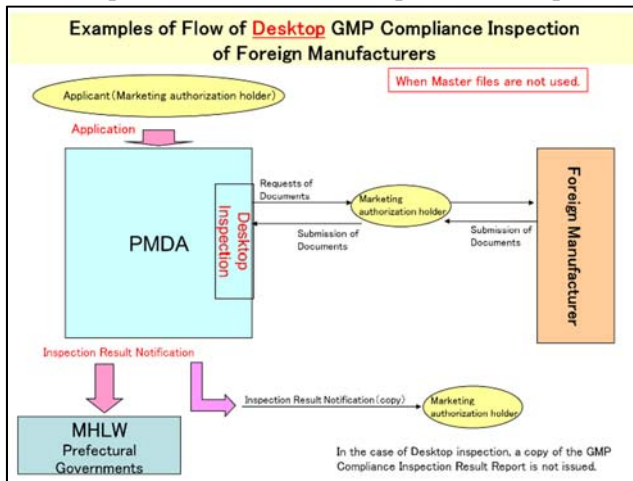
*Note that the flow differs depending on whether Master files are used or not.

• Examples of Flow of onsite GMP Compliance Inspection





• Examples of Flow of desk-top GMP Compliance Inspection



(5) Documents to be attached to the Application of Inspection

Following the application for GMP Compliance Inspection, the applicant shall submit “Documents pertaining to manufacturing control and quality control of product(s)”

concerning the compliance inspection” and “Documents pertaining to manufacturing control and quality control of manufacturing sites concerning the compliance inspection”, at request of the PMDA.

Even applications and attached documents are concerning foreign manufacturing sites, it should be prepared in the Japanese language. If the attachment includes a large volume of documents written in a foreign language, it is acceptable to prepare only an overview of such documents in Japanese.

1. In the cases of ‘Inspections that are conducted at the point of application for new marketing approval or of application for partial changes of approved information’

a. Copies of Compliance Inspection Result Notifications and/or Inspection Report of GMP inspections conducted within two years from the date of the application for the compliance inspection (including those conducted by other authorized compliance inspectorates etc.)

b. In the case of foreign manufacturing sites, as for manufacturing sites in countries with which MRA is concluded, a copy of Compliance Certificate or GMP Inspection Report of that country based on the MRA, as for manufacturing sites in countries with which MOU is exchanged, a copy of Certificate or GMP Inspection Report of that country based on the MOU, and as for manufacturing sites in other countries, WHO Certificate, or Compliance Certificate issued by the country’s relevant authority.

c. Copy of marketing approval application for the applied product(s)

d. Other documents required by the authorized compliance inspectorates(*)

* For the “Other documents required by the authorized compliance inspectorates”, refer to the administrative notice “Documents required by PMDA for the application of GMP compliance inspection” issued by Office of Manufacturing Quality for Drugs, PMDA, June 17, 2019.

2. In the cases of ‘Inspections that are conducted every five years following the obtainment of marketing approval’

a. Copies of Compliance Inspection Result Notifications and/or Inspection Report of GMP inspections conducted within two years from the date of application for the compliance inspection (including those conducted by other authorized compliance inspectorates etc.)

b. In the case of foreign manufacturing sites, as for manufacturing sites in countries with which MRA is concluded, a copy of Compliance Certificate or GMP Inspection Report of that country based on the MRA, as for manufacturing sites in countries with which MOU is exchanged, a copy of Certificate or GMP Inspection Report of that country based on the MOU, and as for manufacturing sites in other countries, WHO Certificate, or Compliance Certificate issued by the country’s relevant authority.

c. Copy of marketing approval

d. Copies of partial change approvals over the past five years

e. Copies of notification of minor changes over the past five years

f. If applications for two or more products are made simultaneously, the applicant shall categorize applications by worksite, workroom, area, equipment etc., select representative products for each category, and submit documents that show reasons for these categorization and selection. (If representative products are selected in line with these rules, documents indicated in a., b. and c. may be limited to those concerning the representative products.)

g. Whether there was product recall concerning the applied product(s) over the past five years (If there was, overview of the recall)

h. Statement (prepared by the applicant)

i. Other documents required by the authorized compliance inspectorates(*)

*Other documents required by the authorized compliance inspectorates' are referred to the Office Memorandum "Documents required by PMDA for the Application of GMP Compliance Inspection" by Office of Compliance and Standards, June 17, 2019.

(6) Inspection Fee

Inspection fee shall be covered by the marketing authorization holder that applies for or obtains

(7) Reference Information

Scope of Drugs subject to GMP Compliance Inspection

Drugs and APIs (the products shows below a. ~ g. and APIs for over-the-counter drugs do not require GMP compliance Inspection.)

a. Drugs that are intended to be used for the extermination or prevention of rats, flies, mosquitoes, fleas and other similar creatures, which are not used directly on human bodies.

b. Drugs that are intended to be used mainly for disinfection and sanitization, which are not used directly on human bodies.

c. Drugs that are, APIs, intended to be mainly used for the manufacturing of drugs indicated in a. or b.

d. Drugs that are manufactured at manufacturing sites that only conduct processes of powdering and/or cutting crude drugs.

e. Drugs that are manufactured and/or marketed by pharmacies.

f. Of gases used for medical purposes, 1) nitrous oxide, 2) oxygen, 3) nitrogen, 4) carbon dioxide, 5) compound of nitrous oxide and oxygen.

g. In addition to a. through f., drugs included in the Japanese Pharmacopoeia, which are designated by the Minister of Health, Labour and Welfare as causing mild action to human bodies (110 items including gum arabic).

(Reference regulatory provisions (excerpts))

* Article 14, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter "the Act")(Approval of marketing of drugs)
A person intending to market a drug shall, for each product, obtain marketing approval of the Minister of Health, Labour and Welfare.

* Article 14, Paragraph 6 of the Act

A person who wishes to obtain the approval or who has been granted the approval specified in Paragraph 1 for a drug shall be subjected to a document inspection or an onsite inspection by the Minister to determine whether the method of manufacturing control or quality control in the manufacturing plant complies with the specifications specified by MHLW ordinance before approval and during a period specified by cabinet order not exceeding 3 years after the approval was granted.

* Article 14-2, Paragraph 1 of the Act (Inspections by the PMDA)

The Minister of Health, Labour and Welfare may have the PMDA conduct the inspection of drugs as specified in Paragraph 1 and Paragraph 6 of the previous Article.

* Article 21 of the Act Enforcement Ordinance(Period of Inspection for Standards for Methods of Manufacturing Control or Quality Control)

The period specified by the government ordinance pursuant to the provisions of Article

14, Paragraph 6 of the Law shall be five (5) years.

*Article 50, Paragraph 1 of the Act Enforcement Regulations(Application for GMP Compliance Inspection)

Application for the inspection specified in Article 14, Paragraph 6 of the Act shall be made by submitting an application using Form No. 25 to the Minister of Health, Labour and Welfare.

* Article 50, Paragraph 2 of the Act Enforcement Regulations

The following documents shall be attached to the application specified in the preceding paragraph.

1 Documents on the manufacturing control and quality control of the product subject to the GMP Compliance Inspection

2 Documents on the manufacturing control and quality control of the manufacturing site subject to the GMP Compliance Inspection

* Article 50, Paragraph 3 of the Act Enforcement Regulations

In the application of the provisions of Paragraph 1 to cases where the Minister has decided to have the PMDA conduct the GMP Compliance Inspection pursuant to the provisions of Article 14-2, Paragraph 1 of the Act, in the same paragraph “to the Minister” shall read “to the PMDA”.

* Article 51 of the Act Enforcement Regulations (Notification of GMP Compliance Inspection Results)

Notification of the results of the GMP Compliance Inspection from authorized compliance to the marketing approval holder licensing authorities or to the approval authorities shall be made by submitting a notification using Form No. 26.

(Sources)

- “Enactment, Revision or Repeal of Ministerial Ordinances and Notices related to Standards for Manufacturing Control(GMP/QMS) of Drugs, Medical Devices etc., following the Enforcement of Laws etc. for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Law”, PFSB/CND Notification No. 0330001 by the Manager of the Compliance and Narcotic Division, PFSB, MHLW, March 30, 2005(revision PFSB/CND Notification No. 0830-1, August 30, 2013)
- “Handling of Standards for Manufacturing Control(GMP/QMS) of Drugs and Quasi Drugs”, PFSB/CND Notification No. 0830-1 by the Manager of the Compliance and Narcotic Division, August 30, 2013
- “Documents required by PMDA for the Application of GMP Compliance Inspection” by Office of Compliance and Standards, PMDA, Feb 2, 2019(revision June 17, 2019)
- “Handling of Application for GMP Compliance Inspection”, PFSB/ELD Notification No 0702-1 and PFSB/CND Notification No, 0702-1 from the Managers of the Evaluation and Licensing Division and the Compliance and Narcotic Division, PFSB, MHLW, July 2, 2015