Tentative Translation (Not Literal Rendering)

Notification No. 0329-9
Dated on March 29, 2024

To: Directors of the Prefectural Health Departments/Bureaus

From: Director of the Compliance and Narcotics Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Notification on Enactment of the GMP Investigation Guide (2024)

Regarding GMP investigations, a notification No.0317-5 from director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated on March 17, 2022, titled "Notification on the Enactment of the GMP Investigation Guide (2022)" (hereinafter referred to as the "former notification") was issued to show the investigation systems, basis of the operations and operational procedures in common for all the GMP inspectorate agencies, in the purpose of suitably addressing cases of manufacturers' non-compliance with the Ministerial Order on the Standard of Manufacturing Control and Quality Control for Pharmaceuticals and Quasi-Pharmaceuticals (Order of the Ministry of Health, Labour and Welfare No. 179 of 2004), as well as ensuring their standardized operations related to GMP in Japan.

This time, since several cases of such non-compliance have still been caused by some manufacturers, in order to further enhance the GMP investigation systems, the renewed GMP Investigation Guide is enacted as attached.

Therefore, you are kindly requested to conduct GMP investigations suitably, taking note of the following descriptions. Upon the implementation of this notification, the former notification is abolished.

Descriptions

1. In the purpose of further enhancement for GMP investigation system, this revision of the GMP investigation guide has been made. Based upon the GMP investigation guide (2024) enacted as by this notification (hereinafter referred to as "this Guide"), each GMP inspectorate agency is expected to build its GMP investigation system according to the assumed workload

including information gathering/compiling/analysis/sharing, which is newly introduced. Therefore, it is requested for each GMP inspectorate agency to improve its conducting system for GMP investigations, which covers securing adequate number of the personnel suitably qualified, considering to increase the number of staff as necessary, implementing training for its personnel, ensuring the official accredited laboratories.

2. Each GMP inspectorate agency is to establish its Quality Manual, in line with essential contents of Quality Manual as shown in Part III of this Guide.

3. From April 1, 2024, each GMP inspectorate agency is to conduct GMP investigations in accordance with this Guide.

Attachment

GMP Investigation Guide (2024)

Contents

Part I. Introduction

This Guide shows matters related to the Quality Management Oversight System in each GMP inspectorate agency, so that each prefectural GMP inspectorate agency and the Pharmaceuticals and Medical Devices Agency (hereinafter shown as "PMDA") can suitably conduct conformity assessments with the Ministerial Order on the Standard of Manufacturing Control and Quality Control for Pharmaceuticals and Quasi-Pharmaceuticals (Order of the Ministry of Health, Labour and Welfare No. 179 of 2004; hereinafter referred to as the "Ministerial Order on GMP"), which are provided in Article 14, paragraph (7) (includes where applied mutatis mutandis as provided in paragraph (15) of the same Article), Article 14, paragraph (9), Article 1-2, paragraph (2), Article 14-7-2, paragraph (3) and Article 80, paragraph (1) of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 145 of 1960; hereinafter referred to as the "PMD Act"), as well as on-site inspections for confirming compliance status with the Ministerial Order on GMP (refers to the inspections as provided in Article 69, paragraphs (1) and (6), and Article 69-2, paragraph (1) of the PMD Act (hereinafter these inspections are referred to as "Article 69 inspections") and the on-site inspections as provided in Article 75-2-2, paragraph (1), items (ii) and (iii), Article 75-2-2, paragraph (4), Article 75-4, paragraph (1), items (i) and (ii), and Article 75-2-2, paragraph (4) applied mutatis mutandis as provided in and Article 75-4, paragraph (3) of the PMD Act) (hereinafter these conformity assessments and on-site inspections are collectively referred to as "GMP investigations").

This Guide consists of commentaries on types of GMP investigations and their legal bases, essential contents of Quality Manual in common among GMP inspectorate agencies, and steps for conducting GMP investigations.

The term "GMP inspectorate agency" as used in this Guide refers to a department/bureau in charge of conducting GMP investigations, in PMDA or each prefectural government. With regard to other terms as used in this Guide, see the "Notification on Pharmaceutical Quality System[i]" (notification dated on February 19, 2010, collaboratively issued from director of the Evaluation and Licensing Division and director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

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[i] **Translation annotation**; notification for implementing *ICH Q10 guideline "Pharmaceutical Quality System"*

Part. II Types of GMP investigations, and their legal basis

1. GMP investigations are categorised into conformity assessment/review (those for which the marketing license holder/manufacturer is to make an application, with regard to manufacture of products concerned with a marketing authorization (includes authorization for partial change of any matter prescribed in an existing marketing authorization), issuance of a confirmation certificate of conformity, evaluation of a Post-Authorization Change Management Protocol (PACMP), or certification of pharmaceuticals/quasi-pharmaceuticals for export), and on-site inspections.

2. Conformity assessment/review is conducted to assess/review whether methods of manufacturing control and quality control at a manufacturing site is complying with the Ministerial Order on GMP or not; which are further categorized into pre-authorization conformity assessment, post-authorization conformity assessment, conformity assessment by types of manufacturing activities, conformity review with regard to post-authorization change management protocol (PACMP), and conformity assessment for certifying pharmaceuticals/quasi-pharmaceuticals for export. Each of those categories consists of investigations as follows, based upon the articles/paragraphs of its legal basis;

(i) Pre-authorization conformity assessment:
(a) Conformity assessment of products concerned with an application for marketing authorization (as provided in Article 14, paragraph (7) of the PMD Act)
(b) Conformity assessment concerned with an application of authorization for partial change of any matter prescribed in an existing marketing authorization (as provided in Article 14, paragraph (7) applied mutatis mutandis as provided in Article 14, paragraph (15) of the PMD Act)
(c) Conformity assessment concerned with an application for exceptional authorization of a product manufactured in a foreign country (as provided in Article 14, paragraph (7) applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the PMD Act)
(d) Conformity assessment concerned with an application of authorization for partial change of any matter prescribed in an existing exceptional authorization of a product manufactured in a foreign country (as provided in Article 14, paragraph (7) applied mutatis mutandis as provided in Article 14, paragraph (15), applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the PMD Act)

(ii) Post-authorization conformity assessment:
(a) Routine conformity assessment concerned with an existing marketing authorization (as provided in Article 14, paragraph (7) of the PMD Act)
(b) For-case conformity assessment concerned with a product which has been authorized for marketing (as provided in Article 14, paragraph (9) of the PMD Act)
(c) Routine conformity assessment concerned with an existing exceptional authorization of a product manufactured in a foreign country (as provided in Article 14, paragraph (7) applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the PMD Act)
(d) For-case conformity assessment concerned with a product manufactured in a foreign country, which has an exceptional authorization (as provided in Article 14, paragraph (9) applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the PMD Act)

(iii) Conformity assessment by types of manufacturing activities (as provided in Article 14-2, paragraph (2) of the PMD Act)

(iv) Conformity review with regard to post-authorization change management protocol (PACMP) (as provided in Article 14-7-2, paragraph (3) of the PMD Act)

(v) Conformity assessment for certifying pharmaceuticals/quasi-pharmaceuticals for export (as provided in Article 80, paragraph (1) of the PMD Act)

3. On-site inspections are categorized as follows, according to their objectives, etc. thereof. Since on-site inspections also include those for confirming compliance status with the Ministerial Order on GMP that are implemented together with other investigations triggered by any whistleblowing, on-site inspections at manufacturing sites with high intrinsic risk should be conducted without informing beforehand (hereinafter referred to as "on-site inspections without announce"). Article 69 inspections are to be performed by pharmaceutical inspectors, or PMDA officials who have been qualified in accordance with the Cabinet Order as provided in Article 69-2, paragraph (4) of the PMD Act.

(i) Regular surveillance:
Those for surveillance/supervision of compliance with provisions in the Ministerial Order on GMP, in regular basis.

(ii) For-case inspections:

Those conducted in the case where ad-hoc inspection of compliance status is needed due to unforeseen problems or other reasons, for performing the following confirmations;

(a) Confirmations into details of rectification (other than those to be implemented as a conformity assessment/review),

(b) Confirmations into compliance status with the Ministerial Order on GMP at the manufacturing sites concerned with those items (products) which have been recalled, rejected by the National Lot Examination, or complained, etc., and/or

(c) Others.

Part III. Quality Manual of GMP inspectorate agencies

Each GMP inspectorate agency is to establish and maintain its Quality Manual that covers the following contents:

1. Objectives

Quality Manual is to prescribe necessary matters for the GMP inspectorate agency in order to establish and effectively implement a operating system for GMP investigations on pharmaceuticals/quasi-pharmaceuticals (hereinafter such system is referred to as "Quality Management Oversight System"), therefore it aims that the GMP inspectorate agency suitably and timely conduct GMP investigations, and sustainably improve quality of those investigations.

2. Scope

Quality Manual applies to operations related to GMP investigations on pharmaceuticals/quasi-pharmaceuticals, that the GMP inspectorate agency conducts.

3. Standards of reference

The following standards and relevant documents are reference for Quality Manual;

PIC/S Quality system requirements for pharmaceutical inspectorate,
WHO Technical report series, No. 902 Annex 8, and
ISO 9001: 2015

4. Responsibility of head of the GMP inspectorate agency

4.1. Commitments by head of the GMP inspectorate agency

In order to conduct suitable GMP investigations, head of the GMP

inspectorate agency is to ensure its Quality Management Oversight System functioning effectively and communicated throughout the organization.

4.2. Quality policy of the GMP inspectorate agency

Head of the GMP inspectorate agency is to ensure the following matters within its quality policy;

- With aiming for distribution of quality pharmaceuticals, based upon its absolute mission to protect lives and health of people, quality policy of the GMP inspectorate agency is to make its operation be executed with timely decision making and highly transparency.
- Quality policy above mentioned is communicated to all GMP inspectors of the GMP inspectorate agency, and understood by them.
- Sustainable effectiveness of the quality policy above mentioned is reviewed regularly.

4.3. Establishment of Quality Management Oversight System

According to its Quality Manual, head of the GMP inspectorate agency is to establish, document, implement, and maintain its Quality Management Oversight System in the agency, which covers the following matters;

- to set quality objectives that enable to assess the matters prescribed in its Quality Manual, and to define procedures for implementing management review, and
- for the purpose of sustainable improvement for its GMP investigation operations, to define procedures for examining issues on Quality Management Oversight System, which are identified by internal audits and/or management review, then taking corrective/preventive actions.

5. Management system of the GMP inspectorate agency

(1) Organization structure of the GMP inspectorate agency, and qualifications and operations of its personnel must be assuring fairness of GMP investigations, etc.

(2) GMP inspectors must not be affected by any commercial, financial, or other pressure which may compromise their investigations. Provisions on declaration, etc. for conflict of interest are to be set within written procedures at each GMP inspectorate agency.

(3) Policies for carrying out processes of GMP investigations to be distinguished from other consultation for manufacturers, etc. must be adopted by the GMP inspectorate agency.

6. Organization

(1) Organization involved with GMP investigation operations, and duties of the responsible officials is to be as shown in Chart I. In line with Chart I, the responsible officials are to be allocated, and the established organization is to be maintained by the GMP inspectorate agency.

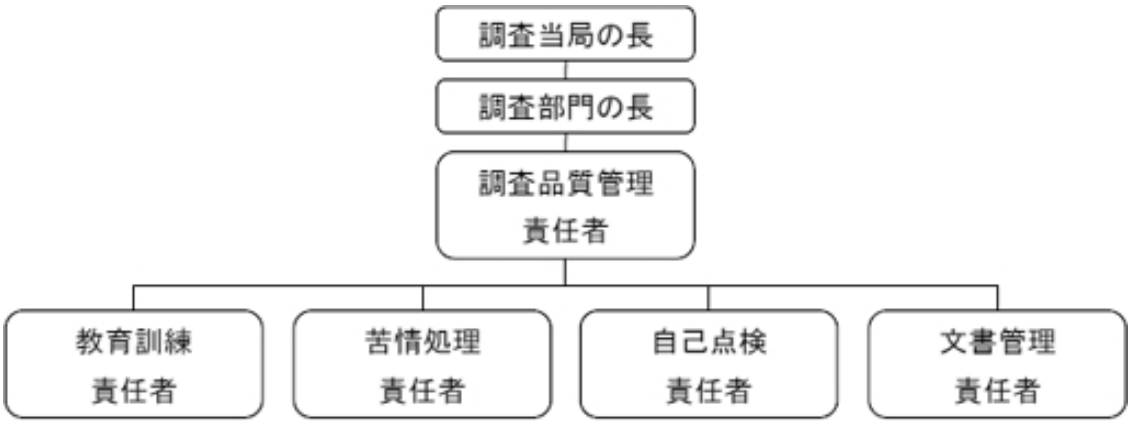

Chart I: Organization involved with GMP investigation operations, and duties of the responsible officials

Quality manager of GMP investigations is to be assigned as the responsible official for GMP investigation operations in the investigation section. In addition, under such quality manager, the following responsible officials are to be assigned:

(i) Responsible official for education/training,
(ii) Responsible official for complaint management,
(iii) Responsible official for internal audits, and
(iv) Responsible official for document management.

(2) In order to maintain Quality Management Oversight System in the GMP inspectorate agency, and for mutual communication with other GMP inspectorate agencies, the constitution which consists of representatives from Ministry of Health, Labour and Welfare (hereinafter shown as "MHLW"), PMDA and prefectural GMP inspectorate agencies (hereinafter such constitution is referred to as the "GMP inspectorate agencies conference") is to perform central functions to facilitate close cooperation through regular meetings, information sharing, etc. (see Chart II). Such mutual communication covers implementation of peer reviews between GMP inspectorate agencies.

- 47 prefectural GMP inspectorate agencies are grouped into 7 regional cluster, in order to establish cooperation scheme within each regional group.
- The GMP inspectorate agencies conference which consists of representatives from each regional group, PMDA and MHLW is to be

organized.

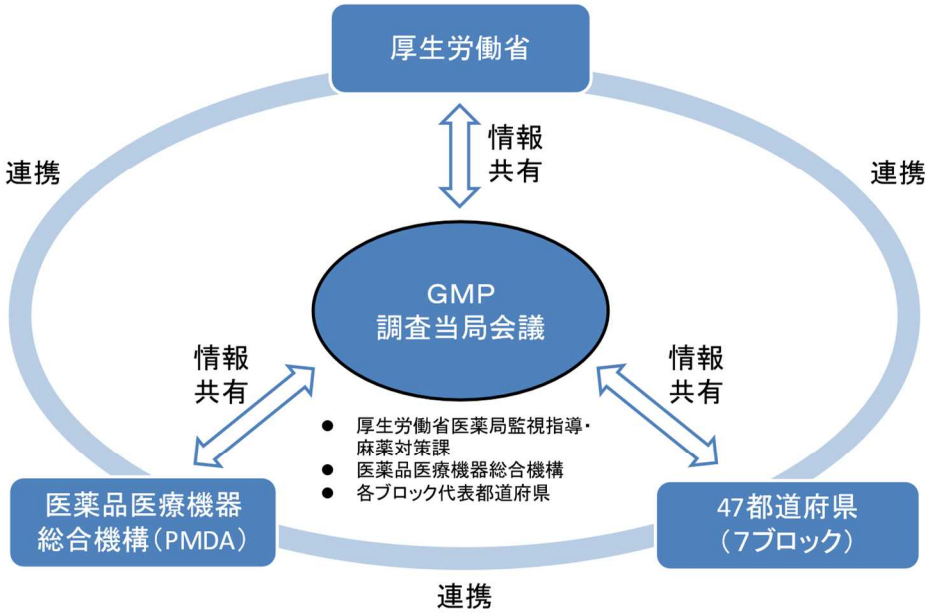

Chart II: Maintaining of Quality Management Oversight System in the GMP inspectorate agency, and mutual communication with other GMP inspectorate agencies

Functions of the GMP inspectorate agencies conference

(i) Harmonization of Quality Management Oversight System among GMP inspectorate agencies (e.g., work for revision of written procedures, implementation of internal audits, etc.),

(ii) Sustainable revision of guidelines on GMP,

(iii) Planning of training/education programme, sharing of materials for training/education,

(iv) Acquisition of information on international harmonization, and information sharing among GMP inspectorate agencies,

(v) Convening meetings for improving quality of GMP investigations, and

(vi) Consultation on matters of guidance, which can be presented by a GMP inspectorate agency or pharmaceutical industries, and publication thereof (it should be paid attention for confidentiality)

(3) Investigation section of the GMP inspectorate agency has operational partnership with other organizations such as follows. Procedures for close cooperation with these organizations should be established by the GMP inspectorate agency.

i) MHLW (relevant divisions in the Pharmaceutical Safety Bureau: the Compliance and Narcotics Division, the Pharmaceutical Evaluation and Licensing Division, and the Pharmaceutical Safety Division),
ii) Each section of the GMP inspectorate agencies (investigation section, evaluation/licensing section, safety section, and official laboratory),
iii) Other GMP inspectorate agencies,
iv) Foreign competent authorities for pharmaceutical GMP, such as partner authorities of Mutual Recognition Agreement (hereinafter shown as "MRA") or Memorandum of Understanding (hereinafter shown as "MOU") regarding pharmaceutical GMP, and other PIC/S participating authorities.

7. Personnel

7.1. Securing resources

In order to implement and maintain Quality Management Oversight System, and continually improve effectiveness thereof, adequate and suitable resources should be secured in the GMP inspectorate agency. In addition, it must be ensured that all GMP inspectors belonging to the GMP inspectorate agency are suitably educated/trained, and capable of performing their operations.

7.2. Qualification for GMP inspectors

Officials who are engaged in GMP investigations must satisfy qualifications as shown in Annex 1. At least one official who satisfies the qualifications for chief inspector or senior inspector as shown in Annex 1 must participate in each of GMP investigations.

7.3. Education/training

For the purpose of qualifying GMP inspectors and implementing suitable GMP investigations, an education/training system should be established in the GMP inspectorate agency, and records of the education/training and qualification should be retained. Such education/training system covers systematic implementation of education/training and periodic reviews for effectiveness thereof (hereinafter referred to as "education/training programme"). It is preferable that officials conducting education/training such as on-the-job training should be qualified as chief inspector or senior inspector.

8. Document Management

8.1. Maintenance of document management system

Document management system as a set of procedures to maintain and

manage all the documents regarding GMP investigations and Quality Management Oversight System should be established by the GMP inspectorate agency. Such document management system covers version control of documents, in order that GMP inspectors can always refer to the current version.

8.2. Documentation system in the GMP inspectorate agency

Necessary documents/records are put in place, based upon documentation system as shown in Chart III.

Chart III: Documentation system

8.3. List of the written procedures

The following written procedures are prepared;

- Procedures for management reviews,
- Procedures for concluding GMP compliance/non-compliance, and for notification on result of a GMP investigation,
- Procedures for complaint management,
- Procedures for internal audits,
- Procedures for education/training,
- Procedures for management of documents/records,
- Procedures for confiscation/acquisition of samples for regulatory examination (testing/analysis), and for cooperation with the official accredited laboratory,
- Procedures for cooperation with surveillance/supervision section and other sections related to GMP investigation operations,
- Procedures for declaration for conflict of interest, and
- Other procedures necessary for performing GMP investigation operations suitably and timely.

8.4. Retention of documents/records

Documents/records are retained for at least the following duration from the date of documentation (in the case of written procedures, etc., from

the date of discontinuance thereof).

a. Thirty-five years, for documents/records regarding GMP investigations concerned with specified biological origin products, or items (products) of biological origin products that are produced from origin materials of human blood,
b. Fifteen years, for documents/records regarding GMP investigations concerned with biological origin products or cell/tissue-based pharmaceuticals,
c. Ten years, for documents/records regarding GMP investigations concerned with items (products) other than biological origin products and cell/tissue-based pharmaceuticals,
d. Five years, notwithstanding a. to c. shown above, for documents/records regarding Quality Management Oversight System, such as education/training, internal audits, etc.

9. Conducting of GMP investigations

9.1. Frequency of GMP investigations

GMP inspectorate agencies are to conduct GMP investigations for each of manufacturing sites in every one to three year, based upon assessment of the intrinsic risks. GMP investigations are to be implemented on-site in principle, however, document-based method may, based upon assessment of the intrinsic risks, also be utilized. In the case of manufacturing sites with high intrinsic risk, on-site inspections without announce are to be conducted once a year, in principle.

9.2. Planning for conducting of GMP investigations

Annual plan for conducting of GMP investigations that covers Article 69 inspection should be adopted every beginning of fiscal year, taking into consideration of previous investigation history, etc. of each manufacturing site, by the GMP inspectorate agency. Upon conducting individual GMP investigations, the GMP inspectorate agency is on its own initiative to collect gather information on the manufacturer[ii]/foreign manufacturer[iii] subjected to the GMP investigation in order to implement the GMP investigation systematically.

[ii] **Translation annotation**; "*Manufacturer*" as used in this Guide refers to manufacturer in Japan that has been licensed as provided in Article 13 of the PMD Act, or registered as provided in Article 13-2-2 of the same Act.

[iii] **Translation annotation**; "*Foreign manufacturer*" as used in this Guide refers to foreign manufacturer that has been accredited as provided in Article 13-3 of the PMD Act, or registered as provided in Article 13-3-2 of the same Act.

9.3. Cooperation on GMP investigations

GMP investigations are to be conducted in cooperation with other GMP inspectorate agencies, as necessary. MHLW is to select manufacturing sites for joint inspection by PMDA and the prefectural GMP inspectorate agency, based upon relative assessment of the intrinsic risks at each manufacturing site in Japan, also taking into consideration of requests from prefectural GMP inspectorate agencies, and make a proposal on plan/schedule for such joint inspection, as necessary.

9.4. Management on outcome of GMP investigations

Records of the conducted GMP investigations should be suitably maintained and managed, and periodically reviewed (with statistical assessment, as necessary) in the GMP inspectorate agency. Results of such periodic review are to be matters of reporting in management review in the GMP inspectorate agency, and to be submitted to MHLW (the Compliance and Narcotics Division, Pharmaceutical Safety Bureau).

10. Internal Audits

Internal audits on operations of the GMP inspectorate agency must, in order to review whether requirements for Quality Management Oversight System are fulfilled, be periodically implemented and documented. Outcome of the internal audits, as well as the subsequent corrective/preventive actions, are to be also matters of reporting in management review in the GMP inspectorate agency.

11. Complaint management

Procedures for managing any complaints against operations of the GMP inspectorate agency, or the execution by its officials or organization are to be established and maintained. Those procedures are to prescribe processes for taking corrective/preventive actions based upon outcome of the investigation for such complaint, as well as for implementing the subsequent verification. Such corrective/preventive actions are to be also matters of reporting in management review in the GMP inspectorate agency.

12. Administrative actions, such as revocation of manufacturer's license/registration, withdrawal of product marketing authorization, etc.

In the case where a GMP investigation has been concluded as GMP compliance, such conclusion is to be shared with relevant prefectural authority competent for the marketing license holder concerned, as well

as relevant authority competent for licensing/registration of the manufacturing site in question, by the GMP inspectorate agency. Such relevant prefectural authority competent for the marketing license holder concerned is, upon receiving the information, to ensure to address in corporation with licensing/registration authorities for the manufacturing site and authority competent for marketing authorizations of the products concerned. As necessary for addressing, the licensing/registration authority for the manufacturing site in question is to take prejudicial disposition (e.g. order for changing the manufacturing supervisor, order for rectifying the defective methods manufacturing control, etc., order for rectifying the defective premises/equipment) and/or other administrative actions (e.g. order for reporting to the authority).

Where found any non-compliance with the Regulation on Premises/Equipment; as necessary, relevant licensing/registration/ accreditation authority is to take prejudicial disposition (e.g. revocation/suspend of the manufacturer's license/registration, order for rectifying the defective premises/equipment) and/or other administrative actions (e.g. order for reporting to the authority) in the case of a manufacturer in Japan, or administrative disposition (e.g. request for rectifying the defective premises/equipment, revocation of accreditation) in the case of a foreign manufacturer.

13. Management of information on suspected quality defects, and rapid alert system

Upon obtaining information on any products suspected quality defects, or where such products are identified during a GMP investigation, the GMP inspectorate agency is to take suitable actions, and share such information with relevant prefectural authority competent for the marketing license holder concerned. In the case where any critical deficiency is identified during a GMP investigation, MHLW (the Compliance and Narcotics Division, Pharmaceutical Safety Bureau) is also to be informed.

In the case where it is deemed recalls of relevant products are needed, the prefectural authority competent for the marketing license holder concerned is to instruct such company to conduct product recalls, etc. suitably in accordance with the "Notification on product recalls of pharmaceuticals/medical devices, etc." (notification dated on November 21, 2014, from Director General of the Pharmaceutical and Food Safety Bureau, MHLW; hereinafter referred to as the "Notification on Product Recalls"), and promptly share such information with MHLW (the Compliance and Narcotics Division, Pharmaceutical Safety Bureau). In accordance with the Notification on Product Recalls, MHLW is to issue a rapid alert notification for foreign competent authorities such as PIC/S participating authorities, as necessary.

14. Cooperation with official accredited laboratories

Regulatory testing/analysis of pharmaceutical samples is to be performed at quality control laboratory accredited by the GMP inspectorate agency (excepting PMDA; the same applies hereinafter in this Section), as official laboratory upon satisfying the qualifications as shown in Annex 2. The GMP inspectorate agency is to conclude a mutual agreement with such official accredited laboratory, with regard to handling of testing/analytical samples and test results, retention of relevant documents/records, etc.

In the case where it will be difficult for the GMP inspectorate agency to conduct regulatory testing/analysis at its official accredited laboratory, and it is deemed to be necessary to perform such regulatory testing/analysis essential for implementing administrative measures, the GMP inspectorate agency may contract such regulatory testing/analysis to the national quality control laboratory (refers to the quality control laboratory accredited by MHLW (the Compliance and Narcotics Division, Pharmaceutical Safety Bureau)), thorough MHLW according to agreement between MHLW and the national quality control laboratory. PMDA performs assessment for accreditation of the national quality control laboratory, based upon a request by MHLW (the Compliance and Narcotics Division, Pharmaceutical Safety Bureau).

Part IV. Steps for conducting GMP investigations

1. Objectives

In the purpose of ensuring execution of GMP investigations in more harmonized manner with regard to the Ministerial Order on GMP, in addition to the operational approaches, etc., as shown in the "Notification on enactment and amendment of related Cabinet Order and Ministerial Orders related to partial enforcement of the amended PMD Act" (notification dated on July 13, 2021, from Director of the Compliance and Narcotics Division, Pharmaceutical and Environmental Health Bureau, MHLW; hereinafter referred to as the "Enforcement Notification") and the "Guide for applications of GMP conformity assessments" (notification dated on July 13, 2021, from directors of the Pharmaceutical Evaluation and Licensing Division and the Compliance and Narcotics Division), the following steps for conducting GMP investigations are provided.

This Guide does not directly apply to assessments for licensing of manufacturing sites and for accreditation on foreign manufacturing sites, as provided in Article 13, paragraph (5) (includes where applied mutatis mutandis as provided in paragraph (9) of the same Article or Article 13-3, paragraph (3)) of the PMD Act, however, in the case where any of such

assessments are implemented together with a GMP investigation, those are to be conducted in accordance with this Guide.

2. How to implement GMP investigations

2.1. Upon planning/implementing GMP investigations

Each GMP inspectorate agency is to conduct GMP investigations suitably taking account of objectives thereof, size of the manufacturing site, number of the items (products) manufactured, dosage forms, production processes, and history of the previous GMP investigations, etc., and suitable instructions is to be given to the manufacturer that have been subjected to a GMP investigation, based upon scientific knowledge and in line with the provisions of the Ministerial Order on GMP. The PIC/S GMP Guide is to be also referred for practical approaches to ensure product quality.

2.2. Frequency of GMP investigations

Taking account of risks that a significant deficiency may arise due to lack of understanding on the current requirements of the Ministerial Order on GMP and other related laws and regulations, each GMP inspectorate agency is to plan GMP investigations at manufacturing sites of each manufacturer, once a year in principle for manufacturing sites with high intrinsic risks, and once every 1-3 years for other manufacturing sites, based upon assessment of risks taking account of the factors as listed in Table I. It is basic for frequency of GMP investigations that main elements (sub-systems) of manufacturing control and quality control at a manufacturing site are totally examined within a valid period for the manufacturer's license/registration (it is also acceptable that those sub-systems are totally examined by conducting multiple partial investigations within a valid period for the manufacturer's license/registration), and flexible approaches are to be implemented taking account of the factors as listed in Table I.

Table I: Factors to be considered upon deciding the scope, frequency, methods, and duration for implementing an GMP investigation

Factors to be considered	Examples
Type of the items (products) manufactured at the manufacturing site	・ Dosage forms, ・ Biological pharmaceuticals or non-biological pharmaceuticals, ・ Aseptic processing or non-aseptic processing ・ Those for use in small dosage, ・ Those for use in narrow therapeutic dosage, ・ Those produced with any peculiar technique,

	・ Type of major products (e.g., whether the products are active ingredients or not, generic products or not, pharmaceuticals with high clinical needs* or not), and ・ Others * Clinically essential pharmaceuticals, such as no alternative products or products with high market share, and with significant impact on medical treatment if any quality problem arises; for example, "pharmaceuticals for secured stable supply" and/or "orphan pharmaceuticals" are applied.
Details of production processes at the manufacturing site	・ Sterile/aseptic operations are involved or not, ・ Type of control for the work environments, ・ Complexity of the production processes/parameters, and ・ Others
Other factors regarding the manufacturing site	・ Number of items (products) manufactured, ・ Number of the personnel concerned, ・ Potential magnitude of impact in the case of any violation, ・ Shared facilities for production or not, and ・ Others
Change history at the manufacturing site	Partial change of any matter prescribed in the existing marketing authorization, for which a GMP conformity assessment is needed, and/or the following changes that may impact on risks of cross-contamination, mixed-up, etc.; ・ Change of the manufacturing site owner (manufacturer/foreign manufacturer), ・ Change of location, etc. of the manufacturing site, ・ Change of any premises/equipment that may impact on product quality, ・ Change of any responsible person or other personnel that may impact on product quality, ・ Introduction of any item (product) of a category to be newly manufactured at the manufacturing site, ・ Introduction of a new equipment/instrument that requires implementation of initial education/training, and ・ Others
Investigation history for the manufacturing site	・ Whether it is the first-time GMP investigation or not, ・ Findings during the previous GMP investigation,

	・ If any product recall or other defective quality information arose after the previous GMP investigation, its details, ・ Whether any confirmation certificate of conformity has been issued regarding the manufacturing site or not, ・ If any other GMP inspectorate agency has conducted a GMP investigation at the manufacturing site, its findings and the conformity conclusion, ・ Period elapsed after the previous GMP investigation, ・ Any GMP information of the manufacturing site, which has been shared by a foreign or other authority, and ・ Others.
Information related to the items (products) manufactured	・ Any report on adverse incident or defective products, and other post-marketing information, ・ Any finding from a surveillance campaign by pharmaceutical authority, ・ Any information related to the items (products) manufactured, which has been shared by a foreign or other authority, and ・ Others.

2.3. Duration for an on-site investigation

In the case of the first-time GMP investigation, since conformity with all of the GMP requirements is to be comprehensively assessed, the conducting GMP inspectorate agency is to have, in principle, two days or more for duration of the GMP investigation. With regard to GMP investigations other than the first-time investigation, the conducting GMP inspectorate agency is to determine duration for each GMP investigation by its own responsibility, taking account of the factors as listed in Table I.

In the case of conformity assessments by types of manufacturing activities, where such investigation applications have been filed for several types of manufacturing activities at a manufacturing site, and where a single GMP inspectorate agency conducts such conformity assessments, the conducting GMP inspectorate agency can implement the GMP investigation for such conformity assessments at once, however, in this case, extended duration for the GMP investigation should be considered, taking account of differences of the control methods for each type of manufacturing activities.

2.4. Methods for GMP investigations

A GMP inspectorate agency which has received an application for conformity assessment/review is to decide either on-site or document-based to conduct the conformity assessment/review, taking account of the factors as listed in Table I, then to convey such decision to the applicant. If any on-site GMP investigation for manufacturing sites of the manufacturer has not been conducted in previous three years before date of the application for conformity assessment/review, the GMP inspectorate agency is to conduct, in principle, on-site GMP investigation for it; however, notwithstanding the above, the GMP inspectorate agency may, taking account of compliance status with relevant laws and regulations, control status, etc., decide to conduct an on-site GMP investigation.

In the case of on-site inspections, taking account of the factors as listed in Table I with point of views to prevent organized concealing, etc., GMP inspectorate agencies is to conduct their on-site inspection without announce, in principle. The mattes to not be informed in advance are everything concerned with the inspection, such as date of the inspection, items (products) to be examined, schedule for the inspection, areas subjected to the inspection, documents subjected to the inspection.

2.5. GMP investigations conducted by another GMP inspectorate agency, etc.

Each GMP inspectorate agency may utilize as reference of investigation findings by another GMP inspectorate agency, etc. that are usable, by its own responsibility.

2.6. Scope for a GMP investigation

Scope for a GMP investigation is to be decided based upon objectives of the GMP investigation, such as whether to focus on a certain item (product) or to examine overall conformity at the manufacturing site, referring the classifications shown in Table II.

Table II. Concepts of scope for a GMP investigation

<table>
<tr><th colspan="4">Type of GMP investigations</th><th>Concepts of scope for a GMP investigation</th></tr>
<tr><td rowspan="4">Conformity assessment</td><td colspan="3">Pre-authorization conformity assessment</td><td>To focus on the item (product) subjected to application of authorization (authorization for partial change of any matter prescribed in an existing marketing authorization); however, in the case of the first-time conformity assessment at the manufacturing site, to examine overall conformity at the manufacturing site.</td></tr>
<tr><td rowspan="3">Post-authorization and other conformity assessment</td><td rowspan="2">Pharmaceuticals/ quasi-pharmaceuticals for export</td><td>Initial assessment</td><td>To focus on the item (product) subjected to application of the conformity assessment; however, in the case of the first-time conformity assessment at the manufacturing site, to examine overall conformity at the manufacturing site.</td></tr>
<tr><td>Second time onwards</td><td>適合性調査申請に係る品目（製品）、又は適合性調査を受けなければならない品目（製品）をまとめての製造所全体、特に前回調査以降変更等のあった部分に重点
To examine overall conformity at the manufacturing site to cover together the items (products) subjected to application of the conformity assessment, or the items (products) for which conformity assessment must be conducted, particularly focusing upon matters changed after the previous GMP investigation.</td></tr>
<tr><td>Routine conformity assessment with regard to an existing authorization</td><td>Initial assessment</td><td>適合性調査申請に係る品目（製品）、又は適合性調査を受けなければならない品目（製品）をまとめての製造所全体
To examine overall conformity at the manufacturing site to cover together the items (products) subjected to application of the conformity assessment, or the items (products) for which conformity assessment must be conducted.</td></tr>
</table>

			Second time onwards	適合性調査申請に係る品目（製品）、又は適合性調査を受けなければならない品目（製品）をまとめての製造所全体、特に前回調査以降変更等のあった部分に重点 To examine overall conformity at the manufacturing site to cover together the items (products) subjected to application of the conformity assessment, or the items (products) for which conformity assessment must be conducted, particularly focusing upon matters changed after the previous GMP investigation.
	Conformity assessment by types of manufacturing activities		Initial assessment	To examine overall conformity at the manufacturing site to cover together the items (products) produced under the type of manufacturing activities subjected to application of the conformity assessment.
			Second time onwards	To examine overall conformity at the manufacturing site to cover together the items (products) that are involved to the type of manufacturing activities subjected to application of the conformity assessment, particularly focusing upon matters changed after the previous GMP investigation.
	Conformity review with regard to post authorization change management protocol (PACMP)			To focus on the item (product) concerned with the PACMP; however, in the case of the first-time conformity assessment at the manufacturing site, to examine overall conformity at the manufacturing site.
On-site inspections	Regular surveillance		Initial regular surveillance	To examine overall conformity at the manufacturing site.
			Second time onwards	To examine overall conformity at the manufacturing site, particularly focusing upon matters changed after the previous GMP investigation.
	For-case inspections			It depends on objectives of the for-case inspection.

(1) Upon conducting a GMP investigation on overall conformity at the manufacturing site, representative items (products) are to be selected for each type of production processes, and documents/records to be examined are suitably specified, in order to plan and implement such GMP investigation so as to totally evaluate for the state of control at the manufacturing site.

Upon conducting a GMP conformity assessment by types of manufacturing activitiess, it should be implemented with taking into consideration that methods of production/quality control may differ in items (products) or marketing license holders among same type of manufacturing activities. Upon conducting a GMP conformity assessment for two or more types of manufacturing activities at once, the processes, etc. concerned with one or more item (product) for each of those types are to be examined in order to assess the conformity with the Ministerial Order on GMP for each type of manufacturing activities.

(2) In the case where a GMP investigation is implemented focusing upon matters changed after the previous GMP investigation, it is to be examined whether changes and deviations, etc. are managed suitably in line with relevant provisions of the Ministerial Order on GMP. For example, records of deviations, records of the quality assurance section's endorsement for changes, records of reviews on the production process after change, records of rejected materials/products, records of testing/analysis on reference samples, records of recalled products, and other records are to be examined intensively. Even where any change has not been found, it should be examined whether production methods, specification and testing/analytical methods, item (products) specifications, and other matters are in line with the product marketing authorization (registration) requirements or matters of the registration of manufacturing for export. And even where any change regarding ingredients and their quantities of a product has not been found, records of testing/analysis on the product/starting materials, records of maintenance on equipment/instruments, and others in addition to the production records are to be examined. Significant deficiencies, in the case where any change has been introduced, may be such as cases where validation is not carried out, or where any significant change has been introduced without notifying the marketing license holder concerned.

2.7. Pre-/post-authorization conformity assessment

Upon conducting a pre-authorization conformity assessment, matters concerned with the Ministerial Order on GMP among matters of the authorization application are also be examined during the assessment. The conducting GMP inspectorate agency is to suitably address based upon matters to note on pre-authorization conformity assessment, such

as timeclock of review processes for the marketing authorization application, as necessary communicating with relevant authority competent for the marketing authorization.

Upon conducting a pre-authorization conformity assessment, it should be particularly focused to examine suitability of protocol for the process validation (as necessary, which covers suitability of the manufacturer's evaluation outcome on matters prescribed within the validation protocol, such as technology transfer, study of conditions for commercial production, study of up-scaling production). In the case of insufficient technical study and validation in order to manufacture high-quality products constantly with reproducibility, it will be high intrinsic risk that defective products may arise during repeated production. Therefore, upon conducting a post-authorization conformity assessment, particularly, occurrence of out of specification/out of trend data, any deviation from the written process control procedures, etc., change management of production scale, and others should be carefully watched.

2.8. Sub-systems for GMP investigations

In the case of GMP investigation to examine overall conformity at a manufacturing site, it is to be collectively and efficiently assessed whether management at the manufacturing site effectively functions, not merely conformity with individual requirements of the Ministerial Order on GMP, based upon the key sub-systems of manufacturing control and quality control as listed in Table III. During a GMP investigation, two or more of the sub-systems that includes quality sub-system are to be examined. In the case of GMP investigation to examine overall conformity at a manufacturing site, at least four of the sub-systems are to be examined. Upon examining the sub-systems, relevant matters among the key matters listed in Table III are to be mainly examined (as necessary, matters listed for other sub-systems are also to be examined), and if any deficiency with regard to a sub-system is identified during the GMP investigation, in-depth assessment on such sub-system should be suitably carried out.

Table III. Sub-systems for GMP investigations on pharmaceuticals/quasi-pharmaceuticals

Sub-systems	Matters to be examined
I. Quality	i) Organizational structure, ii) Pharmaceutical/quasi-pharmaceutical specification files, iii) Document management (includes those for data integrity; hereinafter shown as "DI"), iv) Control of product release (batch certification),

	v) Change management, vi) Deviation management, vii) Management of quality information/quality defect (complaint), viii) Internal audits, ix) Management of recalled products, x) GMP education/training, xi) Conformity with the agreements concluded with relevant marketing license holders (includes compliance with the marketing authorization requirements), xii) Quality policy/quality objectives, xiii) Quality manual[iv] of the manufacturer/foreign manufacturer, xiv) Review of product quality xv) Corrective actions/preventive actions, xvi) Supplier control for starting materials and packaging/labeling materials, xvii) Commitments by senior management (responsible executives) of the manufacturer/ foreign manufacturer, xviii) Management reviews, internal communications, and assignment for resources, xix) Technology transfer, xx) Quality risk management, and xxi) Control of the outsourced contractors.
II. Premises/equipment	i) Management of written procedures/records (includes those for DI), ii) Management of the drawings, iii) Qualifications of premises/facilities (includes work rooms) and equipment (supply of process water, production equipment, air conditioning equipment) iv) Control (maintenance) of equipment/ instruments, v) Control of computerized system, vi) Calibration, vii) Control of supply system for process water, viii) Control of air conditioning system,

[iv] **Translation annotation**; document as provided in *ICH Q10 guideline* and *PIC/S GMP Guide Part I* (equivalent document as provided in Article 3-3, item (i) of the Ministerial Order on GMP)

	ix) Control for shading, x) Control of entrances/exits, xi) Maintenance of premises/buildings, xii) Sanitation/hygiene control, xiii) Control for insect/rat proof, xiv) Prevention of cross-contamination, and xv) Measures for containment.
III. Storage, etc. for products, starting materials, and packaging/labeling materials	i) Management of written procedures/records (includes those for DI), ii) Control for receiving materials, iii) Control for quarantine, iv) Control for labeling, v) Control of stock receipt/dispense, vi) Management of rejected products/materials, vii) Qualification of facilities/equipment, viii) Control of equipment/instruments, ix) Calibration, x) Sanitation/hygiene control, xi) Environmental control, xii) Control for insect/rat proof, xiii) Operations for releasing products, and xiv) Education/training.
IV. Processing; (1) Non-aseptic processing, (2) Aseptic processing, (3) Biological pharmaceuticals, and (4) Radiopharmaceuticals	(1) Non-aseptic processing; i) Written procedures, ii) Management of written production directions/records (includes those for DI), iii) Checks before processing operations, iv) In-process control, v) Prevention of foreign matters/contamination/ mix-up, vi) Control of equipment/instruments, vii) Calibration, viii) Lines of flow, ix) Zoning (partitions) x) Control for insect/rat proof, xi) Control for gowning, xii) Sanitation/hygiene control, xiii) Environmental control, xiv) Microbiological monitoring, xv) Validation, and xvi) Education/training.
	(2) Aseptic processing; i) Written procedures, ii) Management of written production

	directions/records (includes those for DI), iii) Checks before processing operations, iv) In-process control, v) Prevention of foreign matters/contamination/ mix-up, vi) Control of equipment/instruments, vii) Calibration, viii) Lines of flow, ix) Zoning (partitions), x) Control for insect/rat proof, xi) Control for gowning, xii) Sanitation/hygiene control, xiii) Environmental control, xiv) Microbiological monitoring, xv) Validation, xvi) Education/training, xvii) Control for bacterial endotoxins, xviii) Aseptic process simulation (APS), xix) Cleaning (sanitization), xx) Control for drifting particles, xxi) Control for sterilization, and xxii) Control of disinfectants and others.
	(3) Biological pharmaceuticals; i) Written procedures, ii) Management of written production directions/records (includes those for DI), iii) Checks before processing operations, iv) In-process control, v) Prevention of foreign matters/contamination/ mix-up, vi) Control of equipment/instruments, vii) Calibration, viii) Lines of flow, ix) Zoning (partitions), x) Control for insect/rat proof, xi) Control for gowning, xii) Sanitation/hygiene control, xiii) Environmental control, xiv) Microbiological monitoring, xv) Validation, xvi) Education/training, xvii) Procurement, handling and storage control for biological starting materials, and xviii) Process control for elimination/

	inactivation of viruses and other microorganisms
	(4) Radiopharmaceuticals; i) Written procedures, ii) Management of written production directions/records (includes those for DI), iii) Checks before processing operations, iv) In-process control, v) Prevention of foreign matters/contamination/ mix-up, vi) Control of equipment/instruments, vii) Calibration, viii) Lines of flow, ix) Zoning (partitions), x) Control for insect/rat proof, xi) Control for gowning, xii) Sanitation/hygiene control, xiii) Environmental control, xiv) Microbiological monitoring, xv) Validation, xvi) Education/training, xvii) Procurement and storage control for radioactive starting materials, xviii) Control for radiation exposure protection, and xix) Control for radioactive wastes.
V. Packaging/labeling	i) Written procedures/records (includes management for DI), ii) Checks before packaging/labeling operations, iii) Control for labeling materials, iv) In-process control, v) Prevention of contamination/mix-up, vi) Qualification of facilities/equipment, vii) Control of equipment/instruments, viii) Calibration, ix) Sanitation/hygiene control, x) Control for gowning, xi) Lines of flow, xii) Zoning (partitions), xiii) Control for insect/rat proof, xiv) Environmental control, xv) Validation, and xvi) Education/training,
VI. Testing/analysis	i) Written procedures/records (includes

	management for DI), ii) Management for sampling, and control of samples, iii) Control of facilities/equipment (qualification/calibration of equipment/apparatus for testing/analysis, and qualification of testing/analytical methods), iv) Control of equipment/instruments, x) Calibration, xi) Control of testing reagents/solution, and reference standards, xii) Control of water for testing/analysis, xiii) Control of animals for testing/analysis, ix) Evaluation on results of testing/analysis, and management for out of specification results, x) Control of labeling for "passed", and management of such information (e.g., conveying to the personnel in charge of quarantine for the products/materials, or others), xi) Control of reference samples/retention samples, xii) Sanitation/hygiene control, xiii) Stability monitoring, xiv) Validation (validation for testing/analytical methods) xv) Management of outsourced testing/analysis, xvi) Education/training, xvii) Environmental control in the testing/ analytical rooms, xviii) Control for microbiological testing, and xix) Control for sterility testing.
Remarks:	* In the case of GMP investigations on quasi-pharmaceuticals, matters regarding DI, pharmaceutical quality system (including quality policy/quality objectives, review of product quality, supplier control for starting materials/packaging materials, management reviews, internal communication, allocation for resources, quality risk management, control of the outsourced contractors) and stability monitoring are not to apply.

2.9. Document materials for GMP investigations

Document materials which the implementing inspectors can obtain from the manufacturer/foreign manufacturer subjected to a GMP investigation, in advance as necessary are such as shown in Appendix 1. The implementing inspectors are to obtain necessary documents beforehand with point of views for effectively implementing their GMP investigation, as suitably requesting such documents according to scope of the GMP investigation and profile of the manufacturer/foreign manufacturer subjected to the GMP investigation, and prepare for the GMP investigation.

In the case of pre-authorization conformity assessment, or initial conformity assessment on manufacture of pharmaceuticals/quasi-pharmaceuticals for export, the item (product) is to be focused on, and the implementing inspectors are to endeavor to obtain necessary information such as the master files for active ingredients, etc. which are referred within the product authorization application or the exporting product registration. In the case of on-site inspections as well, the implementing inspectors are to endeavor to obtain necessary information beforehand, in similar manner.

2.10. Compiling/analysing, etc. of information on GMP investigations

In order to centrally manage implementation of GMP investigations by each GMP inspectorate agency, MHLW (the Compliance and Narcotics Division, pharmaceutical Safety Bureau) compile and manage information of GMP investigation finding reports, etc., and conduct a project for information gathering, compiling, analysing, sharing, etc. contents of GMP investigation finding reports, to improve cooperating system among the prefectural governments and the Ministry on pharmaceutical surveillance/supervision.

3. Practical flow for conducting a GMP investigation

3.1. Steps for conducting a GMP investigations

A GMP investigation consists of steps such as beforehand preparation, implementation of the GMP investigation on the day, actions/instructions, etc. after the implementation, documentation of the GMP investigation finding report (see Appendix 2), and issuance of the report, etc. Practical flow is as follows;

3.2. Fundamental preparation for a GMP investigation

The GMP inspectorate agency conducting a GMP investigation is to clarify objectives of the GMP investigation, and to lay down fundamental

lines for the GMP investigation based upon the factors as listed in Table I and the obtained material as shown in Appendix 1. In the case where any safety risk for the implementing inspectors be anticipated due to the products manufactured or type of processing, etc. at the manufacturing site to be investigated, suitable safety measures are to be taken (e.g., to exclude personnel with hypersensitivity to a certain drug substance from GMP investigation operation that may expose the implementing inspectors to such drug substance; upon examining areas for handling radioisotopes, for testing/analysis on radioactive products or for radiation sterilization process, etc., to carry a film badge dosimeter, a thermoluminescent dosimeter (TLD) or other devices; upon examining areas with any hazard for infectious bacteria/viruses or toxic gases, etc., to ensure precautions such as for complying with sanitation/hygiene requirements at the manufacturing site to be investigated.).

3.3. Formulation of an investigation team

Upon conducting a GMP investigation, the conducting GMP inspectorate agency is to formulate an investigation team that, in principle, consists of one or more GMP inspector(s) belonging to the GMP inspectorate agency and expert(s) as necessary for the related fields (it is preferable that two or more members for complementing expertise/experience among the team crews, and for ensuring safety of the team crews.). And the conducting GMP inspectorate agency is to designate a responsible inspector for the GMP investigation, and to have such responsible inspector organize the GMP investigation overall, and conduct commentary session on the observations, as well as transmission of the deficiencies identified, and documentation of the GMP investigation finding report. One chief/senior inspector qualified as shown in Annex 1 should be secured within an investigation team for each GMP investigation.

In the case where it is difficult to secure such a qualified inspector within the conducting GMP inspectorate agency, with cooperating among GMP inspectorate agencies, a GMP inspector qualified as such should be secured from another GMP inspectorate agency.

Besides member of the investigation team, any officials from the MRA partner authorities or other relevant organizations can attend the GMP investigation as observers, only in the case where the manufacturer/foreign manufacturer of the manufacturing site to be investigated and the responsible inspector have allowed. In such case, the conducting GMP inspectorate agency is to request such observer(s) to comply with confidentiality and other necessary matters, and each observer must follow that.

3.4. Planning/scheduling for a GMP investigation

Upon conducting a GMP investigation, the conducting GMP inspectorate agency is to have the responsible inspector gather adequate information for the GMP investigation, analyse such information, communicate elaborately within the investigation team regarding approaches to the GMP investigation, and document plan/schedule for the GMP investigation that covers the following matters, taking account of available resources and the timeframe. The investigation plan/schedule may be conveyed to the manufacturer/foreign manufacturer subjected to the GMP investigation as necessary, in order to make the GMP investigation implemented reasonably and suitably. Details of the investigation plan/schedule are to be flexible according to situation at the site during the GMP investigation, in the case where such plan/schedule has been changed, it is to be conveyed to the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation.

(1) Names and titles of the implementing inspectors, and roles for each of them during the GMP investigation,

(2) Objectives of the GMP investigation,

(3) Date/time and location for the GMP investigation;

In the case where a document-based investigation is separately implemented, matters for such document-based investigation are to be included.

(4) Manufacturing site to be investigated;

In the case where any facility related to the manufacturing site, such as a contract laboratory, is also to be investigated, such facility is to be written down as well (in the case of conformity assessment, another investigation application is to be filed regarding such facility, then a written notice of identified deficiencies, and a GMP investigation finding report for such conformity assessment are to be documented separately.).

In the case where the manufacturing site to be investigated is concerned with several quality management system, it should be identified which system among those to be examined.

(5) Language to be used during the foreign GMP investigation; if any arrangement of interpreter for what foreign language to be translated into Japanese,

(6) Scope of the GMP investigation;

i) in the case of GMP investigation on any specified item (product), sub-systems, and production processes relevant to each sub-system (relevant operation areas/zones, concerned sections/units, documents/records, etc. are to be identified as necessary) to be examined, or

ii) in the case of GMP investigation to assess overall conformity at the manufacturing site, sub-systems, and key processes and representative items (products) for each sub-system to be examined,

(7) Timeframe for each key investigation matter to be scheduled,

(8) Time for a commentary session on the observations to be scheduled, and

(9) Predicted date of issuance for the GMP investigation finding report.

3.5. Prior communication

Prior to conducting a GMP investigation, for the purpose of ensuring efficient confirmation of necessary documents/records and attendance of the needed personnel in order to implement reasonable and suitable GMP investigation, the conducting GMP inspectorate agency is to provide necessary information beforehand, in principle, such as date of the GMP investigation, number of the implementing inspectors, size of clothes/shoes for gowning, to the manufacturer/foreign manufacturer subjected to the GMP investigation.

In the case of conformity assessment by types of manufacturing activities, which has been applied by a foreign manufacturer, and where agent person/company in Japan for the application has been assigned, such prior communication is to be made to the agent person/company so that the agent person/company should be requested to convey to the foreign manufacturer.

In the case of Article 69 inspection, and where anyone other than official carrying a certificate for its position as provided in Article 69, paragraph (8) or Article 69-2, paragraph (5) of the PMD Act, joins as an implementing inspector, consent by the manufacturer subjected to the inspection is to be obtained by the time of the inspection.

3.6. Operational steps for a GMP investigation

An on-site investigation proceeds, in principle, by steps as follows;

(i) to ensure manufacturer's understanding of implementing the GMP investigation on-site,
(ii) to confirm basic information for the GMP investigation,
(iii) to implement the GMP investigation,
(iv) to have a commentary session on the observations, and to issue a written notice of deficiencies identified during the GMP investigation,
(v) to receive report(s) on corrective/preventive action plan and/or those action outcome from the manufacturer/foreign manufacturer, and to review on details of the rectification (follow-up investigation), and
(vi) to document a GMP investigation finding report, to issue a copy thereof, and to record on register of the GMP inspectorate agency (includes recording on the administrative disposition register, as prescribed within the operational guide for pharmaceutical surveillance/supervision).

3.7. Ensuring manufacturer's understanding of implementing a GMP investigation on-site

Upon entering the manufacturing site to be investigated, the implementing inspectors are to show a written notice of the GMP

investigation (see Appendix 3) to ensure understanding for that by the manufacturer/foreign manufacturer subjected to the GMP investigation.

3.8. Confirmation of basic information for a GMP investigation

(i) Each implementing inspector is to introduce its name, title and the belonging agency, to the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation. And contact persons for both of the implementing inspectors and the manufacturer/foreign manufacturer subjected to the GMP investigation are to be confirmed.

(ii) A written notice of the GMP investigation is to be handed out, and objectives of the GMP investigation and matters to be examined are to be explained.

(iii) Steps for implementing the GMP investigation are to be explained.

(iv) Both of the implementing inspectors, and the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation are to confirm regarding the above matters.

(v) Utilities for the implementing inspectors (e.g., meeting room for preliminary discussion) are to be ensured.

(vi) Arrangement for a room and schedule of commentary session on the observations is to be confirmed.

(vii) Timeframe for internal discussion by the implementing inspectors, and the predicted closing time for each day during the GMP investigation are to be scheduled.

(viii) In the case of the first-time GMP investigation, basic information written in the application for the GMP investigation (such as name and location of the manufacturer/foreign manufacturer subjected to the GMP investigation) and other necessary matters are to be confirmed.

(ix) An outline explanation regarding organization chart, and summary of production control and quality management at the manufacturing site (includes outlines of the quality policy/quality objectives, as necessary), any changes after the previous GMP investigation, rectification status for the deficiencies that were identified during the previous GMP investigation, and other matters is to be presented by the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation.

3.9. Implementation of a GMP investigation

(i) The conducting GMP inspectorate agency to be ready for addressing any consultation, etc. from the implementing inspectors during their GMP investigation.

(ii) The implementing inspectors are to endeavor to create a good partnership with the manufacturer/foreign manufacturer during the GMP investigation.

(iii) The investigation team is to make mutual communication among the

implementing inspectors in order to maximize its ability as a team (e.g., the investigation team has internal exchanges of views suitably during the GMP investigation, and when the investigation team to be split up several parties to examine different areas at the manufacturing site, the responsible inspector instructs other inspectors for the points to be examined.) and to ensure consistency of guidance/views within the investigation team.

(iv) Upon closing on each day (other than the final day) of the GMP investigation, the responsible inspector is to convey to the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation, that the GMP investigation has not been finished yet. It is sufficient that a written notice of the GMP investigation is handed out once on the first day of the GMP investigation, however, in the case where more extended duration for the GMP investigation than its initial schedule is predicted, the responsible inspector should inform that in advance to the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation.

(v) In the case where any deficiency has been identified during a GMP investigation, the implementing inspectors are to convey it to the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation promptly, in order to avoid for such responsible person to become firstly to know it in the commentary session on the observations.

(vi) Upon examining production records, records of training/education and others, the implementing inspectors are to endeavor sampling of relevant documents/records to be reasonable as risk-based and/or statistically, as far as available resource and timeframe for the GMP investigation.

(vii) Operations during a GMP investigation are to be suitably arranged so that such operations proceed efficiently. For instance, an investigation tour around storage areas, etc. is to be performed firstly in order to early specify information for sampling of cases on rejected materials/products or procedural deviation; and instructions to submit documents/records that take a lot of time and effort to prepare are to be made at early stage of the GMP investigation.

(viii) Each inspector implementing an Article 69 inspection must, pursuant to the provisions of Article 69, paragraph (8) and Article 69-2, paragraph (5) of the PMD Act, carry a certificate for its position, and present such certificate when requested by any person concerned, however, must not provide a copy thereof. In the case where the inspection has been refused, obstructed or avoided, and the inspection cannot be started, the implementing inspectors are to show the contents described in reverse side of a written notice of the inspection to the manufacturer/laboratory for quality control subjected to the inspection, and to explain legal provisions for such case, includes penal provisions of Article 87, item (xiii) in the PMD Act. If the inspection is still refused, the implementing

inspectors are to leave the site/facility to be inspected, after having a written notice of the inspection handed out, and to promptly report that to headquarters of the conducting GMP inspectorate agency. In the case where a part of confirmation of production processes, relevant information or others is refused, obstructed or avoided during an inspection, the inspection is to be continued, after having explanation of the legal provisions above made.

(ix) In the case where any abjuration/signature is requested by the manufacturer/foreign manufacturer subjected to the GMP investigation, with regard to disclaimer of personal injury or confidentiality of company secret or others, the implementing inspectors are to decline it politely. Such a request is to be noted suitably within the investigation finding report and/or other record.

(x) In the case where permission for recording audio/video, etc. during a GMP investigation is asked by the manufacturer/foreign manufacturer subjected to the GMP investigation, it is not necessarily declined, however, with point of views for ensuring accuracy of such recordings, it is to be informed and agreed by the manufacturer/foreign manufacturer that the implementing inspectors are also going to record audio, or that submitting a copy of such recording data is requested for the manufacturer/foreign manufacturer.

(xi) Outsiders who are neither the implementing inspectors, nor personnel of the manufacturer/foreign manufacturer subjected to the GMP investigation are not to be allowed to join during the GMP investigation, in principle. Even in the case where any outsider is allowed to attend there due to an exceptional reason, such outsider is not to affect the GMP investigation at all, and to be ordered to get out upon affecting implementation of the GMP investigation unsuitably. In addition, it should be paid close attention to keep confidentiality of the company secret and others that the implementing inspectors obtained during the GMP investigation. It is to be informed the manufacturer/foreign manufacturer subjected to the GMP investigation, that the implementing inspectors are not responsible for leakage of the company secret and/or other information by such outsiders.

(xii) Each implementing inspector must carefully behave so as not to fall into discredit with the conducting GMP inspectorate agency, such as leakage of confidentiality of another manufacturing site or others due to careless behavior. It is to be paid attention that there can be confidential information even between facilities concerned with manufacturing of the same item (product), including contract laboratories and sterilizing facilities.

(xiii) In the case where the manufacturer/foreign manufacturer subjected to a GMP investigation demands a copy of any records or photos made by the implementing inspectors during the GMP investigation (note; it is to be confirmed with the manufacturer/foreign manufacturer beforehand,

whether carrying a camera into manufacturing areas does not affect the product quality.), such demand is not to be accepted on the spot; it is to be explained that an official procedure for information disclosure at a later date is needed.

(xiv) In the case where it is needed for the implementing inspectors to step into an area/room for aseptic operations, necessary measures such as complying with procedures of sanitation/hygiene control at the manufacturing site being investigated are to be taken, with paying fully attention to suitability of aseptic control there.

(xv) In the case of Article 69 inspections, confiscation of testing samples in minimum amount necessary for regulatory testing/analysis may be carried out: upon such sampling, reliability on results of testing/analysis performed at the manufacturing site being inspected or other facility is to be adequately examined.

In addition, such sample confiscation is to be carried out in mind that results of testing/analysis on the confiscated samples will be notified to the manufacturer subjected to the Article 69 inspection and the relevant marketing license holder.

3.10. Commentary session on observations

(i) The responsible inspector is to have a session to facilitate understanding by the manufacturer/foreign manufacturer subjected to the GMP investigation, regarding any observation which is deemed as deficient by the investigation team at the point of the GMP investigation (hereinafter simply referred to as "observation"); hereinafter such session is referred to as "commentary session". During such commentary session, the investigation team is to wrap up overall of the GMP investigation, and convey the observations, exchange of views on them with the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation. Such commentary session is to be had for the purpose of ensuring proper recognition and understanding by the manufacturer/foreign manufacturer subjected to the GMP investigation, regarding matters observed by the implementing inspectors during the GMP investigation; the responsible inspector is to endeavor to explain them upon facts objectively confirmed during the GMP investigation, and to reply with sincerity for any question to the explanation, so as to convince the manufacturer/foreign manufacturer subjected to the GMP investigation. Transmission of observations is to be carried out distinctly, with exclusively focusing on matters deemed as deficient. Deficiencies, which are commonly observed at different operation areas/zones, etc., are to be suitably summarized for their transmission, with the point of views for facilitating rectification for them. With regard to matters suspected as critical deficiency, the implementing inspectors do not decide by themselves whether those are non-compliance

with laws and regulations or not, to leave an official conclusion at headquarters of the conducting GMP inspectorate agency (e.g., to make those matters as pending and convey at a later date).

(ii) An implementing inspector who gives commentary on observations is, in principle, to be an official of PMDA or the prefectural GMP inspectorate agency in the case of conformity assessment/review, or on-site inspections other than Article 69 inspection; or to be an official carrying a certificate for its position as provided in Article 69, paragraph (8) or Article 69-2, paragraph (5) of the PMD Act in the case of Article 69 inspection. Technical comments related to observations may be made by an implementing inspector (includes an expert) who is specified within written notice of the GMP investigation, even who is not an official mentioned above.

(iii) In the case where the manufacturer/foreign manufacturer subjected to the GMP investigation reported that any deficiency among the observations has been rectified during the GMP investigation, it is preferable to respond for confirmation thereof unless duration of the GMP investigation will be extended unreasonably.

(iv) In the case where any consultation regarding approaches for rectification or others is proposed by the manufacturer/foreign manufacturer subjected to the GMP investigation, upon commentary session on observations, the implementing inspectors are not to respond such consultation at the point, unless able to address with their own responsibilities, and are to instruct to contact for an inquiry with headquarters of the conducting GMP inspectorate agency.

3.11. Classification of deficiencies, and issuance of a written notice of deficiencies identified during the GMP investigation

(i) The investigation team is to carefully review on each of observations identified during the GMP investigation, and to classify deficiencies according to the criteria for concluding GMP conformity (see Annex 3).

(ii) A written notice of deficiencies identified during the GMP investigation is to be documented based upon classification of deficiencies as shown in the 3.11. (i) above, and such notice addressed to the manufacturer/foreign manufacturer subjected to the GMP investigation is to be issued to the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation, in principle within 10 business days after final day of the GMP investigation. At that time, explanation regarding documents to be submitted after issuance of the written notice of deficiencies classified according to the criteria for concluding GMP conformity, procedures, etc. to be taken for decision of the GMP conformity status by the conducting GMP inspectorate agency and others, is to be given. With regard to critical or major deficiency, the manufacturer/foreign manufacturer is to be urged to report the

marketing license holder relevant to the item (product) investigated.

(3) The conducting GMP inspectorate agency is to share a copy of the written notice of deficiencies identified during the GMP investigation, and other relevant materials, with surveillance/supervision section and/or other related sections, in order to be utilized for measures such as instruction for product recalls. In the case where the identified deficiencies are concerned with other marketing license holders as well, the authorities competent for such marketing license holders are to be informed suitably according to procedures as prescribed within the operational guide for pharmaceutical surveillance/supervision.

3.12. Receipt of report(s) on corrective/preventive action plan/outcome, review (investigation) on details of the rectification, and decision of the GMP conformity status

(i) Upon receiving a report on corrective/preventive action plan/outcome from the manufacturer/foreign manufacturer subjected to the GMP investigation, the responsible inspector is to promptly review on details thereof.

(ii) In the case where such report on corrective/preventive action plan/outcome is deemed as inadequate, the manufacturer/foreign manufacturer subjected to the GMP investigation is to be instructed for rectification, and if deficiencies are not rectified still, the conducting GMP inspectorate agency is to deal with such case so that suitable administrative measure be implemented according to the operational guide for pharmaceutical surveillance/supervision and others, and to close the GMP investigation.

(iii) In the case where reasonable rectification is confirmed by review (investigation) on detail of the rectification, and any administrative measure had been implemented based upon the written notice of deficiencies identified during a GMP investigation which such rectification was triggered by, relevant competent department which implemented such administrative measure is to be informed in timely manner.

(iv) Upon receiving a report(s) on corrective/preventive action plan/outcome, attentions are to be paid not to receive any documents that other competent departments should receive (e.g., application for authorization of partial change of matters prescribed in an existing marketing authorization, notification for minor changes of such matters).

(v) Head of the investigation section is to make decision for the GMP conformity status according to the criteria for concluding GMP conformity; however, in the case of for-case inspection conducted based upon any quality information/quality defects found beforehand, conclusion of the GMP conformity status may not necessarily be made by itself, since matters that are examined during such inspection may be so limited due to objectives of such inspection. In the case of "non-

compliance" concluded according to the criteria for concluding GMP conformity, administrative measures are to be implemented according to the operational guide for pharmaceutical surveillance/supervision.

3.13. Documentation of GMP investigation finding report, issuance of copy thereof, notification on result of GMP investigation and others

(i) Upon having conducted a GMP investigation, the conducting GMP inspectorate agency is to have the responsible inspector document a report on findings during the GMP investigation in the form shown as Appendix 2.

(ii) Upon documenting a GMP investigation finding report, each deficiency, which is specified within the written notice of deficiencies identified during the GMP investigation, is to be suitably mentioned for its cause (includes responsible persons concerned with such deficiency) based upon facts (includes definite details of such deficiency) actually confirmed by implementing inspectors during the GMP investigation, and the point is to be described clearly and concisely.

(iii) Matters (includes sub-systems) that have been examined during a GMP investigation are to be described within the GMP investigation finding report.

(iv) Each GMP investigation finding report is preferably to be described so as to be as useful as possible information for improvement by the manufacturer/foreign manufacturer subjected to the GMP investigation. Any personal impressions and self-evident matters are to be avoided to describe as possible; it is sufficient to describe the reference numbers, with regard to matters/contents described within an application dossier for marketing authorization, a written marketing authorization, a product registration for marketing/export, or a master file of active ingredients, etc. that is referred to. Each responsible inspector is to document its GMP investigation finding report, on the assumption of obtaining endorsement by the conducting GMP inspectorate agency; for instance, any measures for surveillance/supervision to be implement under responsibility of the conducting GMP inspectorate agency is to be avoided to mention conclusively within a GMP investigation finding report. Information obtained during a GMP investigation, but not related to the GMP investigation itself, are to be conveyed as necessary to competent section/department, by a note separate from the report.

(v) In the case where any evidence for a deficiency lies in other place than the manufacturing site which has been investigated, and it is concerned that such evidence may be destroyed, the implementing inspectors are to inform it promptly to headquarters of the conducting GMP inspectorate agency. Upon receiving such information, the headquarters is to take necessary actions, such as contact with relevant prefectural authority competent for the marketing license holder concerned.

(vi) The conducting GMP inspectorate agency is to ensure that its GMP

investigation finding report be distinctly concluded as either compliance or non-compliance for comprehensive GMP conformity. In the case of concluding as non-compliance, it should be fully aware that the GMP investigation finding report becomes significant evidence for the subsequent prejudicial disposition, and descriptions thereof should be taken much care.

(vii) Any legal measures such as prejudicial disposition, order for reporting to the authority, or accusation are, in principle, not to be recommended or proposed within a GMP investigation finding report.

(viii) GMP investigation finding report is to be documented promptly, after receiving report on corrective/preventive action plan/outcome and reviewing details thereof.

(ix) A copy of the GMP investigation finding report is, paid close attention to disclosability of information, to be issued to the manufacturer subjected to the GMP investigation and/or the relevant marketing license holder; however, in the case of on-site inspections, issuance of a copy of such GMP investigation report is, taken into account of objective thereof, not necessarily needed.

(x) In the case where a copy of a GMP investigation finding report is requested by MHLW and/or PMDA in written or other means, for a reason such as request form a partner authority of the MRA or MOU, etc. or confirmation upon issuing a GMP certificate, the relevant GMP inspectorate agency is to send it promptly.

(xi) GMP investigation finding reports and their related records are, suitably according to rules/procedures in the GMP inspectorate agency, to be retained as confidential material; however, that this does not apply in the case where such documents/records are requested for information sharing based upon an agreement with the MRA partners, etc.

(xii) With regard to conformity assessment/review (other than conformity assessment by types of manufacturing activities) based upon application thereof, the conducting GMP inspectorate agency is, in accordance with the Enforcement Notification, to notify result thereof to authority competent for the marketing license holder of the item that has been investigated, and authority competent for marketing authorization of the item that has been investigated, as well as the marketing license holder of such item or the manufacturer subjected to the GMP investigation.

(xiii) With regard to conformity assessment by types of manufacturing activities, the conducting GMP inspectorate agency is, in accordance with the Enforcement Notification, to issue confirmation certificate of conformity by the types of manufacturing activities to the manufacturer/foreign manufacturer of manufacturing site assessed for such conformity.

(xiv) From the perspective of centralized management on implementation of GMP investigations by each GMP inspectorate agency, information on each GMP investigation, such as date of implementation, name of the

manufacturing site investigated, product(s) subjected to the GMP investigation, and its GMP compliance status concluded, are to be reported to MHLW (includes in the case where centralized management of those information is contracted to PMDA), in the form shown as Appendix 6, by end of the April for each next fiscal year. In addition, each GMP inspectorate agency is to report information of its GMP investigation finding reports to MHLW, as shown in 2.10.

Appendix 1;
Examples of material to be obtained for preparing a GMP investigation

List of material to be obtained from the manufacturing site, before a GMP investigation (examples for consideration)

1. Overview of the company (e.g., its business activities, history, organi zation, offices, etc.)

2. Overview of the manufacturing site (e.g., organizational chart for GMP, assignment of responsible persons, number of the personnel*1, number of the items manufactured*2, etc.)
   *1 Includes understanding whether suitable allocation for the personnel, and explanation for its justification
   *2 Includes items other than pharmaceuticals/quasi-pharmaceuticals

3. Information on the item subjected to the GMP investigation (e.g., quality characteristics, active ingredient characteristics, starting materials and packaging/labeling materials, storage conditions, shelf-life, etc.)

4. Premises mapping of the manufacturing site (a bird's-eye view of the manufacturing site as whole)

5. Overview of pharmaceutical quality system at the manufacturing site

6. Overview of document/data management system at the manufacturing site

7. List of all the items manufactured (includes those other than pharmaceuticals/quasi-pharmaceuticals)

№	Name of the item	Distinction for active ingredient, intermediate, bulk product, finished product, or others	Whether any products, etc. with strong pharmacological potency or toxicity (e.g., penicillines, β-lactams, or steroids that cause hypersensitivity reactions, etc.) or not	Whether any facilities shared for the product(s) subjected to the GMP investigation or not	Production areas, production lines	Size of batches	Number of batches manufactured in recent one year

8. Material that gives outlines of implementation of appropriate stability monitoring on all the items subjected to GMP requirements*
   * In the case of pre-authorization conformity assessment, it may include an implementation plan for stability testings.

9. Material that gives outlines of implementation of appropriate control on

suppliers of the starting materials and packaging/labeling materials for all the items subjected to GMP requirements

10. Layouts of production areas for the item subjected to the GMP investigation*
    * Such as those that shows name of the work rooms, lines of flow/environmental control classification/pressure differential control between the rooms, and mapping of main equipment

11. Material that gives outlines of the production processes for the item(s) subjected to the GMP investigation*
    * Such as those that shows flow-chart of the production processes, testings for in-process control, whether re-processing/recovering can be implemented or not

12. Copies of production records on the item subjected to the GMP investigation

13. Specifications for intermediate product and final product of the item subjected to the GMP investigation

14. Material that gives outlines of the implementation of appropriate technology transfer and/or industrialisation study (including a list of the matters that have been considered within such study (such as study of conditions for commercial production, study of up-scaling production), and simple summaries of their outcomes) *
    * Only in the case where such material is needed, e.g., pre-authorization (includes authorization for partial change of any matter prescribed in an existing marketing authorization) conformity assessment. Such material may include Quality Overall Summary of Module 2 (such as 2.3.P.2 "Pharmaceutical Development") of the Common Technical Document (CTD)[5] or equivalent.

15. Copy of the report of recent review of product quality on the item subjected to the GMP investigation

16. Material related to validation for the item subjected to the GMP investigation

    16.1 Copy of the validation master plan*
        * Only in the case where such material is needed, e.g., pre-authorization (includes authorization for partial change of any matter prescribed in an existing marketing authorization) conformity assessment.

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[5] **Translation annotation**; ICH M4Q "The Common Technical Document for the Registration of Pharmaceuticals for human use: Quality"

16.2 Copy of the process validation protocol/report*

* Only in the case where such material is needed, e.g., pre-authorization (includes authorization for partial change of any matter prescribed in an existing marketing authorization) conformity assessment.

16.3 Overview for outcome of the aseptic process simulation implemented after the previous GMP investigation*

* Only in the case where production by aseptic operations is implemented.

16.4 Material that gives outlines of implementation of appropriate cleaning control and cleaning validation

16.5 Annual plan for periodic re-validation activities

17. List of changes/deviations/quality information/product recalls concerned with the item subjected to the GMP investigation, which arose after the previous GMP investigation

18. List of out of specification (OOS) cases with regard to the item subjected to the GMP investigation*

* Includes all cases concerned with every item subjected to the GMP investigation, which arose after the previous GMP investigation

※ 必要な場合に製造販売業者より入手する。

19. Others

19.1 Whether any legal offense has been recognized by internal audits/whistleblower in the company, etc., after the previous GMP investigation, or not

19.2 History of periodic audit conducted by relevant marketing license holder, pursuant to the provisions of Article 10 in the Ministerial Order on Quality Management, after the previous GMP investigation, and overview thereof (includes means of the audit, date of the audit, whether any legal offense has been recognized or not, and others) *

* To be obtained from relevant marketing license holder, if needed.

Remarks;

- This list is an example, it is not necessary that all the material are to be obtained in advance, if any reason for difficulty to obtain such material in advance.
- Documents without any changed after the previous GMP investigation are not necessarily to be obtained in advance. With regard to document that has been partially changed, it is considerable that material that shows the changed part is obtained in advance.
- With regard to each material shown in 10., 11., 12., 13., 15., 16. and 17., it is considerable to limit those concerned with the representative items (products) subjected to the GMP investigation.

Appendix 2; Form for GMP investigation finding report

Date of Reporting: YYYY/MM/DD

Report on findings during a GMP investigation

To: [the conducting GMP inspectorate agency]

Responsible Inspector for the GMP investigation:
[name, title, and the belonging department/section]
Other Implementing Inspector(s):
[name, title, and the belonging department/section]

1. Reference number

2. General matters;
(i) Date of implementation for the GMP investigation (includes the time taken for the GMP investigation),
(ii) Name of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, the company's name),
(iii) Address of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, location of the main office),
(iv) Name of the manufacturing site which has been investigated,
(v) Location of the manufacturing site which has been investigated,
(vi) Type, number and date of [license/registration/accreditation] for the manufacturing site which has been investigated,
(vii) Activities at the manufacturing site which has been investigated
(☑ for every applicable),
☐ Manufacture for active ingredients,
☐ Manufacture for finished products,
☐ Manufacture for intermediate products (bulk products),
☐ Manufacture for small portions, packaging and/or labeling processes,
☐ Contract laboratory for quality control,
☐ Certifying finished products for release to the market,
☐ Others [to be specified:].
(viii) Type, number and date of the confirmation certificate of conformity,
(ix) Scope of the GMP investigation,
(x) Findings, etc. during the previous GMP investigation
(date of the conclusion for GMP conformity: YYYY/MM/DD),

3. Details of the GMP investigation;
(i) Objectives of the GMP investigation,
(ii) Type of the GMP investigation
[Conformity assessment/review [on-site / document-based], or
On-site inspections]
(iii) Matters examined during the GMP investigation (the followings are examples for their descriptions);
(i) Overview of the manufacturing site and the item manufactured (type of the manufacturing activities);
- Overview of the organization,
- Summary of production processes for the item (such as information on the preceding/following manufacturing sites),
- Certifying products to release to the market or reject,
- GMP inspections conducted by any foreign competent authority,
- Name/title/belonging section, etc. of responsible persons and other personnel responding to the GMP investigation (as attached list thereof with an appendix*),
- Name/title/belonging section, etc. of observing inspector(s) of the competent authority at the foreign country/region, or attending pharmaceutical inspector(s) of the prefecture, where the manufacturing site locates (as attached list thereof with an appendix*),
- Documents mainly investigated,
- Premises/equipment mainly examined.

* Such appendix lists are to be optional. Format of the appendix lists is free (materials submitted by the manufacturer/foreign manufacturer can be utilised.).

(ii) Sub-system on quality;
- Quality management,
- Management of organizational structure,
- Management of documents/records,
- Internal audits,
- Education/training,
- Review of product quality,
- Sanitation/hygiene control,
- Management of quality information/complaint,
- Management of recalled products and others,
- Validation master plan,
- Change management,
- Deviation management,
- Control of product release from the manufacturing site,
- Control of suppliers and outsourced contractors,
- Others.

(iii) Sub-system on premises/equipment;
- Qualification,

- Utility control;
  - System for supply of process water,
  - Air conditioning system,
- Suitable uses of articles contacting products,
- Maintenance of apparatus/equipment,
- Management of cleaning,
- Cleaning validation,
- Control for preventing contamination,
- Qualification/maintenance of storage facilities,
- Others.

(iv) Sub-system on storage of products, starting materials, and packaging/labeling materials;
- Logistic control of starting materials/intermediate products,
- Control of process water, and gasses used during production process,
- Logistic control of products,
- Management of rejected materials/products,
- Prevention of foreign matters/contamination/mix-up,
- Others.

(v) Sub-system on processing;
- Written production directions/records, and written procedures,
- Production procedures,
- Process control,
- Prevention of foreign matters/contamination/mix-up,
- Process validation (PV),
- Aseptic process simulation (APS),
- Others.

(vi) Sub-system on packaging/labelling;
- Control of labeling materials,
- Line clearance,
- Others.

(vii) Sub-system on testing/analysis;
- Control of equipment/ instruments,
- Data security,
- Control of testing reagents/solution, and reference standards,
- Written procedures/records,
- Validation for testing/analytical methods,
- Management for sampling, and control of samples,
- Management for out of specification (OOS)/out of trend (OOT) results,
- Management for integrity of raw data and retention thereof,
- Stability monitoring,
- Control of reference samples/retention samples,
- Others.

(viii) Suitability with the requirements for biological origin starting materials,

(ix) Compliance with the authorization (authorization application), or the

master file registered for active ingredients or others.

4. Other information for reference;
   - Samples obtained, and others.

5. Identified deficiencies, and rectification status for such deficiencies;

Date of issuance of the written notice of identified deficiencies	: YYYY/MM/DD
Date of receipt of a report on corrective/preventive action plan/outcome	: YYYY/MM/DD
Date of receipt of a follow-up report on corrective/preventive action outcome	: YYYY/MM/DD

Critical deficiency	
(i)	Details of the deficiency:
(ii)	Rectification status:
Major deficiency	
(i)	Details of the deficiency:
(ii)	Rectification status:
Other deficiency	
(i)	Details of the deficiency:
(ii)	Rectification status: Scheduled date of the completion: YYYY/MM/DD

6. Comprehensive conclusion for GMP conformity;
   [Compliance / Non-compliance] as of YYYY/MM/DD

Points to consider for describing a report on findings during a GMP investigation

1. In the case where several manufacturing sites have been practically investigated, a report on findings during such GMP investigation is to be documented for each of such manufacturing sites, in principle.

2. In the case of a report on findings during a GMP investigation with multiple pages, the responsible inspector is to document the report with numbering of page, etc. for each page thereof in order to make clear that it is a series of document.

3. "Other Implementing Inspector(s)" is to be described with name, title, and the belonging department/section for each implementing inspector other than the responsible inspector. In case of the implementing inspector who joined partially the GMP investigation, date and time of its joining is to be additionally indicated within bracket.

4. "General matters" are to be described in the following manner;

(i) "Date of implementation for the GMP investigation" is to be described with the time taken for the GMP investigation, besides the implementation date; e.g., "2021/09/01 (9:30-16:00) – 09/02 (9:30-12:30)".

(ii) "Type, number and date of [license/registration/ accreditation] for the manufacturing site which has been investigated" is described with type and number for license, registration or accreditation of the manufacturing site, and the starting date of such license, registration or accreditation which is indicated on the current license/registration/accreditation certificate. "Type" is to be indicated by any of the following categories;

a. in the case of manufacturing site for pharmaceuticals:
"Biological pharmaceuticals", "Radiopharmaceuticals",
"Aseptic processing", "Processing for non-sterile products",
"Packaging/labeling/quarantine", "Laboratory for quality control", or
"Storage site registered",

b. in the case of manufacturing site for quasi-pharmaceuticals:
"Aseptic processing", "Processing for non-sterile products",
"Packaging/labeling/quarantine", "Laboratory for quality control", or
"Storage site registered".

(iii) "Type, number and date of the confirmation certificate of conformity" is to be described according to the information that is indicated on the current confirmation certificate of conformity within its term of validity.

(iv) "Scope of the GMP investigation" is to be described with names of all the items (products) subjected to the GMP investigation (in the case of conformity assessment by types of manufacturing activities, the type of manufacturing activity subjected to the GMP investigation, and the representative items (products) selected for such manufacturing activity

are to be indicated), and the sub-systems that have been examined during the GMP investigation.

(v) "Findings, etc. during the previous GMP investigation" is to be described with date of the previous GMP investigation, conclusion (conformity or non-conformity) for the previous GMP investigation, and overviews of GMP-related actions taken after the previous GMP investigation by relevant marketing license holder or the manufacturer/foreign manufacturer, such as reporting of product recall, adverse event, etc. due to quality defects.

5. "Details of the GMP investigation" is to be described in the following manner;

(i) "Objectives of the GMP investigation" is to be described with category applicable for the GMP investigations, among those shown in Part II, Section 2., (i) (a)-(d), (ii) (a)-(d), (iii)-(v), and Section 3., (i), (ii) (a)-(c).

(ii) For "Matters examined during the GMP investigation", points of the GMP investigation are to be described clearly and concisely;

(a) With regard to aspect of premises/equipment, the equipment/instruments, work rooms, etc. that have been checked are to be specified suitably.

(b) With regard to aspect of management/operations, documents, such as the product specification files, written procedures, records, etc. that have been checked (if possible, includes their matters examined) are to be specified suitably.

(c) Name of the responsible person (e.g., senor management, pharmaceutical manufacturing supervisor, supervisor for biological origin products, responsible person at the foreign manufacturing site, and others) of the manufacturer/foreign manufacturer subjected to the GMP investigation is to be described; in the case where such responsible person was absent at the GMP investigation, such fact and reason thereof are to be described. An appendix list of key persons at the manufacturing site, among the personnel who practically responded to the GMP investigation, which clearly shows their name and title, is to be attached.

6. "Identified deficiencies, and rectifications for such deficiencies" is to be described in the following manner;

(i) For "Details of the deficiency", their reasons, etc. based upon the facts practically confirmed is to be described clearly and concisely.

(ii) For "Rectification status", cause(s) of the problem, assessment of impact on product quality, corrective/preventive actions and others are to be described clearly and concisely, referring to the submitted materials to prove such rectification. With regard to those submitted as corrective/preventive action plan, scheduled date of the completion is to be indicated.

(iii) With regard to any matter refused to be examined, outline thereof is to be described with titled as "Refused matters during the GMP

investigation".

7. Overview of the manufacturing site subjected to the GMP investigation is to be described concisely and in an easy-to understand manner, taking into consideration that a copy of the report be shared with other GMP inspectorate agency. Any information for reference upon the next GMP investigation, such as information for reference confirmed during the GMP investigation, scheduled change of equipment/organization or others, is to be also described.

8. For "Identified deficiencies", each deficiency which has been classified as critical deficiency, major deficiency or other deficiency in accordance with the criteria for concluding GMP conformity is to be distinctly distinguished, and described clearly and concisely with referring the order of those sub-systems as listed in Table III.

9. For "Comprehensive conclusion for GMP conformity", GMP conformity status is to be decided in accordance with the criteria for concluding GMP conformity. In the case where it is not definitely concluded as "Non-compliance", but has not been confirmed for concluding as "Compliance" from outcome of a for-case inspection or others conducted based upon quality information, etc. obtained beforehand, concluding GMP conformity itself may be omitted.

10. Upon documentation of a report on findings during a GMP investigation, the following elements are preferable to be covered, basically.

(i) For "Identified deficiencies", background thereof and supplementary information are to be described in detail within main text of the report.

(ii) With regard to significant information obtained during the GMP investigation (e.g., information on risks specific to the manufacturing site or the item (product) manufactured and measures to reduce such risks (such as matter of asepsis, cross-contamination, and/or containment), information on management realities with high intrinsic risk (such as degree of intervention to aseptic operation areas, use of old-style equipment, facilities shared with several items (products) manufactured, and/or carry-over of products among product batches), the facts confirmed and their interpretation/evaluation results are clearly described, even when those are deemed as no problem specifically.

Appendix 3; Form for written notice of a GMP investigation

YYYY/MM/DD

Written notice of a GMP investigation

To: Whom concerned at [name of the manufacturing site or other facility to be investigated]

From: [name of the conducting GMP inspectorate agency]

An investigation pursuant to the provisions of Article **, paragraph ** of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 145 of 1960), is to be conducted as follows;

1. Reference number:

2. Name, title and the belonging department/section of each implementing inspector:

3. Objectives of the GMP investigation:

4. Matters to be examined:

5. Date/time for the GMP investigation:
From [starting time] on YYYY/MM/DD to [ending time] on YYYY/MM/DD

6. Name of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, name of the company):

7. Address of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, location of the main office):

8. Name of the manufacturing site to be investigated:

9. Location of the manufacturing site to be investigated:
(Continued on the next page)

The Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Law No. 145 of 1960), (Excerpt)

(Marketing Authorization for Pharmaceuticals, Quasi-pharmaceuticals …)

Article 14 (1) A person/corporation that intends to market pharmaceuticals (excluding pharmaceuticals designated by the Minister of Health, Labour and Welfare, for which the Minister has provided specification standard), quasi-pharmaceuticals (excluding quasi-pharmaceuticals designated by the Minister of Health, Labour and Welfare, for which the Minister has provided specification standard) … must obtain marketing authorization for each such item, by the Minister of Health, Labour and Welfare.

(2) Where falling under any of the following items, the marketing authorization pursuant to the provisions of the preceding paragraph will not be granted:

(i) - (iii) (Omitted)

(iv) in the case where the pharmaceuticals, quasi-pharmaceuticals … which are applied for marketing authorization are those specified by Cabinet Order, where the methods of manufacturing control or quality control for the item at manufacturing sites thereof are not found to comply with the standard provided by Order of the Ministry of Health, Labour and Welfare.

(3) - (6) (Omitted)

(7) A person/corporation that seeks authorization as provided in paragraph (1), or a holder of authorization as provided in the same paragraph must, where the pharmaceutical, quasi-pharmaceutical … subjected to such marketing authorization is of specified by Cabinet Order, undergo a document-based or on-site investigation by the Minister of Health, Labour and Welfare, regarding whether the methods of manufacturing control or quality control for the item at manufacturing sites thereof comply with the standard provided by Order of the Ministry of Health, Labour and Welfare pursuant to the provisions of paragraph (2), item (iv), before obtaining the marketing authorization, and in every period of not less than three years specified by Cabinet Order after obtaining the marketing authorization.

(8) A holder of authorization as provided in paragraph (1), in the case where a confirmation certificate of conformity as provided in paragraph (3) of the next Article has been issued for a manufacturing site where the pharmaceutical, quasi-pharmaceutical … subjected to such marketing authorization is manufactured, regarding the type of manufacturing activity (refers to category specified by Order of the Ministry of Health, Labour and Welfare, with point of views for ensuring quality, efficacy and safety of pharmaceuticals, quasi-pharmaceutical …; the same applies in the next Article) which is categorized as same type of manufacturing activity with that for the item subjected to such marketing authorization, is to be exempted from undergoing the investigation as provided in the preceding paragraph, for such manufacturing site concerning manufacturing activity thereof.

(9) Notwithstanding the provisions of the preceding paragraph, where found necessary taking into consideration of the characteristics and others of the pharmaceutical, quasi-pharmaceutical … subjected to authorization as provided in paragraph (1), the Minister of Health, Labour and Welfare may conduct a document-based or on-site investigation, regarding whether the methods of manufacturing control or quality control for the pharmaceutical, quasi-pharmaceutical … at manufacturing sites thereof comply with the standard provided by Order of the Ministry of Health, Labour and Welfare as provided in paragraph (2), item (iv). In this case, the holder of authorization as provided in paragraph (1) for the item must undergo such investigation.

(10) - (14) (Omitted)

(15) A holder of authorization as provided in paragraph (1) must, where it intends to introduce a partial change to matters authorized for the item (excluding cases where such change is a minor change specified by Order of the Ministry of Health, Labour and Welfare), obtain authorization by the Minister of Health, Labour and Welfare, with regard to the change. In this case, the provisions of paragraphs (2) to (7) and paragraph (10) to the preceding paragraph apply mutatis mutandis.

(16) & (17) (Omitted)

(Issuance, etc. of Confirmation Certificates of Conformity)

Article 14-2 (1) A manufacturer that seeks license as provided in Article 13, paragraph (1), or a manufacturer licensed as provided in the same paragraph, a foreign manufacturer that seeks accreditation as provided in Article 13-3, paragraph (1), or a foreign manufacturer accredited as provided in the same paragraph, or a manufacturer/foreign manufacturer that seeks registration as provided in Article 13-2-2, paragraph (1) or Article 13-3-2, paragraph (1), or a manufacturer/foreign manufacturer registered as provided in Article 13-2-2, paragraph (1) or Article 13-3-2, paragraph (1) may, in the case where the pharmaceuticals … subjected to its manufacture are those specified by the Cabinet Order as provided in the preceding Article, paragraph (7), in accordance with provisions in Order of the Ministry of Health, Labour and Welfare, ask for a confirmation to the Minister of Health, Labour and Welfare, for each type of manufacturing activities for pharmaceuticals, quasi-pharmaceuticals …, regarding whether the methods of manufacturing control or quality control for such pharmaceuticals, quasi-pharmaceuticals … at the manufacturing site subjected to such license, accreditation or registration comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in the same Article, paragraph (2), item (iv).

(2) The Minister of Health, Labour and Welfare, where asked for a confirmation as provided in the preceding paragraph, is to conduct a document-based or on-site investigation thereon.

(3) The Minister of Health, Labour and Welfare, where found that the methods of manufacturing control or quality control at the manufacturing site comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in the preceding Article, paragraph (2), item (iv), from results of the investigation as provided in preceding paragraph, is to issue a confirmation certificate of conformity as of proving that conformity with such standard has been confirmed regarding the manufacturing site, in accordance with provisions in Order of the Ministry of Health, Labour and Welfare, for each type of manufacturing activities for pharmaceuticals, quasi-pharmaceuticals … as provided in paragraph (1).

(4) Validity period for a confirmation certificate of conformity as provided in the preceding paragraph is to be the period specified by Cabinet Order, which begins from the day of issuance for the confirmation certificate of conformity.

(5) A manufacturer that has been issued a confirmation certificate of conformity pursuant to the provisions of paragraph (3) must, where becoming to fall under any of the following items, promptly return the confirmation certificate of conformity to the Minister of Health, Labour and Welfare.

(i) where the manufacturer is ordered as provided in Article 72, paragraph (2), for a reason that methods of manufacturing control or quality control concerning the type of manufacturing activity for pharmaceuticals, quasi-pharmaceuticals … as provided in paragraph (1) subjected to such confirmation certificate of conformity do not comply with the standard which

is provided by Order of the Ministry of Health, Labour and Welfare as provided in the preceding Article, paragraph (2), item (iv), or for a reason that pharmaceuticals, quasi-pharmaceuticals … as provided in Article 56 (includes where applied mutatis mutandis as provided in Article 60 …; the same applies in the next item) or biological origin products as provided in Article 68-20 may arise due to such methods of manufacturing control or quality control.

(ii) where the manufacturer is ordered as provided in Article 72, paragraph (3), for a reason that premises/equipment regarding the manufacturing site issued such confirmation certificate of conformity do not comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in Article 13, paragraph (5), or for a reason that pharmaceuticals, quasi-pharmaceuticals … as provided in Article 56 or biological origin products as provided in Article 68-20 may arise due to such premises/equipment.

(Pharmaceutical Review, etc. by the PMDA)

Artticle14-2-2 (1) The Minister of Health, Labour and Welfare may have the PMDA conduct review for authorization as provided in Article 14 with regard to pharmaceuticals …, quasi-pharmaceuticals … with specified by Cabinet Order, investigation pursuant to the provisions of paragraphs (6) and (7) (includes where these provisions are applied mutatis mutandis as provided in paragraph (15) of the same Article), paragraph (9) and paragraph (13) (includes where applied mutatis mutandis as provided in paragraph (15) of the same Article) of the same Article, and paragraph (2) of the preceding Article, and issuance of confirmation certificate of conformity pursuant to the provisions of paragraph (3) of the same Article and receipt of confirmation certificate of conformity returned pursuant to the provisions of paragraph (5) of the same Article, (hereinafter referred to as "pharmaceutical review, etc.").

(2) The Minister of Health, Labour and Welfare is, where having the PMDA conduct pharmaceutical review, etc. pursuant to the provisions of the preceding paragraph, not to conduct such pharmaceutical review, etc. …

(3) In the case where the Minister of Health, Labour and Welfare decides to have the PMDA conduct pharmaceutical review, etc. pursuant to the provisions of paragraph (1), regarding pharmaceuticals, quasi-pharmaceuticals … specified by Cabinet Order as provided in the same paragraph, an applicant for authorization as provided in Article 14, or an applicant for investigation pursuant to the provisions of paragraph (7) … of the same Article (includes where these provisions are applied mutatis mutandis as provided in paragraph (15) of the same Article) must undergo such review or investigation, or issuance of such confirmation certificate of conformity, which are conducted by the PMDA, and a person/corporation that returns its confirmation certificate of conformity pursuant to the provisions of paragraph (5) of the same Article must return the confirmation certificate of conformity to the PMDA.

(4) (Omitted)

(5) The PMDA must, where having conducted pharmaceutical review, etc. …, notify the outcome of such pharmaceutical review, etc. … to the Minister of Health, Labour and Welfare, in accordance with provisions in Order of the Ministry of Health, Labour and Welfare, without delay.

(6) Any person/corporation that is dissatisfied with a disposition concerned with a pharmaceutical review, etc. conducted by the PMDA (excluding results of pharmaceutical review, etc.) or inaction thereby may file a request for review to the Minister of Health, Labour and Welfare. …

(Certification of Change Management Protocol for

Matters specified in Authorization for Pharmaceuticals …) Article 14-7-2 (1) A holder of authorization as provided in Article 14, paragraph (1) may, applying to the Minister of Health, Labour and Welfare in accordance with provisions in Order of the Ministry of Health, Labour and Welfare, undergo a certification that a protocol for partial change of matters specified within such authorization (hereinafter referred to as "Change Management Protocol" in this Article.) concerning the item authorized fulfils each of the following items. The same applies in the case of such certified Change Management Protocol to be changed. (i) – (iii) (Omitted) (2) During certification as provided in the preceding paragraph, an assessment on quality, efficacy and safety of the pharmaceutical … subjected to the Change Management Protocol (where applied for change pursuant to the provisions of later part in the same paragraph, the changed one; the same applies hereinafter in this Article.) is to be conducted based upon dossier materials submitted by the person/corporation that seeks such certification of the Change Management Protocol. (3) A person/corporation that seeks certification as provided in paragraph (1) or who has undergone certification as provided in the same paragraph must, in the case of the pharmaceutical … to be introduced partial change of any matter specified in the authorization as provided in Article 14 in accordance with the Change Management Protocol subjected to such certification is of specified by the Cabinet Order as provided in the same Article, paragraph (2), item (iv), and where such change is a change of specified by Order of the Ministry of Health, Labour and Welfare as that may impact the methods of manufacturing control or quality control, in accordance with provisions in Order of the Ministry of Health, Labour and Welfare, undergo an review	whether the methods of manufacturing control or quality control at the manufacturing site of the pharmaceutical … subjected to such change comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in the same item. (4) During review as provided in the preceding paragraph, a document-based or on-site investigation is to be conducted regarding whether the methods of manufacturing control or quality control at the manufacturing sites of the pharmaceutical … subjected to the change comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in Article 14, paragraph (2), item (iv). (5) The Minister of Health, Labour and Welfare must, where found that the Change Management Protocol which has been certified as provided in paragraph (1) did not fulfill each of items in the same paragraph, where found that the methods of manufacturing control or quality control which have been reviewed as provided in paragraph (3) did not comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in Article 14, paragraph (2), item (iv), or where found that the applicant has undergone certification as provided in paragraph (1) or an review as provided in paragraph (3) by deception or other wrongful means, revoke such certification. (6) and (7) (Omitted) (8) The Minister of Health, Labour and Welfare may have the PMDA conduct certification as provided paragraph (1) and review as provided in paragraph (3) regarding pharmaceuticals … specified by Cabinet Order as provided in Article 14-2-2, paragraph (1). (9) Provisions of Article 14-2-2, paragraphs (2), (3), (5) and (6) and this Article, paragraph (5) apply mutatis mutandis to the case of having the PMDA conduct certification as provided in paragraph (1) and review

as provided in paragraph (3), pursuant to the provisions of the preceding paragraph. In this case, necessary technical replacement of terms is to be provided by Cabinet Order.

(10) and (11) (Omitted)

(Matters to be Observed by Marketing License Holders, etc. of Pharmaceuticals, Quasi-pharmaceuticals …)

Article 18 (1)-(2) (Omitted)

(3) The Minister of Health, Labour and Welfare may prescribe … matters to be observed by manufactures of pharmaceuticals, quasi-pharmaceuticals … and foreign manufacturers of pharmaceuticals, etc. regarding their business, by Order of the Ministry of Health, Labour and Welfare.

(4) and (5) (Omitted)

(Authorization for Marketing of Pharmaceuticals, etc. Manufactured in Foreign Countries)

Article 19-2 (1) The Minister of Health, Labour and Welfare may, in the case where a person/corporation that conducts manufacture, etc. of pharmaceuticals, quasi-pharmaceuticals … in a foreign country applies to the Minister of Health, Labour and Welfare, regarding pharmaceuticals … as provided in Article 14, paragraph (1), which are those to be exported to Japan, grant authorization for each item, that such authorized item be marketed by a marketing license holder of pharmaceuticals, quasi-pharmaceuticals …, whom such foreign person/corporation has appointed pursuant to the provisions of paragraph (3).

(2) (Omitted)

(3) A person/corporation that seeks authorization as provided in paragraph (1) must, upon applying for such authorization, appoint a marketing license holder of pharmaceuticals, quasi-pharmaceuticals … (limited to person/corporation that is licensed for marketing according to type of the item subjected to such authorization) in order to have such marketing license holder implement necessary measures in Japan to prevent occurrence of public health hazards due to the pharmaceutical, quasi-pharmaceuticals … subjected to such product authorization.

(4) (Omitted)

(5) The provisions of Article 14, paragraph (2) (excluding item (i)) and paragraphs (3) to (17), and Article 14-2 apply mutatis mutandis to authorization as provided in paragraph (1).

(6) (Omitted)

(On-site inspection, etc.)

Article 69 (1) The Minister of Health, Labour and Welfare or each prefectural governor may, where found necessary to confirm whether a marketing license holder or a manufacturer (hereinafter referred to as "marketing license holder, etc." in this paragraph) of pharmaceuticals, quasi-pharmaceuticals … be complying with the following provisions and orders, have such marketing license holder, etc. make necessary reports pursuant to the provisions of Order of the Ministry of Health, Labour and Welfare, or have the officials in charge inspect the factories … and other sites where such marketing license holder, etc. are dealing with pharmaceuticals, quasi-pharmaceuticals … in its business, or examine relevant premises/equipment, records/documents and any other articles, or ask questions to employees and other concerned persons: the provisions of … Article 14, paragraph (2) or paragraph (15), … Article 18, paragraphs (1) to (4), Article 18-2 … Article 80, paragraph (1) … or the orders based upon … Article 72, paragraphs (1) to (3), Article 72-2-2, Article 72-4, …

(2) - (5) (Omitted)

(6) The Minister of Health, Labour and Welfare or each prefectural governor … may, where found it necessary beyond those specified in the preceding paragraphs, have … a marketing license holder, a manufacturer or a seller of pharmaceuticals, quasi-

pharmaceuticals … make necessary reports pursuant to the provisions of Order of the Ministry of Health, Labour and Welfare, or have the officials in charge inspect … the factories … and other sites where pharmaceuticals, quasi-pharmaceuticals … be dealt with in its business, or examine relevant premises/equipment, records/documents and any other articles, or ask questions to employees and other concerned persons, or confiscate articles suspected to be those provided in Article 70, paragraph (1) in minimum amount for testing/analysis samples.

(7) (Omitted)

(8) The officials in charge must, upon implementing on-site inspections, questioning or sample confiscation pursuant to the provisions of the preceding paragraphs, carry the certificate for their status, and show it when requested by any person concerned.

(9) The authorities as provided in paragraphs (1) to (7) must not be construed as those allowed for the purpose of criminal investigation.

(On-site Inspection, etc. conducted by the PMDA)

Article 69-2 (1) The Minister of Health, Labour and Welfare may have the PMDA conduct on-site inspection or questioning pursuant to the provisions of the preceding Article, paragraph (1) … or on-site inspections, questioning or sample confiscation pursuant to the provisions of the same Article, paragraph (6), with specified by Cabinet Order.

(2) Each prefectural governor may have the PMDA conduct on-site inspection or questioning pursuant to the provisions of the preceding Article, paragraph (1) or on-site inspections, questioning or sample confiscation under paragraph (6) of the same Article, with specified by Cabinet Order.

(3) The PMDA must, where conducted an on-site inspection, questioning or sample confiscation specified by Cabinet Order pursuant to the provisions of paragraph (1) pursuant to the provisions of the same paragraph, notify the result of such an on-site inspection, questioning or sample confiscation to the Minister of Health, Labour and Welfare, pursuant to the provisions of Order of the Ministry of Health, Labour and Welfare, or where conducted an on-site inspection, questioning or sample confiscation specified by Cabinet Order pursuant to the provisions of the preceding paragraph pursuant to the provisions of the same paragraph, notify the outcome of such an on-site inspection, questioning or sample confiscation to the prefectural governor, in accordance with the provisions of Order of the Ministry of Health, Labour and Welfare.

(4) PMDA officials who are engaged in operations for on-site inspections, questioning or sample confiscation specified by Cabinet Order as provided in paragraph (1) or paragraph (2) must have been qualified as specified by Cabinet Order.

(5) PMDA officials as provided in the preceding paragraph must, when implementing on-site inspections, questioning or sample confiscation specified by Cabinet Order as provided in paragraph (1) or paragraph (2), carry the certificate for their status, and show it when requested by any person concerned.

(Orders for Rectification, etc.)

Article 72 (1) (Omitted)

(2) The Minister of Health, Labour and Welfare may, in the case where the methods of manufacturing control or quality control for the item at manufacturing sites thereof do not comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in Article 14, paragraph (2), item (iv) …, or where pharmaceuticals, quasi-pharmaceuticals … as provided in Article 56 … or biological origin products as provided in Article 68-20 may occur due to such methods of manufacturing control or quality control, order the marketing

license holder of such pharmaceuticals, quasi-pharmaceuticals … (excluding marketing license holder that has been appointed pursuant to the provisions of Article 19-2, paragraph (3) for marketing foreign-manufactured pharmaceuticals, etc. … ; hereinafter the same applies in this paragraph) or the manufacturers of such pharmaceuticals, quasi-pharmaceuticals … to be exported as provided in Article 80, paragraph (1) …, to rectify such methods of manufacturing control or quality control, or to suspend all or part of the operations until such rectification implemented. (3) - (5) (Omitted)	any of the following items, withdraw all or part of the product authorization obtained by such authorization holder: (i) and (ii) (Omitted) (iii) in the case where the Minister of Health, Labour and Welfare finds it necessary to have the officials in charge inspect relevant premises/equipment or records/documents and any other articles at the factories … and other sites, or ask questions to employees and other concerned persons, at factories of the holder of such authorization or other sites where pharmaceuticals, quasi-pharmaceuticals … be dealt with in its business, and when such inspections are refused, obstructed or avoided, or replies to such questioning are failed without justifiable reasons or false replies are given; (iv) and (v) (Omitted)
(Withdrawal of authorization) Article 74-2 (1) and (2) (Omitted) (3) Beyond the cases specified in the preceding two paragraphs, the Minister of Health, Labour and Welfare may, in the case where a holder of authorization as provided in Article 14 … for a pharmaceutical … falls under any of the following items, withdraw such authorization, or order such marketing authorization holder to change certain part of matters within the marketing authorization: (i) and (ii) (Omitted); (iii) in the case where such marketing authorization holder has violated the provisions of Article 14, paragraph (7) or paragraph (9) …; (iv) (Omitted); (v) in the case where such marketing authorization holder does not obey an order pursuant to the provisions of Article 72, paragraph (2); (vi) and (viii) (Omitted)	(2) The provisions of Article 72, paragraph (2), Article 74-2, … paragraph (3) (excluding … item (iv)) apply mutatis mutandis to product authorization pursuant to the provisions of Article 19-2 …. In this case, with regard to provisions in Article 72, paragraph (2), "order" is to be replaced with "request", "Article 14, paragraph (2), item (iv) …" is to be replaced with "Article 14, paragraph (2), item (iv) applied mutatis mutandis as provided in Article 19-2, paragraph (5) …", and "or to suspend all or part of the operations until such rectification implemented" is not to be applied, … with regard to provisions in Article 74-2, paragraph (3), "the preceding two paragraphs" is to be replaced with "Article 74-2, paragraph (1) and paragraph (2) applied mutatis mutandis as provided in Article 75-2-2, paragraph (2)", "order" is to be replaced with "request", … and "Article 14, paragraph (7) or paragraph (9) …" is to be replaced with "Article 14, paragraph (7) or paragraph (9) … applied mutatis mutandis as provided in Article 19-2, paragraph (5)", …. (3) (Omitted)
(Withdrawal of Authorization for Marketing of Pharmaceuticals, etc. Manufactured in Foreign Countries) Article 75-2-2 (1) The Minister of Health, Labour and Welfare may, in the case where a holder of authorization as provided in Article 19-2 fall under	

(4) The Minister of Health, Labour and Welfare may have the PMDA conduct on-site inspections and questioning pursuant to the provisions of paragraph (1), item (iii), with specified by Cabinet Order. In this case, the PMDA must, where conducted such on-site inspections or questioning, notify the outcome of such on-site inspections or questioning to the Minister of Health, Labour and Welfare, in accordance with the provisions of Order of the Ministry of Health, Labour and Welfare.

(Revocation of Accreditation for Foreign Manufacturers for Pharmaceuticals, etc. …)

Article 75-4 (1) The Minister of Health, Labour and Welfare may, in the case where a foreign manufacturer accredited as provided in Article 13-3, paragraph (1) … falls under any of the following items, revoke whole or part of the accreditation obtained by such accreditation holder:

(i) in the case where the Minister of Health, Labour and Welfare finds it necessary to request the foreign manufacturer been accredited as provided in Article 13-3, paragraph (1) …, to report in needed pursuant to the provisions of Order of the Ministry of Health, Labour and Welfare, and when such report is failed or false report is made;

(ii) in the case where the Minister of Health, Labour and Welfare finds it necessary to have the officials in charge inspect relevant premises/equipment, documents/records or some other item, or ask questions to employees and other concerned persons, at the factories … of the foreign manufacturer accredited as provided in Article 13-3, paragraph (1) or other sites where pharmaceuticals, quasi-pharmaceuticals … be dealt with in its business, and when such inspections are refused, obstructed or avoided, or replies to such questioning are failed without justifiable reasons or false replies are given;

(iii) in the case where the foreign manufacturer does not obey a request pursuant to the provisions of Article 72, paragraph (3) applied mutatis mutandis as provided in the following paragraph;

(iv) in the case where the foreign manufacturer has violated this Act or the other laws and regulations on pharmaceutical affairs which has been specified by Cabinet Order, or any of the dispositions implemented based upon those laws and regulations.

(2) (Omitted)

(3) The provisions of Article 75-2-2, paragraph (4) apply mutatis mutandis to inspections and questioning pursuant to the provisions of paragraph (1), item (ii).

(Pharmaceutical Affairs Inspectors)

Article 76-3 (1) The Minister of Health, Labour and Welfare, each prefectural governor … is to have pharmaceutical affairs inspectors appointed among officials of the government, prefecture …, in order to have such officials in charge execute authorities as provided in Article 69, paragraphs (1) to (6) … .

(2) Besides those provided in the preceding paragraph, necessary matters regarding pharmaceutical affairs inspectors are to be provided by Cabinet Order.

Article 80 (1) Manufacturers of pharmaceuticals, quasi-pharmaceuticals … for export must, in the case where their pharmaceuticals, quasi-pharmaceuticals … manufactured are those specified by Cabinet Order, undergo document-based or on-site investigation by the Minister of Health, Labour and Welfare, regarding whether the methods of manufacturing control or quality control for such items at manufacturing sites thereof comply with the standard which is provided by Order of the Ministry of Health, Labour and Welfare as provided in Article 14, paragraph (2), item (iv), before commencement of manufacture thereof, and in every period of not less than three years specified by Cabinet Order after commencement of manufacture thereof.

(2) - (9) (Omitted)

Article 84-4 (Omitted)

Article 87, and Article 90, item (ii)

A person/corporation falling under any of the following items is to be punished by a fine of not more than 500,000 yen:

(i)-(xii) (Omitted);

(xiii) a person/corporation that has failed reports pursuant to the provisions of Article 69, paragraph (1) to paragraph (6) … or given false reports, or refused, obstructed or avoided an on-site inspection pursuant to the provisions of Article 69, paragraph (1) to paragraph (6) … (includes those conducted by the PMDA pursuant to the provisions of Article 69-2, paragraph (1) and paragraph (2)) or a confiscation pursuant to the provisions of Article 69, … paragraph (6) (includes those conducted by the PMDA pursuant to the provisions of Article 69-2, paragraph (1) and paragraph (2)), or failed replies to questioning pursuant to the provisions of Article 69, paragraphs (1) to (6) … (includes those conducted by the PMDA pursuant to the provisions of Article 69-2, paragraph (1) and paragraph (2)) without justifiable reasons or given false replies;

(xiv)-(xvii) (Omitted).

Appendix 4; Form for written notice of deficiencies identified

Date of issuance: YYYY/MM/DD

Written notice of deficiencies identified during a GMP investigation

To: Name of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of corporation, the company's name)
Mr./Ms. [name of the responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation]

Responsible Inspector for the GMP investigation:
[name, title, and the belonging department/section]
Other Implementing Inspector(s):
[name, title, and the belonging department/section]

This written notice is notifying that deficiencies as shown in the following descriptions have been found during the GMP investigation implemented on YYYY/MM/DD.

Regarding each of the deficiencies, you are requested to submit written report on corrective/preventive action plan or written report on corrective/preventive action outcome, to [the conducting GMP inspectorate agency] by YYYY/MM/DD.

In addition, with regard to critical or major deficiencies, you are requested to report to relevant marketing license holder of the item (product) concerned with such deficiencies.

Descriptions

1. Reference number
2. Name of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, the company's name)
3. Address of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, location of the main office)
4. Name of the manufacturing site which has been investigated
5. Location of the manufacturing site which has been investigated
6. License/Registration/Accreditation number for the manufacturing site which has been investigated
7. Scope of the GMP investigation
8. Identified deficiencies;

(i) Critical deficiencies
(ii) Major deficiencies
(iii) Other deficiencies

Points to consider for describing a written notice of deficiencies identified during a GMP investigation

1. In the case where several manufacturing sites have been practically investigated, a written notice of deficiencies identified during such GMP investigation is to be documented for each of such manufacturing sites, in principle.
2. In the case of a written notice of deficiencies identified during a GMP investigation with multiple pages, the responsible inspector is to document the written notice with numbering of page, etc. for each page thereof in order to make clear that it is a series of document.
3. "Date of issuance" is to be described with the date when the written notice is to be issued for the manufacturer/foreign manufacturer subjected to the GMP investigation.
4. In the case where a written notice of deficiencies identified during a GMP investigation is issued by the organization of GMP inspectorate agency conducting the GMP investigation, "Responsible Inspector for the GMP investigation" and "Other Implementing Inspector(s)" may be replaced with "Conducting GMP inspectorate agency" to describe.
5. "Identified deficiencies" is to be described for each classification of the deficiencies, with referring the order of those sub-systems as listed in Table III.
6. For "Identified deficiencies", their reasons, etc. based upon the facts practically confirmed is to be described clearly and concisely. Matters not based upon the provisions in the Ministerial Order on GMP should not be described.
7. "Identified deficiencies" is to be described so as to show ratios, etc. of the deficiencies confirmed; e.g., "Two deficient records are found among the thirty records examined."
8. In the descriptions of "Identified deficiencies", name of a specific person is not to be shown, which is to be indicated such as "a personnel B". On the other hand, in investigation finding reports, name of a specific person may be indicated as far as not problematic, and as necessary, linkage with descriptions in the written notice of deficiencies during the GMP investigation is to be mentioned.
9. A written notice of deficiencies identified during a GMP investigation is to show clearly points of the identified deficiencies upon specific facts objectively confirmed. In addition, it is to explain their interpretation (e.g., what is the matter, why is the matter, what are risks with the matter.), and to give a course, etc. of their rectification as necessary.

Appendix 5;
Form for written report on corrective/preventive action plan/outcome

Written report on corrective/preventive action plan/outcome for deficiencies identified during a GMP investigation

Name of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, the company's name)	
Address of the manufacturer/foreign manufacturer subjected to the GMP investigation (in the case of a corporation, location of the main office)	
Name of the manufacturing site which has been investigated	
Location of the manufacturing site which has been investigated	
[License/Registration/Accreditation] number for the manufacturing site which has been investigated	
The item (product) or type of manufacturing activity, subjected to the GMP investigation	
corrective/preventive action plan/outcome	

To: the conducting GMP inspectorate agency

Regarding the deficiencies that are notified by the written notice of deficiencies identified during a GMP investigation (Reference number:

XXXX), which has been issued on YYYY/MM/DD, we submit a report on the corrective/preventive action plan/outcome as above. With regard to those that rectification has not been completed, upon rectified shortly according to the corrective/preventive action plan, we will submit follow-up report for that.

Date of the reporting: [YYYY/MM/DD]
Responsible person of the manufacturer/foreign manufacturer subjected to the GMP investigation:
[Name, title, and the belonging department/section]

Appendix 6; Form for annual report on implementation of GMP investigations

Annual report on GMP investigations conducted [from YYYY/MM/DD to YYYY/MM/DD]

Prefectural number	Name of the conducting GMP inspectorate agency	Implementation date of the GMP investigation	Type of the GMP investigation	Name of the manufacturing site investigated	Name of the item (product) subjected to the GMP investigation	GMP conformity status	On-site / Document-based	Remarks
****	Prefectural inspectorate in xxx	YYYY/MM/DD	Pre-authorization conformity assessment	XXX pharma Inc. Ltd. xxx plant	xxx tablets ** mg xxx granules ** %	Compliance	On-site	

[Points to consider for reporting]

1. Implementation of GMP investigations conducted in each fiscal year (from April 1st to March 31st of the next year) is to be reported to the Compliance and Narcotics Division, Pharmaceutical Safety Bureau, MHLW, by end of April for each next fiscal year.
2. This report is to be submitted in electronic form (Excel format). In order to function the spreadsheet for aggregation, any column is not to be inserted/deleted.
3. In the case where two or more types of GMP investigation have been implemented at once, one row is to be entered for each type of the GMP investigation.
4. Each field is to be entered according to the followings;

(1) For the field of "Name of the conducting GMP inspectorate agency", "PMDA" or name of the prefecture is to be entered. In the case of PMDA, "99" is to be entered into the field of "Prefectural number".

(2) For the field of "Implementation date of the GMP investigation", date of the final day for implementation period of the GMP investigation is to be entered.

(3) For the field of "Type of the GMP investigation", any of either "Pre-authorization conformity assessment", "Pre-authorization conformity assessment for partial change of an existing authorization", "Routine conformity assessment with regard to an existing authorization", "Conformity review with regard to PACMP", "Conformity assessment by types of manufacturing activities", "GMP assessment for investigational drugs", "Initial conformity assessment for certifying an exporting product", "Routine conformity assessment for certifying

an exporting product", "Regular surveillance (on-site inspection with announce)", "Regular surveillance (on-site inspection without announce)", "For-case inspection with announce", or "For-case inspection without announce". In the case of on-site inspections, "with" or "without" announce is to be according to whether date of the inspection was informed in advance.

(4) For the field of "Name of the manufacturing site investigated", name of the manufacturing site that is indicated on the license/registration/accreditation certificate is to be entered.

(5) For the field of "Name of the item (product) subjected to the GMP investigation", the representative items (products) subjected to the GMP investigation are to be entered; however, all the items (products) subjected to the GMP investigation may be listed up.

(6) a. For the field of "GMP conformity status", either "Compliance" or "Non-compliance" is to be entered; however, in the case where it has not decided yet upon reporting, "Not decided" is to be entered.

b. In the case where "Not decided" is entered according to the above, "the GMP conformity status is to be shown within the next annual report" is to be described in the field of "Remarks".

c. In the case where conformity status is shown within the next annual report according to the above, upon reporting in the next fiscal year, such GMP investigation for the manufacturing site is to be entered in addition, and "Report for the previous fiscal year" is to be described in the field of "Remarks".

(7) For the field of "On-site / Document-based", method for the GMP investigation (on-site or document-based) is to be entered.

Pharmaceuticals or investigational drugs / Quasi-pharmaceuticals		On-site GMP investigation		*** investigations in subtotal		Document-based GMP investigation		*** investigations in subtotal	
Type of GMP investigation	*** investigations in total (on-site and document-based)	Manufacturing site other than packaging / labeling / quarantine only and storage site	Packaging / labeling / quarantine only or storage site	Laboratory for quality control	Others	Manufacturing site other than packaging / labeling / quarantine only and storage site	Packaging / labeling / quarantine only or storage site	Laboratory for quality control	Others
Pre-authorization conformity assessment									
Pre-authorization conformity assessment for partial change of an existing authorization									
Routine conformity assessment with regard to an existing authorization									
Conformity review with regard to PACMP									
Conformity assessment by types of manufacturing activities									

GMP assessment for investigational drugs [6]									
Initial conformity assessment for certifying an exporting product									
Routine conformity assessment for certifying an exporting product									
Regular surveillance (on-site inspection with announce)									
Regular surveillance (on-site inspection without announce)									
For-case inspection with announce									
For-case inspection without announce									

[6] **Translation annotation**; "Investigational drugs" are not considered as "pharmaceuticals" under the PMD Act. The Notification on GMP for Investigational Drugs (Notification No. 0709004 from Director General of the Pharmaceutical and Food Safety Bureau, MHLW, dated on July 9, 2008) (not the Ministerial Order on GMP) provides GMP requirements for investigational drugs, pursuant to the provisions of Article 17, paragraph (1) and Article 26-3 of the Ministerial Order on GCP (Order of the MHLW No. 28 of 1997).

Annex 1; Qualifications for GMP inspectors

		Regular Inspector	Chief Inspector	Senior Inspector
Criteria for qualification		Having acquired necessary knowledge for GMP inspector.	i) Being capable to perform roles such as planning of a GMP investigation according to characteristics of the item (product) subjected to the GMP investigation, assessment of deficiencies identified, and documentation of a GMP investigation finding report, and ii) Being capable to modify a GMP investigation plan flexibly according to observations at the site.	i) Having acquired knowledge and investigation skill according to characteristics of the item (product) subjected to the GMP investigation, and ii) Being capable to lead and instruct for other GMP inspectors including chief inspector.
How to certify Note (i)		Qualification thereof is to be certified by the quality manager of GMP investigations at the GMP inspectorate agency.	i) Qualification for chief inspector is to be certified for each of five qualification categories ("chemical active ingredients", "non-sterile products", "sterile products note (vi)", "biological pharmaceuticals", and "packaging/labeling/quarantine"), and ii) Qualification thereof is to be certified by the quality manager of GMP investigations at the GMP inspectorate agency.	Qualification thereof is to be certified by the quality manager of GMP investigations at the GMP inspectorate agency.
Requirements for qualification	Attributes	i) Having been educated to acquire knowledge and ability equivalent or more than graduation from a science college, and	i) Satisfying the qualification for regular inspector, ii) Being excellent in observant, adaptability and decision-making, and	i) Satisfying the qualification for chief inspector, ii) Having sufficient competence for practical work and expertise, iii) Being superior autonomous and

	ii) Having personal attributes as shown in ISO 19011.	iii) Having expertise for the qualification category to be certified.	sociable personality, and iv) Having expertise for the qualification category to be certified.
Training Note (ii) and (iii)	To receive education/ training for 40 hours or more (includes on-the-job training), regarding the following items; i) Education on the related law and regulations in Japan (e.g., the PMD Act, the Japanese Pharmacopoeia, the Requirements for Premises/Equipment, the Ministerial Order on GMP, validation guideline, the PIC/S GMP Guide, and other relevant notifications), ii) Concept of GMP, and its practical approaches, and iii) Education on processes of GMP investigations (e.g., the current GMP Investigation Guide, procedures, etc. for GMP investigations, on-site inspections, and sample confiscation).	To receive education/training systematically, regarding the following items, however, regarding items of ii)-iv) are to be subjected to education/training as necessary; i) Training/education on technique for GMP investigations (planning of individual GMP investigations, assessment for identified deficiencies, and how to document GMP investigation finding report (includes on-the-job training)), ii) Education on international trend (e.g., understanding of quality assurance system of ISO 9000 or others, knowledge of MRA and other bilateral agreements, understanding of regulatory implementations in overseas (EDQM, ICH, PIC/S, WHO)), iii) Technical knowledge according to type of items (products) (e.g., production technologies at manufacturing sites for pharmaceutical preparations and their active ingredients, characteristics of production facilities and utilities, methods for	To receive education/training systematically, regarding the following items; i) Education/training on knowledge and skill as an instructor for other GMP inspectors, and ii) Further advanced and up-to-date knowledge and concept on GMP.

		validation, analytical technique, microbiological knowledge), and iv) Up-to-date knowledge and concept on GMP (e.g., understanding of relevant ICH guidelines on pharmaceutical development/risk management/pharmaceutical quality system and others, knowledge of computerized system).	
Experience Note (ii) and (iii)		Being experienced as listed in the following items; i) Job experience engaging in GMP related work; Four years or more (in the case of person licensed as a pharmacist, two years or more in principle) of such job experience (includes job experience engaging in pharmaceutical surveillance/supervision or review of pharmaceutical authorization applications, as well as job experience engaging in pharmaceutical quality assurance work/pharmaceutical development at a pharmaceutical company Note (iv)), and one year or more of job experience engaging in GMP investigations Note (v) among such period above is required, ii) Having participated in one or more	

			joint mock-inspection (includes joint inspection exercise convened by National Institute of Public Health) or joint GMP investigation with PMDA (refers to a GMP investigation implemented by GMP inspectors of both of a prefectural GMP inspectorate agency and PMDA, on site of the same manufacturing site; however, excludes attendance for observing of GMP investigation), iii) Other than in the case of qualification category of packaging/labeling/quarantine, having experienced GMP investigations covering all sub-systems (processing, testing/ analysis, packaging/labeling, quarantine, control for starting materials and packaging/labeling materials, quality system), and being evaluated as having understanding on those sub-systems, and iv) With regard to the qualification category to be certified (each of "chemical active ingredients", "non-sterile products", "sterile products Note (vi)", "biological pharmaceuticals", and "packaging/ labeling/quarantine"), having	

			experienced five or more GMP investigations (include joint mock-inspection, and attendance for observing a GMP investigation).	
	Follow-up after qualified Note (ii) and (iii)	To receive education/ training in accordance with annual programme (for 10 days or more a year, covers self-learning, seminars, study session, conferences, on-the-job training, etc.)	i) To receive education/training in accordance with annual programme (for 10 days or more a year, covers self-learning, seminars, study session, conferences, on-the-job training, etc.), and ii) Experience in on-site GMP investigations as chief inspector and qualification thereof is to be certified.	i) To receive education/training in accordance with annual programme (for 10 days or more a year, covers self-learning, seminars, study session, conferences, on-the-job training, etc.), and ii) Experience of senior inspector and instructor, etc., and qualification thereof is to be certified.
Requirements for coming back to GMP inspector after blank of the job		To acquire knowledge on the law and regulations, guidelines, and written procedures, etc. that have been changed during blank of the job.	i) To acquire knowledge on the law and regulations, guidelines, and written procedures, etc. that have been changed during blank of the job. ii) To acquire knowledge for each qualification category that has been changed during blank of the job, and knowledge necessary for implementing GMP investigations.	i) To acquire knowledge on the law and regulations, guidelines, and written procedures, etc. that have been changed during blank of the job. ii) To acquire knowledge for each qualification category that has been changed during blank of the job, and knowledge necessary for implementing GMP investigations.

Points to consider

Note (i); In the case of an official who has experience in GMP investigations in former times, and where records of its education/training are not retained, such officials may be qualified after received necessary education/training again, and when certified for relevant qualification requirements.

Note (ii); Each prefectural GMP inspectorate is to establish its education/training programme in order to meet qualification requirements for chief inspector of necessary qualification categories, according to types of the manufacturing sites located in its prefecture.

Note (iii); Records of education/training for each individual official are to be documented and retained.

Note (iv); Job experience engaging in pharmaceutical surveillance/supervision includes such as regulatory operations for manufacturers of pharmaceuticals/quasi-pharmaceuticals, medical devices/in-vitro diagnostics and regenerative products (GMP, QMS and GCTP and manufacturing licensing/registration), regulatory operations for marketing license holders thereof (GQP, GVP and marketing licensing), compliance operations for credibility of clinical/non-clinical study (GCP and GLP) and other authorization related operations, regulatory operations for pharmacies/pharmaceutical sellers, regulatory testing/analysis operations on pharmaceuticals and others.

Completion of the 5-week training course convened by National Institute of Public Health is equivalent to one-year job experience in pharmaceutical surveillance/supervision; however, it is not to be counted as job period engaged in GMP investigations.

Note (v); With regard to job experience engaging in GMP investigations, number of GMP investigations involved is also to be taken into consideration.

Note (vi); With regard to qualification category for radiopharmaceuticals, it is sufficient that such qualification is to be certified after receiving necessary education/training to be chief inspector for qualification category for sterile products.

Annex 2; Qualifications for official accredited laboratories

Qualifications to be satisfied by official accredited laboratories, which perform regulatory testing/analysis on pharmaceuticals, etc.

1. Scope

This Annex specifies qualifications for official accredited laboratories, which perform regulatory testing/analysis on pharmaceuticals and quasi-pharmaceuticals (hereinafter these are referred to as "pharmaceuticals, etc."), so that such official accredited laboratories are suitably managed, and suitability of testing/analytical results to be provided is ensured.

2. Terminology

(i) The term "official accredited laboratory" means an organization which has been officially accredited by MHLW or a prefectural authority, as quality control laboratory for performing testing/examination contracted by a GMP inspectorate agency.

(ii) The term "samples" (refers to pharmaceuticals, etc. to be subjected to regulatory testing/analysis) means testing/analytical samples that have been taken and obtained by MHLW, PMDA or prefectural authority, or samples that have been confiscated pursuant to the provisions of Article 69, paragraph (6) in the PMD Act, and Article 69-2, paragraphs (1) and (2) in the same Act.

(iii) The term "entruster" means an organization outsourcing testing/analysis on pharmaceuticals, etc.; in the case of a national quality control laboratory, MHLW, and in the case of a prefectural quality control laboratory, the prefectural authority.

3. Organization

Head of an official accredited laboratory must, in order to ensure integrity of testing/analytical data, put in place a person/group engaging in reliability assurance activities that is independent from section engaging in testing/analytical operations (hereinafter referred to as "reliability assurance unit").

4. Personnel

Head of an official accredited laboratory must, in order to enable to implement suitable and timely testing/analytical operations and reliability assurance activities, appoint responsible persons in each of section/unit engaging in testing/analytical operations and reliability assurance activities.

5. Premises/equipment

An official accredited laboratory is to have facilities necessary for performing testing/analysis to be undertaken, testing/analytical equipment, and relevant utilities.

6. Written procedures

Head of an official accredited laboratory must, in order to perform testing/analysis suitably at each of the facility, establish documents specifying procedures, etc. as listed in the following (hereinafter refers to as "written procedures, etc."), and maintain such written procedures;

(i) Matters of agreement regarding the contract for testing/analysis to be undertaken,
(ii) Procedures for receiving samples,
(iii) Procedures for performing testing/analysis (includes sanitation control, calibration, validation for testing methods, and others),
(iv) Procedures for issuing reports on testing/analytical results,
(v) Procedures for management of information on suitability of testing/analytical results, and of deficit matters, etc. during testing/ analytical operations,
(vi) Procedures for change management,
(vii) Procedures for deviation management,
(viii) Procedures for internal audit,
(ix) Procedures for education/training,
(x) Procedures for management of documents/records,
(xi) Procedures for implementing management review,
(xii) Procedures for declaration for conflict of interest and others, and
(xiii) Other procedures necessary for performing suitable and timely testing/analysis.

7. Agreement

Head of an official accredited laboratory must, with regard to entrusted testing/analysis on samples, document an agreement with head of the entruster (e.g., retention of documents/records, audits by the entruster, instructions for improvement of the operations), and retain such agreement.

8. Testing/analysis

(i) Testing/analytical section must, in accordance with the written procedures, etc., implement systematical and suitable operations of testing/analysis on samples.
(ii) With regard to sampling for testing/analysis, sample retention, preparation of testing/analytical reagents, testing/analytical operations, calculation processing of testing/analytical data, and others, records

thereof must be documented and retained.

(iii) Equipment and instruments related to testing/analysis must be regularly checked and maintained, and records thereof must be documented and retained. In addition, measuring instruments must be suitably calibrated, and records thereof must be documented and retained.

9. Issuance of reports on testing/analytical results

(1) Each official accredited laboratory is to document a report on testing/analytical results, that results of the testing/analysis performed are described, and to issue such report to the entruster.

(2) Upon issuing a report on testing/analytical results, head of the official accredited laboratory must have its appointed section conduct, in accordance with the written procedures, etc., tasks suitably evaluating results of the testing/analysis, and having documentation of the report on testing/analytical results.

10. Suitability verification for testing/analytical methods

Head of an official accredited laboratory must have its appointed personnel conduct the following tasks in accordance with its written procedures, etc.;

(i) In the following cases, to verify suitability of the testing/analytical methods;

(a) in the case where any testing/analysis is newly introduced, or

(b) in the case where any major change of testing/analytical procedures is introduced,

(ii) to verify suitability of the testing/analytical methods, in regular basis.

11. Change management

Upon introducing any change of testing/analytical procedures or other which may cause impact on the testing/analytical data, head of the official accredited laboratory must, have its appointed personnel conduct the following tasks in accordance with its written procedures, etc.;

(i) to assess impact on the testing/analytical data by the change, and based upon outcome of such assessment, to have endorsement by the reliability assurance unit for introducing the change, and to document and retain records thereof, and

(ii) to revise relevant documents, to conduct education/training for relevant personnel, and to take other necessary actions, upon implementing a change with endorsement by the reliability assurance unit pursuant to the provisions in the preceding item.

12. Deviation management

In the case where any deviation from testing/analytical procedures, etc., or any testing/analytical data out of the specification has occurred, head of the official accredited laboratory must have its appointed personnel conduct the following tasks in accordance with the written procedures, etc.;

(i) to record details of the deviation,

(ii) In the case where any significant deviation has occurred, to conduct the following tasks;

(a) to assess impact on the testing/analytical data by the deviation, and to take necessary actions,

(b) to document and retain records of outcome of the assessment and actions taken as provided in the preceding (a), and to report them in written to the reliability assurance unit, and

(c) to have the assessment outcome and actions reported pursuant to the provisions of the preceding (b) checked by the reliability assurance unit.

13. Management of information on suitability of testing/analytical results, and of deficit matters, etc. during testing/analytical operations

In the case where any complain, etc. on an issued report on testing/analytical results has been received, head of the official accredited laboratory must have its appointed personnel conduct the following tasks in accordance with the written procedures, etc.;

(i) to investigate the cause of matters concerning such complain, etc., and in the case where any rectification with regard to testing/analytical operations or others is needed, to take necessary actions, and

(ii) to document and retain records describing detail of such complain, etc., the investigation outcomes, and the actions for rectification, to report such records in writing to the reliability assurance unit, and to have such records checked by the reliability assurance unit.

14. Internal audit

Head of an official accredited laboratory must have its appointed personnel conduct the following tasks in accordance with its written procedures, etc.;

(i) to conduct regular internal audits on testing/analytical operations overall at the official accredited laboratory, and

(ii) to document and retain records of the internal audit outcomes.

15. Education/training

Head of an official accredited laboratory must have its appointed personnel conduct the following tasks in accordance with its written procedures, etc.;

(i) for personnel that are engaging in reliability assurance or testing/analytical operations, to systematically implement necessary education/training, and

(ii) to document and retain records of the education/training.

16. Management of documents/records

Head of an official accredited laboratory must have its appointed personnel conduct the following matters regarding documents/records specified within this Annex, in accordance with its written procedures, etc.;

(i) upon establishing or revising a document, to endorse, distribute, archive, etc. such document,

(ii) upon establishing or revising written procedures, etc., to record dates of the establishment/revision on such written procedures, etc., and to retain records of the history of previous revisions, and

(iii) to retain documents/records specified within this Annex, in accordance with the agreement.

17. Management review

Head of an official accredited laboratory must, in accordance with its written procedures, etc., implement management review for each fiscal year in principle, to confirm that its Quality Management Oversight System has been maintained, and take actions for rectifying problems occurred.

18. Declaration for conflict of interest and others

Head of an official accredited laboratory must, in order to ensure reliability of testing/analytical data, have its appointed personnel conduct the following tasks in accordance with its written procedures, etc.;

(i) to have the personnel concerned comply with the code of ethics and others prescribed at the official accredited laboratory, and to confirm their declaration for conflict of interest every fiscal year in principle, and

(ii) to ensure that any personnel with conflict of interest not to be engaged in testing/analytical operations.

19. Oversight

Head of an official accredited laboratory must seek confirmation of conformity with this Annex, to its entruster every fiscal year.

Annex 3; Criteria for concluding GMP conformity

Criteria for concluding GMP conformity

1. Conformity with the Ministerial Order on GMP is to be assessed for each item (product) or each type of manufacturing activities. Matters required regardless of item or type of manufacturing activity are also to be evaluated as matters concerned with the item (product) or the type of manufacturing activity, which is subjected to GMP conformity assessment.

2. Classification of deficiencies

Upon concluding GMP conformity, it is to be decided for each matter found by the GMP investigation whether it is a deficiency (refers to a matter violating any provision in the Ministerial Order on GMP, or a matter needed for any rectification in order to ensure more suitable operations of production control/quality control; hereinafter the same applies) or not; and each deficiency is to be classified according to the following concepts. Related matters may be treated comprehensively, and classified as one deficiency.

(1) Critical deficiency:

A case where a deficiency identified is a violation of any provision in the Ministerial Order on GMP, and falls into any of the followings;

- Any products hazardous to patients (consumers) have been manufactured, or any significant risk which may cause such products has been identified, or
- With regard to products or records, any falsification or false statement or dishonest alteration by the manufacturer/foreign manufacturer has been identified.

(2) Major deficiency;

A case where a deficiency identified is a violation of any provision in the Ministerial Order on GMP, but does not fall into “critical deficiency”.

(3) Other deficiency;

A case where a deficiency identified is not definitely a violation of any provision in the Ministerial Order on GMP, but a matter needed for any rectification in order to ensure more suitable operations of production control/quality control.

3. Concluding GMP conformity status

Whether the GMP conformity status is falling under Article 14, paragraph (2), item (iv) of the PMD Act (includes applied mutatis mutandis as provided in Article 19-2, paragraph (5) of the same Act, and referred in Article 80, paragraph (1) of the same Act and Article 96 of the Enforcement

Regulation of the PMD Act (Order of the MHLW No. 1 of 1961); the same applies hereinafter) is to be decided according to the following concepts, based upon each of deficiencies classified as shown in the Section 2. above. For deciding as "compliance" in result of a GMP conformity assessment, it is needed that prospective validation on critical steps of manufacturing processes (includes validation for changing such processes) are completed, in principle.

(1) In the case where any deficiency is not identified:

Since the methods of manufacturing control and quality control at the manufacturing site are not falling under Article 14, paragraph (2), item (iv) of the PMD Act, the GMP conformity status can be decided as "compliance".

(2) In the case where identified deficiencies are "other deficiencies" only:

Since the methods of manufacturing control and quality control at the manufacturing site are not falling under Article 14, paragraph (2), item (iv) of the PMD Act, the GMP conformity status can be decided as "compliance"; however, each of the deficiencies are to be pointed out for the manufacturer/foreign manufacturer subjected to the GMP investigation by means of issuing a written notice of deficiencies identified during the GMP investigation, and submitting a written report on corrective/preventive action plan/outcome for such deficiencies is to be requested. After confirming details of such reported corrective/preventive action plan/outcome, the GMP investigation is to be closed. In this case, rectification status thereof is to be examined upon conducting the next routine GMP conformity assessment or other.

(3) In the case where any "major deficiency" is included with the identified deficiencies:

With regard to such "major deficiency", the manufacturer/foreign manufacturer subjected to the GMP investigation is to be requested to submit (i) a detailed report on corrective/preventive action outcome, or (ii) a report on practical corrective/preventive action plan, within 30 business days after the date of issuance for the written notice of deficiencies identified during the GMP investigation. After confirming details of such reported corrective/preventive action outcome/plan, unless those are considered as justifiable, the GMP conformity status is to be decided as "non-compliance" in principle. In the case where details of (i) or (ii) above are considered as justifiable, the GMP conformity status can be decided as "compliance"; however, when it is decided as "compliance" based upon (ii) submitted, a report on corrective/preventive action outcome is to be requested for being submitted promptly after completion of such corrective/preventive actions, so that the rectification status is to be examined. In addition, with regard to "other deficiency" identified, it is to be addressed according to (2) above.

(4) In the case where any “critical deficiency” is included with the identified deficiencies:

Unless corrective/preventive actions for such “critical deficiency” is completed within 15 business days after the date of issuance for the written notice of deficiencies identified during the GMP investigation, and those are considered as justifiable by the conducting GMP inspectorate agency, the GMP conformity status is to be decided as “non-compliance” in principle. In the case where such corrective/preventive actions considered as justifiable is completed, the GMP conformity status can be decided as “compliance”; however, it cannot be considered that rectification for “critical deficiency” is implemented for the reason that spontaneous recall of the items (products) concerned with critical deficiency have been commenced.

In addition, “major deficiency” and “other deficiency” identified are to be addressed according to (2) and (3) above.