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Comprehensive Research Projects for Regulatory Science of Pharmaceutical
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Study Related to Quality Management Systems for Pharmaceutical Products
and Medical Devices based on Science and Risk Management

Yukio Hiyama, Ph. D., Section Chief
Division of Drugs, National Institute of Health Sciences

GMP Guideline for Drugs and Quasi-drugs
(Drug Products)

● Study Group Members for Preparation of “GMP Guideline for Drugs and Quasi-drugs, Drug Products” ●

Study Director:

Yukio Hiyama, Ph. D. (Drug Department, National Institute of Health Sciences)

Study Group Members:

Yasuto Koyama (Eli Lilly Japan K.K.,
currently working at Shionogi & Co., Ltd.)
Yoshinori Ii (Ono Pharmaceutical Co., Ltd.)
Yuji Ishii (Shizuoka Prefectural Government)
Kazuhiro Kagawa (Tokyo Metropolitan Government)
Hiroshi Kawamura (Shizuoka Prefectural Government)
Yoshiaki Kii (Mercian Corporation)
Yoko Kurihara (Osaka Prefectural Government)
Yoshiaki Hara (Sartorius K.K.,
currently working at Sartorius Stedium Japan K.K.)
Yoshihiko Yanagihara, Ph. D.
(Pharmaceuticals and Medical Devices Agency)

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The regulatory requirements for the manufacturing control and quality control at manufacturing sites, i.e., the minimum standards to be followed, which may accompany enforcement measures including improvement orders when a nonconformity occurs, include the following: “Ministerial Ordinance for Good Manufacturing Practice for Drugs and Quasi-drugs” (MHLW Ministerial Ordinance No. 176, 2004) (hereinafter referred to as “GMP Ministerial Ordinance for Drugs and Quasi-drugs”) that was revised and issued in accordance with the revised Pharmaceutical Affairs Law that is to come into effect from April 2005, “Regulations for Buildings and Facilities for Pharmacies, etc.” (MHW Ministerial Ordinance No. 2, 1961) (hereinafter referred to as “Regulations for Buildings and Facilities), and the notification “Concerning Establishment and Amendment/Abolition of Ministerial Ordinance and Notifications Related to Manufacturing Control and Quality Control (GMP/QMS) for Pharmaceuticals and Medical Devices in association with the enforcement of the laws related to partial revisions of the Pharmaceutical Affairs Law and Regulations for Agencies of Blood Collection and Donation” (MHLW-PFSB-CND Notification No. 0330001, dated March 30, 2005) (hereinafter referred to as “Enforcement Notification”), in which the interpretations, etc. of the aforementioned regulations are shown, and other related notifications. However, beyond such compliance with the regulatory requirements, further efforts for continuous improvements are required for actual implementation of manufacturing control and quality control of drugs and quasi-drugs (limited to those to which the GMP Ministerial Ordinance for Drugs and Quasi-drugs is applied; the same is applied in the following) by incorporating voluntarily and positively the ICH Q7 Guideline (hereinafter referred to as “Q7”) and requirements shown in the standards and guidance adopted in Western countries, as well as other control methods on which a global consensus has been reached with the progress of knowledge and technology.

1. Introduction

1.1 Objective

In regard to general matters on manufacturing control and quality control of drug products (except for matters related to production of specified drug products such as sterile drugs and biological-origin drugs, etc.), this guideline has been prepared with the

intention of providing, as specifically as possible, control methods that are not clearly specified as requirements in the GMP Ministerial Ordinance for Drugs and Quasi-drugs and other related laws, and that need to be voluntarily addressed according to current knowledge, etc. In this guideline, the word "should" indicates recommendations for applying the relevant matters unless there are alternative control methods that can provide equivalent levels of manufacturing control and quality control. This guideline is not intended to cover safety and health for personnel or environmental protection.

2. Quality Management System

2.1 Principles

- 2.10 Each manufacturer should establish, document, and implement an effective system for supervising quality control. To establish and maintain a quality management system, control supervisors and personnel engaging in manufacturing operations should be actively involved.
- 2.11 The components of the quality management system should encompass the activities necessary for manufacturing control and quality control of drugs or quasi-drugs, as well as organizations and other required resources to implement the activities. In establishing the quality management system, all quality-related activities should be defined and documented.
- 2.12 The quality unit defined under the provision of Article 4, Paragraph 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (including cases to which Article 32 is applied; the same hereinafter) can take the form of multiple divisions or be a single individual, depending upon the size and structure of the organization.
- 2.13 All quality-related activities should be documented at the time they are performed, and the documents should be archived.

- 2.14 Any deviation from established procedures should be documented and explained, and the documents should be archived. Critical deviations for which impacts on product quality cannot be completely ruled out should be handled as defined under the provision of Article 15, Paragraph 1-c of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.
- 2.15 Neither the decision for release from manufacturing sites defined under the provision of Article 12, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as “release decision”), nor the use of products, etc., and packaging/labeling materials in subsequent processes should be implemented before completion of evaluation by the quality unit, unless there are appropriate systems in place to allow for such use (e.g., release from manufacturing sites under quarantine or the use of products or packaging/labeling materials pending completion of evaluation).

2.2 Responsibilities of Quality Unit

- 2.20 The quality unit should be involved in all quality-related matters.
- 2.21 The quality unit should appropriately review, confirm and approve all quality-related documents.
- 2.22 The main responsibilities of the quality unit should not be delegated in order to preserve the independence of the unit. These responsibilities should be documented, and should include but are not necessarily limited to:
- 1) Establishing and maintaining a system for deciding release or rejection for receipt or use of products and packaging/labeling materials in subsequent processes;
 - 2) Reviewing all manufacturing instructions, completed batch records and laboratory control records of critical processes for the lots concerned when the

- release from manufacturing sites is decided¹ ;
- 3) Approving the manufacturing control standard code, hygienic control standard code, and master manufacturing instructions;
 - 4) Approving all procedures influencing product quality;
 - 5) Confirming the results of self-inspections;
 - 6) Approving contract matters related to quality aspects concluded with suppliers of raw materials (except for the contracted matters concluded between Licensed Marketing Approval Holders and suppliers);
 - 7) Confirming the plans and results of validation reported as defined under the provision of Article 13, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs²;
 - 8) Confirming whether an efficient system is used for periodic inspections and maintenance of important buildings and facilities, in addition to those related to laboratory testing/inspection;
 - 9) Confirming whether stability data, from which the date of retest or expiry for use and storage conditions of products can be identified, are available, when necessary.
 - 10) Reviewing product quality (refer to Chapter 2.5); and
 - 11) Confirming the status of implementation of education and training.

¹ With respect to the provision of Article 10, Paragraph 9 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, this guideline stipulates that the quality unit should review whether manufacturing control is appropriately implemented from the standpoint of a third party.

² In this guideline, this is stipulated considering that approval of a validation plan and validation results is originally the responsibility of the quality unit, and that it is necessary for the quality unit to be actively involved in validation.

2.3 Responsibilities of Production Unit

The responsibilities of the production unit should be documented, and should include but are not necessarily limited to:

- 1) The manufacturing instructions defined under the provision of Article 10, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should be prepared in accordance with the product master formula, manufacturing control standard code and hygiene control standard code, as well as the review, approval and distribution of the completed manufacturing instructions;
- 2) Reviewing batch records of all production lots to ascertain whether the instructions made for the relevant lots are completed, and ensuring that the batch records are appropriately prepared, signed and sealed³;
- 3) Making sure that all deviations noted at production are reported to the person predesignated under the provision of Article 15, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, and that the results of the deviation assessments made by the designee are confirmed by the quality unit;
- 4) Confirming hygiene of buildings and facilities defined under the provision of Article 10, Item 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs; while making sure that the relevant buildings and facilities are sanitized and sterilized when necessary;
- 5) Making sure that validation plans and reports that have been prepared by persons predesignated under the provision of Article 13, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs are reported to and reviewed and approved by the quality unit;
- 6) Involving persons predesignated under the provision of Article 14 of the GMP

³ A seal that has been registered for the manufacturer should be used, and it is necessary to establish a control system for use of the relevant seal (locking control by the user, or always carrying the seal, etc).

Ministerial Ordinance for Drugs and Quasi-drugs in assessing impacts of changes in manufacturing procedures on product quality where appropriate; and

- 7) Making sure that new and, when appropriate, modified facilities and equipment are qualified, in addition to the validation-related operations defined under the provision of Article 13 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.

2.4 Self-inspection

2.40 In addition to the self-inspection for manufacturing sites defined under the provision of Article 18 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, self-inspection across the entire operation of the manufacturer should be performed periodically in accordance with the approved schedule.⁴

2.41 Self-inspection results and the required measures to be taken should be brought to the attention of control supervisors. The relevant measures should be completed in a timely and effective manner.

2.5 Product Quality Review

2.50 Regular quality reviews of the products should be conducted by the quality unit with the objective of verifying the consistency of the manufacturing process (hereinafter referred to as “product quality review”). The product quality review should be conducted at least annually, and documented and archived. In addition to the periodic reviews of process control, reviews of at least the following matters should be included in the product quality review:

- 1) A review of results of critical matters related to acceptance testing/inspection of

⁴ In addition to the self-inspection defined under the GMP Ministerial Ordinance for Drugs and Quasi-drugs, quality assurance at manufacturing sites may be implemented as part of the overall quality assurance at the manufacturer. For example, handling of quality information, recall handling, contracts between outsourcers and trustees, and confirmation whether self-inspection has been performed appropriately are included in the operations of self-inspection.

raw materials and packaging/labeling materials, and testing/ inspection related to in-process control, and testing/inspection of products;

- 2) A review of all batches or control units that failed to meet established specification(s);
- 3) A review of all critical deviations or non-conformances and related investigations;
- 4) A review of any changes carried out related to the processes or analytical methods;
- 5) A review of results of the stability monitoring program⁵;
- 6) A review of quality-related returns, complaints and recalls; and
- 7) A review of adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. When corrective actions are required, the reason should be documented, and the documents should be archived. Agreed corrective actions should be completed in a timely and effective manner.

2.6 Technology Transfer⁶

2.60 There are two types of technical transfer including that from the R&D to

⁵ This stability monitoring program includes both time-associated stability evaluation by stability monitoring tests and periodic confirmation of product quality (post-marketing stability evaluation).

⁶ The consistency in product quality between the pivotal manufacturing batch in the development stages and the actual manufacturing batch (validated batch) is important for technical transfer from R&D to production. The same has been described in the Q7 12.52. The pivotal manufacturing batch refers to that related to investigational drugs used for phase III clinical studies or biological equivalence studies, and that related to the samples to be used for stability tests for approval application. The aim and importance of assurance of product quality consistency before and after technical transfer should be the same also in the post-marketing technical transfer for contract manufacturing.

production and that after commercialization. In each case, technical information (including quality-related information) subject to the transfer should be documented, and the necessary information should be shared between the parties involved in the transfer.

- 2.61 The information (documents) to be shared includes the following as examples:
- 1) **Product Development Report:** The document that summarizes the manufacturing technique-related information obtained by research and development, which includes the quality design of drug products, specifications of raw materials and packaging/labeling materials and laboratory testing methods, as well as the justification for establishing these matters.
 - 2) **Technical transfer documents:** A series of documents including product specifications that describe the manufacturing method and test methods of the drug product subject to the transfer, as well as the technical transfer plan prepared on the basis of product specifications.
- 2.62 The responsibilities of the organization and the management system related to the technical transfer should be clarified for both the transferring party and the receiving party.
- 2.63 All the matters related to technical transfer should be approved or confirmed by the quality unit.
- 2.64 The consistency of manufacturing quality before and after the relevant technical transfer should be confirmed at the final step of the technical transfer by the process validation, etc.

3. Personnel

3.1 Personnel Qualifications

- 3.10 All the employees involved in the manufacturing control and quality control of drugs or quasi-drugs should understand GMP.

3.2 Education and Training

- 3.20 An education and training program should be prepared for each task of the personnel who are to receive the education and training. The education and training program should be prepared by the production unit, quality unit and other related divisions, and it should be approved by the person who has been predesignated under the provision of Article 19 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as “Education and Training Manager”). In addition, the education and training program should be regularly reviewed.
- 3.21 The Education and Training Manager should report the implementation status of the education and training program to the quality unit and this should be confirmed by the quality unit.
- 3.22 Special education and training should be given to the employees who work in the areas where contamination would cause problems; for example, the clean area, aseptic area, and working rooms for the operations related to products that are easily scattered or spilt and could cause anaphylactic reactions if present even in trace amounts, or those having major impacts on other products through cross-contamination.
- 3.23 Visitors or employees who have not received any education or participated in a training program should not be allowed to enter the working areas and the areas for testing operations (hereinafter referred to as “testing areas”). In unavoidable

circumstances, these persons should be appropriately instructed, such as by notifying them of precautions in advance.

3.3 Personnel Hygiene Control

- 3.30 Personnel should wear clean work clothing suitable for the operations in which they are involved, and the clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand and arm coverings, should be worn when necessary, to protect products from contamination.
- 3.31 Personnel should avoid direct contact with objects that may affect product quality wherever possible.
- 3.32 Smoking, eating, and the storage of food should be restricted to certain predesignated spaces separate from the working areas.
- 3.33 Personnel having health conditions that may have impacts on product quality (for example, having an infectious disease or wounds, etc.) should not be engaged in manufacturing operations. Any person shown by medical examination or supervisory observation to have an apparent illness or open lesions should be excluded from operations where the health condition could adversely affect product quality until the condition is rectified or qualified medical personnel determine that the person's inclusion would not jeopardize product quality.

4. Buildings and Facilities

4.1 Design, etc. of Buildings and Facilities

- 4.10 Buildings and facilities should be designed so that mix-ups, contamination or cross-contamination of the flow lines of products and packaging/labeling materials, as well as of personnel, in manufacturing sites can be avoided.

- 4.11 There should be defined areas in manufacturing sites for the following operations, and a control system should be established for these operations⁷:
- Receipt, identification, sampling, quarantine and pending release of raw materials and packaging/labeling materials;
 - Storage of rejected products and packaging/labeling materials that have been separated from accepted ones, for example, in locked containers;
 - Quarantine of recovered or returned products;
 - Aseptic operation (only in the case of manufacturing of aseptic preparations)
 - Storage of products pending release or rejection
 - Storage of products where it has been decided to release them from manufacturing sites;
 - Storage of products that are not allowed to be released from manufacturing sites;
 - Testing and inspection; and
 - In-process control testing and inspection (when appropriate)
- 4.12 Washing facilities defined under the provision of Article 6, Item 3 of the Regulations for Buildings and Facilities should be provided with a hot water supply as appropriate. In addition, soap or detergent, air driers or single service towels should be provided. The hand washing and toilet facilities should be separated, but easily accessible, from manufacturing working spaces. When necessary, an appropriate facility for taking showers should be installed.
- 4.13 In principle, testing and inspection laboratory areas should be separated from manufacturing working spaces. However, testing and inspection laboratory areas are allowed in the manufacturing working spaces provided that the manufacturing operations and products are not adversely affected, and those related to in-process control are allowed in the manufacturing working spaces provided that the precision of the relevant laboratory testing/inspection is not adversely affected. In addition, testing and inspection laboratory areas can be

⁷ When decision on release to the market or rejection is made at manufacturing sites, it is necessary to specify the place of storage of the relevant products. Moreover, an isolation area, etc., separate from the specified area, should be considered as a measure for prevention of cross-contamination and chemical hazards, as appropriate.

located in the manufacturing working spaces provided that manufacturing operations and products are not adversely affected.

- 4.14 The testing and inspection laboratory rooms should be appropriately designed for the operations to be conducted there. Appropriate management should be made such as providing a sufficient space to prevent mix-ups, contamination and cross-contamination. A sufficient and appropriate space for storage of collected samples and records should be provided.

4.2 Buildings and Facilities for Utilities

- 4.20 Appropriate monitoring should be performed to check whether all the utilities (e.g., steam, gases, compressed air, etc.) that may affect product quality conform to the predefined specifications. Necessary measures should be taken when data have exceeded the allowable limits.⁸
- 4.21 Buildings and facilities necessary for adequate ventilation, air filtration and exhaust should be provided. These building and facilities should be designed and constructed to minimize the risks of contamination and cross-contamination.
- 4.22 If there are no impediments to air recirculation in the manufacturing working spaces and in the testing and inspection laboratory areas, appropriate measures should be taken for the buildings and facilities to minimize the risks of contamination and cross-contamination.

⁸ The control specifications for steam are related to contamination by foreign matter, particulate matter, and pipe cleaning agents, etc. In addition, control specifications for gases and compressed air include oil content, foreign matter, particulate matter, and those related to dew points. In any case, control items and control specifications (limits) are set in consideration of product quality.

- 4.23 Permanently installed piping should be identified in an appropriate manner (for example, labeling of individual lines, etc.). Piping should be located to avoid the risks of product contamination.⁹
- 4.24 Drainpipes should be of an adequate size and should be provided with an air break device¹⁰ and other suitable devices to prevent backward flow, when appropriate.

4.3 Buildings and Facilities for Process Water

- 4.30 It should be demonstrated that process water is suitable for its intended use. When any water outside the specifications listed in the compendium, such as the Japanese Pharmacopoeia, is used, internal specifications with valid grounds should be established and documented.¹¹
- 4.31 Unless otherwise justified, process water should at least meet the water quality standards based on the Japanese Pharmacopoeia, or the Tap Water Law or the World Health Organization (WHO) guidelines for drinking water quality.
- 4.32 If the purity level of process water is insufficient to assure product quality, and more strict biological and physicochemical control limits are required, appropriate specifications should be established for necessary items among physicochemical characteristics, total microbial count¹², count of specified microorganisms and endotoxin level.

⁹ Piping is identified, normally, by direct labeling or by attaching a tag, etc. to it. With regard to insulated piping, when removal of the identification labels, etc. is unavoidable for the operations of replacement of the insulating materials, identification by labeling should be made immediately after completion of the relevant operations.

¹⁰ “Air break device” is denoted as a device that is aimed at prevention of backflow from drains; for example, it corresponds to an air break, etc. equipped with a funnel for pressure reduction to atmospheric level.

¹¹ It is desirable to identify process water for which internal specifications have been established by use of such terms as “ultrafiltration water” or “ion-exchange water,” to avoid mix-ups with the water to be used for drug manufacturing (purified water, water for injection, etc.) listed in the compendium, such as the Japanese Pharmacopoeia.

¹² (Reference) According to the USP and EP specifications, total microbial count is specified as 10 cfu/100 mL for water for injection (excluding water that is sealed in an air-tight container and is specified as sterile), while it is specified as 100 cfu/mL for purified water.

- 4.33 When water is purified to achieve a defined quality for use in a manufacturing process, the purification process should be verified and monitored by establishing appropriate control limits; for this purpose, suitable buildings and facilities should be provided.

4.4 Sewage and Waste Materials

- 4.40 Sewage and waste materials from manufacturing sites (including the sewage or waste materials formed as by-products in the manufacturing process) should be disposed in a sanitary, safe and timely manner. Containers and/or pipes for waste materials should be clearly distinguished from those for products and packaging/labeling materials by identification labeling.

4.5 Sanitation and Maintenance

- 4.50 The items defined under the provision of Article 6, Paragraph 4 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include the responsibilities and the control system related to hygiene control. Plans related to the cleaning of buildings and facilities, and matters related to the use of buildings and facilities, and chemicals, etc., should be included in the hygiene control standard code defined under the provision of Article 8, Paragraph 1 of GMP Ministerial Ordinance for Drugs and Quasi-drugs.
- 4.51 Matters related to the use of the chemicals, such as rodenticides, insecticides, fungicides, disinfectants, and cleaning agents, etc. should be included in the hygiene control standard code.

- 4.52 Buildings and facilities that are used for manufacturing of other drugs and quasi-drugs should not be used for the operations (including weighing, milling and packaging) related to manufacturing of highly toxic agrochemicals, such as herbicides and insecticides, etc. Such highly toxic agrochemicals should be handled and stored separately from drugs and quasi-drugs.

4.6 Design and Set-up of Buildings and Facilities

- 4.60 Buildings and facilities that may adversely affect product quality due to their surfaces coming into contact with products should be set up so that such contact can be avoided.¹³
- 4.61 Buildings and facilities should only be used within their qualified operating range.
- 4.62 Major buildings and facilities used for manufacturing of products (e.g., blender, tableting machine, etc.) should be appropriately identified by labeling.
- 4.63 Substances, such as lubricants, heating fluids, and coolants, etc. should not contact products as these substances may adversely affect product quality. It is desirable to use food grade oils as an alternative.¹⁴

¹³ Buildings and facilities that may contact products include tanks, pipes, filters, ion-exchange resins, hoses, gaskets, chromatographs, etc. Specific items to be considered are as follows: (1) chemical resistance (products do not react with or corrode the contact area); (2) extractables (extract from the contact area does not adversely affect product quality; particular attention should be paid to extractables from high-molecular materials (hoses, gaskets, filters, columns, and linings, etc.), and if necessary, data on extractable characteristics should be obtained from suppliers to confirm information on contraindications with products and reactivity with products, etc. based on the chemical characteristics of such extractables. Moreover, safety evaluation data (toxicity studies, etc) related to the surface materials should be obtained from suppliers. The same is also described in the 21CFR, 211.65(a) and (b)); (3) adsorption (evaluation of adsorption to high-molecular weight materials is important particularly in cases of liquid agents. Effects of the substances extracted from the surface of high-molecular weight materials on product quality should be assessed.)

¹⁴ Areas where lubricants, heating fluids, and coolants, etc. may contact products include, for example, shaft and pump, etc. for stirring.

- 4.64 If necessary, closed or contained equipment should be used. Where open equipment is used, or equipment is opened, appropriate preventive measures should be taken to minimize the risk of contamination.
- 4.65 A set of drawings related to the current construction should be maintained for critical buildings and facilities (e.g., instrumentation, utility-related equipment, etc.).

4.7 Maintenance and Cleaning of Buildings and Facilities

- 4.70 Procedures for cleaning of the buildings and facilities that are used for manufacturing control and quality control of products (including the detailed procedures necessary for cleaning with an efficient and reproducible method by personnel) and those related to subsequent release for use of the relevant buildings and facilities in the next batch should be included in the hygiene control standard code. These procedures should include:
- A complete description of the methods for cleaning (including the methods for dilution of cleaning agents), as well as the materials and chemicals, etc. to be used for cleaning;
 - Instructions for disassembling and reassembling each structural component of buildings and facilities if required to ensure proper cleaning;
 - Instructions for removal or obliteration of previous batch identification;
 - Instructions for protection of clean buildings and facilities from contamination prior to use
 - Testing/inspection of buildings and facilities for cleanliness immediately before use, if feasible; and
 - When appropriate, the maximum time that may elapse from completion of the process-related operations to cleaning of buildings and facilities, and the cleaning expiry date after cleaning.¹⁵

¹⁵ The risk of contamination of the process equipment during the period from cleaning of buildings and facilities to the next batch of production should be considered (e.g. possible risk of negative pressure, contamination from accessory piping, and contamination from drain piping).

- 4.71 Buildings and facilities should be cleaned to prevent contamination or carry-over of a material that may adversely affect product quality. When appropriate, buildings and facilities should be sanitized, disinfected or sterilized.
- 4.72 Where buildings and facilities are used for continuous production by successive batches of the same product or production of only the relevant product during a specified period (campaign production), they should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradation products or objectionable level of microorganisms).
- 4.73 Non-dedicated buildings and facilities should be cleaned in each case of changeover of product items to prevent cross-contamination.
- 4.74 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents suitable for the residues should have been defined and justified.
- 4.75 Buildings and facilities should be labeled by appropriate methods¹⁶ to identify their contents and cleanliness status.
- 4.76 It should be confirmed that filters to be used at the final stage of the product manufacturing process do not release fibers.¹⁷

4.8 Calibration

- 4.80 For calibration of equipment related to the manufacturing control defined under the provision of Article 10, Item 8 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, and that related to the inspection defined under the provision of Article 11, Item 4 of the ministerial ordinance, a list of measuring instruments should be prepared, the risks related to product quality should be assessed, and the necessity of calibration as well as the calibration frequency should have been

¹⁶ For example, “before cleaning,” “completion of cleaning,” “during production,” etc.

¹⁷ With respect to discharge of fibers and other foreign matter from the filter itself, when appropriate, flushing cleaning, etc. should be considered prior to use based on the data provided by the supplier.

specified in advance.

- 4.81 Calibration of equipment should be performed using methods that are traceable to the certified standards, if national standards are available.
- 4.82 The current calibration status of critical equipment should have been specified. A calibration seal should be affixed to the calibrated equipment, in which the calibration results, the scheduled date of the next calibration, etc. should be described.
- 4.83 Measuring equipment that does not meet the calibration criteria should not be used. Any measuring equipment that does not meet the calibration criteria or whose calibration validity has expired should be labeled as “not permitted for use,” etc.
- 4.84 In cases of deviations of critical measuring equipment from approved calibration standards, investigations should be made to assess the impacts of the relevant deviations on the quality of the product that have been manufactured using the relevant equipment after the previous calibration. Investigation methods, for example, may include checking the presence or absence of any problems by testing/inspection with proper measuring equipment based on the quality standard determined by the equipment using the reference product manufactured after the last successful calibration. If any abnormality has been detected as a result of investigation, necessary actions to be taken should be discussed.

4.9 Computerized Buildings and Facilities and Procedures

- 4.90 Computerized buildings and facilities and procedures related to manufacturing control and quality control of products should be validated. The degree and scope of the validation should be decided considering the diversity, complexity and importance of the computerized buildings and facilities.

- 4.91 Installation qualification and operational qualification should be appropriately performed for the hardware and software related to the computerized buildings and facilities and procedures.
- 4.92 Commercially available software that has been qualified does not require the same level of testing as that required for a computer system designed originally for the relevant manufacturing process. If existing computerized buildings and facilities and procedures have not been validated at the time of installation, a retrospective validation may be conducted using appropriate records.
- 4.93 Data of computerized buildings and facilities and procedures should be sufficiently controlled to prevent unauthorized access to or change in data. The data should be controlled to prevent their omission. In the event data are changed, previous data, name of person who made the change, and the date of change should be documented, and the documents should be archived.
- 4.94 A procedural manual should be prepared for implementation and maintenance of the computerized buildings and facilities and procedures.
- 4.95 In the case of the manual entry of critical data, such data need to be reviewed by a second party to confirm whether or not accurate entry has been made. This reconfirmation review can be conducted by a second operator or by the computer system related to the relevant computerized buildings and facilities and procedures.
- 4.96 Any failure in computerized buildings and facilities and procedures that may affect the reliability of product quality, should be investigated and documented, and the documents should be archived.
- 4.97 Changes in the computerized buildings and facilities and procedures should be made in accordance with the manual for change control. All changes, including modifications and extensions, which have been made for the critical parts of the

hardware and software of the computer system related to the computerized buildings and facilities and procedures should be documented, and the documents should be archived. These documents should demonstrate that the relevant computerized buildings and facilities and procedures are ultimately maintained in a validated state.

- 4.98 If breakdowns or failures of the computer system related to the computerized buildings and facilities and procedures may result in the permanent loss of records, a back-up system should be provided. A measure of ensuring data protection should be established for the manufacturing control and quality control-related computer system.

5. Documentation Control and Records

5.1 Documentation Control

- 5.10 The documentation and record control manual, defined under the provision of Article 8, Paragraph 4, Item 9 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should specify the preparation, defined under the provision of Article 20, Items 1 and 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, abolition and recovery procedures.
- 5.11 The documents should be prepared in a language and context that are understandable to the personnel who are engaged in activities related to the manufacturing control and quality control of products at manufacturing sites.
- 5.12 The documents should be prepared so as to demonstrate clearly how they are related to other documents.
- 5.13 When preparing records, the name of the person who made entries should be inscribed using an indelible means in a predefined space directly after operations. Any correction to entries should be dated and signed or sealed, and the original

entry should be kept in a legible state. In the case of correction of records that may affect product quality (yield, analytical values related to process control, etc.), the reason for the corrections should be provided.

- 5.14 The original records or their copies should be readily available during their archiving period at the manufacturing site where the relevant operations have been performed. Records that can be promptly retrieved from an archiving site other than the relevant manufacturing site by electronic or other means are acceptable.
- 5.15 Where reduction techniques such as microfilming or electronic records are used for archiving of product master formulae, instructions, manuals and copies of original records (photocopies, microfilm, microfiche, and other accurate copies of the original records), suitable retrieval equipment and a means to produce a hard copy should be readily available.

5.2 Manufacturing Instructions and Batch Records

- 5.20 Manufacturing instructions should mention the criteria used when deciding release to the subsequent processes.¹⁸ When master manufacturing instructions are prepared, a person at the production unit who is responsible for preparation of the master manufacturing instructions should enter the date and affix his/her signature or seal. The relevant quality unit should confirm the content of the master manufacturing instructions, which should be dated and signed or sealed by a person in the relevant unit, who is responsible for the confirmation.
- 5.21 The batch record should be confirmed by a person at the production unit who is responsible for preparation of the batch record to assure that the batch record is a

¹⁸ Concrete matters to be described in manufacturing instructions include product name, list of raw materials and packaging/labeling materials, accurate description of the quantity or ratio of the raw materials and packaging/labeling materials (including measuring units), working spaces and critical buildings and facilities, order of operations, related process parameters, instructions for sampling, judging standards for laboratory testing/inspection related to in-process control, limit times of individual processes or the overall process, range of anticipated yield, and storage conditions of products, as well as conditions for storage of packaging/labeling materials.

correct version and has been prepared legibly in accordance with the appropriate manufacturing instructions.

- 5.22 In the case of continuous production, the lot number to be described in the manufacturing instructions and batch records can be replaced by the date of manufacturing and manufacturing code for identification until the final lot number is assigned.
- 5.23 The items related to major processes, which should be documented in the batch records, include the following (in addition to items defined by other regulations, such as Enforcement Notification, etc.):
- 1) Date and, where applicable, time;
 - 2) Amount, lot number or control number of the raw materials and packaging/labeling materials used in the manufacturing process;
 - 3) Major buildings and facilities used;
 - 4) Records of sampling;
 - 5) Records of packaging and labeling;
 - 6) Records of critical process parameters;
 - 7) Any deviation noted, its evaluation, and results of investigation conducted as appropriate (or reference to the investigation results when the relevant results have been separately archived);
 - 8) Results of decision for release to the subsequent processes; and
 - 9) Signatures or seals of the persons who have performed and directly supervised

the operations in each critical process.

5.3 Buildings and Facilities Cleaning and Use Records

- 5.30 The buildings and facilities cleaning (including sanitation, disinfection and sterilization) and periodic maintenance and etc. records, which are defined under the provisions of Article 9, Item 1, and Article 10, Items 6 and 8 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, date, time (only when applicable), name and lot number of the products manufactured using the relevant buildings and facilities, and name of the persons who have been engaged in the operations of cleaning and maintenance should be provided in use record.
- 5.31 If buildings and facilities are dedicated to the manufacture of only one product, preparation of individual use records is not necessary provided that the lot number of the product follows a traceable sequence. In cases where dedicated buildings and facilities are used, the records of cleaning, periodic maintenance and use can be part of the batch record.

5.4 Packaging and Labeling Materials Records

- 5.40 The records related to storage and inventory of the materials, defined under the provision of Article 10, Item 5 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should provide the name and identification number of the supplier (if available) and any matters defined under the Enforcement Notification. The records related to conformity judgment on the materials, defined under the provision of Article 10, Item 4 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should provide the contents of the final handling of the packaging and labeling materials that have been judged to be non-conforming.
- 5.41 Approved original labeling materials (master labels) should be archived for comparison with the labeling materials that have been used for each lot of products (those used for the representative lot should be attached to batch

records).

5.5 Testing/Inspection Records

5.50 The testing/inspection records, defined under the provision of Article 11, Paragraph 1, Items 1 and 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs and the Enforcement, should provide the following contents and any matters:

- 1) Descriptions of the name of the suppliers, and where applicable, the quantity of the samples collected for testing/inspection;
- 2) Comments and other references related to the testing/inspection method used;
- 3) Descriptions of the quantity of samples used for each testing/inspection, reference standards, reagents, preparation of standard solutions, and other cross-references;
- 4) Complete records of all raw data obtained by each testing/inspection, graphs, charts and spectra, etc. obtained from analytical instruments (these should be properly identified to show the specific materials, etc., and their lot or control number);
- 5) Records of all calculations performed in connection with the testing/inspection, including units of measure, conversion coefficient, and equivalence coefficient, etc.; and
- 6) The signature or seal of a responsible person at the quality unit and the date to show that the original records have been reviewed for accuracy, completeness, and compliance with established specifications.

5.51 Complete records should be archived for the following matters:

- 1) Contents of any modifications of established analytical methods;
- 2) Results obtained by all stability tests performed on products; and
- 3) Results of investigations made on the causes of deviations from specifications

6. Control of Raw materials and Packaging/Labeling Materials

6.1 General Control

- 6.10 Suppliers of critical raw materials and packaging/labeling materials should be jointly evaluated with Licensed Marketing Approval Holders.¹⁹
- 6.11 Raw materials and packaging/labeling materials should be purchased from suppliers approved by the quality unit in conjunction with Licensed Marketing Approval Holders.
- 6.12 If a supplier of critical raw materials and packaging/labeling materials is not itself the manufacturer of the materials, the name (corporate name) and address (address of the main body of the corporate) of the supplier should be provided.
- 6.13 Change in suppliers of critical raw materials and packaging/labeling materials should be handled in accordance with the procedures for change control.

6.2 Receipt and Quarantine of Raw Materials and Packaging/Labeling Materials

- 6.20 Upon confirmation of receipt of packaging/labeling materials defined under the provision of Article 10, Item 4 of the GMP Ministerial Ordinance for Drugs and

¹⁹ In addition to onsite audit, methods for evaluation of suppliers include the following: (1) receipt of a GMP Certificate issued by the relevant regulatory authority in the case of overseas manufacturers; (2) confirmation of past record of ISO accreditation (however, GMP Certificate is prioritized for GMP-applied sites), etc.

Quasi-drugs, as well as raw materials, a visual inspection should be performed to check the labeling of each container of the raw materials and packaging/labeling materials (and make sure that the descriptions are different but the information is essentially the same), and to check for container damage, broken seals, evidence of tampering, and contamination, etc. Raw materials and packaging/labeling materials should be held under quarantine separately from other products and materials until approval for use after the testing/inspection defined under the provision of Article 11, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.

- 6.21 In the case where newly received raw materials and packaging/labeling materials are mixed with existing stocks (including solvents, etc., in a large-volume storage tank), the incoming material should be tested in advance to confirm their appropriateness. The necessary procedures should be established to ensure that any mix-up of incoming raw materials and packaging/labeling materials with existing stocks is prevented.
- 6.22 In the case where raw materials and packaging/labeling materials are transported by non-dedicated tankers, etc., it should be confirmed that there is no cross-contamination mediated by the relevant tankers, etc. Thereby, confirmation may be made by application of the following methods:
- 1) Receipt of a certificate of cleaning;
 - 2) Testing for trace impurities; and
 - 3) Onsite audit of the supplier
- 6.23 Large-volume storage containers, their installed piping, filling and discharge lines for raw materials and packaging/labeling materials should be appropriately identified.
- 6.24 Containers for raw materials and packaging/labeling materials should be labeled

appropriately. The labeling should provide at least the following information. The status of each lot should be identified by labeling in the event the lot is relocated or if the control unit of the lot is changed. When completely and appropriately computerized buildings and facilities and procedures²⁰ are employed, it is not necessary to make all of the labeling contents visually readable.

- 1) Product name;
- 2) Lot number or control number;
- 3) Control condition of the contents (e.g., “under isolation,” “under testing,” “accepted,” “rejected,” “returned material,” “recalled material,” etc.); and
- 4) Where applicable, expiry date or expiry for use, or the date of retest.

6.25 For a lot number or control number to be assigned to the received raw materials and packaging/labeling materials, attention should be paid to the following matters:

- 1) Even in the case of an identical lot at the supplier, an independent lot number or control number should be assigned at the time of receipt, when the lot is received in installments.
- 2) Even in the case where the lot number or control number is the same, when the lot is placed in two or more containers, a control method should be adopted so that each container can be identified, if necessary.²¹

²⁰ This corresponds to the case in which non-visual information has been controlled by a computer system using barcode labeling and RFID tags, etc.

²¹ Irrespective of the lot and control unit at receipt of raw materials and packaging/labeling materials, the possibility that storage status may be different in each container should be considered; for example, the number of package openings may be different. Therefore, this was stipulated, considering the necessity to specify containers for sampling. However, it is not necessarily required to assign a lot number or control number to each container, provided that another control method to identify each container is adopted.

6.3 Sampling and Testing/inspection of Packaging/Labeling Materials at Receipt

- 6.30 In the case where some of the items for testing are omitted at receipt of raw materials and packaging/labeling materials defined under the provision of Article 11, Paragraph 11, Items 1 and 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, such materials should be assessed based on sufficient evidence (e.g., quality history of the raw materials and packaging/labeling materials supplied in the past) that suppliers have a system to supply raw materials and packaging/labeling materials conforming to the specifications, and it should be confirmed whether their test data of the relevant items are stable and that the items do not have the potential to become non-conforming considering the range of the specifications. Thereby, at least 3 lots or 3 control units should be tested in advance based on full analyses to ascertain the validity of the test data by confirming the continuous consistency of the test data obtained by both parties. Even when several of the acceptance tests have been omitted, full analyses should be performed at appropriate intervals to ascertain the reliability of the Certificate of Analysis issued by the supplier.
- 6.31 In the case where special equipment or techniques are necessary due to the explosiveness, harmfulness, etc. of the raw materials used for manufacturing of the drug substance, the test results described in the appropriate Certificate of Analysis issued by the supplier can be utilized as part of the acceptance test data of the relevant raw materials. In the case where the acceptance test is omitted, the reason for the omission should be clearly documented in the product master formula after prior approval by the quality unit.²²
- 6.32 Collected samples should be representative of the lot or control unit. Sampling procedures including the number of containers to be sampled, as well as sampling points in the containers and sampling amount, should be predefined in

²² Such a case is also predicated on evaluations of suppliers and transportation conditions. If the evaluation results are undesirable, measures, such as confirmation using the samples for testing/inspection, etc. should be taken.

consideration of the importance of the relevant raw materials or packaging/labeling materials, quality variability, quality history of the materials supplied from the relevant suppliers in the past, and the quantity needed for proper testing.

- 6.33 Sampling of the materials defined under the provision of Article 11, Paragraph 1, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should be conducted at predefined locations in accordance with the procedures designated to prevent contamination of the sampled raw materials and packaging/labeling materials, as well as other products and materials.
- 6.34 Samples defined under the provision of Article 11, Paragraph 1, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should be collected in accordance with the following procedures²³:
- 1) The containers of components selected shall be cleaned where necessary, by appropriate means;
 - 2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures;
 - 3) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing;
 - 4) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample; and
 - 5) Containers from which samples have been taken shall be marked to show that samples have been removed from them. (attachment of a label describing “sampled,” etc.).

²³ The same have been stipulated also in the 21CFR 211.84(c).

6.4 Storage

- 6.40 Raw materials and packaging/labeling materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.
- 6.41 Containers for storage of raw materials and packaging/labeling materials should be stored off the floor and suitably spaced to permit cleaning and testing.
- 6.42 Raw materials and packaging/labeling materials should be stored in a proper manner so that the oldest stock is used first, except for particular cases.

6.5 Re-evaluation

- 6.50 In the case where received raw materials and packaging/labeling materials have been stored for a period that exceeds the expiry date, or they have been exposed to heat or humidity, re-evaluation should be performed to determine their suitability for use. However, indefinite storage based on repeated re-evaluations should be avoided.

7. Production and In-Process Control

7.1 Manufacturing Operations

- 7.10 Prior to start of the manufacturing operations, cleaning of the buildings and facility, defined under the provision of Article, 10, Item 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should be confirmed, and whether products, packaging/labeling materials, and documents that are not required for the relevant operations do not remain in the working spaces for the operations.
- 7.11 Raw materials should be weighed or measured under appropriate conditions that do not affect product quality, etc. Weighing and measuring devices should be of

suitable accuracy for the intended use.

- 7.12 If raw materials are subdivided for manufacturing processes to be performed later, appropriate containers should be used, and the following information should be placed on the labels of the relevant containers:
- Name, lot number or control number of the raw material;
 - Subdividing number, when necessary;
 - Weight or volume of the raw material in the relevant container; and
 - Where applicable, expiry date or expiry for use, or date of retest
- 7.13 Critical weighing, measuring, or subdividing operations should be witnessed by personnel other than those who perform the operations (this does not apply to the case where the operations can be controlled under equivalent conditions by other methods). Prior to use, the personnel who perform the operations should make sure that products and packaging/labeling materials are those specified in the manufacturing instructions.
- 7.14 Other critical operations should be witnessed by personnel other than those who perform the operations (this does not apply to the case where the operations can be controlled under equivalent conditions by other methods).
- 7.15 Actual yields (net yields) should be compared with theoretical yields at the predefined steps in the manufacturing processes. A theoretical yield with appropriate ranges should be established based on laboratory testing data, pilot-scale data or the data obtained in the actual production scale. Deviations in yields in critical processes should be investigated to determine their impacts on the resulting quality of affected lots, and the results confirmed.
- 7.16 The operation status of equipment should be indicated on their main part (this does not apply to the case when the operations can be controlled under equivalent conditions by a computerized control system).

7.17 Any products excluded from the manufacturing process (e.g., products excluded from the manufacturing process by reason of filling failure, tableting failure, etc.) should be stored in places differentiated from those for storage of other products. This should be documented and archived.

7.2 Time Limits

7.20 If time limits for process completion are to be specified in the manufacturing instructions, they should ensure the manufacturing control and quality control of products.²⁴ Deviations in time limits should be assessed and documented, and the documents should be archived. However, in the case where processes with specific target values are running, such as pH adjustment or drying to predetermined specifications, setting of time limits is inappropriate. The time of completion of such processes should be determined by in-process sampling and testing/inspection.

7.3 In-Process Control

7.30 Written procedures should be established to monitor the progress and control the status of processes that affect the quality characteristics of products (content, titer, dissolution profile, etc.). In-process control and the acceptance criteria should be determined based on the information obtained during development stages or actual production data.

7.31 Acceptance criteria, and type and scope of testing related to in-process control should be established depending on the quality characteristics of products, content of the process and impacts of the relevant process on product quality.

7.32 Critical in-process control (and monitoring of critical processes) should be documented, and then approved by the quality unit.

²⁴ Particularly, in the case of storage of intermediate products for a long term, storage conditions (storage place (temperature and humidity, etc.), storage container, storage period, etc.) that have been confirmed in advance should be documented so that product quality does not deteriorate during the storage period.

- 7.33 When process adjustments are made by personnel at the production unit without prior approval by the quality unit, the adjustments should be made within the limits predefined and approved by the quality unit. All tests and results related to in-process control should be documented as a part of manufacturing records.
- 7.34 Samples to be used for process controls should be representative of the lot. Sampling procedures (including sampling points and sampling amount) should be based on scientifically valid methods.²⁵
- 7.35 Investigations on the cause of out-of specification (OOS) results are not usually needed for in-process testing/inspection that is performed for the purpose of monitoring or process adjustment.
- 7.36 In-process sampling should be conducted in accordance with the procedures for preventing contamination of products and ensuring the integrity of the samples after sampling.

7.4 Lot-Blending Process

- 7.40 Any lot that has been judged to be out-of specification from test results should not be blended with other lots for the purpose of meeting specifications.
- 7.41 The lot-blending process (this refers to the process of blending products within the same specifications²⁶ to produce a homogenous lot²⁷) should be appropriately controlled and documented in accordance with the manufacturing instructions, and the documents should be archived. A new lot produced in the lot blending

²⁵ “Samples to be used for process controls” are different from those to be used for “in-process testing/inspection that is performed for the purpose of monitoring or process adjustment” described in Chapter 7. 35. They are used for confirmation related to on-process control that is particularly necessary for manufacturing of a final product of consistent quality.

²⁶ In the case where processes before and after the lot-blending process are performed consecutively, or that the quality of individual (small) lots has been confirmed to be equivalent, it is not mandatory to perform testing/inspection of individual (small) lots; therefore, it is not required to confirm the specification conformity of individual (small) lots.

²⁷ Manufacturing of products by blending of residual materials formed in the manufacturing process of a previous lot with a new lot (namely, rescue), and blending with other lots for the purpose of meeting specifications of a non-conforming lot do not apply to the “lot-blending process” defined here.

process (hereinafter referred to as “blended lot”) should be tested as appropriate to ascertain whether it meets the predefined specifications.

- 7.42 The record of the lot-blending process should be prepared to allow traceability back to the original individual lots used for the blending process.
- 7.43 Procedures for the lot-blending process should be based on scientifically valid methods.
- 7.44 In the case where the physicochemical homogeneity of blended lots critically affects product characteristics (e.g., drug products of oral solid preparation), validation of the lot-blending process should be performed from the viewpoint of homogeneity of the blended lot. The validation should include testing of critical characteristics (e.g., particle size distribution, bulk density, etc.) that may be affected by the lot-blending process.
- 7.45 If the lot-blending process may have adverse impacts on the stability of blended lots, stability testing should be performed to decide whether the blended lots are suitable for release.
- 7.46 The shelf life or expiry for use of blended lots should be based on the manufacturing date of the oldest lot or leftover lots among the lots used for blending.

7.5 Contamination Control

- 7.50 Residual materials that are carried over into successive lots (e.g., residues adhering to the wall of the milling machine or granulator, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the materials to the next process) should be controlled so that they do not adversely affect product quality.

- 7.51 Manufacturing operations should be conducted in a manner that will prevent contamination by materials other than the product.
- 7.52 Measures to prevent contamination should be taken for intermediate products being manufactured.
- 7.53 Methods for preventing contamination should be periodically inspected in accordance with the written procedures, etc.

7.6 Microbiological Contamination Control

- 7.60 Even in the case of drug products where sterility is not required, appropriate written procedures should also be established and complied with to prevent undesirable microbiological contamination.

8. Packaging and Labeling

8.1 General Matters

- 8.10 Packaging and labeling materials should be controlled as defined in this chapter, and where applicable Chapter 6 (Control of Raw Materials and Packaging/Labeling Materials). This chapter (Chapter 8) applies to the packaging and labeling materials that are used for drug products that will be released from manufacturing sites, but not to intermediate products that are temporarily stored at manufacturing sites.

8.2 Control of Packaging Materials

- 8.20 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. Containers should be appropriately controlled to maintain their cleanliness, etc., where applicable.

8.3 Control of Labeling Materials

- 8.30 Access to the label storage areas should be limited to authorized personnel, except in the case where an equivalent level of control can be achieved by other methods.
- 8.31 Labels used on containers of drug products should include the name, the lot number and quantity of the products, as well as shelf life or expiration date, or retest date, and storage conditions where applicable.
- 8.32 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).
- 8.33 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels which bear neither lot number nor other lot-related information should be retained and stored in a manner that prevents mix-ups and provides proper identification.
- 8.34 Obsolete and out-of-date labels should be destroyed.

- 8.35 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.
- 8.36 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.
- 8.37 A printed label, which is representative of those used, should be included in the batch production record.

8.4 Packaging and Labeling Operations

- 8.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.
- 8.41 Prior to the start of packaging and labeling operations, it should be confirmed whether the building and facilities defined under the provision of Article 10, Item 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs are clean, and whether products, packaging/labeling materials and documents that are not required for the relevant operations do not remain in the work area for the relevant operations. The confirmation results should be documented and retained.
- 8.42 Packaging operations should be monitored to prevent contamination, cross-contamination, and mix-up, and should be physically and spatially separated from the operations related to other products. Labeling operations should be monitored to prevent mix-up, and should be physically and spatially separated from the operations related to other products.
- 8.43 Prior to the start of packaging and labeling operations, the production unit should confirm whether the name of products and packaging/labeling materials, the lot

number or the control number and quantity conform to the content of the relevant manufacturing instructions. The confirmation results should be documented, and the documents should be archived.

- 8.44 The name and lot number of the product subject to packaging operations should be posted in a visible position in the packaging room and by the packaging process line.
- 8.45 In the case where samples collected from the packaging and labeling process lines for in-process testing/inspection are returned to the labeling process lines, the operations should follow the predefined procedures. In the case where the packaging and labeling operations are stopped due to the occurrence of an abnormality and then restarted, special investigations should be made, and operations should begin again only after approval by authorized personnel. The investigation results should be documented and retained.
- 8.46 In where case products became temporarily unidentifiable as a result of packaging operations, the subsequent process should be advanced as rapidly as possible until identifiable conditions are obtained. If prompt transfer of the operation to the next process is difficult, appropriate measures should be taken to prevent mix-up and labeling errors.
- 8.47 Products containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the packages have been opened during transport.

9. Storage and Release from Manufacturing Site

9.1 Storage Operations

- 9.10 Buildings and facilities should be available for the storage of products under appropriate conditions (e.g., controlled temperature and humidity, when

necessary). Records of the storage conditions should be prepared and retained if they are necessary for maintaining product quality characteristics.

- 9.11 In the case of storage of intermediate products, they should be placed in predefined containers, appropriately labeled, and cleaned if necessary, and then stored in specified areas. When necessary, the stability of the relevant intermediate products should be assessed under the predefined storage conditions.

9.2 Operations of Release from Manufacturing Site

- 9.20 Products should be transported in a manner that does not adversely affect their quality.
- 9.21 It should be ensured that the contract carriers of products understand and comply with appropriate conditions of transport and storage.
- 9.22 If a potential risk to the quality of the products to be used for manufacturing at other manufacturing site has been found after release from the manufacturing site, immediate contact should be made with the receiving manufacturer.

10 Laboratory Control

10.1 General Control

- 10.10 Any out-of-specification (OOS) data obtained should be investigated and documented in accordance with a written procedure, and the documents should be retained. This procedure requires analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective action, and conclusions. Re-sampling and re-testing after obtaining OOS results should be performed in accordance with a written procedure. Even in cases other than OOS results, any re-sampling and re-testing of samples should not be performed without a valid reason. When re-sampling is performed, the reason should be

documented, and when re-testing is performed, the reason and handling of test results should be documented, and the documents should be retained.²⁹

- 10.11 Reagents and reference standards received should be controlled in accordance with written procedures, and should be labeled with the date of purchase, the expiration date, and where applicable, the date of seal opening. Test solutions, etc. that need preparation should be prepared in accordance with the written procedures, which should be documented, and the documents should be retained. Expiration date of the prepared test solutions, etc. should be determined appropriately based on their characteristics. Prepared test solutions, etc. should be labeled with the item name, preparation number, date of preparation, name of the personnel who performed preparation, expiration date, and where applicable, the storage conditions, and conversion coefficient, etc. Containers for subdividing water and solvents to be used for testing should also be labeled with the item name, etc.
- 10.12 Primary reference standards should be obtained as appropriate for the testing of products. Suppliers of the primary reference standards should be documented, and the documents should be archived. Primary reference standards should be stored and used in accordance with the supplier's recommendations, which should be documented, and the records should be retained. Primary reference standards obtained from an officially qualified supplier can usually be used without testing, provided they are stored under conditions that are consistent with the supplier's recommendations.
- 10.13 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity³⁰ and purity of the primary reference standard. Appropriate documentation of this testing should be retained.

²⁹ Even where OOS results, limitations in re-sampling and re-testing were set while taking into consideration current status of implementation of re-sampling and re-testing.

³⁰ Identification of a compound based on structural determination by such techniques as nuclear magnetic resonance spectroscopy and infrared spectroscopy, etc. may be considered as an example of identity verification.

- 10.14 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each lot of the secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with written procedures.
- 10.15 Water for test purposes having a quality that does not affect the test results should be available. In the case of in-house preparation of water for tests, the equipment to be used for water purification should be controlled and the water quality should be checked regularly. The process and results should be documented, and the documents should be retained.³¹
- 10.16 Reference samples should be representative of the product lots from which they are taken. Other samples may also so be taken to monitor the most unstable stage (e.g., at the start and end of production).

10.2 Certificate of Analysis

- 10.20 Certificate of Analysis should be issued for each lot of product on request.
- 10.21 The Certificate of Analysis should include the name of the product, the lot number, the specifications, the numerical results obtained, and results of overall assessment.
- 10.22 The Certificate of Analysis should be dated and signed or sealed by the person at the quality unit who is responsible for the testing with descriptions of the name (the corporate name), address (location of the major office of the corporate) and telephone number of the manufacturer or testing institutions.

10.3 Monitoring of Product Stability

³¹ This was set to enhance awareness of the control of test water.

- 10.30 To confirm product stability, stability should be monitored for at least one lot per year (except when no batch is produced in the year), and stability testing should be performed at least once a year. Stability of products to be released to other manufacturers should be monitored in the same manner where applicable.
- 10.31 Test procedures for stability monitoring should be validated and be appropriate for stability assessment.
- 10.32 Samples to be used for stability monitoring should be collected from the products, the release of which from the manufacturing site has been approved. If there is no impediment to doing so, samples can be collected from intermediate products under packaging conditions that ensure product stability.
- 10.33 Storage conditions should be consistent with the stability-related ICH guidelines, where applicable.

10.4 Expiry Date or Expiry for Use

- 10.40 When expiry date or expiration date, or date of re-testing, is applied to products to be released to other manufacturing sites, information to ensure stability (e.g., published data, test results, etc.) should be available.

10.5 Reserve Samples (related to Article 11, Paragraph 1, Item 3 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs)

- 10.50 To avoid misuse, reserve samples should be labeled as such.

11. Validation

11.1 Validation Policy

- 11.10 Documents on the validation operating procedure defined under the provision of Article 8, Paragraph 4, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include overall policy and manufacturer's intention, and methods adopted for validation of manufacturing processes, cleaning procedures, analytical methods, in-process test procedures, as well as validation of computerized buildings and facilities and procedures, plan, review, approval and documentation at each stage of validation.
- 11.11 Critical process parameters and product characteristics (usually, these should be identified during development stages or based on actual production data) should be defined within a range necessary for reproducible operations (these should include the following):³²
- Identification of process parameters that may affect critical quality characteristics of the relevant products; and
 - Determination of ranges for each critical process parameter to be used for routine process control

11.2 Validation Documentation

- 11.20 The validation protocols and documents related to validation results should be reported by the person responsible for validation to the quality unit in accordance with the procedures defined under the provision of Article 13, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, which should be reviewed and approved by the quality unit and other predesignated personnel.
- 11.21 The validation protocol should specify the type of validation to be conducted (e.g., retrospective, prospective, or concurrent validation), validation method, number of process runs, and critical processes, in addition to the matters defined under the

³² For deciding validation range and degree, appropriate use of the concept of risk management (refer to ICH/Q9, etc.) is recommended.

Enforcement Notification, etc.

- 11.22 A validation report corresponding to the validation protocol defined under the provision of Article 13, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should summarize the validation results obtained, and the report should outline the causes of any deviations found, provide appropriate conclusions, and where applicable, proposals for necessary corrective actions (including changes) should be made.

11.3 Qualification

- 11.30 Qualification of equipment and their operational performance at the time of installation, reequipping or maintenance, which are defined under the Enforcement Notification, should be carried out, usually, by conducting the following operations, individually or in combination.
- 1) Design Qualification (DQ): Documented verification to confirm whether the requirements for the manufacturing equipment ascertained in the process development studies performed for the purpose of manufacturing products having an intended quality are scientifically and reliably reflected in the basic design of the equipment used in the actual production. This procedure is usually performed by confirmation, etc. of design specifications and design drawings.
 - 2) Installation Qualification (IQ): Documented verification to confirm whether the installed or modified manufacturing equipment complies with the approved (notified) design and the manufacturer's requirements.
 - 3) Operational Qualification (OQ): Documented verification to confirm whether the installed or modified manufacturing equipment to be used for actual production can be operated in compliance with the intended performance in the range of expected operating conditions after conducting IQ and calibration of the equipment.

- 4) Performance Qualification (PQ): Documented verification to confirm whether manufacturing procedures, etc. can be performed effectively and reproducibly; namely, the manufacturing equipment to be used for actual production demonstrates the intended performance in accordance with the manufacturing procedures, etc.³³, which have been established based on the results of the efficiency study (refer to Chapter 11.4), and products with the intended quality can be manufactured by performing operations in compliance with the established specifications.³⁴

11.4 Efficiency Study

- 11.40 After conducting OQ of the manufacturing equipment to be used for actual production, a series of process development studies should be conducted under the same manufacturing conditions as those in the actual production, and manufacturing procedures, etc. necessary for the transfer to the next PQ stage should be established and documented (hereinafter referred to as “efficiency study”)³⁵.

11.5 Approaches to Validation

- 11.50 The system for the actual production; namely, the system of the production unit and the quality unit, should have been established, and PQ should have been

³³ These include process parameters.

³⁴ DQ, IQ and OQ are the procedures for evaluation and confirmation, which are applied only to buildings and facilities, while the major objective of PQ rests on evaluation and confirmation of whether buildings and facilities “exert intended performance” in consideration of actual production. For instance, an installed capsule-filling machine may not work at the specified precision when it comes to filling an actual product, even when it has been confirmed that the machine works in compliance with established specifications. Although PQ is a verification operation using actual machines and actual drugs (placebo may also be used), it is not necessary to perform it on actual production scale, and it is allowable to perform it on a scale suited to the verification objective.

³⁵ It is considered that operating conditions and process parameters, etc. are finally established in some cases based on examinations, such as a scale-up experiment, etc. as a matter of practice using the actual manufacturing equipment and active drugs or placebo. In this guideline, these operations are regarded as process development studies separately from the OQ and PQ operations that are performed as part of validation operations, and newly positioned as an “efficiency study” pursuant to the Enforcement Notification, because any judgments on “acceptance criteria” are not made in these operations. An efficiency study is not limited to examinations using the actual machine, but could also involve examinations at the laboratory level or examinations of the actual production data of existing products that have been obtained in the past.

completed. In addition, all matters, including raw materials and personnel, etc., should have been qualified.

- 11.51 As an exception, retrospective validation can be performed instead of confirmation by actual manufacturing for some adequately established processes that ensure critical product quality, provided the following conditions are met:
- 1) Critical quality characteristics and critical process parameters of the relevant processes have been identified;
 - 2) Appropriate acceptance criteria and control methods for in-process testing of the relevant processes have been established;
 - 3) There have been no failures in critical processes or products that can be attributed to causes other than operator errors, or equipment failures unrelated to equipment suitability; and
 - 4) Quality characteristics have been established for existing products manufactured by the relevant processes.
- 11.52 Lots selected for retrospective validation should be representatives of all lots manufactured during the review period, including any lots that fail to conform to the specifications. They should be sufficient in number to demonstrate the consistency of the relevant processes. Reserve samples may be tested to obtain data for retrospective validation.
- 11.53 Prior to conducting process validation on an actual production scale, a tentative maintenance program should be established based on the findings of IQ and OQ, and preparations should be made for the measures designed to optimize the maintenance program including the timing and items subject to maintenance after the validation.

11.6 Cleaning Validation

- 11.60 Cleaning validation should be performed on the processes where contamination or incidental carryover of products has major impacts on product quality.
- 11.61 Cleaning validation should reflect patterns of actual use of the equipment to be cleaned. In the case where equipment used for manufacturing of various products is cleaned in accordance with the same procedures, a representative product can be selected for the relevant cleaning validation. This selection should be based on the residue limit estimated in consideration of solubility, difficulty in cleaning, as well as potency, toxicity, and stability.
- 11.62 The cleaning validation protocol should describe the equipment to be cleaned, procedures, packaging/labeling materials, acceptable cleaning level, process parameters for monitoring and controlling, analytical methods, type of samples to be collected, and sampling and labeling methods.
- 11.63 In order to detect both insoluble and soluble residues, an appropriate sampling method should be selected among the swab method, rinse method, and alternative method (e.g., direct extraction) for cleaning validation. The sampling method should ensure quantitative measurement of the levels of residues remaining on the equipment surfaces after cleaning. The swab method may be impractical when the product contact surface is not easily accessible due to equipment design or process limitations (e.g., inside of pipes and parts of the filling machine in contact with liquids, and small-sized complex instruments, etc.).
- 11.64 For cleaning validation, validated analytical methods having adequate sensitivity to detect residues and contaminants at the detection limit level should be used. The recovery level attainable by the relevant analytical methods should be established. Residue limits should be practical and achievable, and the method should be capable of verifying the measurement at levels below the relevant limits, and be based on the data of the most highly toxic residues or those with the

greatest impact on the product quality. Residue limits should be established based on the minimum dose level of known pharmacological, toxicological, and physiological activity of the most toxic substance among the product ingredients.

- 11.65 Operations of cleaning, sanitation and disinfection of equipment should be appropriate in consideration of contamination by microorganisms and endotoxins in the manufacturing processes where control of the microbial count or endotoxin level in the product is necessary, or their contamination may become problematic.
- 11.66 Cleaning procedures should be monitored periodically at appropriate intervals even after validation in order to ensure that these procedures are effective in routine production. The hygiene level of the equipment to be cleaned may be monitored by analytical testing, and where applicable, by visual inspection. Visual inspection may allow detection of gross contamination concentrated in small areas that cannot be detected by sampling and analysis.

11.7 Analytical Method Validation

- 11.70 In the case where the analytical methods to be adopted are not listed in the compendium, such as the Japanese Pharmacopoeia, etc., and other acknowledged references³⁶, the relevant analytical methods should be validated. All the testing methods should be validated under actual usage conditions, which should be documented, and the documents should be archived.
- 11.71 Analytical methods should be validated in consideration of the ICH guidelines for analytical method validation. The degree of analytical method validation should reflect the purpose of the targeted analytical method and the step of the manufacturing process to which the relevant analytical method is applied.
- 11.72 Analytical instruments to be used for testing/inspection of products and

³⁶ The analytical methods listed in the compendium, such as the Japanese Pharmacopoeia, etc. or other acknowledged references are general methods, and are not necessarily applicable to all analytical targets; therefore, it is necessary to have their compatibility verified by analytical validation and other appropriate methods.

packaging/labeling materials should be appropriately qualified.

- 11.73 In the case where validated analytical methods are to be modified, analytical method validation should be conducted depending on the degree of the modification. The results of the analytical method validation and the relevant modification should be documented, and the documents should be archived. The documents should include the reason for the modification and appropriate data to verify that the modified analytical method gives results as accurate and reliable as the established method.

12. Change Control (related to Article 14 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs)

- 12.10 In addition to changes attributable to complaints and recall, those attributable to regulatory requirements should also be covered by change control.
- 12.11 The document related to change control procedures prepared in accordance with Article 8, Paragraph 4 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as “change control procedures”) should include changes to the quality management system, raw materials and packaging/labeling materials (including changes of suppliers), specifications, manufacturing methods, testing methods, and buildings and facilities (including related software).³⁷
- 12.12 Changes should be drafted and reviewed by an appropriate division, and should be approved by the quality unit.

³⁷ According to Article 14, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, changes (plans) should be approved by the quality unit. “Involvement of the quality unit in all quality-related matters” (refer to Chapter 2.20) is the basic concept of this guideline, and it is recommended that the results of changes, like the plans, are also approved by the quality unit.

12.13 The change control protocols should include the following matters:

- 1) The evaluation defined under the provision of Article 14, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include evaluation of the necessity of revalidation, the necessity of additional testing required to justify the changes, and the necessity of partial change application;
- 2) Prior to the changes, methods for evaluation of product quality (including accelerated stability tests, stability monitoring program, etc.) and evaluation criteria should be determined in advance;
- 3) Prior to changes, methods for revision of documents related to the changes and methods for education and training of personnel should be determined in advance, and the document revision and the education and training should be conducted in a reliable manner;
- 4) Prior to the changes, “other necessary actions” defined under the provision of Article 14, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, such as the necessity of changes to specifications, testing methods, expiry dates or expiry for use, and labeling should be determined in advance.

12.14 After the changes, the first two or more lots manufactured or tested under the changed conditions should be evaluated.

13. Non-conforming Products

13.1 Non-conforming

13.10 Products that have failed to meet established specifications (hereinafter referred to as “non-conforming products”) should be identified by labeling and

quarantined.

- 13.11 The final disposition of non-conforming products and raw materials and packaging/labeling materials should be documented, and the documents should be archived.

13.2 Returns

- 13.20 Returned products should be discarded unless their quality is proven to be acceptable on the basis of the conditions of storage or transport after release from the manufacturing site until return, elapsed time, appearance of the containers, etc., and results of testing conducted after return, etc.
- 13.21 The following matters related to the returned products should be documented, and the documents should be archived:
- Name and address of the consignee;
 - Name and lot number of returned product, date of release, and date and quantity returned;
 - Reason for return; and
 - Actions taken for the returned product

14. Quality Information

14.10 The quality information management system defined under the provision of Article 16, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include procedures for assessing the necessity of improving the quality management system and recall, etc., which are attributable to complaints or the like.³⁸

15. Recall Management (related to Article 17 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs)

15.10 The documented procedures for management of recalls defined under the provision of Article 8, Paragraph 4, Item 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should clearly describe the personnel to be engaged in information evaluation, the procedures for judgment on recall, where and how to transmit the recall information, as well as methods for storage and handling of recalled products.

15.11 Records of recall management defined under the provision of Article 17, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include the results of investigation of causes and corrective actions taken.³⁹

³⁸ It is important for the operations in the quality information management system to assess “causes,” “trends,” “frequency related to products,” “importance,” and “assessment of corrective actions,” and to use them as materials to be utilized for subsequent activities to improve product quality assurance. In addition to the matters defined under the provision of Article 16 of the Ministerial Ordinance for Drugs and Quasi-drugs and Enforcement Notification, etc., name and address of the provider of the quality information, date of receipt of the quality information, measures that have been taken initially (including date of the measurements and name of the personnel in charge), and responses made to the quality information provider (including date of reply), final decision related to the measures taken for the quality information target lot, and improvement measures, etc. should be documented.

³⁹ The records of recall management defined under the provision of Article 17, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should describe the reason for recall, dates of start and completion of recall, recall method (including methods for recall information transmission and confirmation of the presence or absence of recalled products at the recall site), scope of recall (medical institution where recall has been performed, name and address of distributors, etc), recalled amount, marketing status of the recalled product, results of investigations on reserve samples, results of investigations on the records related to the recalled lot, and other matters including methods and results of investigations on causes, status or results of corrective actions, etc.

**Health and Labour Science Research of Fiscal Year 2005
(Comprehensive Research Business of Regulatory Science of Pharmaceuticals and
Medical Devices):
A Study on Quality Management Systems for Pharmaceutical Products and
Medical Devices based on Science and Risk Management**

Yukio Hiyama, Section Chief, Division of Drugs, National Institute of Health Sciences, The
Ministry of Health Labour and Welfare

**Guideline on Control of the GMP Quality Control Laboratory for
Drugs and Quasi-drugs**

**Project Team for Preparation of
“Guideline on Control of the GMP Quality Control Laboratory for Drugs and Quasi-drugs”**

Researcher in Charge:

Yukio Hiyama (Division of Drugs, National Institute of Health Sciences)

Co-researchers:

Shinichi Tadaki (Saitama Institute of Public Health)
Masatoshi Ikutoh (Santen Pharmaceutical Co., Ltd)
Masao Izaki (Mitsubishi Pharma Corporation.)
Noriko Katori (National Institute of Health Sciences)
Tomoaki Sakamoto (National Institute of Health Sciences)
Tomoko Sagawa (Teijin Pharma Limited)
Shuhei Deguchi (Dainippon Sumitomo Pharma Co., Ltd.)
Koei Hatada (Sumika Chemical Analysis Service, Ltd.)
Yozo Hamachi (Institute of Applied Medicine, Inc.)

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1. Preface

1.1 Introduction

In the manufacturing and marketing of drugs, it is important to deliver drugs of a constant quality into the market in order to assure the safety and efficacy that has been proven and abides by the standards for manufacturing control and quality control. In line with this, “Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-Drugs” (hereinafter referred to as “GMP Ministerial Ordinance on Drugs and Quasi-drugs”) was established according to the Pharmaceutical Affairs Law, marketing approval holders are required to comply with these standards for the manufacturing control and quality control at their manufacturing sites as one of the approval conditions. Furthermore, manufacturers are obliged to observe the Standards.

The implementation of analysis and testing has an important significance for the objective verification of the manufacturing control and quality control of products related to drugs; however partially because many of the stipulations for the analysis and testing in GMP Ministerial Ordinance on Drugs and Quasi-drugs are in rather comprehensive expression and partially because after the enforcement of the Revised Pharmaceutical Affairs Law, it becomes possible to totally entrust the analysis and testing to external testing institutions by manufacturers’ own responsibility and judgment or other reasons, and highly necessary to have a guideline which shows concrete methods for the control of analysis and testing.

In the meantime, now is the time when, in association of the increase in international business transaction or others, quality-related-standards agreed upon in ICH, management methods of international standard basis including ISO and others prevail in Japan, so the guideline must also be one that boosts the credibility of analysis and testing at Japanese manufacturing sites in the global society.

Taking all these things into consideration, the “Guideline on Control of the GMP Quality Control Laboratory for Drugs and Quasi-drugs” has been prepared.

1.2 Objectives of the Guideline

This Guideline intends to concretely show as many recommendation items as possible that are necessary for manufacturers when they conduct analysis and testing duties as the quality control specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, and for external testing institutions when they conduct analysis and testing duties appropriately. These recommendations include items indirectly related to quality control such as quality assurance or manufacturing control, etc., depending on items.

1.3 Scope of Application

- 1) This Guideline is subjected to all of the analysis and testing (including those entrusted to others) to be done as the quality control in accordance with the stipulations in GMP Ministerial Ordinance on Drugs and Quasi-drugs. The analysis and testing includes those related to physiochemical, microbiological, veterinary and other fields, however, detailed items in a specific field are not handled in this Guideline.
- 2) This Guideline is targeted to all of the organizations that perform analysis and testing as the quality control specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, regardless of the size or form, etc. of business, or regardless of whether the organization is a testing institution performing analysis and testing exclusively or unit performing analysis and testing as a unit responsible for the analysis and testing in a manufacturer’s organization.
- 3) Although the recommendation items in this Guideline complement the stipulations of GMP Ministerial Ordinance on Drugs and Quasi-drugs, these matters, excluding those required in the Ordinance or in other Laws, are expected to be applied and utilized selectively in accordance with the size, form or others of actual business. It is not necessary to carry out all of the recommendation items in this Guideline; only applicable parts need to be carried

out.

- 4) In this Guideline, “analysis and testing unit” means an organization that relates to the analysis and testing duties performed by the quality unit as a part of the manufacturing control and quality control.

2. Recommendation items for the control

2. 1 Organization

- 1) A manager should be appointed to manage and control analysis and testing duties in accordance on the basis of Article 6, Paragraph 1 and Paragraph 2 of GMP Ministerial Ordinance on Drugs and Quasi-drugs. The content and scope of the responsibility and authority of the manager should be defined in the document specified in Article 6, Paragraph 4 of GMP Ministerial Ordinance on Drugs and Quasi-drugs.
- 2) The analysis and testing unit should perform analysis and testing for the quality control and is responsible for the results of the analysis and testing.
- 3) The analysis and testing duties should be carried out by a sufficient number of employees who received appropriate education and training (refer to section 3.1) including those employees (including temporary employees) who perform the analysis and testing. The responsibility and scope of duties of the employees should be defined in advance in the document specified in Article 6, Paragraph 4 of GMP Ministerial Ordinance on Drugs and Quasi-drugs.
- 4) In preparation for cases of absence of the manager, a representative of the manager should be designated in advance from among employees who are well informed of the contents of duties.

2. 2 System for Management and Control of Quality related to Analysis and Testing

- 1) In order to maintain the System for Management and Control of Quality that has already been established in a manufacturer for the obedience of the stipulations specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, the manager of the analysis and testing unit should include “a system, for the employees engaged in analysis and testing duties, and for the duties of the analysis and testing unit” as a part of the System for Management and Control of Quality.
- 2) Documents related to the System for Management and Control of Quality related to Analysis and Testing Duties contain the following contents. Meanwhile, these documents may sometimes be prepared as a part of various operating procedures which are prepared pursuant of the stipulations of GMP Ministerial Ordinance on Drugs and Quasi-drugs.
 - a) Organization, personnel and training and education
 - b) Control of documents and records
 - c) Control of deviation and changes
 - d) Control of self-inspection and internal audit
 - e) Control items related to external entrusting
 - f) Control of environment
 - g) Grasping of specifications and standards, and suitability evaluation of analysis and testing methods
 - h) Control of buildings and facilities
 - i) Control of reagents, test solutions and reference standards
 - j) Control of sample collection, and collected samples

- k) Assurance of results of analysis and tests
 - l) Procedures for planning, implementation, acceptance or rejection judgment, and reporting of analysis and testing
 - m) Control of reference samples
 - n) Stability monitoring
- 3) The documents related to the System for Management and Control of Quality related to Analysis and Testing Duties should be reviewed periodically in accordance with the changes in the organization or in contents of duties and be revised appropriately.
 - 4) Procedures related to the System for Management and Control of Quality related to Analysis and Testing Duties should be checked and approved by related sections in the quality unit.

2.3 Control of document

- 1) As an operating procedure for the management of all documents used for the analysis and testing duties among the written operating procedures prepared pursuant of the stipulations in Article 8, Paragraph 4, Item 9 of GMP Ministerial Ordinance on Drugs and Quasi-drugs, operating procedures that are clearly specified in Article 20, Item 1 of the Ordinance should be prepared and implemented, in addition to operating procedures that are for the review at the time of preparation or revision and for the recall at the time of document destruction.
- 2) Documents should be prepared in a way that mutual relationships among documents are easily understood.
- 3) In all cases when analysis and testing duties take place, the latest version of documents approved by the quality unit should always be used.
- 4) The following is an example of the layout of the documents, including operating procedures for analysis and testing, based on the stipulations in Article 8, Paragraph 5 of GMP Ministerial Ordinance on Drugs and Quasi-drugs. In the meantime, when electronic media are used as documents, the documents should remain easy to access .
 - a) Operating procedures and validations reports for analysis and testing methods: Inside of an analysis and testing room
 - b) Operating procedures for the operation of analysis and testing instruments: Places which are near the instruments and easy-to-reach
 - c) Operating procedures for the control of reagents and test solutions: Places which are near the storage place of reagents and test solutions and easy-to-reach
- 5) All of the documents should be stored appropriately and safely, without being tampered with, for a specified period in a place which is devised for protection from loss or serious damage.

2.4 Control of records

- 1) Each of all of the duties related to the analysis and testing duties should be recorded in control records of an analysis and testing room at the time when it is implemented, if it is defined to do so, or, if it is considered necessary to do so even though there is no definition.
- 2) At the time of preparation of records, filling-up should be done in a predetermined space in an easy-to-read way, and with not an easy-to-erase manner; and the date of the entry and the name of the filling-up person should be clearly described.
- 3) When a correction of the recorded items is made, the reason for the correction and the date of the correction should be described together with the signature and seal of the person making the correction. In addition, the pre-revision record should be maintained to be legible.

- 4) Analysis and testing records should contain complete data and descriptions related to all of the analysis and testing that are performed to confirm that the products, and labeling and packaging materials meet the specifications. Demanded contents include the following:
 - a) In addition to descriptive matters indicated in Chapter 3, 3-11 of Enforcement Notification, records on samples collected or obtained for analysis and testing should contain: names of manufactures or suppliers (if it is a juridical person, the name of the juridical person) (places where the samples were collected, if necessary); date of the collection of samples; and the date of acceptance of samples for analysis and testing (this is limited when this date is different from the date of collection of samples).
 - b) Description and reference matters (when corresponding matters are mentioned in published literatures, cite the source) related to the analysis and testing methods implemented should be given. Usually it is acceptable to describe information such as the number of operating procedures, etc., from which it is possible to specify the analysis and testing method
 - c) In addition to the descriptive matters indicated in Chapter 3, 3-11 of Enforcement Notification, records of the content of analysis and testing should contain: amounts of samples; reference standard materials (reference standard products); reagents; standard solutions; major analysis and testing equipment and instruments used; and judgment criteria of the results of analysis and testing.
 - d) All of raw data related to each analysis and test (including the process leading to the final result from which measurement units, conversion factors and equivalency factors become clear) should be identified appropriately in a way that makes the relation between the samples used and the lots or control units clear.
 - e) Signature, date of signing/applying seal and date of the review (records of double checking by a third party) of the person who reviewed the validity, completeness and compliance with established specifications of the master production records.

- 5) In addition to the analysis and testing records of products, and labeling and packaging materials, complete records on the following items should be prepared, checked and preserved.
 - a) At the time of change of analysis and testing method, the records on the evaluation of the change defined in Article 14, Item 1 of GMP Ministerial Ordinance on Drugs and Quasi-drugs should contain: the reason of the change; the results of verification proving that the changed analysis and testing method gives similar, correct and reliable results as the pre-changed method; and the data used for the verification (refer to Sections 2.6 and 3.4).
 - b) Checks, maintenance and periodic calibration of equipment, instruments, apparatuses and tools in the analysis and testing room.
 - c) All stability tests performed for products.

- 6) For all of the records and their copies, mutual interrelation and retrieval should be easy to control. Recorded matters should be easily picked up at the testing institutions where the matters were implemented. In the meantime, when the system is made that such records are available at the said testing institution by transfer from a storage place other than the said analysis and testing institutions using an electronic method or other methods whenever necessary, this system is allowed to be used. The following are examples of the control methods of records.
 - (a) To file related raw data and records for each fiscal year, after classifying them for each product, or labeling and packaging material, for lot number or control unit number, etc.
 - (b) Utilization of electronic media with retrieval system

- 7) All records or their copies should be stored appropriately and safely, without being tampered with, for a specified period in a place which is devised for protection from loss or serious damage.

2. 5 Control of deviation

- 1) Contents of deviations from procedures of analysis and testing duties should be made clear, and should be reported to the manager of the analysis and testing unit regardless whether they are serious or not. These procedures should be documented.
- 2) The manager of analysis and testing unit should conduct cause investigations, evaluate the influence on quality and judge about the measures of his/her analysis and testing unit, taking into consideration of the degree or conditions, etc. of the deviation.
- 3) When it becomes clear that a deviation is one of those previously specified for which the manager can take disposal action by his/her own authority as a result of the cause investigation and evaluation, the manager should instruct actions corresponding to the content directly to persons in charge in the analysis and testing unit. On the other hand, if it is judged, as a result of the cause investigation, that the deviation may relate to the quality of product, for example, cause serious influence on the judgment for product release from the manufacturing site, the manager should report the content and evaluation results, etc. of the deviation, a conclusion of his/her analysis and testing unit, and opinions on desirable actions and others to the person in charge of deviation control in the quality unit.
 - a) Examples of deviations for which the manager of analysis and testing unit can take actions by his/her authority:

In cases when a deviation is clear in its cause and relatively moderate in its degree, it is possible in some cases that the manager of analysis and testing unit can take easy and appropriately actions under the responsibility of the unit, for example, when the unit holds a sufficient amount of equivalents preserved samples. For example,

 - When there is a deviation from the regulations in the operating procedures for analysis and testing methods such as weighing error, miss operation at sample preparation, etc. → When analysis and testing is under way, it should be stopped and repeated from the appropriate step according to the instruction from the manager. It should be judged whether or not additional analysis and testing or reanalysis and retesting is necessary, according to necessity.
 - When it becomes clear that the expiration date of a reagent had passed after the completion of analysis and testing → It should be judged whether or not additional analysis and testing or reanalysis and retesting is necessary. The influence on results of analysis and testing in the past up to the expiration date should be evaluated.
 - When analysis and testing is carried out without performing a defined calibration of analysis and testing equipment and tools → The influence on results of analysis and testing should be evaluated and it should be judged whether or not additional analysis and testing or reanalysis and retesting is necessary. Calibration of analysis and testing equipment and tools should be immediately instructed.
 - When necessary items are not described on the label of a sample → Necessary information should be confirmed immediately and should be described correctly.
 - b) Examples of deviations that may relate to quality:

These are such critical deviations which may markedly damage the credibility of results of analysis and testing, or deviations which are found in such a condition that equivalent samples are no longer available, or that was found only after the judgment of the analysis and testing was made, being not able to take actions by the analysis and testing unit only. The following are examples:

 - When it is a kind of deviation mentioned in the above a), but it was found only after the end of the judgment of analysis and testing and additionally judged necessary to carry out additional analysis and testing or reanalysis and retesting → It should be instructed to again carry out analysis and testing of the said items, and if necessary, it should be instructed to again carry out the collection of samples or other necessary works.
 - When it becomes clear that the defined analysis and testing has not been completed in some

items → It should be instructed to carry out analysis and testing of the said items, and if necessary, it should be instructed to again carry out the collection of samples or other necessary works.

- When it becomes clear that analysis and testing was done using a wrong analysis and testing method → The analysis and testing should be carried out again using the correct analysis and testing method. It should be instructed to re-collect samples, if necessary. Both cases a) and b) are given only as an example to the last, and therefore each case should be appropriately judged and dealt with following the respective content of the deviation. In addition, such actions for the prevention of recurrence as the review of education and training program or others, according to necessity, should be taken.
- 4) Records should be preserved in a form from which the relationship between the content of the deviation and the investigation, judgment and actions for the deviation is confirmed in the future. These procedures should be documented.

2. 6 Change control

- 1) When procedures for analysis and testing duties are to be changed for some reason, a defined procedure, which contains the following contents, should be documented in advance and the change should be carried out following this procedure. In the meantime, the procedure after b) should be carried out not only by the analysis and testing unit but by depending on results of consultations with the quality unit and other related units.
- a) Proposal for the change of procedures of analysis and testing duties. The proposal should be made according to the pre-determined method.
 - b) Acceptance of the change proposal in the quality unit, and primary evaluation of the influence of the said change.
 - c) Decision making for the action measures based on the content of change and the results of influence evaluation. In the meantime, it may go directly to procedure f) in some cases depending on the result of the said evaluation. The following are examples of evaluations and actions:
 - In cases when words in sentences are to be corrected, no specific validity investigation is needed if the content of procedures before the change is judged to be practically maintained.
 - In cases when analysis and testing methods are to be changed, whether or not actions such as re-validation or additional analysis and testing are necessary for the change should be investigated; and if it is judged necessary, a plan for the analysis and testing related to the said actions should be established.
 - In cases when it is judged that approval application or notification for the change is required according to the Pharmaceutical Affairs Law, the fact should be notified to related units.
 - d) The protocol related to the investigation of the validity of the change should be prepared according to necessity. The protocol should contain standards for the evaluation of the validity.
 - e) The investigation of the validity of the change should be conducted according to necessity. A report about the results of the investigation should be prepared in a way that makes the degree of influence of the change on the quality of products clear.
 - f) A draft for the content of the change should be prepared (if necessary, attach the reports, etc. of the investigation of the validity of the change).
 - g) The content of the draft should be confirmed as the quality unit, and if the validity of the change was investigated, the reports thereof should be evaluated as the final evaluation.
 - h) Approval or disapproval of the change by the quality unit.
 - i) The changes of all of the specifications and standards related to the change and the revision and destruction of related procedures, etc. should be carried out.
 - j) Employees should be well informed with the content of the change, and education and

training for the implementation should be carried out.

- 2) All documents related to the change from proposal to approval, including the protocol and report of the investigation of the validity related to the changes in analysis and testing method, should be reviewed by related units and the approval from the quality unit should be obtained.
- 3) When analysis and testing duties are to be implemented based on the approved change, revision or destruction of related documents and education and training of employees, etc. should be completed beforehand.
- 4) Works related to the change control of analysis and testing should be recorded; and the records should be preserved. In addition, history records showing the changed date and reasons of the change should be prepared and retained for all of the documents which were changed so that time course of the change becomes clear.

2. 7 Self-inspection and internal audit

- 1) The analysis and testing unit should take the initiative in complying with GMP Ministerial Ordinance on Drugs and Quasi-drugs and other laws, and should conduct, in addition to the self-inspection specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs, periodic internal audit according to the predetermined procedures, in order to ensure that the part of analysis and testing in the System for Control and Management of Quality are operated appropriately. Analysis and testing duties subjected to the self-inspection and internal audit include the following duties. Meanwhile, concerning external testing institutions, refer to section 2.8.
 - a) Judgment of results of analysis and testing.
 - b) Actions for the out-of-specification results of analysis and testing
 - c) Control of all serious deviations in analysis and testing.
 - d) Control of all changes in analysis and testing methods.
 - e) Implemented corrective actions (including actions for the results of previous self-inspection and internal audit).
- 2) Those who perform internal audit should not be those who are engaged by themselves in duties subjected to the internal audit, as a rule, similarly as in the case of the self-inspection mentioned in the Enforcement Notification. Meanwhile, those who perform the self-inspection or internal audit should be qualified in advance for the duties; and it is desirable to establish a certification system for the qualification.
- 3) Results of the internal audit and subsequent corrective actions should be documented, similarly as in the case of the self-inspection mentioned in the GMP Ministerial Ordinance on Drugs and Quasi-drugs. In addition, they should be reported to responsible persons concerned, in order to alert them to appropriate operation of the relevant parts of analysis and testing in the System for Control of Quality Control.
- 4) Corrective actions related to the analysis and testing that are decided to perform according to the results of self-inspection and internal audit should be implemented at an appropriate time, and with an effective method, and if necessary, the subsequent effect should be confirmed.

2. 8 Confirmation items in the contract analysis

- 1) In cases when an analysis and testing specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs is entrusted to an external testing institution, the institution is subject to the stipulations of the Ordinance; the institution should pay special attention to the following points, in deep consideration of business form.
 - a) Prevention of contamination and cross-contamination of samples

- b) Maintenance of analysis and testing data traceability
 - c) Confirmation of actions for samples, and analysis and testing methods, in advance of the implementation of the analysis and testing
 - d) Securing safe, and reliable methods for the transportation of samples
- 2) The contract-giver and contract-acceptor should prepare documents for the agreement concerning the contract analysis. In the agreement, responsibility assignment of each party for performing the analysis and testing specified in GMP Ministerial Ordinance on Drugs and Quasi-drugs should be concretely described as well as those specified in Enforcement Notification.
 - 3) In the agreement document, the contract-giver should be given the privilege of inspecting the contract-acceptor's facilities in order to facilitate confirmation of the compliance with GMP Ministerial Ordinance on Drugs and Quasi-drugs. The contract-giver should conduct the periodic inspection on the external testing institutions and make evaluation; the targets of the inspection and evaluation should include not only technological level of the analysis and testing, but also whether or not predetermined procedures, etc. are appropriately performed and also whether or not the contract-giver functions as the person concerned with the analysis and testing parts in the System for Control of Quality Control.
 - 4) Both parties of the contract-giver and contract-acceptor should conclude an agreement in writing between them for storage condition of data of records related to the analysis and testing performed at the external testing institution (the condition should be based on the regulations in GMP Ministerial Ordinance on Drugs and Quasi-drugs or other related laws). When it is decided that the external testing institution preserves raw data of the records related to the analysis and testing, it should be made that the data are available for use immediately upon request of the contract-giver.
 - 5) Any of the changes related to analysis and testing methods or judgment criteria in external testing institutions should not be implemented by its own judgment of the external testing institution unless otherwise approved by the contract-giver.
 - 6) In cases of the occurrence of a critical deviation related to analysis and testing or a result of out of specification in the analysis and testing, both parties of the contract-giver and contract-acceptor should conclude an agreement in writing in advance for the reporting system of such occurrence.

3. Recommendation items for Technological Aspects

3. 1 Personnel and Training

- 1) Employees who engaged in analysis and testing duties should be those who are well informed of GMP and the quality system related to analysis and testing duties, and received sufficient training corresponding to the content of duties.
- 2) The manager of an analysis and testing unit should objectively evaluate results of the training performed for the employees in the analysis and testing unit, and perform periodic review of the education and training program in order to appropriately reflect the review results on the program. Items of the objective evaluation include, for example, confirmation of task performance capacity or technological accomplishment level of the analysis and testing, or confirmation of the consistency of training records of persons in charge of training and those receiving training.
- 3) Corresponding to the degree of past history of receiving training and the degree of job experience, a more professional education and training program should be imposed and the

result thereof should be confirmed, if necessary, in consideration of the specificity of the content of sampling or analysis and testing duties. Establishment of a certification system for the qualification is one example for this confirmation.

- 4) Persons in charge of training who teach how to practice sampling, analysis and testing operations, etc. by means of practical demonstration at sites should be those who have sufficient experience and knowledge about the said duties. Since persons in charge of training are expected to be able to convey knowledge and experience appropriately through the training to trainees, it is desirable to qualify them by some type of qualification. And this qualification is desirable to be renewed periodically, after the competency or fitness has been evaluated based on the effect of the training or on others. Items for the evaluation of competency, for example, include the degree of consistency of training records, results of questionnaires of trainees, and the evaluation of training results of trainees by a third party, etc. Objective evaluation is important in all evaluations.
- 5) All education and training programs, and training records and evaluation records of the training performed based on the programs should be arranged each employee, and preserved.

3. 2 Facilities and Environment

- 1) A quality unit should have an analysis and testing room(s) of an appropriate environment that can be used freely according to necessity, and sufficiently assures data reliability.
- 2) The analysis and testing room should be separate from manufacturing working places. If analysis and testing for the process control is conducted in manufacturing working places, it should be confirmed that manufacturing does not exert a undesirable influence on the analysis and testing and in addition, the analysis and testing duties related to the quality control do not exert an undesirable influence on the manufacturing and quality of products.
- 3) Requirements for the control of the analysis and testing room and the maintenance of environment should be decided upon and documented in advance.
- 4) The analysis and testing room should be designed corresponding to the duties carried out inside the room, by securing sufficient and appropriate space for preventing mix-up, contamination, and cross-contamination from occurring and for storing collected samples and analysis and testing records, etc.

3. 3 Grasping of Specifications and Standards

- 1) In the analysis and testing unit, the latest specifications and testing methods for the products, and labeling and packaging materials subject to the analysis and testing should be prepared as documents, and the documents should be kept in a way that the employees who perform analysis and testing duties can utilize them at any time.
- 2) Contents of the specifications and testing methods which are prepared as documents in the analysis and testing unit should be consistent with the contents described in the Marketing Approval Letter (Notification Letter) or official compendia (including self-imposed specifications, if any). (It should be arranged so that referring to the master of the Marketing Approval Letter (Notification Letter) is possible.)
- 3) In the analysis and testing unit, documents of the analysis and testing methods and judgment criteria related to the in-process control, which is carried out as part of the manufacturing control, should be prepared according to necessity. These analysis and testing methods and judgment criteria, which are not defined in the Marketing Approval Letter (Notification Letter) or official compendia, should be established based on the information obtained during

the development stages.

- 4) The analysis and testing methods and judgment criteria related to the in-process control, which is carried out as part of the manufacturing control, should also be reviewed and approved by the quality unit similarly as in the case of the analysis and testing methods related to the quality control specified in the Product Master Formula.

3. 4 Qualification Evaluation of Analysis and Testing Methods

- 1) All analysis and testing methods should be scientific and appropriate so that they can assure the compliance of products, and labeling and packaging materials with pre-determined specifications/standards.
- 2) All of the specifications and testing methods, including their changes, should be drafted by an adequate unit, reviewed and subsequently approved by the quality unit.
- 3) The analysis and testing unit should confirm the validity of an analysis and testing method, and the unit should also obtain such bases of the validity as validation data, etc. which were acquired during the research and development stages in order to maintain the consistency of the analysis and testing method. As for the analytical method used for the analysis and testing, it should be confirmed that validation for the analytical method was performed appropriately in consideration of attributes, etc. included in the ICH guidelines on validation of analytical methods.
- 4) When an analytical method used in the analysis and testing is not described in the official compendia including the Japanese Pharmacopoeia or in other published literatures, validation for the analytical method should be done in an appropriate unit. The scope and degree of the validation should be decided according to the object of the analytical method or the stage of manufacturing process or others.
- 5) Qualification of all of the analysis and testing methods used for the analysis and testing, including cases when an analytical method used in the analysis and testing is described in the official compendia including the Japanese Pharmacopoeia or in other well recognized literatures, should be verified under the actual condition (including equipment, instruments, reagents and test solutions which are used) in the analysis and testing room, and accordingly, records of the results should be prepared. Analysis and testing methods are occasionally technology transferred: between a research & development unit and analysis and testing unit at a manufacturing site; between plural numbers of analysis and testing units of manufacturers; or between an analysis and testing unit in a research & development unit or at manufacturing sites and external testing institutions. In any one of these cases, it is important to confirm in advance about whether expected reasonable results are surely obtained or whether precision of the analysis and testing has no problem, by implementing the analysis and testing for obtaining data, using the equipment and instruments, reagents and test solutions, and standard reference substances, all of which are expected to be used, under a test environment in the analysis and testing room, to where the method is to be transferred, prior to the actual business operation of the analysis and testing at the transferred place.
- 6) When the analytical method is to be changed, analytical method validation should be implemented according to the degree of the said change. All of the changes implemented for the said analytical method based on the results of the analytical method validation should be documented, which should be preserved together with the protocol and reports of the analytical method validation. The said reports should contain the reason of the change and appropriate and concrete data in order to make possible verifying that it is possible to obtain data by the changed method similarly and as accurate and reliable as the pre-changed analysis and testing method.

- 7) Documents of the latest analytical method validation on analysis and testing methods, including data thereof, should be displayed in a way that employees who perform analysis and testing duties can access them at any time when it becomes necessary.

3. 5 Equipment/Instruments and Calibration

- 1) In the analysis and testing room, equipment and instruments that are required for assuring data reliability sufficiently should be installed.
- 2) In order to clearly indicate that it is in compliance with applicable control items, labeling on equipment and instruments, etc. or other measures should be implemented in accordance with necessity.
- 3) Duties related to calibration are allowed to be entrusted to external organizations under the responsibility of the quality unit if they are defined so beforehand in quality control standard code, etc.
- 4) At the time of calibration of equipment or instruments, etc., when there is a standard procedure that makes inspection of the standards of weighing possible, such procedure should be used.
- 5) The condition of the status of the calibration of important equipment and instruments can be proven should be maintained. One example of the measures is placing a label indicating the result of calibration and the next planned calibration date, etc. on equipment and instruments.
- 6) Equipment or instruments, etc. not complying with the calibration standard should not be used. As measures to prevent the miss-use of such equipment or instruments, etc., one example is placing a label indicating “not for use” on the equipment or instruments, etc. that are not in compliance with the standards for calibration, or overrun the calibration period.
- 7) Operational performance confirmation of the equipment or instruments, etc. to be used should be done using appropriate procedures including system suitability tests.
- 8) In cases where it becomes known that one piece of equipment or one instrument, etc. related to critical analysis and testing items is deviated from the calibration standards, it is required to make necessary investigations for judging whether or not the deviation has exerted influence on results of the analysis and testing carried out using the equipment or instruments, etc. since the previous calibration. One example method of the investigation is to implement analysis and testing on products manufactured during the same said period by using normal equipment or instruments, etc. in order to confirm the existence or non-existence of problems in specifications of quality that were to be assured by the analysis and testing performed with the use of the said equipment or instruments, etc. If abnormality should be found as a result of the investigation, actions should be taken quickly by having discussion with a related section, etc., according to necessity.

3. 6 Reagents / Test Solutions

- 1) Concerning reagents and test solutions, procedures concerning purchasing or procurement, safety handling, preparation methods, storage, and use should be defined and documented in advance.
- 2) Reagents should be controlled according to the procedures, and should be indicated by name, safety information, storage condition, date of purchase, expiration date, and, if necessary, the date of opening.

- 3) Already prepared materials including test solutions should be controlled according to the procedures, and records on the preparation should be prepared. The expiration date of the already prepared test solutions, etc. should be established appropriately in consideration of the characteristics and stability of the materials. Already prepared materials should be indicated by name, preparation number or date of preparation, name(s) of person(s) who prepared the materials, expiration date, and, if necessary, storage condition and conversion coefficient, etc. It is also necessary to indicate name, etc. for containers of water for analysis and testing, as well as dispensed solvents for analysis and testing.
- 4) Water for the analysis and testing of enough quality that does not exert influence on results of analysis and testing should be secured. In cases when water for the analysis and testing is purchased and used, the quality should be confirmed according to necessity, and records should be prepared on it. In cases when water for the analysis and testing is manufactured using in house equipment, the equipment should be maintained and controlled, and the quality of water should be checked periodically; and records should be prepared for it.
- 5) Reagents and test solutions should be those that can be applicable to the analysis and testing, and the samples. If necessary, the suitability of them should be evaluated beforehand.
- 6) For safely and stable handling of reagents, relevant laws and regulations should be abided by, and at the same time, information related to the said reagents should be collected.

3. 7 Reference Standards Materials

- 1) In order to prevent contamination and degradation, etc. of the reference standard materials from occurrence, procedures for the purchase or other procurement methods, safety handling, transportation, storage and use should be defined and documented.
- 2) Primary reference standard materials should be procured appropriately, and stored according to the condition designated by the suppliers. When primary reference material is accepted, a record on necessary items such as name, purity, safety information, storage condition, where it is procured from, date of procurement, expiration date and others should be prepared, and should be controlled after indicating necessary items on the containers in a way that they can be easily identified. Reference standard materials (reference standards) should be stored according to the pre-defined storage condition.
- 3) In cases when a primary reference standard cannot be procured from an officially authorized supplier, an “in-house primary standard” should be established. The in-house reference standard material should be prepared by implementing purification procedures, according to necessity, on material procured appropriately. It should be confirmed that the material is the said compound (“identification”) by determining the structural formula using nuclear magnetic resonance spectroscopy and infrared absorption spectroscopy, etc. In addition, the entity of impurities should be identified as much as possible, and after that, appropriate analysis and testing should be implemented to absolutely prove the purity. Records on raw materials, purification, identification and purity should be prepared and reserved.
- 4) When a primary reference standard is used, the object of the use and the amount of used should be recorded, and the records should be preserved.
- 5) When a secondary reference standard is prepared, its lot suitability should be evaluated by implementing the comparison with the primary reference standard prior to the first use of it. In addition, the primary reference standard used in the comparison should be identified. The secondary reference standard should be re-evaluated periodically according to the procedures specified beforehand.

- 6) During the period that the product is being shipped from the manufacturing site and used, the reference standard material of necessary and sufficient amount for the analysis and testing should be controlled in a way that the material is available anytime when it becomes necessary.

3. 8 Planning of Analysis and Testing

- 1) In the quality unit, following procedures that are necessary for analysis and testing duties should be defined, and specified in written operating procedures, etc. in advance.
 - a) Procedures for concrete analysis and testing operations;
 - b) Procedures for sampling and for judgment of analysis and testing;
 - c) Procedures for the preparation and approval of the analysis and testing protocols or analysis and testing instructions (hereinafter referred to as “the analysis and testing protocols, etc.”).
 - d) Procedures for the implementation of analysis and testing based on the analysis and testing protocols, etc.
 - e) Other procedures necessary for the appropriate implementation of analysis and testing
- 2) Written procedures for analysis and testing operations should be prepared independently for each product. Operating procedures of the analysis and testing room should be more concrete and more specific in operational procedures than those generalized expressions of analysis and testing seen in the Marketing Approval Letter (Notification Letter) or in official compendia, so that it facilitates the easy implementation of accurate analysis and testing.
- 3) It is desirable to prepare written procedures by several employees. At the preparation, the manager of analysis and testing unit, a person(s) who is qualified as a trainer (for example, a person indicated in section 3.1-4) or a person(s) who is recognized as having equivalent experience and technology level, and a person(s) who is well informed with the content of analysis and testing should participate according to necessity. It is desirable that the procedure prepared is reviewed by several persons (excluding the person(s) who prepared the procedure) who have equivalent experience and a technology level as high as the person(s) who prepared the procedure.
 - 4) When preparing the analysis and testing protocols, etc., the following matters should be confirmed.
 - a) Written procedures for the analysis and testing corresponding to samples are adjusted and made available at any time for employees related to analysis and testing duties.
 - b) The validation data or suitability confirmation data related to analysis and testing methods exist, and they are arranged in a way that employees in the analysis and testing unit can utilize at any time necessary.
 - c) Equipment and instruments are those that correspond to the analysis and testing methods and samples.
 - d) Reagents and test solutions are those that correspond to the analysis and testing methods and samples.
- 5) In cases of contract analysis, a contract-giver’s approval for written procedures prepared for independently for each product and the analysis and testing protocols, etc. should be obtained. As for a plan for accepting samples, the contract-giver and the contract-acceptor should sufficiently discuss and make an agreement for the procedures for acceptance and also for action procedures at the time of the change of the procedures in advance.

3. 9 Sampling

- 1) Sampling methods should be scientific and appropriate for assuring that the products, and labeling and packaging materials meet pre-determined quality standards.
- 2) In advance of implementing the sampling, a sampling plan should be prepared for each

- implementation. The sampling plan should usually be prepared by an appropriate unit in consideration of the production schedule, etc. Preparation is allowed as a part of analysis and testing protocol. In cases of contract analysis, it is desirable to make an agreement beforehand in details about: section for the preparation of the protocol for sampling; section or person or title who performs the sampling; methods for the transfer-in and transfer-out of samples; and schedule, etc.
- 3) The samples should be representative ones of the lot or control unit, and be appropriate for the object of analysis and testing; and the ground thereof should be documented.
 - 4) Sampling should be done by a person in the analysis and testing unit as a rule, however, sampling by a designated person of the manufacturing unit, who has undergone necessary training, is also allowed under the responsibility of the quality unit when there is an appropriate reason, for example, in cases when the sampling must be done under aseptic conditions or in cases when the sampling must be done depending on the condition of process, etc. When the sampling is to be done by a person of the manufacturing unit, which should be clearly mentioned in the quality control standard code, etc., additionally, in order to secure the appropriate implementation of the sampling, attention is required, for example, by the manager of analysis and testing unit and the manager of the manufacturing unit keeping close communication regarding the matter.
 - 5) At describing the sampling procedures in the quality control standard code, the procedures should be established in consideration of the significance of products, and labeling and packaging materials, dispersion of quality, past quality history of the suppliers, and necessary amount for analysis and testing, etc. It is desirable to specify the procedures using drawings, etc. showing sampling places according to necessity so that it facilitates the certain implementation of the sampling.
 - 6) At the time of implementing a change or giving a special instruction for the sampling amount decided beforehand, it should be arranged so that such change or instruction is implemented only after clearly describing the content and reason of the change in the sampling protocol, and the recording of the works is surely done; and at the same time, special attention should be paid in order to avoid mistakes in analysis and testing afterward.
 - 7) The sampling should be done at a pre-determined place, using a procedure that prevents the contamination of samples and the contamination to other raw materials, labeling and packaging materials, and products.
 - 8) Concerning the raw materials, labeling and packaging materials, and products from which samples were taken, they should be controlled so as not to be used in the subsequent manufacturing process or to be put in the market mistakenly, using some clearly acknowledgeable measures, for example, by placing a label indicating “under analysis and testing”.
 - 9) Sampling should be done while paying attention to the following points:
 - a) If necessary, containers subjected to the sampling should be cleaned before the sampling.
 - b) If necessary, sampling should be done by aseptic sampling method using aseptic sampling utensils.
 - c) When special conditions are established for sampling, the sampling should be done according to the conditions. One example is a condition in which each sample collected from upper, middle or lower parts of a container is prohibited to mix.
 - d) In order to prevent a mix-up of samples, a container for collected samples should be indicated by necessary items including: name of sample, lot number or control number, sampling date and name of sample collector, etc.

- e) When sampling is complete for a container, the container should be indicated clearly that a sample has already been taken (for example, by fixing a label indicating “under analysis and testing”).
- f) At the time of sampling for the in-process control, the integrity of the collected samples should be assured.

3. 10 Control of Samples

- 1) The quality unit should take necessary action so that the appropriate sample distinction of collected samples is done in order to avoid the mix-up with other samples. Placing a label or bar-code indicating necessary items is an example measure for avoiding mix-up with other samples.
- 2) Information for the appropriate sample distinction includes: name, lot number or control number, number of the analysis and testing of sample, sampling date, name of sample collector, sampling place, sampling amount, and storage condition, etc. This information should be indicated on the sample container according to necessity. If necessary, it should also be indicated whether it is before or after the implementation of analysis and testing, and whether it was qualified or disqualified in the analysis and testing, etc.
- 3) The samples should be stored using a method for preventing contamination or cross-contamination, under a storage condition specified for the prevention of degradation or alteration. According to necessity, the control status of the temperature during storage should be recorded, and records should be preserved.
- 4) The receipt and distribution, name of distributor, destination of the distribution, and date of distribution should be recorded, and a record should be preserved.
- 5) In cases when analysis and testing are entrusted to external testing institutions, samples should be transported by a safe and certain method, and a record on the acceptance of the sample should be prepared and preserved. The control status of temperature during transportation should be recorded according to necessity, and the records should be preserved.
- 6) Prior to the implementation of analysis and testing, the person in charge from the analysis and testing unit should confirm that the distributed samples are those corresponding to the planned analysis and testing.

3. 11 Implementation of Analysis and Testing

- 1) The manager of the analysis and testing unit should establish in advance a procedure as to how the person in charge of analysis and testing report the result of analysis and testing, and obtain the approval of the quality unit.
- 2) The person in charge of analysis and testing duties should receive training about the operational procedures of analysis and testing and understand them sufficiently, prior to the implementation of the analysis and testing.
- 3) The person in charge of analysis and testing duties should implement the analysis and testing, in accordance with the instructions from the manager, according to the analysis and testing protocols, etc. as well as to the written procedures related to analysis and testing operations. At the time of implementing analysis and testing, work sheets and flow charts, etc. should be used according to necessity in order to make the implementation procedures certain.
- 4) All raw data obtained during the course of implementation of analysis and testing should be confirmed by persons other than the person(s) in charge, and records on the confirmation

should be prepared.

- 5) The person in charge in the analysis and testing unit should report the result of analysis and testing, including those confirmation records by person(s) other than the person in charge, to the manager in writing.

3. 12 Assurance of Results of Analysis and Testing

- 1) Person(s) other than the person in charge in the said analysis and testing unit should confirm that the result of analysis and testing was obtained by implementing the specified analysis and testing methods corresponding to the collected samples, according to the operational procedures. Confirmation methods include confirmation of written procedures used for the said analysis and testing, and review of records on the said analysis and testing, etc.
- 2) The quality unit should appropriately define in advance the specifications for the control in addition to the specifications in the Marketing Approval Letter (Notification Letter) or in the Japanese Pharmacopoeia or other official compendia, and use these specifications at the time of the judgment of results of analysis and testing. The specifications for the control as well as the specifications in the Marketing Approval Letter (Notification Letter) or in the Japanese Pharmacopoeia or other official compendia, should be those that sufficiently assure the quality of the products, and labeling and packaging materials subjected to the analysis and testing, from statistics and other scientific prospects.
- 3) Having discussions with other related units about the out-of-specification in the results of analysis and testing, the quality unit should define and document the procedures for the cause investigation and counter measures as well as the responsibility and authority in advance for the case. It is desirable to consider the following points, in consideration of the effects on quality of products.
 - a) When an out-of-specification in the result of analysis and testing is confirmed, it should be reported promptly to the manager of analysis and testing unit.
 - b) Upon receiving a report of the out-of-specification in the analysis and testing, including in the case of discovery by oneself, the manager of analysis and testing unit should take actions according to the pre-determined cause investigation and action procedures.
 - c) As initial actions, the analysis and testing unit should, for example:
 - Confirm the content of the result and make judgment promptly about appropriate action.
 - Make necessary communication with related units according to the procedures.
 - Investigate whether or not there are any deviations during the implementation of analysis and testing concerning each of the results of out-of-specification, and take records.
 - Perform the investigation to specify the scope of influence of the results of out-of-specification.
 - When it becomes necessary to carry out the re-sampling or reanalysis and retesting after the discovery of the results of out-of-specification, issue an instruction in writing.
 - d) The manager of analysis and testing unit should report the result of the cause investigation carried out by the analysis and testing unit to necessary related units after, if necessary, adding its opinions on whether or not a critical problem is present, etc. excluding cases where it is defined in advance that the problem is allowed to be dealt with under his/her own responsibility and authority. Examples of cases where the manager of analysis and testing unit is allowed to deal with his/her own responsibility and authority include cases when a problem is caused by simple cacography or minor mistakes in analysis and testing, or similar matters.
 - e) In cases where there is a deviation whose influence on quality of products cannot be denied or possibility of the influence is judged high by the analysis and testing unit, the content and results of the cause investigation carried out by the analysis and testing unit,

together with the opinions on the possible influence on the quality of products, should be documented and promptly reported to the related units. Meanwhile, concerning external testing institutions, refer to Section 2.8, Item 6.

- f) The quality unit should review the content and results of all investigations and decide whether it is approvable or not, prior to making a decision (yes or no) for the product release from the manufacturing site. And, if it is necessary to impose improvement in some points, necessary actions should be taken timely. Auditing on related unit(s) should be done according to necessity.
 - g) Training should be carried out corresponding to the results of the out-of-specification in the analysis and testing.
- 4) In cases of the implementation of analysis and testing, re-sampling or reanalysis and retesting should not be carried out without reason. In cases when a re-sampling or reanalysis and retesting is to be carried out based on a formal instruction, the reason or the reason and actions in response to the results of the analysis and testing, respectively, should be recorded.

3. 13 Judgment and Reporting of Results of Analysis and Testing

- 1) The quality unit should define the following items in written procedures and observe them.
 - a) Establishment of the judgment criteria and method of the acceptance or rejection of the analysis and testing.
 - b) Reporting and approving of the result of judgment of the analysis and testing
 - c) Reporting and actions at the time of occurrence of the result of out-of-specification in the analysis and testing.
 - d) Judgment of the necessity of the reanalysis and retesting.
 - e) Disposal of rejected products
 - f) Issuance of certificate of analysis
- 2) The manager of analysis and testing unit should review the reports from the person in charge in the analysis and testing unit and make judgment about acceptance or rejection of the result of analysis and testing. In the meantime, this acceptance or rejection judgment constitutes the base for the approval or disapproval of the product release from the manufacturing site, so the judgment criteria should be those that assure the compliance with the specifications in Marketing Approval (Notification) Letter or in the Japanese Pharmacopoeia or other official compendia.
- 3) In order to prevent mix-up, a container of the products, and labeling and packaging materials subjected to the judgment should be indicated the result of the judgment whether it is accepted or rejected, by fixing a label showing “qualified” or “not-qualified”, or by other methods, so that clear distinction becomes possible.
- 4) The manager of analysis and testing unit should report the result of analysis and testing of products and labeling and packaging materials, from which the judgment of acceptance or rejection was made, to the quality unit. The reporting should be done according to the predetermined procedures.
- 5) At the time of issuance of the certificate of analysis, the following items should be observed.
 - a) The quality unit should issue the certificate of analysis for each lot or control lots of the product, or labeling and packaging materials, upon request.
 - b) The certificate of analysis should be made so that it can be clearly identified that it is a certificate of analysis, and it should be indicated by: name of the object subjected to analysis and testing; lot number or control number; specifications; numerical results (only when the result of analysis and testing is numerical data); and judgment result, etc.
 - c) In the certificate of analysis, a person designated beforehand in the quality unit, should enter the date and subscribe or apply a stamp/seal. It should be indicated by the name of the

manufacturers (name of a juridical person, if it is a juridical person) (following to the Enforcement Notification, if it is an external testing institution), etc., according to necessity.

3. 14 Control of Reference Samples

- 1) It should be reminded that the reference sample is a reserve for the possible occasion of the evaluation of quality of an already released lot in the future, and not for monitoring the stability of the lot.
- 2) Products of drug substances:
The reference samples should be stored in a similar packaging form to the products of drug substances, or be stored in a form that is protected equivalent to or greater than the packaging form for normal release from the manufacturing site.
- 3) Products of drug products (for only those which are subjected to the qualification judgment for product release into the market):
As a rule, the reference sample should be stored in the same packaging form as the marketed products.
- 4) In order to avoid mistaken use, the reference samples should be labeled clearly so that there is no confusion regarding sample identification.
- 5) All of the reference samples preserved should be controlled in a way that the history of each of them becomes clear.

3. 15 Stability Monitoring

- 1) The plan for continuous monitoring of the stability should be established and implemented for: the evaluation and confirmation of time-course stability of a product's quality; confirmation of the appropriate storage condition of drug substance products and retest date or expiration date, etc. The implementation procedures for stability monitoring should be established independently for each product and documented.
- 2) Items for analysis and testing of the stability monitoring should be those that are sufficient for appropriate evaluation of the stability. Also, analysis and testing methods used for the monitoring should be those which are implemented with analytical validation.
- 3) The samples used for the stability monitoring should be collected from the products in the final packaging form (excluding intermediate products). Collecting samples from intermediate products packaged in a form that is guaranteed the stability is allowed, if there is no problem. Concerning drug substance products, the samples should be stored in a container of equivalent quality to the container for the marketing. For example, in cases when a drug product is released from the manufacturing site after packaging in a fiber drum having an inner bag as a primary container, the sample should be stored in a bag of the same material or in a small scale drum having the same or identical composition of materials to the marketing product (additionally, for details of the stability monitoring of the drug substances, refer to the "Good Manufacturing Practice Guideline for Active Pharmaceutical Ingredients").
- 4) The stability monitoring should be carried out independently for each product and for more than one lot per year as a rule (excluding cases when there is no production in that corresponding year). In the meantime, the frequency of the analysis and testing should be at level from which the stability is able to be evaluated sufficiently, and possible to increase or decrease according to the accumulation of information, etc. related to the stability. However, the base of the decision should be documented.

- 5) The storage condition should be based on the regulations specified in the ICH stability guideline, according to necessity.
- 6) In cases when it is judged that assurance of the shelf-life or expiration date may become impossible as a result of the stability monitoring, evaluations of reference samples of other lots should also be performed; and according to the results, appropriate actions should be implemented.