

The Welfare and Labor Science Research in 2005
Report on
“Study related to the concept of latest quality system
and techniques for drugs”
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GMP Guideline for Drug Products

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Preface and Acknowledgment

In the Welfare and Labor Science Research in 2003 “Study related to the concept of latest quality system and techniques for drugs” (chief study director: Yukio Hiyama, Ph. D.), our study group reported “A Proposal for Drug GMP Guidance.” For preparation of this guidance, “Draft Drug Product GMP Guideline” by Japanese Pharmaceutical Manufacturer’s Association” was used as a reference, and a lot of helpful comments were given by those concerned in the industry.

In 2004 we issued “A Proposal for Drug GMP Guidance” to ask for public comments, and prepared this research report “GMP Guideline for Drug Products” based on a lot of ideas given by the GMP Committee of the Federation of Pharmaceutical Manufacturers’ Associations of Japan and Parenteral Drug Association Japan Chapter (PDA Japan), as well as companies and individuals.

Although some people may consider the roles of GMP for Drug Products as different from those presented in this guideline, we would appreciate it very much if reference is made to the rationale for our ideas given in “II. Explanation” of this guideline. We would like to express our deep appreciation to all who gave us helpful information.

We look forward to contribution of this guideline to voluntary activities of companies in relation to GMP.

March, 2006
Study Group for GMP Guideline for Drug Products

Introduction

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 unconformity occurs, are the following: “Ministerial Ordinance for Good Manufacturing Practice for Drugs and Quasi-drugs” (MHLW Ministerial Ordinance No. 179, 2004, hereinafter referred to as “GMP Ministerial Ordinance for Drugs and Quasi-drugs”) that was revised and issued according to the revised Pharmaceutical Affairs Law to be effective on April 2005, and the Regulations for Buildings and Facilities for Pharmacies etc. (MHW Ministerial Ordinance No. 2, 1961, hereinafter referred to as “Regulations for Buildings and Facilities”). On the other hand, beyond such compliance with the regulatory requirements, further efforts for continuous improvement are required for actual implementation of manufacturing control and quality control of drug products, while incorporating voluntarily and positively ICH Q7A Guideline (hereinafter referred to as “Q7A”), and requirements shown in standards and guidance in Europe and USA, as well as control methods that are being globally and commonly acknowledged with the progress of knowledge and technology.

From the view point of supporting such efforts, in regard to general matters on manufacturing control and quality control of drug products (except for specified drug products such as sterile drugs and biological products, etc.), this “GMP Guideline for Drug Products” was prepared to provide as specifically as possible the control methods that are related to the requirements of the GMP Ministerial Ordinance for Drugs and Quasi-drugs and the Regulations for Buildings and Facilities as well as the “Ministerial Ordinance for Good Quality Practice for Drugs, Quasi-drugs, Cosmetics and Medical Devices” (MHLW Ministerial Ordinance No. 136, 2004, hereinafter referred to as “GQP Ministerial Ordinance”) but are not legally required or not clearly specified as requirements, and that need to be voluntarily addressed according to current knowledge, etc. The format of a guideline makes it possible to flexibly deal with future necessity of review in this field with significant progress in knowledge and technology.

Structure of GMP Guideline for Drug Products

This guideline consists of 2 parts: “I. Text” and “II. Explanation.” The rationale for the text of the guideline, points to consider, or the relationship to Q7A referred to preparation of this guideline are explained in “II. Explanation.”

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I. GMP Guideline for Drug Products: Text

1 Introduction

1.1 Objective

In regard to general matters on manufacturing control and quality control of drug products (except for specified drug products such as sterile drugs and biological-origin drugs, etc.), this guideline intends to provide as specifically as possible the control methods that are related to the requirements of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (and the GQP Ministerial Ordinance) but are not legally required or not clearly specified as requirements, and that need to be voluntarily addressed according to current knowledge, etc.

Consequently, this guideline covers the manufacturing control and quality control of drug products to which the GMP Ministerial Ordinance for Drugs and Quasi-drugs is applicable.

In this guideline “manufacturing” includes receipt of APIs, raw materials and labeling/packaging materials, production, packaging, labeling, examination/testing, storage, release from manufacturing sites, and other all operations related to manufacturing control and quality control at manufacturing sites for drug products. In this guideline the term “should” indicates recommendations for applying the relevant item unless there are alternative control methods that can provide equivalent levels of manufacturing control and quality control.

This guideline does not intend to cover safety and health for the personnel nor 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 the quality management system, the active participation of control supervisors and appropriate manufacturing staff should be involved.
- 2.11 The components of the quality management system should encompass the activities necessary for manufacturing control and quality control of drug products, as well as organizations and other required sources to implement the activities. In establishing the quality management system, all quality-related activities should be defined and documented.
- 2.12 The quality unit, independent of production units under the provision of Article 4, Paragraph 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, can be in the form of a separate unit or a single individual or group, depending upon the size and structure of the organization.
- 2.13 All quality-related activities should be recorded at the time they are performed.
- 2.14 Any deviation from established procedures should be documented and explained. As to critical deviations for which the effect on product quality cannot be denied, the quality unit should confirm the results of evaluation and necessary actions by the decision of release from the manufacturing site at the latest, under the provision of Article 15, Paragraph 1, Item 3 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.
- 2.15 Neither the decision of release from manufacturing sites under the provision of Article 12, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, nor the use of raw materials, packaging/labeling materials or intermediate products in the next 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 raw materials or intermediate products 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 review, confirm and approve all appropriate quality-related documents.
- 2.22 The main responsibilities of the independent quality unit should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:

- 1) Making decision of release from manufacturing site or rejection (hereinafter referred to as “decision of release”), and evaluating and deciding the use of intermediate products in the next processes in case they are used outside the control of the manufacturing company;
- 2) Establishing a system to release or reject raw materials, intermediate products, packaging and labeling materials;
- 3) Reviewing all manufacturing instructions, completed batch records and laboratory control records of critical processes of concerned lots when deciding the release of products from manufacturing sites;
- 4) Prior to deciding the release of products from manufacturing sites, making sure that critical deviations are investigated and resolved;
- 5) Approving the product master formula, manufacturing control standard code, hygienic control standard code, and all specifications and master manufacturing instructions;
- 6) Approving all procedures influencing product quality;
- 7) Confirming the results of self inspections and internal audits;
- 8) Approving contract matters on the quality aspects of suppliers of APIs and intermediate products;
- 9) Approving changes that potentially affect product quality
- 10) Confirming the plans and results of validation reported under the provision of Article 13, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs;
- 11) Making sure that effective systems are used for maintaining and calibrating critical equipment;
- 12) Testing raw materials and packaging/labeling materials appropriately;
- 13) Making sure that there is stability data to support retest or expiry dates and storage conditions of APIs and/or intermediate products where necessary;
- 14) Performing product quality reviews (as defined in Chapter 2.5);
- 15) Making sure that training is performed; and
- 16) Constructing, maintaining, and managing a liaison system between the manufacturing distributor and manufacturing sites for the technical transfer and change control.

2.3 Responsibility of Production Unit

The responsibility of production units should be described in writing, and should include but not necessarily be limited to:

- 1) Preparing the master manufacturing instructions according to the product master formula, manufacturing control standard code and hygienic control standard code under the provision of Article 10, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, as well as reviewing, approving and distributing the completed manufacturing instructions;
- 2) For all production lots, reviewing manufacturing instructions and batch records and ensuring that the instructions are completed, the records are appropriately prepared, and both are signed or sealed.
- 3) Making sure that all production deviations are reported to and evaluated by persons predesignated under the provision of Article 15, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, and that critical

- deviations are investigated and the conclusions are recorded;
- 4) Confirming cleanliness of buildings and facilities under the provision of Article 10, Paragraph 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 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) Evaluating proposed changes in product, process or equipment; and
 - 7) Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4 Self Inspection and Internal Audits

2.40 In order to verify compliance with the principles of GMP for drugs, regular self inspection and internal audits should be performed in accordance with an approved schedule. While the self inspection is performed by each manufacturing site, the internal audits are conducted across the whole manufacturer by an auditing team consisting of internal and external staffs of the manufacturing site. Confirmation under the GQP Ministerial Ordinance that can provide equivalent levels of confirmation can substitute the internal audits.

2.41 Self inspection or internal audit findings and the resulting corrective actions should be documented and brought to the attention of control supervisors. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product Quality Review

2.50 Regular quality reviews of products should be conducted by the quality unit with the objective of verifying the consistency of the process. Such reviews should be conducted and documented at least annually, and should include at least:

- 1) A review of results of critical ones among acceptance testing of raw materials and packaging/labeling materials, in-process control, and inspection and testing 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 to the processes or analytical methods;
- 5) A review of results of the stability monitoring program;
- 6) A review of all 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. Agreed corrective actions should be completed in a timely and effective manner.

2.6 Technical Transfer

- 2.60 There are two types of technical transfer, that is, the technical transfer from the R&D to production, and the technical transfer after commercialization. In each case, technical information and quality 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 to be shared (documents) includes the following as examples:
R&D report - The report that summarizes the information on the manufacturing technique and quality obtained by research and development. That is, the information that clearly shows the quality design of drug product, as well as the raw materials and packaging/labeling materials, manufacturing method, specifications and test methods, and that also shows the justification for establishing these matters.
Technical transfer documents - Product specifications that prescribe the specifications and product quality including the manufacturing method and assessment method of the drug products subject to technical transfer, and technical transfer plan/report prepared on the basis of product specifications.
- 2.62 The system for the responsibility in the organization related to transfer should be clarified for both parties (the transferring party and 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 technical transfer should be confirmed by the process validation, etc. at the final step of technical transfer.

3 Personnel

3.1 Personnel Qualifications

- 3.10 All the employees involved in the manufacture and quality of drug products should understand GMP.
- 3.11 For the purpose of appropriate conduct of jobs and supervision, the manufacturer should position an appropriate number of those who have received appropriate education and training or those who have had experiences.
- 3.12 The responsibilities of persons working in the production unit and quality unit and the management system should be prescribed in documents.

3.2 Education and Training

- 3.20 The persons predesignated under the provision of Article 19 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as “training and education manager”) should conduct initial and continuous training (including the training related to hygiene) that is required for all the employees involved in the manufacture and quality of drug products (that is, staffs who enter the manufacturing area or laboratory area, including those engaged in the maintenance and cleaning, as well as staffs of the quality unit, etc.). The training and education records should be periodically evaluated.
- 3.21 The employees who are to be engaged in a new job should receive the education and training appropriate for the job including the basics of GMP. Continuous education and training thereafter should also be conducted.
- 3.22 An education and training program should be prepared for each job of those who are to receive education and training. The education and training program should be prepared by the production unit, quality unit and other departments involved. The program should be approved by the training and education manager. The education and training program should be regularly reviewed.
- 3.23 The quality unit should confirm the education and training program with its implementation records.
- 3.24 Special education and training should be given to the employees who work in the areas where contamination causes problems, for example, the clean area and the area where physiologically active, toxic and highly infectious or sensitizing substances are handled.
- 3.25 Visitors or employees who have not received education and training should not be allowed to enter the manufacturing area and laboratory area. In unavoidable cases, these persons should be appropriately instructed, such as notifying them of precautions in advance.

3.3 Personnel Hygiene Control

3.30 Appropriate health care of personnel should be practiced.

3.31 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect raw materials and products from contamination.

3.32 Personnel should avoid as much as possible the direct contact with the object that may affect product quality.

3.33 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.34 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising product quality. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect product quality until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the products.

4 Buildings and Facilities

4.1 Design and Construction of Buildings and Facilities

- 4.10 Buildings and facilities should be located, designed, and constructed to facilitate cleaning, maintenance, and operations there as appropriate to the type and stage of manufacture of the products. The facility should also be designed to minimize potential contamination and cross-contamination. Where microbiological limits have been established for the product, facilities should also be designed to eliminate the exposure to objectionable microbiological contaminants as appropriate.
- 4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and raw materials to prevent mix-ups and contamination or cross-contamination.
- 4.12 Appropriate buildings and facilities, where raw materials and packaging/labeling materials are stored in a manner to avoid contamination by microorganism and foreign matters, should be provided.
- 4.13 Buildings and facilities should be designed so that the flow of raw materials, packaging/labeling materials and personnel through the manufacturing site can prevent mix-ups and contamination or cross-contamination.
- 4.14 There should be defined areas or other control systems in manufacturing sites for the following activities:
- Receipt, identification, sampling, quarantine and pending release or rejection of raw materials and packaging/labeling materials;
 - Storage of rejected raw materials and rejected packaging/labeling materials that were separated from accepted ones, for example in locked containers;
 - Storage of accepted raw materials, containers and plugs
 - Manufacturing and processing
 - Storage of returned products
 - Storage of intermediate products (when appropriate)
 - Sterilization operation (only in the case of sterile drug product)
 - Packaging and labeling
 - Storage of products pending release or rejection
 - Storage of products decided to be released
 - Storage of products decided to be rejected
 - Inspection and testing
 - In-process control inspection and testing (when appropriate)
- 4.15 Washing facilities prescribed in the Article 6, Paragraph 3 of the Regulations for buildings and facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separated from, but easily accessible from, manufacturing areas. When necessary, an appropriate facility for taking a shower and changing clothes should be installed.

- 4.16 Laboratory areas/operations should normally be separated from manufacturing areas. Some laboratory areas, in particular for in-process controls, can be located in manufacturing areas, provided that the operations of the manufacturing process do not adversely affect accuracy of the inspection/testing, and the laboratory and its operations do not adversely affect manufacturing processes or products.
- 4.17 The laboratory should be appropriately designed for the operations conducted there. Appropriate arrangement should be made such as providing sufficient space to prevent any mix-ups, contamination and cross-contamination. Sufficient and appropriate space for storage of collected samples and records should be provided.
- 4.2 Buildings and Facilities for Utilities
- 4.20 As to all utilities that could affect product quality (e.g., steam, gases, compressed air, etc.), appropriate monitoring should be performed to check whether they conform to the specifications predefined to control them. Necessary actions should be taken when limits are exceeded.
- 4.21 Buildings and facilities necessary for adequate ventilation, air filtration and exhaust should be provided. These buildings and facilities should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of room pressure, microorganisms, dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where products are exposed to the air inside the manufacturing site.
- 4.22 If air is recirculated to manufacturing areas, appropriate measures should be taken on the buildings and facilities to minimize risks of contamination and cross-contamination.
- 4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of products.
- 4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent backward flow, when appropriate.
- 4.3 Buildings and Facilities for Purifying Water
- 4.30 Purifying water should be demonstrated to be suitable for its intended use. When any water outside the standards listed in the compendium is used, the internal standard with valid ground should be established and documented.
- 4.31 Unless otherwise justified, purifying water should, at a minimum, meet the water quality standards based on Japanese Pharmacopoeia or Tap Water Law, or World Health Organization (WHO) guidelines for drinking water quality.

- 4.32 If purifying water is insufficient to assure product quality, and enhanced microbiological/physicochemical control limits are called for, appropriate specifications for necessary items among physicochemical attributes, total microbial counts, numbers of specific microorganisms and/or endotoxins should be established.
- 4.33 Where water used in the process is purified by the manufacturer to achieve a defined quality, the purification process should be validated and monitored by establishing appropriate control limits, and for this purpose, necessary buildings and facilities should be provided.
- 4.4 Buildings and Facilities for Containment
- 4.40 Dedicated manufacturing areas, which can include facilities, air treatment equipment and/or process equipment, should be employed in the production of highly sensitizing drug products, such as penicillins or cephalosporins. Sufficient attention should be given to prevention of cross-contamination and containment in inspection/testing of the sensitizing products in the laboratory.
- 4.41 Dedicated manufacturing areas should also be considered when drug products with high pharmacological activity or toxicity are involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.
- 4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, raw materials and packaging/labeling materials moving from the above dedicated manufacturing areas to another dedicated area.
- 4.43 Any manufacturing activities (including weighing, milling, or packaging) of highly toxic agricultural products such as herbicides and pesticides should not be conducted using the buildings and facilities and/or equipment being used for the manufacturing of other drug products. Handling and storage of these highly toxic agricultural products should be separated from other drug products.
- 4.5 Sewage and Refuse
- 4.50 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) from manufacturing sites and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly distinguished from those for products, raw materials and packaging/labeling materials by labeling of identification.
- 4.6 Sanitation and Maintenance
- 4.60 Buildings and facilities used in the manufacture of products should be properly maintained, repaired and retained in a clean condition.

- 4.61 Written procedures should be established assigning responsibility for sanitation of the building and facilities and describing the cleaning schedules, methods, equipment, and materials to be used.
- 4.62 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, and products.

5 Process Equipment

5.1 Design and Construction

- 5.10 Equipment used in the manufacturing control and quality control of products (hereinafter referred to as “process equipment”) should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.
- 5.11 Process equipment should be constructed so that surfaces that contact products do not alter the quality of the product beyond the official or other established specifications.
- 5.12 Process equipment should only be used within its qualified operating range.
- 5.13 Major process equipment (e.g., blender, tableting machine) used during the manufacturing of products should be appropriately identified.
- 5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact products so as not to alter their quality beyond the official or other established specifications. Wherever possible, food grade lubricants and oils should be used.
- 5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.
- 5.16 A set of current drawings should be maintained for process equipment and critical installations (e.g., instrumentation and utility systems).

5.2 Maintenance and Cleaning of Process Equipment

- 5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of process equipment.
- 5.21 Written procedures should be established for cleaning of process equipment and its subsequent release for use in the manufacture control and quality control of products. Cleaning procedures should contain sufficient details to enable operators to clean each type of process equipment in a reproducible and effective manner. These procedures should include:
- Assignment of responsibility for cleaning of process equipment;
 - Cleaning schedules, including, where appropriate, sanitizing schedule;
 - A complete description of the methods and materials, including dilution of cleaning agents used to clean process equipment;
 - When appropriate, instructions for disassembling and reassembling each article of process equipment to ensure proper cleaning;
 - Instructions for the removal or obliteration of previous batch identification;
 - Instructions for the protection of clean equipment from contamination prior to

- use;
 - Inspection/testing of equipment for cleanliness immediately before use, if practical; and
 - Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate. Establishing the cleaning expiry date for equipment cleaning implementation, when appropriate.
- 5.22 Process equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter product quality beyond the official or other established specifications.
- 5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or product, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of micro-organisms).
- 5.24 Non-dedicated equipment should be cleaned between productions of different products to prevent cross-contamination.
- 5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.
- 5.26 Process equipment should be identified as to its contents and its cleanliness status by appropriate means.
- 5.27 Confirm that filters to use at the last stage of product manufacturing process do not discharge fiber.
- 5.3 Calibration
- 5.30 Control, weighing, monitoring and test equipment that is critical for assuring product quality should be calibrated according to written procedures and an established schedule. A list of measuring instruments for each unit of equipment should be prepared, the risk related to product quality should be assessed, and the presence or absence of calibration as well as the calibration frequency should be clarified.
- 5.31 Calibration of process equipment should be performed using standards traceable to certified standards, if existing.
- 5.32 The current calibration status of critical equipment and measuring instruments should be known and verifiable. A calibration seal should be affixed to each equipment and measuring instrument. The contents of such seal include the result of calibration, scheduled date of next calibration.
- 5.33 Measuring instruments that do not meet calibration criteria should not be used. Any measuring instruments that do not meet the calibration criteria or any

measuring instruments whose calibration expiry date has expired should be labeled as “not permitted for use.”

- 5.34 Deviations from approved standards of calibration on critical measuring instruments should be investigated to determine if they could have had an effect on quality of products manufactured with this equipment after the last successful calibration.
As to investigation methods, for example, there is a method to check the presence or absence of any problems by conducting tests with proper measuring instruments on the quality standard determined by those instruments using the stored product (reserve sample) manufactured after the last successful calibration. If any abnormality is detected as a result of investigation, implementation of necessary actions should be discussed.
- 5.4 Computerized Systems
- 5.40 Computerized systems related to manufacturing control and quality control of products should be validated. The degree and scope of the validation should be decided considering diversity, complexity and criticality of the computerized application.
- 5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- 5.42 Commercially available software that has been qualified does not require the same level of testing as that for the computerized systems designed specifically for the process. If an existing system was not validated at time of installation but appropriate documentation is available, a retrospective validation can be conducted.
- 5.43 Data of computerized systems should be sufficiently controlled to prevent unauthorized access to or change in the data. Data should be controlled to prevent their omissions. In case that any data are changed, all changed data, previous entry, name of person who made the change, and date/time when the change was made should be recorded.
- 5.44 Written procedures should be available for the operation and maintenance of computerized systems.
- 5.45 In case that critical data are entered manually, whether the accurate entry was made should be reviewed. This review can be conducted by the second operator or by the system itself.
- 5.46 Any failure in computerized systems that can affect product quality, or the reliability of records or test results should be recorded and investigated.
- 5.47 Changes to the computerized system should be made according to a change

procedure, and the content of the change should be approved ultimately by the quality unit, documented and investigated. Records should be retained of all changes, including modifications and enhancements made to the hardware, software and any other critical components of the system. These records should demonstrate that the system is ultimately maintained in a validated state.

- 5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems related to GMP.
- 5.49 Data can be recorded by another means in addition to the computerized system.

6 Documentation and Records

6.1 Documentation

- 6.10 All documents related to the quality management system should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.
- 6.11 Written procedures should be prepared to control appropriately the issuance, revision, superseding and withdrawal of all documents. The latest version should be controlled by maintaining all document histories.
- 6.12 A procedure should be established for retaining all appropriate documents (e.g., development history records, scale-up reports, technical transfer reports, validation protocols/reports on manufacturing processes, equipment and analytical methods, product master formula, hygienic control standard code, manufacturing control standard code, quality control standard code, written procedures, master manufacturing instructions, manufacturing instructions and corresponding batch records, records on cleaning/use/calibration of equipment, raw material records, laboratory control records, inventory records, and training records). The retention periods for these documents should be specified.
- 6.13 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.
- 6.14 The documents should be prepared so as to demonstrate the mutual relation among the documents clearly.
- 6.15 When preparing records, the name of the person who made entries should be written by indelible way in predefined spaces directly after performing the activities. Corrections to entries should be dated and signed or sealed, and the original entry should be kept readable. In case of correction of records that would affect the product quality (yield, analytical values of process control, etc.), reason for the corrections should be provided.
- 6.16 The original records or their copies should be readily available during their retention period at the site where the relevant activities have been performed. Records that can be promptly retrieved from another archiving site by electronic or other means are acceptable.
- 6.17 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.
- 6.18 If electronic signatures are used on documents, they should be certified and assured

of specific use by each individual.

6.2 Specifications

6.20 Specifications should be established and documented for raw materials used for manufacturing of products. As to packaging/labeling materials used for manufacturing that may critically affect product quality, specifications should be established where applicable. For in-process control items, acceptance criteria should be predefined and documented.

6.3 Manufacturing Instructions and Batch Records

6.30 Manufacturing instructions should mention the standards for decision of release to the next processes. When master manufacturing instructions should be prepared, a person in the production unit who is responsible for preparation of the master manufacturing instructions should enter the date and sign or seal on the master manufacturing instructions. The quality unit should confirm the content of the master manufacturing instructions, and enter the date and sign or seal of a person in the unit, who is responsible, on the master manufacturing instructions.

6.31 Product manufacturing records prepared for each lot (hereinafter referred to as “batch record”) should include the complete information related to the manufacturing control of each lot. The batch record should be confirmed by a person in the production unit who is responsible for preparation of the batch record to assure that the batch record is a correct version and has been prepared legibly and accurately according to the appropriate manufacturing instruction.

6.32 When manufacturing instructions and batch records are issued, they should be dated and signed or sealed, and numbered with specific lot numbers or identification numbers. In continuous production, the product code together with the date and time should be used as the specific identifier until the final number is allocated.

6.33 The items to be documented on the major processes in the manufacturing instructions and batch records should include:

- 1) Dates and, where applicable, times;
- 2) Major equipment used;
- 3) Specific identification of each lot, including weights, measures, and lot numbers or control numbers of raw materials and packaging/labeling materials used during manufacturing;
- 4) Results recorded for critical process parameters;
- 5) Any sampling performed;
- 6) Signatures or seals of the persons performing and directly supervising or checking activities in each critical process;
- 7) In-process and laboratory test results;
- 8) Actual yield at appropriate steps or times;
- 9) Description of packaging and label for products;
- 10) Any deviation noted, its evaluation, investigation conducted (where

applicable) or reference to that investigation results if stored separately; and
 11) Results of decision for release to the next processes.

6.4 Equipment Cleaning and Use Record

6.40 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should provide the date, time (where applicable), product name, and lot number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.41 If equipment is dedicated for manufacturing one product, the individual equipment records are not necessary if the lot number of the product follows in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.5 Use Records of Labeling and Packaging Materials

6.50 Use records of labeling and packaging materials used for the product should be prepared per lot or control unit of the product and should include:

- For each lot and each receipt; name of supplier, identification number of supplier (if available), control number at the time of receipt, and date of receipt;
- Results of testing on conformity with predefined specifications and results of the decision;
- Records of inventory and use of materials; and
- The final actions to deal with rejected labeling and packaging materials.

6.51 Approved master labels for labeling and packaging materials should be retained and maintained for comparison to the used labels per lot or control unit of the product.

6.6 Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with the established specifications, as follows:

- 1) Descriptions of samples collected for testing, including the name of raw materials and packaging/labeling materials, supplier name, lot number or control unit number, date of sampling, and sampling quantity where applicable;
- 2) Comments or reference to each testing method used;
- 3) Descriptions of the quantity of samples used for each test, measured values, reference standards, reagents, preparation of standard solutions, and other cross-references;
- 4) Complete records of all raw data obtained in each test, in addition to graphs, charts, and spectra from laboratory instruments, which should be properly identified to show the specific materials and their lots tested;
- 5) Record of all calculations performed in connection with the test, including

- units of measure, conversion coefficients, and equivalency coefficients;
- 6) Descriptions about the evaluation of test results and the comparison with acceptance criteria;
 - 7) Signatures or seals of persons who performed each test and dates when the tests were performed; and
 - 8) A signature or seal of a responsible person in the quality unit and the date to show that the original records have been reviewed for accuracy, completeness, and compliance with established specifications.
- 6.61 Complete records should be maintained for:
- 1) Any modifications to established analytical methods;
 - 2) Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
 - 3) All stability testing performed on products; and
 - 4) Out-of-specification (OOS) investigations

7 Control of Raw Materials and Packaging/Labeling Materials

7.1 General Controls

- 7.10 The quality control standard codes defined in Article 8, Paragraph 3 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include descriptions about receipt, identification, storage, handling, sampling, testing, procedure for approval or rejection, and reassessment of raw materials and packaging/labeling materials.
- 7.11 A system for assessment of suppliers of critical raw materials and packaging/labeling materials should be provided.
- 7.12 Raw materials and packaging/labeling materials should be purchased from suppliers approved by the quality unit, and only those that conform with the predefined specifications should be accepted.
- 7.13 If a supplier of critical raw materials or packaging/labeling materials is not itself the manufacturer of them, the name and address of the manufacturer of the relevant raw materials or packaging/labeling materials with their quality information should be provided.
- 7.14 Change of suppliers of critical raw materials and packaging/labeling materials should be treated as defined in Chapter 13 (Change Control).

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

- 7.20 Upon receipt and before approval of use, visual inspection should be performed to check labeling of each container or group of containers of raw materials and packaging/labeling materials (including description of correlation between the labeling by suppliers and the in-house labeling, if they are different), container damage, broken seals and evidence of tampering or contamination. Raw materials and packaging/labeling materials should be held under quarantine during sample collection and required testing, and until approved for release for use.
- 7.21 In case that newly received raw materials and packaging/labeling materials are to be blended with existing stocks (e.g., solvents in a large volume storage tank), the incoming materials should be tested in advance and identified as appropriate, and then blended. Procedures should be available to prevent inadequate mix-up of incoming raw materials and packaging/labeling materials with existing stocks.
- 7.22 In case that raw materials and packaging/labeling materials are transported by non-dedicated tankers, confirm that no cross-contamination occurs in the tankers. Confirmation method can include the following:
- Certificate of cleaning
 - Testing for minute impurities
 - Onsite audit of the supplier
- 7.23 Large volume storage containers, their equipped piping, filling and discharge lines

for raw materials and packaging/labeling materials should be appropriately identified.

- 7.24 Each container or group of containers containing raw materials and packaging/labeling materials should be assigned and identified with a distinctive labeling. The labeling should provide at least the following information, and be used in changing the location of each lot. A system should be available in place to identify the status of each lot.
- 1) Product name;
 - 2) Lot number of control number;
 - 3) Control condition of contents (information such as “under isolation,” “under testing,” “accepted,” “rejected,” “returned material,” “recalled material” etc.); and
 - 4) Where applicable, information on expiry date or the date when re-test becomes necessary.

When a completely computerized storage system for raw materials and packaging/labeling materials is employed, it is not necessary for the system to make all the above information readable.

- 7.25 For lot numbers or control numbers to be given to the received raw materials and packaging/labeling materials, attention should be paid to the following:
- 1) Even in the case of identical lot at the supplier, if the lot is received in installments, an independent lot number or control number should be given at the time of receipt.
 - 2) Even when the lot number or control number are the same, when the lot is placed in two or more containers, a control method should be required to specify each container, if necessary.

7.3 Sampling and Testing of Incoming Raw Materials and Packaging/Labeling Materials

- 7.30 Raw materials and packaging/labeling materials should be tested per lot or control unit, with the exception described in Chapter 7.32. A supplier's Certificate of Analysis can be used in place of a part of tests, provided that the manufacturer has a system to evaluate suppliers.
- 7.31 Suppliers should be approved based on sufficient evidence (e.g., results of evaluation of suppliers, quality histories of raw materials and packaging/labeling materials supplied in the past) for consistent supply of raw materials and packaging/labeling materials that meet specifications. When intended to omit part of items of in-house testing upon receipt (hereinafter referred to as “acceptance testing”), at least 3 lots or 3 control units should be tested in advance on full analyses to ascertain the validity. Even when part of acceptance testing has been omitted, full analysis should be performed at appropriate intervals to ascertain the reliability of the suppliers' Certificates of Analysis.
- 7.32 When opening the containers of raw materials and packaging/labeling materials for

sampling for acceptance testing affects the quality of the materials, test results described in suppliers' proper Certificates of Analysis can be used for a part of acceptance testing. In case that acceptance testing is omitted, the reason should be explained appropriately and described in the quality control standard code.

- 7.33 Samples should be representative of the lot or control unit. The number of containers to be sampled, sampling points in the containers and sampling amount should be predefined in the sampling plan in consideration of criticality of the relevant raw materials and packaging/labeling materials, quality variability, quality histories of materials supplied in the past by the relevant suppliers, and quantity needed for proper testing.
- 7.34 Sampling should be conducted at predefined locations by procedures designed to prevent contamination of the sampled raw materials and packaging/labeling materials as well as contamination of other materials.
- 7.35 Samples should be collected by the following procedure:
- 1) The container from which samples are collected should be made clean before sample collection, when necessary.
 - 2) Containers from which samples are collected should be opened carefully, and reclosed immediately after sampling.
 - 3) Sterile instruments and sterile methods for sampling should be employed, when necessary.
 - 4) When a sample has to be collected from the top, middle and bottom of container, the samples collected should not be mixed with each other.
 - 5) To avoid mix-up of samples, the container in which the samples are placed should have labeling that describes the name of sampled raw materials or packaging/labeling materials, lot number or control number, container from which the samples were collected, sampling date, and person who sampled.
 - 6) Containers from which samples were collected should be marked to indicate that samples were collected from the relevant containers.
- 7.4 Storage
- 7.40 Raw materials or packaging/labeling materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.
- 7.41 Containers for storage of raw materials or packaging/labeling materials should be placed off the floor and suitably spaced to permit cleaning and testing.
- 7.42 Raw materials or packaging/labeling materials should be stored under proper conditions for a suitable period to assure their quality, and should be controlled so that the oldest stock is used first, except for particular cases.
- 7.43 Rejected raw materials or packaging/labeling materials should be properly identified and stored under quarantine to prevent mix-up of use in manufacturing processes.

7.5 Re-evaluation

- 7.50 Raw materials or packaging/labeling materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage over predefined period or exposure to heat or humidity).

8 Production and In-Process Controls

8.1 Manufacturing Operations

- 8.10 Prior to starting the manufacturing operations, it should be confirmed that the working areas and equipment are clean, and that raw materials, products, and documents that are not needed for the relevant operations do not remain there. Appropriate measures should be taken when necessary.
- 8.11 Raw materials for manufacturing products should be weighed or measured under appropriate conditions that do not affect the product suitability. Weighing and measuring devices should be of suitable accuracy for the intended use.
- 8.12 If raw materials are subdivided for later manufacturing processes, appropriate containers should be used to receive the materials, and the following information should be labeled on the containers:
- Name, lot number or control number of the raw material;
 - Subdividing number, when necessary;
 - Weight or volume of the raw material in the container; and
 - Where applicable, information on expiry date or dates when re-testing becomes necessary
- 8.13 Critical weighing, measuring, or subdividing should be witnessed by a person other than those who perform the operations, or be controlled under the equivalent level of conditions. Prior to use, the personnel who perform operations should verify that the raw materials are those specified in the manufacturing instructions for the intended product.
- 8.14 Other critical operations should be witnessed by a person other than those who perform the operations, or be controlled under the equivalent level of conditions.
- 8.15 Actual yields should be compared with expected yields at predefined steps in the manufacturing processes. Expected yields with appropriate ranges should be established based on laboratory data, pilot-scale data or production data. Deviations in yields associated with critical processes should be investigated to determine their effect or potential effect on the resulting quality of affected lots.
- 8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computerized control systems, or alternative means.
- 8.17 The intermediate products excluded from the manufacturing process (materials excluded from the process) should be controlled with clear differentiation from the products accepted in the process.
- 8.18 Any disposal of materials excluded from the process should be recorded. In case that materials excluded from the process are re-processed, the procedure should follow the provision of Chapter 14.2 (Reprocessing).

8.2 Time Limits

- 8.20 If time limits for completion of processes are specified in the manufacturing instructions, these time limits should ensure the manufacturing control and quality control of products. Deviations of time limits should be documented and evaluated. In case that processes go on with specific target values (e.g., pH adjustment, drying to predetermined specification), setting of time limits is inappropriate because the completion of such processes are determined by in-process sampling and testing.
- 8.21 Intermediates to be further processed should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process Sampling and Controls

- 8.30 Written procedures should be established to monitor the progress of processes that affect the quality characteristics of products (content, potency, dissolution, etc.) and to control the process conditions. In-process controls and their acceptance criteria should be determined based on the information obtained during development or on the actual production data.
- 8.31 Acceptance criteria, type and scope of testing can depend on the characteristics and processes of products being manufactured, and on the degree of variation of the product quality affected by the process.
- 8.32 Matters related to critical in-process controls (and monitoring of critical processes), including the control points and methods, should be documented and approved by the quality unit.
- 8.33 Adjustments of processes as in-process controls can be performed by personnel in production units without approval of the quality unit in advance, only when the adjustments are within limits predefined and approved by the quality unit. All tests and their results should be recorded as a part of the lot record.
- 8.34 Samples used for in-process controls should be representative of the lot. Sampling plans (including sampling points and sampling amounts) and sampling procedures should be based on scientifically valid method.
- 8.35 Investigations on out-of-specification (OOS) results are not usually needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the processes.
- 8.36 In-process sampling should be conducted using procedures designed to prevent contamination. Procedures should be established to ensure the integrity of samples after collection.

8.4 Lot Blending

- 8.40 In this chapter, “lot blending process” refers to a process of blending some intermediate products within the same specification to produce a homogeneous lot.
- 8.41 Out-of-specification lots should not be blended with other lots for the purpose of meeting specifications.
- 8.42 Lot blending processes should be appropriately controlled and recorded according to the manufacturing instructions. A new lot produced in the lot blending process (hereinafter referred to as “blended lot”) should be tested where applicable whether it meets the predefined specifications.
- 8.43 The record of lot blending process should be prepared to allow traceability back to the individual lots used for the blending process.
- 8.44 Procedures for lot blending process should be based on scientifically valid method, and written procedures for the relevant operation should be prepared.
- 8.45 In case that physicochemical homogeneity of blended lots critically affects product characteristics (e.g., solid oral dosage forms), 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) that may be affected by the lot blending process.
- 8.46 If the lot blending could potentially have adverse effects on stability of blended lots, stability testing should be performed on the final blended lots.
- 8.47 The expiry dates of blended lots should be based on the manufacturing date of the oldest lots or left-over parts used in the blending.
- 8.5 Contamination Control
- 8.50 Even under appropriate control, residual materials can be carried over into successive lots of the products. Examples include residues adhering to the wall of milling machines or granulators, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next process. Nevertheless, such carryover should not adversely affect products.
- 8.51 Manufacturing operations should be conducted in a manner that will prevent contamination by materials other than the product.
- 8.52 Preventive actions against contamination should be taken for intermediate products under manufacturing.
- 8.53 Methods to prevent contamination and their effectiveness should be regularly inspected according to the written procedures.
- 8.6 Microbiological Contamination Controls

- 8.60 As to drug products whose sterility is not required, appropriate written procedures should be established and complied with to prevent undesirable microbiological contamination.

9 Packaging and Labeling

9.1 General

9.10 Control of packaging and labeling materials should be conducted as defined in this chapter, in addition to the control defined in Chapter 7 (Control of Raw Materials and Packaging/Labeling Materials). This chapter applies to the packaging and labeling materials that are used for the drug products and intermediate products to be released to other manufacturers. This chapter does not apply to the in-process products that are tentatively stored at the site of manufacturer.

9.2 Control of Packaging Materials

9.20 If necessary considering product characteristics, packaging materials should be cleaned and sterilized before use so as to assure the compliance with the intended use. Packaging materials should be appropriately controlled to maintain the cleanliness where applicable.

9.3 Control of Labeling Materials

9.30 Labeling materials should be stored in the storage area where only authorized personnel can access, or stored by the method that allows equivalent or higher levels of control.

9.31 Contents to be labeled should include the product name, lot number, quantity, expiry date, and storage condition where applicable. For drug products to which expiry dates are not applied, description of expiry dates is not required on labels.

9.32 Numbers of labeling materials issued, used, and returned should be confirmed. In case of discrepancies found between the number of containers/packages with the labeling materials applied and the number of issued labeling materials, the causes of the discrepancies should be investigated, and the results should be reported to and approved by the quality unit.

9.33 All excess labeling materials bearing lot numbers or other lot-related information should be destroyed. As to excess labeling materials that bear neither lot numbers nor other lot-related information and that are returned to be reused, mix-up should be prevented, and appropriate methods for storage should be taken to ascertain absence of mix-up.

9.34 Obsolete and/or out-dated labeling materials should be destroyed.

9.35 Printing devices used to print labeling items on labeling materials and those used to print lot numbers on packaging materials should be controlled so that all items defined in the manufacturing instructions should be printed.

9.36 Labeling materials issued for specific lots should be examined for conformity to specifications defined in the manufacturing instructions and for appropriate

labeling, and the results should be recorded.

- 9.37 Records should be prepared by the methods that demonstrate use of appropriate labeling materials. For example, labeling materials representative of those used in the labeling operations should be attached to the batch records for individual lots as a part of the labeling operation record.
- 9.4 Packaging and Labeling Operations
- 9.40 Written procedures to ensure appropriate use of packaging and labeling materials should be available.
- 9.41 Prior to start of packaging and labeling operations, it should be confirmed that the working areas and equipment are clean, and that raw materials, packaging/labeling materials, products, and documents that are not needed for the relevant operations do not remain there. Records of the confirmation should be maintained.
- 9.42 Packaging operations should require attention to prevention of cross-contamination, contamination and mix-up, and should be physically and spatially separated from the operations related to other products. Labeling operations should require attention to prevention of mix-up, and should be physically and spatially separated from the operations related to other products.
- 9.43 As to the products, packaging and labeling materials released from storage, the production unit (persons responsible for receipt of released materials, manufacturing operators, etc.) should confirm before operations that product name, lot number or control number and quantity conform to the contents of the relevant manufacturing instructions.
- 9.44 The name and lot number of the product subject to the operations should be indicated at each packaging room and packaging line.
- 9.45 In case that samples taken from the packaging and labeling lines for in-process testing are returned to the relevant original lines, written procedures should be followed. In case that the packaging and labeling operations are stopped due to occurrence of abnormality and then restarted, products should be returned to the relevant operations only after receiving special testing/investigation and obtaining approval by an authorized person. Detailed records should be maintained in such case.
- 9.46 In case that the products became unidentifiable temporarily as a result of packaging operation, the subsequent processes should be pushed ahead as promptly as possible until reaching the identifiable packaging condition. If prompt progress of the operation is difficult, appropriate actions should be taken to prevent mix-up and labeling mistakes.
- 9.47 Packaged and labeled products should be tested to confirm that the containers and packages for the lot are correctly labeled. This testing should be part of the

packaging operation. Results of the testing should be recorded in the batch records or control records for individual lots.

- 9.48 As to the products to be released to other manufacturer and to the market, their packages should be sealed in a manner to allow the recipient notice if packages have been opened during transport.

10 Storage and Release from Manufacturing Site

10.1 Storage Operations

10.10 Building 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 maintained if they are critical to maintain product characteristics.

10.11 When intermediate products are stored, they should be placed in predefined containers, appropriately labeled, cleaned if applicable, and then stored in predefined areas. When necessary, the stability under the predefined storage conditions should be assessed.

10.2 Operations of Release from Manufacturing Site

10.20 Products should be released from manufacturing sites only after approval by the quality unit. As to the product whose release from the manufacturing site was approved as the results of the product assessment, they can be transferred to another unit within the same company having marketing approval.

10.21 Products should be transported in a manner that does not adversely affect their quality.

10.22 Manufacturers should ensure that the contract carriers of products understand and follow the appropriate conditions of transport and storage.

10.23 If a potential risk on the quality of the products to be used for manufacturing in other manufacturing site is found after release from the manufacturing site, immediate contact should be made with the receiving manufacturer.

11 Laboratory Controls

11.1 General Controls

- 11.10 The quality unit should have appropriate laboratory facilities and equipment that are available uninhibitedly where necessary for those who perform testing.
- 11.11 There should be documented procedures describing sampling, testing, approval or rejection of products, raw materials and packaging/labeling materials, records of laboratory control and their storage. Records of laboratory control should be archived according to Chapter 6.6.
- 11.12 All specifications, sampling procedures and testing procedures should be scientifically sound and appropriate to ensure that raw materials, products, and packaging/labeling materials conform to established quality standards. Specifications and test procedures should be consistent with those included in the approval document. Some testing items can be added other than the contents of the approval document. All specifications, sampling procedures and testing procedures, including changes to them, should be drafted by the appropriate unit and approved by the quality unit.
- 11.13 Any out-of-specification (OOS) results obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resamplings and/or retestings after OOS results should be performed according to a written procedure. Even in the case other than OOS results, resampling and retesting of samples should not be performed without valid reason. When resampling, the reason should be maintained. When retesting of samples, the reason and handling of test result should be maintained.
- 11.14 Reagents and reference standards obtained should be controlled according to written procedures, and should be labeled with the date of purchase, expiry date and, where applicable, the date of seal opening. Reagent solutions that need preparation should be prepared following procedures, and the preparation should be recorded. Expiry dates should be determined appropriately based on the characteristics of prepared test solutions, etc. Prepared test solutions should be labeled with the item name, preparation No. preparation date, name of person who performed preparation, expiry date, and where applicable, the storage conditions and conversion factors. Containers for subdividing water and solvent for testing should also be labeled with the item name, etc.
- 11.15 Primary reference standards should be obtained as appropriate for the testing of products. Suppliers of primary reference standards should be recorded. Primary reference standards should be stored in accordance with the supplier's recommendations, and the use records should be maintained. Primary reference standards obtained from an officially qualified supplier can be usually used without testing if stored under conditions consistent with the supplier's recommendations.

- 11.16 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 fully establish the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.
- 11.17 Secondary reference standards should be obtained or appropriately prepared, identified, tested, approved, and stored. The suitability of each lot of secondary reference standards should be determined by comparing to a primary reference standard prior to first use. Each lot of secondary reference standards should be periodically requalified in accordance with written procedures.
- 11.18 Test water with a quality that does not affect the test result should be available. In the case of in-house preparation of test water, the facility for manufacturing the water for testing should be controlled, the water quality should be checked regularly, and the record should be maintained.
- 11.2 Testing of Products
- 11.20 For each lot of products, appropriate testing should be conducted to determine conformance to specifications.
- 11.21 Samples of product to be tested should be representative of the lot. Other than such ones, samples may be collected from the most unstable window (e.g., at the start or end of production) of the processes for monitoring.
- 11.3 Validation of Analytical Methods - See Chapter 12.9.
- 11.4 Certificates of Analysis
- 11.40 Certificates of Analysis should be issued for each lot of products on request.
- 11.41 Certificates of Analysis should include the name of product, lot number, specifications, numerical results (if test results are numerical) and overall judgment.
- 11.42 Certificates of Analysis should be dated and signed or sealed by personnel of the quality unit who performed the testing, with descriptions of the name, address and telephone number of the manufacturer.
- 11.5 Monitoring of Stability of Products
- 11.50 To confirm the stability of products, at least 1 lot per year should be monitored for the stability (except when no batch is produced in the year). Stability of products to be released to other manufacturer should be monitored in the same manner where applicable.

- 11.51 Test procedures used in stability monitoring should be validated and appropriate to assess the stability.
- 11.52 Samples for monitoring product stability should be collected from the products. If there is no problem, samples can be collected from intermediate products under the packaged condition whose stability is assured with the products.
- 11.53 Storage conditions should be consistent with the ICH guidelines on stability, where applicable.
- 11.6 Expiry Date
 - 11.60 When expiry dates are to be applied to intermediate products, information to ensure stability (e.g., published data, test results) should be made available.
 - 11.7 Reserve Samples (related to Article 11, Paragraph 1, Item 3 of GMP Ministerial Ordinance for Drugs and Quasi-drugs)
 - 11.70 As to storage of reserve samples defined in Article 11, Paragraph 1, Item 3 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, “twice or more of amount required for predefined testing per lot” is defined. The testing is deemed to exclude the sterility test and endotoxin test. As to reserve samples for the sterility test and endotoxin test, necessary amount should be secured so that the relevant tests can be appropriately conducted.
 - 11.71 To avoid misuse, reserve samples should be labeled as such. Storage conditions of reserve samples should be the same as that determined for products.

12 Validation

12.1 Validation Policy

12.10 Validation master plans should be documented and include the following information: the intentions, policy and methods of validation on manufacturing processes, cleaning procedures, analytical methods, in-process test procedures and computerized systems; the design, review and approval of each validation; persons responsible for documentation; and other matters common and necessary across all validations in the relevant manufacturing site.

12.11 Critical parameters/characteristics should usually be identified during development stages or by actual production data, to define ranges necessary for the reproducible operations. These should include:

- Characteristics of the relevant drug products;
- Identifying process parameters that could potentially affect the critical quality characteristics of the relevant products; and
- Determination of ranges for each critical process parameter to be used in the routine process control.

12.12 Validation should extend to those operations determined to be critical to the quality and characteristics of the relevant drug products.

12.2 Validation Documentation

12.20 The validation protocols should clearly describe how to conduct each validation of a specific process of a specific product or a manufacture support system, etc. The validation protocols and records should be confirmed/reviewed and approved by the quality unit and other personnel designated in advance.

12.21 The validation protocol should specify the type of validation to be conducted (e.g., retrospective, prospective or concurrent), method, number of process run, critical processes and acceptance criteria, etc.

12.22 A validation report corresponding to the validation protocol should be prepared, where results are summarized, causes of any deviations observed are investigated, appropriate conclusions are drawn, and recommended changes to correct deficiencies are included.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and attendant equipment should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- 1) Design Qualification (DQ): Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose; It should be confirmed and documented that the requirements for the manufacturing facility and equipment or system that were grasped in the

formulation studies (process development) for the purpose of manufacturing products with intended quality are scientifically and reliably reflected in the basic design of facility and equipment or system used in the actual production. This procedure is usually performed by confirmation of design specifications and design drawings.

- 2) Installation Qualification (IQ): Documented verification that the equipment or systems, as installed or modified, complies with the approved design and the manufacturer's recommendation.
- 3) Operational Qualification (OQ): Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges; After conducting IQ and calibration of the facility and equipment or system used in the actual production, it should be confirmed and documented that the facility and equipment or system can be operated in compliance with the established specifications.
- 4) Performance Qualification (PQ): Documented verification that the equipment and its ancillary devices/systems can perform effectively and reproducibly based on the approved manufacturing methods and specifications; It should be confirmed and documented that the facility and equipment or system used in the actual production demonstrate the intended performance by functioning in compliance with established specifications, and enable the manufacture of products with the intended quality, according to the manufacturing procedure and control parameters established as a result of performance assessment (Chapter 12.4).

12.4 Efficiency Study

- 12.40 After conducting OQ of the facility and equipment or system used in the actual production, a series of process development with the same manufacturing conditions as that of actual production should be conducted as efficiency study, where manufacturing procedures and control parameters necessary for the transfer to the next stage PQ should be developed, established and documented.

12.5 Approaches to Process Validation

- 12.50 Process Validation (PV) is the documented evidence that the process operated within established parameters can perform effectively and reproducibly to produce intermediate products and products that meet predetermined specifications and quality characteristics; With a prerequisite that the system for actual production, that is, the system of production unit and the quality unit has been completed at this stage, all of the manufacturing facilities, equipment, raw materials, personnel should have been qualified. In conducting PV, it should be confirmed in the actual production scale and documented that the intended goals are achieved for each facility and equipment and system as well as product quality, and that constant production with the relevant manufacturing processes can be secured. Three batches are usually manufactured for this purpose.
- 12.51 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used.

These approaches and their applicability are shown below.

- 12.52 Prospective validation should usually be performed for all manufacturing processes of drug products, as defined in Chapter 12.12. Prospective validation performed on manufacturing processes of drug products should be completed before the launch of the relevant drug products.
- 12.53 Concurrent validation (validation concurrently performed in actual production) can be conducted when data from repeated production runs are unavailable due to the following reasons:
- Only limited numbers of lots are manufactured;
 - Products are rarely manufactured;
 - Part of lots of the relevant product batches are manufactured by a validated process that has been modified.
- 12.54 As an exception, retrospective validation can be performed for some established processes that ensure the critical quality of drug products free from variation caused by changes in raw materials, equipment, systems, facilities or manufacturing processes. This validation is applicable when the following conditions are available:
- 1) Critical quality characteristics and critical process parameters have been identified;
 - 2) Acceptance criteria and controls for in-process testing have been appropriately established;
 - 3) There have been no failures in critical processes or products that are attributable to causes other than operator error, or equipment failures unrelated to equipment suitability; and
 - 4) Quality and stability have been established for the existing drug products.
- 12.55 Lots selected for retrospective validation should be representative of all lots manufactured during the review period, including any lots that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Reserve samples and/or retained samples may be tested to obtain data to retrospectively validate the process.
- 12.56 Prior to conducting process validation, the prototype of maintenance program should be established on the basis of IQ/OQ findings, and the preparations should be made for the measure to optimize the maintenance program including the timing and items of maintenance after the validation.
- 12.6 Process Validation Plan
- 12.60 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validations, three consecutive successful production lots should be used as a guide, but there may be situations where additional process runs are accepted to demonstrate consistency of the process (e.g., complex manufacturing processes or prolonged manufacturing processes whose completion

were delayed). For retrospective validation, generally data from ten to thirty consecutive lots should be examined to assess process consistency, but fewer lots for examination can be accepted if justified.

- 12.61 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.
- 12.62 Process validation should confirm that the quality and stability of the product are within the specified limits. The quality and stability of the product manufactured in the process validation should be comparable to or better than actual production data, and where applicable, the quality and stability determined during process development, or the quality and stability of lots used in pivotal clinical trials and toxicological studies.
- 12.7 Periodic Review of Validated Systems
- 12.70 Systems and processes should be periodically evaluated to verify that they are still operating in valid conditions. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing intermediate products meeting specifications, revalidation is not usually required.
- 12.8 Cleaning Validation
- 12.80 Cleaning procedures should be validated in principle. In general, cleaning validation should be performed on the process where contamination or incidental carryover of APIs, raw materials and intermediate products has the greatest effect on the quality of drug products.
- 12.81 Validation of cleaning procedures should reflect patterns of actual use of equipment to be cleaned. If various products are manufactured with the same equipment and the equipment is cleaned by the same method, a representative product can be selected for the relevant cleaning validation. This selection should be based on the residue limits estimated in consideration of solubility, difficulty of cleaning, potency, toxicity, or dose levels.
- 12.82 The cleaning validation protocol should describe the equipment to be cleaned, procedures, raw materials, acceptable cleaning levels, parameters for monitoring and controlling, analytical methods, type of samples to be collected, sampling methods, sampling points, and how to indicate the above items on labels.
- 12.83 For cleaning validation, in order to detect both insoluble and soluble residues, appropriate sampling method should be selected among the swab method, rinse method, and alternative methods (e.g., direct extraction). The sampling method used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. The swab method may be impractical

when product contact surfaces are not easily accessible due to equipment design and/or process limitations, e.g., inside of piping, inside of liquid contact parts of filling machines, and inside of equipment for powder processing.

- 12.84 For cleaning validation, validated analytical methods should be used that have sensitivity to detect residues or contaminants. The detection limits for each analytical method should be sufficiently sensitive to detect the established acceptable levels of the residues or contaminants. The method's attainable recovery levels should be established. Residue limits should be achievable and practical, and be capable of verifying the measurement below the limits, and be based on the data of residues most toxic or with the greatest effect on the product quality. Residue limits should be established in consideration of the highest dose level of the product, and the lowest observed effect level of known pharmacological, toxicological, or physiological activity related to the API or the most toxic component of the product.
- 12.85 Cleaning, sanitization and sterilization of equipment to be cleaned should be appropriate operations in consideration of microbiological and endotoxin contamination in the process where control of total microbiological count or endotoxins in the product is required during manufacturing, or in other processes where such contamination could be of concern.
- 12.86 Cleaning procedures should be monitored periodically at appropriate intervals even after validation, in order to ensure that these procedures are effective when used in routine production. Cleanliness of 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 could not be detected by sampling and/or analysis.
- 12.9 Analytical Method Validation
- 12.90 Analytical method validation should be conducted unless the method to be employed is included in Japanese Pharmacopoeia or other acknowledged references. If the method is listed in Japanese Pharmacopoeia or other acknowledged references, the method should be verified to be sufficiently applicable to the target of analysis. In each case, all the test methods to be applied should be verified to be appropriate under the actual usage conditions, and the results should be recorded.
- 12.91 Analytical methods should be validated in consideration of characteristics provided in the ICH guidelines on analytical method validation. The degree of analytical method validation should reflect the purpose of the targeted analytical method and the manufacturing process step which the relevant analytical method is applied to.
- 12.92 Appropriate qualification of analytical equipment to be used for testing of products, raw materials and packaging/labeling materials should be conducted.
- 12.93 In case that analytical methods are to be modified, analytical method validation

should be conducted depending on the degree of the modification. Records should be prepared on the results of the analytical method validation and all the changes made to the analytical method, and should be archived. The records 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.

13 Change Control

- 13.10 The change control system should be established to control all changes in the quality management system established in advance.
- 13.11 The change control system should also cover changes attributable to complaints, recall and regulatory requirements.
- 13.12 The document on change control procedures prepared according to Article 8, Paragraph 4 of GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as “change control procedures”) should include changes to the quality management system itself, raw materials and packaging/labeling materials (including change of suppliers), specifications, manufacturing processes, testing methods, buildings and facilities (including manufacturing support system, computer hardware) and computer software.
- 13.13 The change control procedures should include the followings:
- 1) The protocol should be prepared in advance, when changes are to be made;
 - 2) The evaluation defined in Article 14, Item 1 of GMP Ministerial Ordinance for Drugs and Quasi-drugs should include evaluation on the necessity of revalidation, the necessity of additional testing required to justify the changes, and the necessity of partial change application;
 - 3) Prior to the changes, methods of assessment of the product quality after the change (including accelerated stability tests, stability monitoring program, etc.) and assessment criteria should be predetermined;
 - 4) Prior to the changes, methods for revision of documents related to the changes and methods for training of personnel should be predetermined, and the document revision and the training should be conducted prior to the changes; and
 - 5) Prior to the changes, “other necessary actions” defined in Article 14, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, such as the necessity of changes to specifications, testing methods, expiry dates and labeling should be predetermined.
- 13.14 All protocols and reports related to the changes should be drafted by an appropriate unit, reviewed by related units and approved by the quality unit.
- 13.15 After the changes, the first two or more lots manufactured or tested under the changed conditions should be evaluated.

14 Rejected Products and Reprocessing

14.1 Rejection

- 14.10 Products failed to meet established specifications (hereinafter referred to as “rejected product”) should be identified with labeling and quarantined.
- 14.11 The final disposition of rejected raw materials and packaging/labeling materials should be recorded.
- 14.12 Any actions on products that were rejected upon decision on release from the manufacturing site should be confirmed by the person who made the decision on release (hereinafter referred to as “person responsible for decision on release”) in advance.

14.2 Reprocessing

- 14.20 In this guideline, reprocessing refers to returning of products or rejected products to the manufacturing process of the relevant products and repeating of a part of or whole the predefined manufacturing process. “Predefined manufacturing process” refers to the process associated with the relevant product among the approved manufacturing methods for the drug product.
 - 14.21 Reprocessing should be conducted according to the predefined procedure, after evaluation of its effect on the stability or other quality of the product.
 - 14.22 The product reprocessed after the decision on release should be given a new lot number, after providing the traceability to its initial lot number given at initial decision on release, so that the reprocessed product can be differentiated from products before reprocessing.
 - 14.23 Testing items, number of samples, and stability assessment or the like of each lot of reprocessed products should be approved by the quality unit.
 - 14.24 Testing items, number of samples, and stability assessment of each lot of products reprocessed after decision on release should be evaluated by the person responsible for the testing, confirmed by the person responsible for decision on release for the relevant products, and approved by the quality unit.
 - 14.25 Records on reprocessing should be prepared and archived in the same manner as usual batch records and laboratory records.
- ### **14.3 Returns**
- 14.30 Returned products should be identified as such and quarantined.
 - 14.31 Returned products should be discarded unless their quality is proven to be permissible on the basis of the conditions of storage or transport from the time of

release from the manufacturing site until return, elapsed time, appearance, conditions of containers, and results of testing conducted after return, etc.

14.32 Records of returned products should be prepared and archived. For each return, the record should include:

- Name and address of the consignee
- Name and lot number of the returned product, date of release, and date and quantity of the return
- Reason for the return
- Actions taken for the returned product

14.33 Redistribution or reprocessing is permitted when the quality of the returned products was assessed by the person responsible for the testing according to documented procedures, confirmed by the person responsible for decision on release of the relevant products, and approved by the quality unit.

14.34 Returned products in this section also include those returned due to recall. For recalled products, however, actions on recall processing should be given priority.

14.4 Redistribution

14.40 In this guideline “redistribution” refers to a process where the product once released from the manufacturing site and thus not under control of the site is received again by the manufacturing site for the reason of return or the like, and is tested to confirm its quality, without reprocess, and is decided again on release from the manufacturing site based on the test results, and then is released.

14.41 Testing items, number of samples, and stability assessment or the like of each lot of products to be redistributed should be evaluated by the person responsible for the testing, confirmed by the person responsible for decision on release for the relevant products, and approved by the quality unit, on the basis of the conditions of storage or transport from the time of release from the manufacturing site, elapsed time, appearance, and conditions of containers, etc.

14.42 Records on redistribution should be prepared and archived together with the initial batch records and laboratory records for the relevant redistributed products.

15 Quality Information

- 15.10 For the quality information defined in Article 16, Paragraph 1 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, the processing system should be constructed and documented, and the investigation should be conducted according to the documented procedures, and records should be prepared.
- 15.11 The quality information processing system should include the procedures for judgment of necessity of improving the quality management system and recall, etc. attributable to complaints or the like.

16 Recall Processing

- 16.10 The recall processing system applied to the licensed marketing approval holder and the system of notification to regulatory authorities in case of the recall conducted for the reason of the product quality should be defined in the documented procedures for recall processing defined in Article 8, Paragraph 4, Item 6 of GMP Ministerial Ordinance for Drugs and Quasi-drugs.
- 16.11 The recall procedures should clearly describe those people involved in the information assessment, procedures for determination of recall, where and how to transmit the recall information, as well as methods of storage/control and disposal of recalled products.
- 16.12 Recall processing records defined in Article 17, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs should describe the results of investigation of causes and corrective actions.

II Guideline for Drug Product GMP: Explanation

1 Introduction

In this guideline, the term “quality control” is limitedly used as explained in Chapter 2.12 of Part II (Role of quality unit), while in Japan the term “manufacturing control and quality control” has been used as a term corresponding to GMP, and thus, as long as the term “quality control” means the latter, this term is used with a different intention of this guideline.

- 1.1 This guideline does not apply to therapeutic gas. In Japan, GMP Ministerial Ordinance is not applicable to therapeutic gas, and in this regard, the scope of this guideline is defined in Chapter 1.1 as “drug products to which the GMP Ministerial Ordinance for Drugs and Quasi-drugs is applicable.”

2 Quality Management System

Terms (review, confirmation, approval)

The terms “review,” “confirmation,” and “approval” are used in this guideline to include the meaning below in principle. These terms are used in Q7A as translation of “review,” “making sure,” and “approval” respectively.

- Review: To carefully examine the contents of GMP activities that are documented, followed by decision on acceptance/rejection or right/error on the contents of the activities.
- Confirmation: To check on documents that GMP activities have been implemented according to predefined methods, and reviewed/approved by predefined personnel. Not necessarily intended to examine the contents of the activities.
- Approval: To give final approval to GMP activities, and to complete them on documents.

2.1 Principles

2.10 Quality Management System

In relation to the revised Pharmaceutical Affairs Law, GMP is applicable to both the manufacturing distributors and manufacturing sites (manufacturers). In both cases, the quality management system is a basic requirement for globally certified quality assurance that is defined in ISO9001:2000, and is not restricted to the quality assurance system established by the manufacturing distributors. The important points of quality management system defined in ISO9001:2000 are as follows: 1) Responsibility and authority up to the management, 2) Documentation, and 3) Audit by a third party. These points should be remembered as the concept of quality assurance in GMP. This guideline is especially aimed at the establishment of self-directed GMP systems in manufacturing sites, which are led mainly by the relevant manufacturing sites themselves. Chapter "2. Quality Management System" illustrates the basic concept and methods.

2.12 The role of the quality unit is outlined below.

According to Q7A (Chapter 20, terminology), the role of the quality unit is defined as fulfilling both responsibilities for quality assurance (to ensure that quality systems are maintained) and quality control (to confirm/test conformity to specifications).

On the other hand, in the conventional GMP Ministerial Ordinance for Drugs and Quasi-drugs (MHLW Ministerial Ordinance No. 16, 1999, hereinafter referred to as “old GMP Ministerial Ordinance for Drugs and Quasi-drugs”), the role of the quality unit has been limited to conducting testing at manufacturing sites. Against such background, there seem to be various views on the role of the quality unit from company to company. Therefore, some guidelines should be established on the role of the quality unit, considering that the main role of the quality unit have been clearly defined in the new GMP Ministerial Ordinance for Drugs and Quasi-drugs.

In this guideline, based on the GMP Ministerial Ordinance for Drugs and

Quasi-drugs, the concept of Q7A on the quality unit is brought into shape, and the role to be fulfilled by the quality unit is defined as follows:

Role of quality unit = "quality assurance activities + quality control activities"
+ laboratory activities

The above three kinds of activities related to the quality unit are outlined below.

Quality assurance activities and quality control activities:

Quality assurance activities are intended for establishing across-the-board quality policies and confirming the status of compliance with the policies. Quality control activities are intended to bring the across-the-board quality policies into shape as requirements for each manufacturing site, to promote the compliance with the requirements, and to confirm or approve GMP-related activities. In other words, quality assurance activities aim at time-series quality improvement from the aspect of quality requirement by demonstrating the required levels, while quality control activities aim at the quality improvement, maintenance or control from the aspect of satisfying the quality requirements to be complied with.

An important point is that quality assurance activities and quality control activities are positioned as staff activities, while laboratory activities mentioned later are the practice in the laboratory (line activities), because one of the basics of the quality management system is that quality-related staff activities should be a third party against line activities.

Of course, the concept of quality assurance activities and quality control activities should be defined by each company, and the activities may not necessarily be considered in two different parts, nevertheless this guideline illustrates these ideas as a concept to clarify the role of the quality unit. Examples of quality assurance activities and quality control activities are shown below.

Quality assurance activities:

- Establishment of in-house GMP system
- Implementation or confirmation of internal/external audits

Quality control activities:

- Decision on release
- Review of batch records and test records for each lot
- Acceptance testing of raw materials
- Approval of manufacturing procedures and test procedures
- Confirmation of deviation processing and approval of change processing
- Confirmation of validation plans and reports
- Quality information processing and recall processing
- Confirmation of self inspection
- Confirmation of training
- Maintenance and control of liaison systems with consignors/consignees

In the GMP Ministerial Ordinance for Drugs and Quasi-drugs, among the above quality control activities, quality information processing and recall processing are defined as matters to be reported to the quality unit and to be confirmed, and self inspection and

training are not included in the activities of the quality unit. However, this guideline positions these activities as responsibilities of the quality unit, according to the basic concept “The quality unit should be involved in all quality-related matters. (Chapter 2.20)”. As the GQP Ministerial Ordinance requires manufacturing distributors to have responsibility for quality-related control of contract manufacturers, maintenance and control of liaison systems with consignors/consignees are the responsibility of contract manufacturers. See also Chapter 2.22 Explanation (Paragraphs 7, 15, 16).

In the GMP Ministerial Ordinance for Drugs and Quasi-drugs, the quality unit is defined as a manufacturing-site-level organization under supervision by product security pharmacists, while the quality unit defined in this guideline is intended, based on its concept, to include the corporate function of head office of the manufacturer having two or more manufacturing sites. In this case, quality assurance activities and quality control activities at manufacturing sites can be regarded as the activities of head office that are localized in manufacturing sites (site activities against corporate activities).

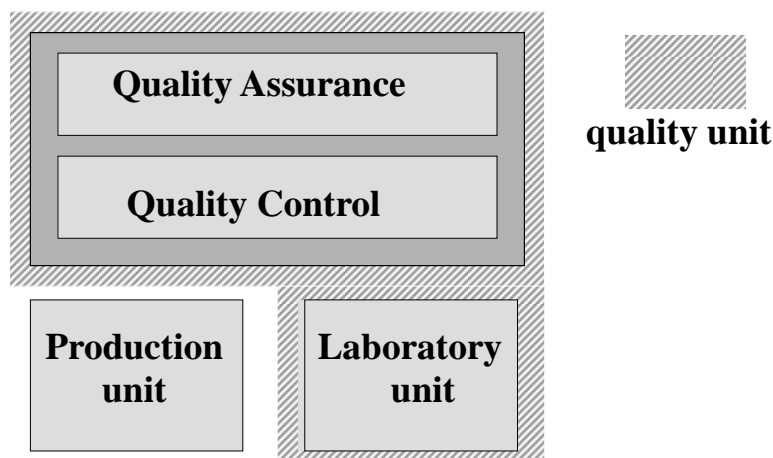
Although the GQP Ministerial Ordinance refers to the quality assurance unit of manufacturing distributors, in this guideline, the target to be considered is the role of quality assurance activities in the quality unit, assuming establishment of self-directed GMP systems of manufacturing sites (manufacturers).

Laboratory activities:

Laboratory activities are those performed in laboratories, that is, line activities like manufacturing activities. It is important to clearly distinguish laboratory activities from activities on quality assurance and quality control, which are staff activities.

In Japan, the unit responsible for laboratory activities (laboratory units) may be often referred to as the quality control department (section), and even in such case, the unit activities may be considered to include staff activities associated with quality assurance and quality control. In this guideline, the term “quality control” is used to limitedly mean quality control activities of the quality unit as mentioned in the above section, while the term “laboratory activities (unit)” is used to clearly define the activities on testing as line activities.

The relation between the quality unit and production unit can be illustrated as follows. In the manufacturing site, there are two line units schematically, i.e., the production unit as well as the laboratory unit of the quality unit, while there are staff units responsible for quality control and quality assurance in the quality unit, and thus it should be noted that these two different line and staff functions are integrated to form the GMP system.



2.14 Points to consider on deviation control are shown below:

- 1) Deviation means departing from predefined procedures or standards.
- 2) Any deviations should be recorded.
- 3) As to critical deviations whose effect on the product quality cannot be completely denied, the quality unit should evaluate the presence or absence of effect on the product quality and provide a conclusion.
- 4) In case that cause investigation of deviation is required, causes of matters related to the deviation should be investigated. In case that improvement of controls in the production unit and the quality unit are required, appropriate corrective actions should be taken.
- 5) All records related to deviation should be approved by the quality unit.
- 6) Prior to the release, the quality unit should confirm that critical deviations have been investigated and resolved.

As deviation means occurrence of abnormality (or possible occurrence of abnormality), and has potential effect on product quality, it is necessary to establish rules on deviation and to provide a system to prevent release of any defective products. In this regard, confirmation of deviation processing and confirmation that the deviation has been resolved upon product release should be the responsibility of the quality unit. Furthermore, if the result of cause investigation of deviation indicates the necessity of changes, the changes should be made immediately.

On the other hand, as deviation may serve as a clue to improvement of product quality and quality management system, all deviations occurred (regardless of degree and type of deviation) should be recorded (at least records on what kind of deviation occurred).

It is sometimes difficult to judge at the operator level whether the deviation is a critical one whose effect on the product quality cannot be completely denied. In this regard, all deviations should be recorded in order to ensure reporting of the deviation to the responsible persons (in the same manner as in Articles 2.3 and 11.14 of Q7A, CGMP,

and EU GMP). One of the responsibilities of the quality unit is to be involved in all quality-related matters (Chapter 2.20), and thus, when the related units judges whether the deviation is critical, the quality unit should confirm or approve the judgment as a third party.

2.2 Responsibilities of quality unit

2.2.2 Main responsibilities of the quality unit

Paragraph 1) In the old GMP Ministerial Ordinance for Drugs and Quasi-drugs, the responsibilities of the manufacturer (management) were considered to be ensured by

- 1) Appointment of three GMP-related staffs (security pharmacist, manufacturing control manager, quality control manager); and
- 2) Establishment of four major standard codes (manufacturing control standard codes, quality control standard codes, manufacturing hygiene control standard codes and product master formula)

for the manufacturing site. Therefore, when the responsibilities of quality control manager defined in the old GMP Ministerial Ordinance for Drugs and Quasi-drugs are transferred to the quality unit according to the current GMP Ministerial Ordinance for Drugs and Quasi-drugs, the person responsible for control and supervision of duties should be appointed by the manufacturer or those authorized by the manufacturer, in order to clarify the responsibility of the manufacturer (management). As decision on release is one of the focal responsibilities of the quality unit, the person responsible for decision on release shall be appointed by the manufacturer or those authorized by the manufacturer.

Paragraph 3) According to Article 10, Item 9 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, the production unit should confirm that manufacturing control is appropriately performed, and the result should be reported to the quality unit in writing. In this guideline, the quality unit is intended to confirm as a third party that manufacturing control is appropriately performed, and to review all manufacturing instructions and batch records (laboratory control records) related to critical processes (in the same manner as in Chapter 2.22 of Q7A).

Paragraph 5) See Chapter 6.3 Explanation for master manufacturing instructions.

Paragraph 7) See Chapter 2.4 Explanation for self inspections and internal audits. Because it is stipulated in Article 18, Paragraph 1, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs that the result of self inspections should be reported to the security pharmacist in writing, the responsibilities of the quality unit shall include confirmation of results of self inspections and internal audits.

Paragraph 8) In the contract manufacture, it is necessary to arrange various matters in addition to basic contracts related to business transactions. The quality unit has the responsibilities about the quality-related contract matters as represented by “Quality Agreement.”

Paragraph 10) Because it is stipulated in Article 13, Paragraph 1, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs that the validation plan and result should be reported to the quality unit in writing, the responsibilities of the quality unit shall include confirmation of validation plans and results. Approval of validation plans and results is considered originally as a responsibility of the quality unit (according to Chapter 2.22 of Q7A, review and approval of validation protocols and reports are responsibilities of the quality unit), and active involvement of the quality unit in validation activities is expected.

Paragraph 16) Because it is stipulated in Article 19, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs that the progress/state of training and education should be reported to the security pharmacist in writing, the responsibilities of the quality unit shall include confirmation of implementation of training and education.

Paragraph 17) In association with the liberalization of contract manufacture by the revised Pharmaceutical Affairs Law, this paragraph was added. Remember that the quality management system is not intended for manufacturing distributors alone but also for the manufacturers (manufacturing sites). The bi-directional liaison between the two parties on the critical GMP matters such as change control or deviation control is considered as the basis of quality assurance system in the contract manufacture.

2.3 Responsibility of Production Unit

In the old GMP Ministerial Ordinance for Drugs and Quasi-drugs, the responsibilities of the manufacturer (management) were considered to be ensured by

- 1) Appointment of three GMP-related staffs (security pharmacist, manufacturing control manager, quality control manager); and
- 2) Establishment of four major standard codes (manufacturing control standard codes, quality control standard codes, manufacturing hygiene control standard codes and product master formula)

for the manufacturing site. Therefore, when the responsibilities of manufacturing control manager defined in the old GMP Ministerial Ordinance for Drugs and Quasi-drugs are transferred to the production unit according to the current GMP Ministerial Ordinance for Drugs and Quasi-drugs, the person responsible for control and supervision of duties should be appointed by the manufacturer or those authorized by the manufacturer, in order to clarify the responsibility of the manufacturer (management).

The person responsible for control and supervision should not necessarily perform all the duties of items 3) - 7), but should perform at least 3) Confirmation of deviation and 6) Evaluation of change control. As approval of manufacturing instructions and confirmation of batch records are the focal responsibilities of the production unit, the person responsible for the duties shall be appointed by the manufacturer or those authorized by the manufacturer.

Paragraph 2) Signature and seal. The seals registered in the GMP organization should be used. The control system that enables a specific individual can use the relevant seal

(locking by the user, always carried by the user) should be available.

2.4 Self Inspection and Internal Audits

In Chapter 2.4 of Q7A, the self inspection and internal audits are both described, but not differentiated clearly. In this guideline, they are clearly differentiated from each other, and are considered both essential.

According to the GMP Ministerial Ordinance for Drugs and Quasi-drugs, the scope of self inspection is limited to manufacturing control and quality control at manufacturing sites (at least such impression is given). However, quality assurance at manufacturing sites is not limited to matters in manufacturing sites alone, but is performed as a part of quality assurance system applied by the company as a manufacturer in across-the-board scale. For example, processing of quality information like complaints, and recall processing, contracts with consignors/consignees, or confirmation of appropriate conduct of self inspection. As to self evaluation of such matters, self inspection alone is not sufficient, and thus, internal audits by a third party other than the manufacturing site are necessary.

According to the GQP Ministerial Ordinance, the audit is an activity of confirming the quality assurance system in the manufacturing site under the responsibility of the manufacturing distributor, that is, confirmation of compliance to the quality policy of the manufacturing distributor who is the manufacturing consignor. On the other hand, in this chapter, the internal audit is intended to establish self-directed GMP systems in manufacturing sites, and to confirm the compliance to the in-house quality policy which is performed under the responsibility of the manufacturing site itself. Thus, the self inspection and internal audit are implemented with different intentions. However, considering the current state that the audit of contracted manufacturing sites is obliged by the GQP Ministerial Ordinance, this chapter defines “Confirmation under the GQP Ministerial Ordinance that can provide equivalent levels of confirmation can substitute for the internal audits.”

2.5 Product Quality Review

Deviations and changes are evaluated and processed at each onset. However, some of abnormality (hereinafter referred to as “potential abnormality”) or risks cannot be detected by case-by-case evaluation. Review of product quality is necessary from the viewpoint of secure the consistency of product quality by aggressively detecting and eliminating the potential abnormality or risks.

Review of product quality is essential from the viewpoint of securing (including improving) the consistency of product quality, which is requirement of the Q7A and CGMP. For example, in the Q7A, review of product quality can be classified into “review on abnormality,” which means review of complaints, recalls and non-conformity, and “review on consistency of product quality,” which means review of critical process control and important test results for all lots. In the “Notification about Validation Standards” (PMSB Notification No. 0330001, 2005, hereinafter referred to as “Validation standards”), “periodic review of process control” is defined, and this review shall include “review on consistency of product quality.”

Manufacturer’s preparation of annual reports on review of product quality is highly beneficial, because it can be a rationale for the document review at the GMP Compliance

Review every five years.

Paragraph 5) Stability monitoring includes both the chronological stability assessment and periodic quality confirmation (post-marketing stability assessment).

2.6 Technical Transfer

Recently, importance is placed on the scientific and rational ground for technical transfer from research & development to commercial production. In view of the liberalization of contract manufacture by the revised Pharmaceutical Affairs Law, this paragraph was newly added.

In technical transfer of drug products from research & development to production, consistency of the quality of pivotal manufacturing batches in the development and that of commercial production batches (process validation batches) is the basis of the product quality, including safety of efficacy, of drug products in the market. In other words, the objective of technical transfer is to secure consistency of manufacturing quality before and after the transfer. The same purport is found in Chapter 12.52 of Q7A, and is also described in Chapter 12.62 of this guideline on drug products. In this regard, pivotal manufacturing batches in development stage refer to investigational drug products used in the important phase III clinical studies, investigational drug products used in the bioequivalence test, and samples used in the stability test for approval application.

The objective and importance of securing consistency of manufacturing quality before and after the technical transfer are the same in the technical transfer after marketing such as contract manufacturing, etc.

Therefore, in the technical documents including R&D reports related to technical transfer, the data and context that rationally and scientifically demonstrate “how to achieve (or to have achieved) the consistency of manufacturing quality in the technical transfer concerned” are required, rather than simply citing the items and data.

As to technical transfer, refer to the Welfare & Labor Science Research in 2004 “Guideline for Technical Transfer.”

3 Personnel

3.2 Training and Education

In Chapters 3.20 - 3.25, necessary matters for training and education such as the scope, rules on training/education programs are defined. It is also defined to prepare a training/education program for each job. According to Article 6, Paragraph 4 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, responsibilities of all personnel working in the production unit and the quality unit are defined to be documented as a job description.

It is helpful for understanding the training/education status of personnel to prepare the following items in a package for each person engaged in the manufacturing of drug products: job description, training/education program, results and history of training/education.

Chapter 3 covers employees, but does not describe training and education of management who is not included in the employees. However, one of the focal points of the quality management system defined in the ISO9001:2000 is training and education of management, and thus quality-related training and education of management are required to be conducted.

- 3.20 “The persons pre-designated” under the provision of Article 19 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs is hereinafter referred to as “training and education manager.” According to this article, the main body of this chapter shall be the training and education manager.
- 3.23 Because it is stipulated in Article 19, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs that the training and education manager should implement systematically the training and education program, the training and education manager shall approve the training and education program.
- 3.24 Because it is stipulated in Article 19, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs that the training and education manager should report the progress/state of training and education to the security pharmacist in writing, the responsibilities of the quality unit shall include confirmation of implementation of training and education.

4 Buildings and Facilities

- 4.1 Design and Construction of buildings and facilities
- 4.10 Methods for easy cleaning, maintenance and operation include the following: making rounded surface between the wall and floor, using a vacuum cleaner or central vacuum equipped with HEPA filters for vacuum cleaning of working rooms. As to environmental control levels for manufacturing non-sterile products, it is effective to decide the levels based on the general information of Japanese Pharmacopoeia “Microbial Attributes of Nonsterile Pharmaceutical Products,” and USP <1111> “Microbiological attributes of nonsterile pharmaceutical products.”
- 4.11 Attention should be paid especially to cleaning and the maintenance space as well as prevention of cross-contamination.
- 4.12 Attention should be paid, for example, by storing materials on shelves and pallets avoiding direct contact with the floor.
- 4.14 “Storage of products pending release or rejection” and “storage of products decided to be released” are defined on the assumption that the products are released from the manufacturing site. Other than these cases, when decision on release for markets associated with manufacturing/distributing is made at the manufacturing site, providing another storage area for the relevant products is required.
Separately from this rule about the specific area, consideration should be given to providing an isolation area to deal with cross-contamination and chemical hazard where applicable.
- 4.16 In case that the area for “in-process control testing” is to be located within the manufacturing area, risks on the relevant testing caused by microbiological contamination and particulate contamination should be evaluated, and installation of walls or partitions should be considered where applicable. Vibration and voltage variation should also be evaluated.
- 4.17 For arrangement of the laboratory, attention should be paid to the activities such as repair, maintenance and calibration of critical measuring instruments, and appropriate space necessary for the activities should be provided.
- 4.2 Utilities
- 4.20 Control specifications for steam include foreign materials, particulates, contamination by boiler compounds, etc. Control specifications for gases and compressed air include oil contents, foreign materials, particulates, dew point, etc. For all of them, control items and control specifications (limits) should be determined in consideration of product quality.
- 4.22 This item should be evaluated together with Chapter 4.40.

- 4.23 Piping should be identified usually by direct labeling on the surface of piping, or using tags. In case of heat insulation piping, labeling for identification of piping should be performed immediately after completion of replacing the heat insulation materials.
- 4.24 “Air blocking device” is intended to prevent backflow from the drain pipe, and includes a funnel for setting back to atmospheric pressure and air break, etc.
- 4.3 Buildings and Facilities for Manufacturing Water
- 4.30 For identification of purifying water when in-house specifications are to be determined, use of names such as “ultrafiltered water” and “ion-exchanged water” is preferable, in order to prevent mix-up with water for medical use listed in the compendium (purified water, water for injection, etc.).
- 4.32 Specifications for viable counts in USP and EP define 10 cfu/100mL for water for injection (excluding those of sterile-grade packaged in sealed containers), and 100 cfu/mL for purified water.
- 4.4 Buildings and Facilities for Containment
- 4.40 Drugs that require dedicated manufacturing areas for the measure against cross-contamination are defined in Article 9, Item 5 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs as “products which are easy to disperse and cause hypersensitive reactions in small quantities or which have serious effects on other products due to cross-contamination.”
- 4.41 For cleaning of manufacturing equipment for drug products with high pharmacological activity or toxicity, consider disassembling joints of piping and equipment thoroughly to clean them, depending on the case.

5 Process Equipment

5.1 Design and Construction

5.11 Process equipment that contacts products includes tanks, piping, process equipment, filters, ion-exchange resin, hoses, gaskets, chromatography, etc. The equipment surface that contacts products should be considered to prevent altering product quality. Concrete points to take into consideration are shown below. Especially the substances dissolved and released from the surface of polymer parts contacting products should be evaluated on their effect on product quality.

1) Chemical resistance

To prevent the products from reacting and corroding the surface of equipment through contact with it.

2) Dissolution

Product quality should not be deteriorated by substances dissolved and released from equipment surface that contacts products. Particular caution is necessary against the dissolution from polymer parts (hoses, packing, filters, columns, lining, etc.). Where necessary, data on dissolution characteristics should be obtained from suppliers to check the incompatibility and reactivity with the products. To secure the safety of the materials of equipment surface that contacts products, it is important to obtain data on safety assessment (toxicity test, etc.) from suppliers. Similar description on this requirement is also given in CGMP 21CFR 211.65 (a) and (b).

3) Adsorption

An especially critical point is to evaluate adsorption of liquid preparations to polymer parts.

5.14 When products may contact with lubricating oil, heat or cold refrigerant (e.g., rotating equipment such as shafts of stirrers, pumps, etc.), safe fluid materials such as of food grade in this chapter should be employed.

5.2 Maintenance and Cleaning of Process Equipment

5.21 Taking into account the risk of contamination of process equipment during the period between cleaning/washing of the process equipment and the next use in manufacturing (e.g., possibility of becoming negative pressure, contamination from attendant piping, contamination from drain piping), maximum permissible time from the cleaning until the next manufacturing, and re-cleaning immediately before use in manufacturing should be considered.

5.23 In this case, potential mix-up of batches due to residue products remaining in equipment, and possibility of deterioration in quality by degeneration/spoilage should be considered.

5.26 Indication of process equipment condition refers to the indication of cleanliness

and status of manufacturing activities such as “before cleaning,” “cleaning completed,” and “during manufacture.”

- 5.27 As to fiber from the filter itself and discharge of foreign materials, flush cleaning before use should be considered based on the data obtained from suppliers, where applicable.

6 Documentation and Records

6.1 Document Control System

- 6.10 Although the old GMP Ministerial Ordinance for Drugs and Quasi-drugs did not give any clear provision for document control, procedures for document control has been stipulated in Article 20 of the new GMP Ministerial Ordinance for Drugs and Quasi-drugs. It is necessary to unify the understanding of those involved, by documenting all matters related to the quality management system (quality assurance) including manufacturing control and quality control of drug products. In this regard, it is stated in this guideline as “all documents related to quality management system” to expand the scope without limiting it to the “production” of products.
- 6.11 A document once prepared is to be revised, abolished and withdrawn. By keeping the document histories, tractability of relevant document including its history is secured, and “Latest version control” that is particularly important in the document control becomes possible.
- 6.12 Many documents that are related to matters on the research & development, commercial production, and post-marketing activities are prepared and archived. Providing an archiving rule, it is necessary to show what types of documents are present and how they are retained, even at the time of personnel reshuffling. For the future approval application of manufacture/distribution, companies are required to provide consistency of the development process from research to commercial production. In this regard, retention of documents becomes all the more important.

Examples of documents to be prepared and retained at manufacturing sites are shown below.

A: Product master formula

This refers to the document defined in Article 7 of GMP Ministerial Ordinance for Drugs and Quasi-drugs. Product master formula is defined as documents that state the “manufacturing approval matters” and “manufacturing procedures” of the drug product to be manufactured. In addition, it states details that cannot be incorporated in the “manufacturing approval document,” and also provide the standards for the manufacturing control and quality control of drug products to be manufactured. As to product master formulas, refer to Chapter 6.3 Explanation (Manufacturing instructions).

B: Various standard codes

Standard codes refer to documents that define the outline of manufacturing control and quality control in a large control area (manufacture, quality). In other words, they refer to “hygiene control standard codes,” “manufacturing control standard codes,” and “quality control standard codes” that are defined in Article 8, Paragraphs 1, 2 and 3 of GMP Ministerial Ordinance for Drugs and Quasi-drugs. “GMP control rules” should also be regarded as standard codes, which describe the corporate policies on overall manufacturing control and quality control, and the scope of authorities associated with the

responsibilities of each unit.

In the case of “quality control standard codes” that state the rules to be applied after receipt of raw materials and packaging/labeling materials at manufacturing sites, it should be considered that “qualification for purchase of raw materials and packaging/labeling materials to be used” should be defined in the quality control standard codes, from the viewpoint of the quality management system.

C: Written procedures

Written procedures are documents that state specifically the details of procedures to carry out each of the provisions of various standard codes. Examples are shown below.

- Procedures release procedure
Detailed written procedures that state the rules for release of products from manufacturing sites (including decision on release).
- Deviation/Failure control procedure
Documents that describes the policies and rule for investigation and corrective action in case of deviations/failure from the predefined manufacturing control, laboratory control and quality assurance rule, and the relevant procedure.
- Change control procedure
Document that defines the policy in case of changes in manufacturing control, laboratory control and quality assurance rules for products.
- Quality information and quality defect processing procedure
Document that describes the measures, policy and rule as well as the procedure for dealing with quality information and quality defect of released product, which is raised by third parties including the destination party.
- Product recall procedure
Document that describes the policy and rule as well as the procedure for the recall of released product.
- Self inspection procedure
Document that describes the policy and rule as well as the procedure for periodic self inspection of the status of manufacturing control and quality control at manufacturing site.
- Training and education procedure
Document that describes the educational policy and rule as well as the procedure for improvement of understanding about GMP and each responsibility, and of skills of the management, executives of relevant departments including manufacturing site, responsible persons, and staffs.
- Document and record control procedure
Procedure defined in Article 8, Paragraph 4, Item 9, and Article 20 of GMP Ministerial Ordinance for Drugs and Quasi-drugs
- Validation procedure
Document that describes the rule about method, plan, implementation and evaluation of validation, as well as the procedure.
- Record
Document aimed at describing the process and result of implementation of the defined procedure. To avoid differences in the description items among the staffs who makes entry, it is advisable to make the description in a predefined format.

- 6.13 In view of the globalization in the future, it is stipulated that the documents should be prepared “in a language and context that are understandable” to the personnel actually engaged in activities, because the documents prepared in such a way are considered necessary when those engaged in the production of drug products manufactured abroad and imported into Japan understand a language such as English, or Chinese, etc. other than Japanese.
- 6.14 Documents prepared are versatile with their complicated mutual relations. There is few cases to use a small number of documents independently. A large number of documents and records are used in combination in many cases. Therefore, it is stipulated that “The documents should be prepared so as to demonstrate clearly the mutual relation among the documents.” It is expected that errors in operation may be reduced by clarifying the relation among documents.
- 6.15 This chapter concerns a basic matter in preparation of records, which needs care in the routine activities in the production site for drug products. Some of values to be recorded have influence on the decision on release or the quality of the products (yield, or analytical values of process control), thus, “reasons for the corrections” shall be described, in case of corrections to entries that would affect product quality.
- 6.16 This chapter is provided considering the cases involving one ore more manufacturing sites and electronic recording in mind.
- 6.17 This chapter defines methods of archiving documents. This chapter is essential nowadays when electronic and optical records are being developed.
- 6.18 In addition to the above, rules for dealing with electronic signatures are defined.
- 6.3 Manufacturing Instructions and Batch Records

In many cases, manufacturing instructions are photocopies of the original, and these copies are used for each lot manufacturing. The original is referred to the master manufacturing instructions. To certify the contents of master manufacturing instructions are correct and of the latest version, signatures and seals of two or more responsible persons (one of them should be from the quality unit) were stipulated. Master manufacturing instructions can be referred to as “master batch records” abroad.

Matters to be described in manufacturing instructions are shown below.

- Name of the product to be manufactured. Document control number, if provided.
- A complete list of raw materials and packaging/labeling materials designated by names or codes sufficiently specific to identify any particular quality characteristics.
- Accurate statements of the quantity or ratio of raw materials and packaging/labeling materials to be used, including unit of measure. Where the quantity is not defined, each lot size or calculation of ratios used in production should be included. Variations in quantities should be included

- where they are justified.
- Working areas and major process equipment.
 - Details of manufacturing instructions shall include:
 - operation procedure;
 - ranges of process parameters employed;
 - sampling instructions and in-process testing with their acceptance criteria, where applicable;
 - time limits for completion of individual process steps or of the whole process, where applicable;
 - expected yield ranges at appropriate steps or time points of processes;
 - where appropriate, special notations, precautions, or cross-references to them; and
 - instructions to retain products to guarantee the appropriateness for use, including packaging/labeling materials, and, where applicable, particular storage conditions with specified time frame.

Contents of product master formulas are defined in Article 7 of GMP Ministerial Ordinance for Drugs and Quasi-drugs. Product master formulas are prepared generally consisting of three parts, i.e., the part summarizing manufacturing approval matters or the like, the part related to manufacturing, and the part related to testing. It is preferable to incorporate the contents of manufacturing instructions shown above into the part related to manufacturing in the product master formula, where applicable. Composing master manufacturing instructions as a part of product master formulas causes no inconvenience.

Attention should be paid to the following four points in preparing product master formulas:

- 1) Product master formulas should be prepared by manufacturers (GMP Ministerial Ordinance for Drugs and Quasi-drugs). That is, product master formulas are the documents that secure the responsibility of the manufacturing sites of the manufacturer (management) for the relevant product with regard to quality management system (Chapters 2.2 and 2.3 Explanation).
- 2) Contents of product master formulas should be ensured consistency with the approved items of the relevant product.
- 3) Product master formulas should be official documents to provide specific manufacturing know-how of the relevant product.
- 4) In relation to the preceding paragraph, product master formulas should also be documents for change control, which should clearly describe histories of changes in manufacturing methods including testing.

6.5 Use Records of labeling and Packaging Materials

Materials for labeling and packaging used in drug products are part of the products, and contents to be described on them are legally defined. Providing “master labels” is considered necessary to confirm the contents of labeling of packaging/labeling materials used per manufacturing or per control unit.

6.6 Laboratory Control Records

In this chapter, laboratory control records are focused on testing conducted as the release test, but also to be applied to testing for process control.

7. Control of Raw Materials and Packaging/Labeling Materials

7.1 General Controls

7.13 It is assumed that information on raw materials and packaging/labeling materials is sometimes not disclosed by suppliers. However, quality of raw materials and packaging/labeling materials is considered to have potentially critical effect on product quality, thus, the sentence “quality-related information should be provided” was added. Obtaining the following information is considered as means for confirmation of quality systems at suppliers that provide backgrounds for quality assurance of raw materials and packaging/labeling materials.

- 1) Results of inspection of manufacturers of raw materials and packaging/labeling materials
- 2) In the case of an overseas manufacturer, the GMP certificate issued by the government to the manufacturing site of the exporter
- 3) ISO certification records (GMP is given priority in case of facilities that GMP is applied to)
- 4) Quality assurance records of manufacturers of raw materials and packaging/labeling materials

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

7.24 Detailed description is given with reference to EU GMP and WHO GMP.

- 1) Concerning Item 3), there is a method to provide separated storage areas in addition to the method of control by labeling. Especially for rejected, returned or recalled products, it is speculated that separated storage areas should be provided.
- 2) Objective of labeling in Item 4) is to clearly identify usable raw materials and packaging/labeling materials.
- 3) Completely computerized storage systems for raw materials and packaging/labeling materials include applying bar-codes where the information is visually unreadable but controlled on the computer. In such cases, it is considered possible to establish systems where any expired raw materials and packaging/labeling materials are never used in manufacturing even when expiry dates are not indicated on the materials.

7.25 1) Even when the same lot number is provided by the supplier, quality conditions may differ under different transport conditions. Therefore, it is stipulated that a control method is required to identify the receiving date by providing a lot number or control number at each time of receiving.

7.25 2) Even when the lot number of incoming raw materials and packaging/labeling materials is the same, storage conditions may differ from container to container, for example, difference in frequency of opening containers. This rule is defined also for the necessity of specifying the containers when sampling is performed. However, if a control method to specify the containers can be employed, it is considered not necessary to provide lot numbers for each container.

7.3 Sampling and Testing of Incoming Production Materials and Packaging/Labeling Materials

1) Omission of acceptance testing (Chapters 7.30, 7.31)

Although it is possible to omit acceptance testing of raw materials and packaging/labeling materials by using Certificates of Analysis provided by suppliers, the following attention is necessary in such cases.

- 1: In order to utilize Certificates of Analysis provided by suppliers, it is essential that a system is available to appropriately evaluate the suppliers including transport conditions, and that the suppliers meet requirements of the evaluation.
- 2: Periodic in-house testing is also required to be conducted.
- 3: Even if Certificates of Analysis provided by the supplier are used, at least confirmation by appearance tests, etc. is required as acceptance testing for each lot.
- 4: In the case of suppliers without use records, past quality histories are sometimes not available, thus, results of evaluation of suppliers were added.

7.32 Even in such cases, in order to omit testing, evaluation of suppliers and transport conditions is the prerequisite, as above Item 1. If the evaluation result is insufficient, further investigation becomes necessary for confirmation using samples for testing.

7.35 Contents of FDA 21 CFR 211.84-(c) were added.

7.4 Storage

7.42 Examples for “particular cases” include the case of crude drugs for which the first-in first-out system cannot be applied, because two or more lots of raw materials are used.

7.5 Re-evaluation

7.50 The sentence “to determine their suitability for use” includes the meaning that unlimited prolongation of the shelf life should not be performed by repeated re-evaluation of raw materials and packaging/labeling materials.

8. Production and In-Process Controls

8.1 Manufacturing Operations

8.17 “The intermediate products excluded from the manufacturing process (materials excluded from the process)” are those removed from manufacturing lines for the reason of process control such as defective filling or tableting, and those used as samples for operation check of equipment. In order to prevent them from being mixed into manufacturing lines, control by labeling and quarantine is required.

8.2 Time Limits

1) Storage of intermediate products

1: In case that the product is stored in the intermediate state, especially for a long term, storage conditions confirmed in advance should be documented and followed, in order to prevent deterioration in quality during storage. The storage conditions to be investigated include the following.

- 1) Storage areas (temperature and humidity, etc.)
- 2) Storage containers
- 3) Storage deadlines

2: Refer to Chapter 9.42 for labeling of intermediate products, and Chapter 10.1 for their storage.

8.3 In-process Sampling and Controls

8.34 Unlike samples used for “in-process tests that are performed for the purpose of monitoring and/or adjusting the processes” as specified in Chapter 8.35, “samples used for in-process controls” are those intended for confirmation of the control of processes on the way that is particularly required for manufacturing finished products with a specific level of quality (e.g. pH control of preparation processes). Thus, if the collected samples are inappropriate for judging validity of the relevant processes, they are of no value. In this regard, sampling procedures are necessary to be investigated from the development stage (refer to Chapter 11.21). “In-process tests that are performed for the purpose of monitoring and/or adjusting the processes” include control of filling weight/volume in the filling process.

8.4 Lot Blending Process

1) “Lot blending process” in this chapter refers to the case where sub-lots are blended to make a larger-sized lot, for the reason of manufacturing equipment, etc. (e.g. due to a size reduction machine with smaller capacity compared to other machines to be used in the subsequent processes, several lots are produced in the size reduction process, followed by blending them to form one lot). Thus, the following cases do not correspond to “lot blending.”

- 1: Residues from the manufacturing processes of the previous lot are mixed into the current lot to produce products (so-called “salvaging operation”).
- 2: Out-of-specification lots are blended with other lots for the purpose of meeting specifications (Chapter 8.41).

- 2) Confirmation of conformity to specifications for each sub-lot is not required, because testing is not always conducted for each sub-lot, when the processes before and after the lot blending are continuously conducted, or when the quality of all sub-lots has been confirmed to be identical.
- 3) Any variation in product quality attributable to lot blending should be avoided. Especially there are cases where manufacturing dates greatly vary from sub-lot to sub-lot, or where sub-lots in different sizes are used. Therefore, the procedures defined in Chapter 8.44 should include some restrictions for the purpose of quality assurance.

8.5 Contamination Control

Causes of contamination include the following.

- 1) Carryover (Chapter 8.50)
- 2) Cross-contamination caused by other than intermediate products, products or raw materials derived from them
- 3) Contaminants caused by insects or personnel
- 4) Microbiological contamination (Chapter 8.6)
- 5) Others

In this guideline, controls for the above 2), 3) and 5) are summarized in Chapters 8.51 and 8.52, while confirmation of overall contamination control is summarized in Chapter 8.53.

8.6 Microbiological Contamination Controls

With reference to FDA 21CFR 211-13, controls of microbiological contamination were added.

9 Packaging and Labeling

Packaging and labeling activities of drug products are very complicated, compared with that of APIs. As packaged drug products are supplied to a medical institution, activities related to packaging and labeling of drug products are critical processes. In this regard, improvement in contents of this chapter was intended.

9.1 General

As to general controls such as receipt and storage of packaging and labeling materials, refer to Chapter 7 (Control of Raw Materials and Packaging/Labeling Materials).

9.2 Control of Packaging Materials

As to packaging materials for drug products, specific material quality is selected during dosage form designing and stated in the manufacturing approval document (data summary), and thus is not cited in this chapter.

9.3 Control of Labeling Materials

Unlike APIs, because not only labels but also printed boxes may be used for drug products, the term “labeling materials” was employed.

9.32 Contents of this chapter are included in deviation control, nevertheless they were clearly described here because of the importance of controlling numbers of labeling materials. In case that deviation such as discrepancy in numbers occurs, on-site investigation of causes should be conducted at the manufacturing site, and on this basis, the record describing the consideration of validity of the causes for the discrepancy should be maintained, which should certainly be confirmed by the third-party quality unit.

9.4 Packaging and Labeling Operations

Packaging and labeling activities of drug products are very complicated, compared with that of APIs, and are the final processes for drug products. In addition, reprocessing of packages (packaging or labeling activities are performed again due to stain, scratch, or breakage of packaging/labeling materials) is routinely performed. Therefore, Chapter 9.41 was added to define line clearance, and Chapters 9.44 - 9.46 were added with the intention of tightening of activities related to packaging and labeling.

10 Storage and Release from Manufacturing Site

10.2 Operations of Release from Manufacturing Site

Although recall of products is described in Chapter 16, there is no description for the case where a potential risk on the quality of intermediate products is found, after they were released to other manufactures (inappropriate calibration of measuring instruments, etc.), thus Chapter 10.23 was added.

11 Laboratory Controls

The role of laboratory control was evaluated in The Welfare and Labor Science Research in 2005, and organized in “Guideline for Laboratory Controls.”

11.1 General Controls

11.13 Considering that resampling and retesting of samples are performed routinely even in the case other than out-of-specification results, restrictions on resampling and retesting were defined.

11.14 Labeling information on commodities is the basic principle of control. Therefore, complete control of labeling on purchased reagents and reference standards, prepared test solutions and subdivided products is required in the same manner as manufacturing control.

11.18 Control of water for testing was added with the intention of increasing awareness of the relevant control.

11.5 Monitoring of Stability of Products

Stability of drug product is clarified in detail. Monitoring of stability required in this chapter means confirmation of the no change in stability, which is one of the items of product quality review.

11.6 Expiry Date

Since drug products have the approved shelf life, description about expiry dates for drug products is not necessary. Only for intermediate products to which expiry dates are applied, the rationale should be provided.

11.7 Reserve Samples

Details on the quantity of reserve samples to be stored are described. To avoid misuse of reserve samples, labeling on reserve samples is required.

12 Validation

12.1 Validation Policy

12.10 Explanation was given with examples of summarizing the outline of validation as “validation plan” which is called as “validation master plan” abroad.

12.11 For determining the range and degree of validation, use of the concept of risk assessment under evaluation by FDA and ICH (Q9) is recommended.

12.2 Validation Documentation

12.20 In Article 13, Paragraph 1, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, it is stipulated that validation plans and results should be reported to the quality unit in writing. Thus, the responsibility of the quality unit shall include confirmation of the validation plans and results (Chapter 2.22, Item 10 of this guideline).

In Q7A, approval of validation plans and results is defined as the responsibility of the quality unit (See Chapter 2.22, Item 10 of Explanation of this guideline). On the other hand, in Article 13, Paragraph 1 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, it is stipulated that those predesignated should be responsible for validation activities, thus, another system can be considered where such predesignated personnel approves the validation plans and results.

12.21 “Concurrent validation” can be translated as “ongoing validation.” However, “ongoing validation” is a term defined in the former “validation standards” (PAB Notification No. 158, 1995, hereinafter referred to as “old validation standards”), and it is to be noted that the concept is different from that of concurrent validation defined in the current validation standards and in Chapter 12.53 of this guideline (the same as the description in Chapter 12.43 of Q7A).

12.3 Qualification

As to the concept for each step of validation, there is a lack of consistency in some points between Q7A (IQ, OC, etc.) and the validation standards (qualification of equipment). In considering Chapters 12.3 and 12.5, each step of these validations was re-evaluated according to Q7A.

The concept of validation has been already reviewed by the Technical Education Committee (Chairperson: Dr. Kaoru Morikawa, department head, National Institute of Public Health, at the time) of PDA Japan with reference to Q7A. Referring to their report, PDA Japan “Validation of solid dosage forms” (2000), and in accordance with the chapter “Pharmaceutical development and validation,” description about qualification was provided in more detail.

12.30 4) Performance Qualification (PQ)

DQ/IQ/OQ are qualification targeting only facilities and equipment, while PQ is aimed at confirming that the facilities or equipment “demonstrates the intended performance” in order to secure the intended product quality, where a

product-dependent element “drug products” is included. This point is different from OQ that is aimed at confirming that the facilities or equipment operates “according to the established specifications.” That is, even if equipment operates according to the established specifications, it does not always demonstrate the intended performance (for example, with a capsule filling machine, the relevant drug product cannot be filled with predefined precision). Verification of such point is an important objective of PQ.

PQ is an activity of verification with actual production machines, where active drug products (placebos in some cases) are used. However, the batch size is not necessarily of an actual production scale, and PQ can be conducted in a scale appropriate for its purpose. In addition, if scientifically sufficient data have been obtained by challenge tests, etc. in the performance evaluation cited below, verification by PQ seems not necessary in some cases, depending on assessment items.

12.4 Efficiency Study

In the conventional OQ or PQ, experimental studies such as virtual scale-up tests using active drug products or placebos have been likely conducted with actual production equipment under the name of “validation” in many cases. In such activities, operating conditions and control parameters may be determined. However, these activities are out of the category of validation, which should be recognized as research activities called process development, and be clearly differentiated from validation. It is because process development itself is not aimed at decision on “acceptance/rejection” by setting “acceptance criteria” that are prerequisite for completion of validation. In order to clarify that such process development like scale-up tests is different from the concept of validation, another concept of efficiency study for such activities was introduced, and it was stipulated that “manufacturing procedures and control parameters necessary for the transfer to PQ should be developed, established and documented.” Although the term “efficiency study” is used in this guideline, understanding of the concept without being constrained by the term is anticipated.

Scale-up tests mean various kinds of examination with actual production equipment, while efficiency study is not limited to such examination with actual production equipment. As examples of approaches to efficiency study, operation procedures and control parameters for actual production equipment may be developed in the examination in laboratory-scale, or transfer to actual production may be implemented by establishing manufacturing conditions for a new product based on the scientific evaluation of past data related to manufacturing of other existing products.

The concept of efficiency study has been reviewed also by the Technical Education Committee of PDA Japan. Referring to the report, PDA Japan “Validation of solid dosage forms” (2000), and in accordance with the chapter “Pharmaceutical development and validation,” description about efficiency study was provided.

12.5 Approaches to Process Validation

12.50 Process validation

Description in this chapter is in accordance with the chapter “Pharmaceutical development and validation” of the PDA Japan “Validation of solid dosage forms”

(2000).

Needless to say, it is not possible to confirm by testing only three lots in PV that the products with intended quality can be manufactured consistently. For such confirmation, accumulation of scientific data, i.e. formulation studies, and overall results of activities from DQ to PV are required. In addition, it is also important to establish maintenance programs for manufacturing facilities and equipment. It is necessary to emphasize that these two factors enable consistent manufacturing of products with intended quality, and secure the quality of the drug products.

12.55 Concerning lots failed to meet specifications, the cause should be investigated. Based on the cause, if the relevant lot cannot be regarded as a “representative lot,” such lot should be excluded from the targets of retrospective validation.

12.56 Maintenance program

Description on maintenance program that is essential for consistent production was added in accordance with the chapter “Pharmaceutical development and validation” of the PDA Japan “Validation of solid dosage forms” (2000).

In actual production after PV, it is not exaggeration to say that quality of drug products depends on how appropriately the maintenance of facilities, equipment and system is conducted. It is because in the process, so-called product development, from formulation design until clinical supplies or start of actual production, it is impossible to evaluate the chronological changes in the actual manufacturing facilities and equipment for drug products (aging such as abrasion, peeling and rust, deviation from the true values of measuring instruments such as balances and gauges). Therefore, it is crucial to determine the items and frequency of maintenance in the earliest stage of actual production, and to prepare them into a program.

12.7 Periodic Review of Validated Systems

Periodic review cited in this chapter includes “periodic review of process control” defined in the validation standards. Refer to Chapter 2.5 (Product Quality Review).

12.9 Analytical Method Validation

The role of laboratory control was evaluated in The Welfare and Labor Science Research in 2005, and organized in “Guideline for Laboratory Controls.”

12.90 Even if the analytical method is listed in Japanese Pharmacopoeia or other acknowledged references, it is still a general method and is not always applicable to the target of the relevant analysis. Therefore, it is necessary to verify the appropriateness of the analytical method by validation of analytical methods or other proper ways.

12.93 Based on the importance of change control, validation shall be conducted depending on the level of changes.

13 Change Control

In Article 14, Item 1 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, it is stipulated that changes (plans) should be approved by the quality unit. The basic idea of this guideline is that “the quality unit should be involved in all quality-related matters” (Chapter 2.22), and it recommends that results of changes should also be approved by the quality unit as in the case of the plan. In Article 14 of the above Ministerial Ordinance, it is stipulated that those predesignated should be responsible for implementation of change control, thus, another system can be considered where such predesignated personnel performs planning of changes and reporting of results.

- 13.10 Since the concept of “quality management system” was introduced, the change control system in a broader sense is considered necessary to be established.
- 13.11 Control procedures including manufacturing method may be sometimes changed due to quality information about product quality, product recall or regulatory requirements (i.e. changes in specifications due to the revision of Japanese Pharmacopoeia), thus, such case was defined in this chapter.
- 13.12 The scope of change control was defined. This scope should be predefined in the “change control procedures.”
- 13.13 Procedures for changes and matters to be considered are cited. The following two points are considered to require particular attention when changes are made.
- When changes may have potential effect on the quality of drug products, the notification to that effect should be made to the manufacturer and manufacturing distributor in advance.
 - When changes conflict with the manufacturing approval matters, or when changes may have effect on the quality, efficacy and safety of products, it is necessary to submit “application for partial change in manufacturing approval” or “application for minor change” about the implementation of changes to the regulatory authorities in advance, to obtain their approval or authorization.
- 13.15 This chapter was added, because it is necessary to evaluate the effect of changes implemented on product quality.

14 Rejected Products and Reprocessing

14.1 Rejection

14.12 It was clearly described that any matters related to decision on release should be confirmed by the person responsible for decision on release of the relevant products. That is, disposal or reprocessing of products after the decision on release should be confirmed by the person responsible for the decision on release. It is because the initial decision on release may be reversed in some cases as a result.

14.2 Reprocessing

14.20 Reprocessing was clearly described and the term is defined as “returning of products or rejected products to the manufacturing process of the relevant products and repeating of a part of or whole the predefined manufacturing process.” And “predefined manufacturing process” shall refer to “the process associated with the relevant product among the approved manufacturing methods for the drug product.”

Examples of reprocessing include the following.

1. After the decision on release, products including returns whose quality is acceptable, are returned to the manufacturing process, and then a part of or whole the manufacturing process is repeated.
2. After the decision on release, products including returns that meet the predefined quality specifications, are mixed into another lot of the same product during the manufacturing process.
3. Intermediates whose quality is acceptable are mixed into the same or another lot of the same product during the manufacturing process (excluding the case where such processing is a part of the predefined process that is required in the routine manufacturing control).

Examples that are not regarded as reprocessing include the following.

1. In case that the relevant process was found uncompleted by in-process control testing, continuation of subsequent processes is regarded as a part of routine process, and is not as reprocessing. More specifically, so-called consequential manufacturing processes such as granulation, drying and coating are conceivable.
 2. In case that products are processed at a place other than the approved manufacturing site, or processed by a method other than the approved manufacturing method, thereby deviating from the contents of approval matters, such processing is not regarded as reprocessing.
- 14.22 It is clearly described that the lot number should be changed when products were reprocessed after the decision on release. It is because, products before reprocessing and that after reprocessing should be differentiated since they were

produced by different manufacturing processes and received different decisions on release.

14.24 The purport of this chapter is the same as that of Chapter 14.11 Explanation.

14.3 Returns

14.33 Description of this chapter was intended to clarify that redistribution and reprocessing are sometimes permissible for returns. Based on this, in Chapter 14.40 “redistribution” was defined as “the process where the product once released from the manufacturing site and thus not under control of the site is received again by the manufacturing site for the reason of return or the like, and is tested to confirm its quality, without reprocessed, and is decided again on release from the manufacturing site based on the test results, and then is released.”

Basic concept: There is no legal regulation to prohibit “redistribution,” while there is a rule corresponding to redistribution in WHO GMP, thus, it is possible to perform redistribution. However, redistribution should be performed under the responsibility of companies, and needless to say, there should not be unconformity to the regulation in the process or result of redistribution. This is specifically described in Chapters 14.3 and 14.4.

The purport of description in this chapter that “confirmed by the person responsible for decision on release of the relevant products” is the same as that of Chapter 14.1 Explanation. That is, as the returned products were once evaluated acceptable upon decision on release, their disposal, redistribution and reprocessing shall be confirmed again by the person responsible for the decision on release.

14.34 It is stated that the returned products in recall processing may be redistributed or reprocessed in some cases. The purport is “Just because it is a recalled products, it does not stand to reason that any redistribution and reprocessing are never approved.” Consideration was given to the situations that most of recalls in Japan nowadays are voluntarily conducted by companies for the reason of potential defectives, thus, many of recalled products are not corresponding to defectives actually. Needless to say, it was clearly stated that “for recalled products, actions on recall processing should be given priority,” to avoid misunderstanding.

14.4 Redistribution

As stated in Chapter 14.33 Explanation, a paragraph on redistribution was provided.

Cautions for redistribution

1. Redistribution of products after decision on release is not permissible when a deviation from the contents of approved matters is caused by activities such as performing tests related to approved specifications at facilities other than the approved laboratories, or conducting evaluation that does not comply with the approved specifications and testing methods.
2. When intermediate products or products after decision on release are received and released by a manufacturing site other than those who have released them,

this is not regarded as redistribution.

- 14.41 In this chapter, the purport of requiring confirmation by the person responsible for decision on release for the relevant product is the same as that of Chapter 14.1 Explanation. That is, as the returned products were once evaluated acceptable upon decision on release, their evaluation methods and items shall be confirmed again by the person responsible for the decision on release.

Supplement to Chapter 14

1. Reworking

No paragraph corresponding to reworking is provided in this guideline.

Reason: Reworking of drug products is regarded as a deviation from the approved manufacturing process under the currently enforced system in Japan, and drug products of reworking may be regarded as “non-approved drugs.” In addition, it is considered sufficient to appropriately define “reprocessing” alone in the case of drug products. However, the deletion of “reworking” does not mean to negate the reworking. If reworking for drug products is authorized in the future, separate investigation in this regard is considered necessary. There is a rule corresponding to reworking in Q7A (Chapter 14.3).

2. Recovery of intermediate products, APIs and solvents

No paragraph corresponding to recovery of intermediate products, APIs and solvents is provided.

Reason: For drug products, it is considered that few cases correspond to this activity. If any of such case for drug products, controlling them according to Q7A is considered sufficient. There is a rule corresponding to recovery of intermediate products, APIs and solvents in Q7A (Chapter 14.4).

15 Quality Information

As to activities in the quality information processing system, it is important to evaluate the “cause,” “trend,” “frequency related to drug products,” “importance” and “corrective actions,” and to use the data in the subsequent activities for improvement of product quality assurance. In case that improvement or changes of procedures for manufacturing control or quality assurance is required on the basis of the evaluation results, it is necessary to report to those who have responsibility and authority, and for notifying related organizations such as licensed marketing approval holder or regulatory authorities.

Records on “quality information” include matters defined in Article 16 of GMP Ministerial Ordinance for Drugs and Quasi-drugs. It is preferable to describe the following items.

- 1) Name and address of person who offers the quality information
- 2) Name (and job title, if applicable) of and where and how to contact the person who submits the quality information
- 3) Details of quality information (including the name, dosage form, packaging form and lot number of product)
- 4) Date and time of receiving quality information
- 5) Action taken first (including the date of action and the name of person in charge)
- 6) All the follow-ups conducted
- 7) Response to the person who offers the quality information (including the date of response)
- 8) Final decision on the actions taken for the lot subject to quality information
- 9) Details of corrective actions and conclusion

16 Recall Processing

16.10 In Article 11, Paragraph 2, Item 2 of GQP Ministerial Ordinance, it was clearly stipulated that decision of recall should be made under the responsibility of licensed marketing approval holders. Actual recall activities should be conducted under the good cooperation between licensed marketing approval holders and manufacturers. Manufacturers should also establish recall processing system, including handling of recalled products that are defined in Article 8, paragraph 4, Item 6, and in Article 17 of GMP Ministerial Ordinance for Drugs and Quasi-drugs.

Conventional recall processing systems give an impression as if they are limited to “recall attributable to physicochemical quality of products,” however, considering the future quality assurance for drug products, it cannot be denied that product quality can induce adverse events related to “efficacy” and “safety” that are taken account at the final stage of drug use. Therefore, information exchange is also necessary among the departments concerned.

16.12 In the recall processing records defined in Article 17, Item 2 of GMP Ministerial Ordinance for Drugs and Quasi-drugs, it is preferable to include the following items, as well as those described in the text of this guideline.

- 1) Reason for recall
- 2) Name, approval/license date and number, dosage form, packaging form, quantity, lot number or batch number, and date of manufacture (import) of the drug subject to recall
- 3) Name, address, license date and number of the manufacturing site that produced the drug subject to recall (including contract manufacturing sites)
- 4) Dates of recall initiation and completion
- 5) Method of recall (including methods for transmission of recall information, and for confirmation of presence/absence of recall products at the sites of recall)
- 6) Scope of recall (name and address of medical sites and distributors from which the products are recalled)
- 7) Quantity, distribution status and usage status of recalled products
- 8) Results of review of reserve samples
- 9) Results of review of records related to the recalled lot including manufacturing, testing, storage, and hygiene control records
- 10) Method of investigation of causes and the results
- 11) Status or results of corrective actions
- 12) Other than the above, details of actions taken to prevent the onset or spreading of damage on health

End of GMP Guideline for Drug Products

Scientific Research Granted by the Ministry of Health, Labor and Welfare in 2004

Research on Current Quality System of Drug Products

Research Report

Yukio Hiyama, Chief Researcher, Division of Drugs, the National Institute of Health Sciences

Guideline for Technology Transfer (Final Draft)

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Introduction

This research is intended to provide appropriate guidance for technology transfer of which importance is expected to increase under the new manufacturing and marketing approval system to be implemented by the revised Japanese Pharmaceutical Affairs Law, and supplement the GMP regulations to be revised soon. The research is also intended to propose some regulations to realize technology transfer necessary for high quality and stable manufacturing of new drugs and existing products by reviewing technology transfer based on the following principles.

In this research, draft guideline has been established on the basis of the following principles.

- The technology transfer means actions to transfer information and technologies necessary to realize quality of design of drugs during manufacturing.
- Appropriate technology transfer is important to upgrade the quality of design to be the quality of product, and ensure stable and high quality of the product.
- It should be noted that drugs may have a great impact on human lives and health, and their raw materials, compositions and manufacturing methods are subject to various changes during their long term manufacturing and marketing.
- To assure the drug quality, it is required to make sure 5 W's and 1 H, that is what, when and why information should be transferred to where and by whom and how to transfer, then share knowledge and information of the drug product between transferring and transferred parties.
- The technology transfer does not mean transient actions taken by the transferring party toward the transferred party, but means continuous information exchange between the both parties to maintain the product manufacturing.

Basic Policies on the Establishment of the Guideline for the Technology Transfer

The basic policies on the establishment of the guideline are shown as follows.

1) Assurance of consistency of new drug from development through manufacturing

- When a drug is launched into the market, the quality of design of the drug should be reproducible as the quality objectives so that the drug can have indications as confirmed in clinical studies conducted at the development phase.
- The transferring party in charge of development should fully understand what kind of technical information is required for the technology transfer, and should establish an appropriate evaluation method to determine whether a drug to be manufactured meets the quality of design.
- It is important to fully refer to product information of the past, while understanding that technical information of new drugs are generated from data of a limited amount of batches, various standards have been established within a narrow range, and quality evaluation method established in the development phase is not always sufficient in the manufacturing phase.

2) Consistency Between Quality and Specification

- It is required to verify that the product specification adequately specifies the product properties and quality.
- The product specification should ensure that the quality of design specified in the development is assured as the quality objectives, and the product satisfies the quality of design.
- It should be fully understood that quality assurance in the manufacturing is based on the product specification. Relations between upper and lower limits of setting range of manufacturing formula (compositions and manufacturing methods) and upper and lower limits of specification values in the product specification should be fully understood, and appropriate specifications and the specification range should be established to maintain the consistency between the quality objectives and product specification.
- For specifications of raw materials, labeling and packaging material, intermediates, semimanufactured products, and in-process test, consistency between test items, specification range, and product specifications should be maintained.
- Since initial manufacturing formula and product specification are established based on limited information, the consistency between the quality and specification after the start of manufacturing should be fully verified, and these should be improved through appropriate change controls, if necessary.

3) Documentation Management and Update of Technical Information

- Responsibility system should be established in view of responsibility for giving sufficient information (Accountability) and responsibility for consequences of actions (Responsibility). For this purpose, appropriate documentation management of technology transfer is required.
- In light of the fact that drugs have long product life, the documentation management should be performed assuming that the technology transfer would occur several decades after the completion of development.
- Since the control range of formula to realize planned quality objectives has been specified within a narrow range at the early phase of manufacturing, the control range might be revised due to information accumulation accompanied with repeated manufacturing, and the product quality is not fixed one but may be improved and involved in the revision of specification and test methods. Taking these into consideration, initial technical information should be reviewed at regular intervals on the basis of the quality of design, and then the information should be updated.

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The table of contents is shown as follows. The 1st chapter addresses background and the scope of the guideline. The 2nd to 4th chapters address items to be noted when the technology transfer is implemented as well as the process of technology transfer, while the 5th chapter shows detailed procedure and documentation of technology transfer. In addition, the 6th and latter chapters show considerations necessary for the implementation of technology transfer, and exemplify items to be listed in the technology transfer documentation.

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Guideline for Technology Transfer

1. Preface

1.1 Background

In the drug approval system, the manufacturing approval was replaced with the manufacturing and marketing approval in April 2005, resulting in a big change in the Japanese pharmaceutical system and regulations. Under these circumstances, in order to continue providing effective and safe drugs to the public as in the past, it is required to restructure a quality assurance system of drugs at all stages through research and development (R&D), manufacturing and marketing in line with the trends by reviewing the current quality assurance system and its methods including existing Good Manufacturing Practice (GMP) to comply with the new system and adopting achievements of technological progress and international harmonization of pharmaceutical regulations.

In recent years, there is a growing awareness that an appropriate transfer of manufacturing technologies (technology transfer) is important to upgrade drug quality as designed during R&D to be a final product during manufacturing as well as assure stable quality transferred for many reasons between contract giver and contract acceptor during manufacture. Also, to assure the drug quality in the transferred party, it is required to make sure 5 W's and 1 H, that is what, when and why information should be transferred to where and by whom and how to transfer, then share knowledge and information of the technology transfer each other among parties related to drug manufacturing. For this purpose, it is required to establish an appropriate guideline for technology transfer and help to restructure the quality assurance system. This guideline categorizes information generated in the processes through pharmaceutical R&D and manufacturing as well as the information flows, discusses information necessary for the technology transfer and communication route, and proposes ideal technological transfer.

1.2 Objective

The objectives of this guideline are:

- 1) To elucidate information necessary to transfer technology from R&D phase to actual manufacturing phase by sorting out various technical information obtained during R&D of new drugs;
- 2) To elucidate information necessary for technology transfer occurring between different manufacturing plants when the manufacturing plants of existing products, etc. are changed; and
- 3) To exemplify specific procedures and points of concern for the two types of technology transfer in the above to contribute to smooth technology transfer.

1.3 Scope

This guideline applies to the technology transfer through R&D and manufacturing of drugs (chemically synthesized drug substances and drug products) and the technology transfer related to changes in manufacturing plants of already marketed drugs. The both technologies include those of manufacturing and quality control (manufacturing methods and tests).

1.4 Organization

This guideline consists of the followings:

- Explanation of technology transfer process
- Explanation of considerations for technology transfer
- Explanation of procedures and necessary documents for technology transfer
- Examples of technical information to be transferred
- Points of concern for documenting technology transfer

2. Technology Transfer Process of New Drugs from Development Phase through Manufacturing Phase

The quality of design of drugs is designed based on basic data concerning efficacy, safety and stability of drugs (drug substances) obtained from various studies in preclinical phases and data concerning efficacy, safety and stability of drug products obtained from clinical studies. The quality of design will be almost completed in Phase II clinical

study. Various standards for manufacturing and tests will be established by reviewing pilot research during the period of Phase III study to realize the quality of design, and the quality of design will be verified in various validation studies, and will be upgraded to be the quality objectives, and the actual production will be started. The technology transfer consists of actions taken in these flows of development to realize the quality as designed during the manufacturing. Even if the manufacturing starts, the technology transfer will take place in processes such as changes in manufacturing plants. The processes are classified broadly into the following five categories.

2.1 Quality Design (Research Phase)

The quality design is to design properties and functions of drugs, and performed mainly in phases from late preclinical studies to Phase II clinical study. For drug products, the quality design corresponds to so-called pharmaceutical design to design properties and functions such as elimination of adverse reactions, improvement of efficacy, assurance of stability during distribution, and adding usefulness based on various data such as chemical and physical properties, efficacy, safety and stability obtained from preclinical studies. For drug substances, the quality design is to determine starting materials and their reaction paths, and basic specifications of the drug substances.

2.2 Scale-up by Pilot Research, and Detection of Quality Variability Factors (Development Phase)

To manufacture drugs with qualities as designed, it is required to establish appropriate quality control method and manufacturing method, after detecting variability factors to secure stable quality in the scale-up validation that is performed to realize pilot research of drugs designed on the basis of results from small-scale experiments. In general, this process is called the pilot research where the quality of design will be upgraded to be the quality objectives. Adequate data accumulation in the pilot research is important for successful technology transfer.

2.3 Technology Transfer from Development Phase to Manufacturing Phase

Transfer of technical information is necessary to realize that actual products are manufactured in manufacturing facilities using compositions and manufacturing methods established in the above. In the past, the technology transfer was mainly seen as standard transfer or as technology instruction from development department to manufacturing department within the same company. In future, since contract manufacturing is expected to increase under the revised Pharmaceutical Affairs Law, the technology transfer between companies will increase. In principle, how accurately transfer technical information from transferring party to transferred party is important, and it is essential to establish responsibility system and prepare documents clarifying 5 W's and 1 H, and have adequate technology exchange between the both parties for successful transfer.

When transfer technology of new products from research and development department to manufacturing department, it is recommended to compile technical information to be transferred as research and development report (hereinafter referred to as "the development report"), and use the development report as a part of technology transfer documentation.

2.4 Validation and Manufacturing (Manufacturing Phase)

Manufacturing is implemented after various validation studies verify that it is able to stably manufacture based on transferred manufacturing formula. While the manufacturing facility accepting technology is responsible for validation, the research and development department transferring technology should take responsibility for validations such as performance qualification (PQ), cleaning validation, and process validation (PV) unique to subject drugs. For validations such as installation qualification (IQ) and operational qualification (OQ), which are not unique to the subject drugs, it is possible to effectively use data of already implemented validations.

2.5 Feedback of Information Generated from Manufacturing Phase

As a result of technology transfer, products are manufactured and brought to the hands of consumers. Since manufacturing and quality evaluation methods established in the early phase of manufacturing is not always the best ones, it is required to accumulate various technical information obtained through repeated manufacturing. Also, it is important to appropriately modify various standards established before on the basis of these information. For this purpose, appropriate feedback system for technical information at transferred parties and documentation management

of technology transfer at transferring parties should be established. For drugs as they have long product life, documentation management should be performed assuming that the technology transfer would occur several decades after the completion of development. Also since product improvements and changes of specifications and methods are often implemented, the initial technical information should be reviewed and updated at regular intervals. For this kind of documentation management and information updating, it is desirable to establish product specification describing entire characteristics of the product in addition to the development report, which is to be revised and updated regularly.

3. Three Requirements to be Considered for Technology Transfer

It is important to satisfy the following three requirements in order to steadily implement the technology transfer through the processes described in the chapters 2.1 to 2.5.

3.1 Assurance of Consistency from Development through Manufacturing

To make developed new drugs have efficacy and safety as predetermined in clinical studies, the quality of design should be reproducible as the quality objectives (assurance of consistency). For this purpose, the transferring party in charge of development should fully understand what kind of technical information is required by the manufacturing plant which receives technology transfer, and should establish an appropriate evaluation method to determine whether a drug to be manufactured meets the quality of design. It should be recognized that technical information of new drugs at the early phase of manufacturing are generated from data of a limited amount of batches, various standards obtained from the limited data are established only within a narrow range, and quality evaluation method established in development phase is not always sufficient for latter phases including pilot research. For stable manufacturing of consistent products, it is fundamental to fully refer to and review information of research and manufacturing of existing products when the pilot research is implemented, and this is a key to successful technology transfer.

3.2 Consistency between Quality and Specification

When the product specification is established on the basis of the quality objectives determined in the above, it is required to verify that the specification adequately specifies the product quality (consistency between quality and specification). That is, it is required to ensure the quality predetermined in the quality design as the quality objectives, and assure in the product specification that the product satisfies the quality of design.

In reviewing pilot research, since manufacturing methods are established with limited amount of lots and limited resources of raw materials, the product specification should be established based on data from study results with limited lots; however, relations between upper and lower of control limits of compositions and manufacturing methods and upper and lower of control limits of the product specification should be fully understood, and the consistency between the quality objectives and specification should be maintained.

Also, since initial manufacturing formula and specification are established based on limited information, the consistency between the quality and specification should be fully verified after the start of manufacturing, and the consistency should be improved through appropriate change controls, if necessary.

3.3 Update of Documentation Management and Technical Information

For both of new drugs and existing products, concerned parties should make clear the responsibility system in order to fulfill the responsibility for giving sufficient information (Accountability) and responsibility for consequences of actions (Responsibility) in view of the quality of design and quality objectives of the product. For this purpose, appropriate documentation management of technology transfer is important and required. In light of the fact that drugs have long product life, it should be fully understood that it is essential to perform the documentation management assuming that the technology transfer would occur several decades after the completion of development. In addition, appropriate documentation management of various technical information accompanied with technology transfer should be established, and storage period should be set up according to the importance of data. Since the quality objectives have been stipulated within a narrow range at the early phase of manufacturing, the control range might be revised due to information accumulation accompanied with repeated manufacturing, and the

product quality is not fixed one but may be improved and involved in the revision of specification and test methods according to technology progress. Taking these into consideration, initial technical information should be reviewed at regular intervals on the basis of the quality of design, and then the information should be updated.

4. Technology Transfer of Existing Products

Since manufacturing plants of existing products are often changed for many reasons after the launch of a new drug, already standardized test methods and manufacturing methods of the existing products are sometimes transferred to other offices or other companies. In addition, for certain reasons, qualities of the existing products might be improved.

In case of the change in manufacturing plants of the existing products, no alteration of product quality before and after the change (assurance of uniformity) is required rather than assurance of consistency needed for new drugs. Products manufactured in a new manufacturing plant should satisfy the product specification, while it is required to confirm that there is no alteration of trends of each control value of manufacturing, test and inspection processes which may affect the product quality. Although there are no significant differences between existing products and new drugs in terms of implementation of technology transfer, many of existing products have already established standards of manufacturing, test and inspection processes. Therefore, transferring and reproducibility validation of established standards become actual technology transfer in case there is no significant alteration of these standards which may affect the product quality and no possibilities to affect the product quality due to technology transfer. However, in case where alterations of facilities or manufacturing scales often occurring due to technology transfer may possibly affect the product quality, it is required to confirm whether there is any influence on the quality, establish manufacturing standard not affecting the product quality as much as possible, and revise various specification, test methods and inspection standards if necessary. In these cases, it should be always noted that each standard has been established within a narrow range at the early stage of manufacturing after the technology transfer as in the case of new drugs, and revised quality evaluation method of specification, test methods, etc. are not always the most ones. When revising manufacturing standard, specification test, etc., close attention is required, since equivalence evaluation of quality objectives (including bioequivalence) may be required in terms of change control.

In case quality objectives of the product are improved, quality equivalence including bioequivalence should be assured. That is, since examinations similar to those of generic products are required, Guideline for Bioequivalence Studies of Generic Products should be fully referred. Technology transfer in this case should be handled as in the case of new drugs. Since items stated in the chapters 2.3 to 2.5 shall apply to both of developed and existing products, it is desirable that technical information to be transferred should be compiled in forms such as product specification. For this purpose, Drug Product Standard Code is an important document. Also as in the case of developed products, responsibilities for the technology transfer should be clearly defined, documentation of technology transfer should be prepared, and the technology transfer should be implemented through adequate exchanges of technical information.

4.1 Assurance of Consistency, Equivalency, and Uniformity between Quality and Specification of Existing Products

Unlike new drugs, the quality of existing product is considered being stable. However, the quality of product may possible change due to various revisions (such as places, operators, raw materials, labeling and packaging material, facilities, test methods, etc.) accompanied with technology transfer. If the product specification does not fully stipulate the quality of product, changes in quality may be overlooked. Therefore, for the technology transfer, it should be confirmed that the product specification fully stipulates the product quality as in the case of developed products (assurance of consistency between the quality and specification).

Essential difference between assurance of consistency of new drugs and assurance of uniformity and equivalency of marketed products is whether approval is necessary or not. Concerning new drugs, their qualities are officially authorized by the regulatory approval granted after the technology transfer, while the quality of existing products has been officially authorized since they have already been approved. Therefore, in case of the above changes, the quality of existing product should be improved or not be altered. As such, if the quality is improved in

the technology transfer, equivalence including bioequivalence of other qualities should be assured, and if the quality is not changed, the uniformity before and after the changes should be assured. For this purpose, results of changes accompanied with the technology transfer should be fully evaluated. If necessary, appropriate change control procedures should be taken after the processes of quality of design, pilot research, and validation, and required legal procedures should be taken as in the case of developed products.

5. Procedures and Documentation of Technology Transfer

To properly transfer technology according to the above processes, documentation of technology transfer including appropriate procedures and technical documents is required. Procedures and documentation of technology transfer are indicated as follows. Items to be specified in the documentation will be referred in detail in the 6th chapter.

5.1 Organization for Technology Transfer

One of the most significant elements for successful technology transfer is close communication between transferring and transferred parties. Therefore, organization for technology transfer should be established and composed of both party members, roles and scope of responsibilities of each party should be clarified, and adequate communication and feedback of information should be ensured.

If view of the fact that results of technology transfer is reflected to GMP conformity after the start of manufacturing, it is important to establish an organization of transferred parties with due consideration for transferring to final GMP system.

5.2 Development Report

To realize quality assurance of new drugs at all stages from drug development to manufacturing, transfer of technical documents concerning product development or corresponding documents should be considered. The development report is a file of technical information necessary for drug manufacturing, which is obtained through development process, and the research and development department is in charge of its documentation. This report is an important file to indicate rationale for the quality of design of drug substances and drug products including information such as raw materials, labeling and packaging material, manufacturing methods, specifications and test methods. The development report should also include the above rationales, and it is desirable to complete the documentation before the approval inspection if possible or before the pre-approval inspection at the latest. Although the development report is not prerequisite for the application for approval, it can be used at the pre-approval inspection as valid document for the quality design of new drug. Also, this report can be used as raw data in case of post-marketing technology transfer of existing products. The following exemplifies information to be contained in the development report.

- Background of development of drug substances and drug products at stages from early development phase to final application of approval
- Rationale for the selection of raw materials, labeling and packaging material, and synthetic route
- Rationale for designs of dosage form, formula designs, and manufacturing methods
- Rational and change histories of important processes and control parameters
- Quality characteristics of manufactured batches (including stability data)
- Specifications and test methods of drug substances, intermediates, drug products, raw materials, and labeling and packaging material, and their rationale (validity of specification range of important tests such as contents, impurities and dissolution, rationale for the selection of test methods, reagents, and columns, and traceability of raw data of those information)

5.3 Technology Transfer Documentation

Technology transfer documentation is generally interpreted as documents indicating contents of technology transfer for transferring and transferred parties. The raw data of the documents (such as development report) should be prepared and compiled according to purposes, and should be appropriately managed so that the data can be referred any time. For successful technology transfer, task assignments and responsibilities should be clarified, and acceptance criteria for the completion of technology transfer concerning individual technology to be transferred should be established beforehand.

In principle, it is desirable to prepare product specification with detailed information of product (drug substances or

drug products) subject to transfer, then proceed with the technology transfer according to the technology transfer plan established on the basis of this specification, and document the results as the technology transfer report.

5.3.1 Product Specification (Product Specification File)

The product specification is to compile information which enables the manufacture of the product, and to define specification, manufacturing and evaluation methods of the product and its quality, and the transferring party is responsible for documenting the file.

For new products, the development report can be used as a part of product specification file.

The product specification file should be reviewed at regular intervals, and revised as appropriate incorporating various information obtained after the start of manufacturing of the product.

The product specification file should contain the following.

- Information necessary for the start and continuation of product manufacturing
- Information necessary for quality assurance of the product
- Information necessary for assurance of operation safety
- Information necessary for environmental impact assessment
- Information of costs
- Other specific information of the product

} Including the contents
of the development
report

5.3.2 Technology Transfer Plan

The technology transfer plan is to describe items and contents of technology to be transferred and detailed procedures of individual transfer and transfer schedule, and establish judgment criteria for the completion of the transfer. The transferring party should prepare the plan before the implementation of the transfer, and reach an agreement on its contents with the transferred party.

5.3.3 Technology Transfer Report

The technology transfer report is to report the completion of technology transfer after data of actions taken according to the technology plan is evaluated and the data is confirmed pursuant to the predetermined judgment criteria. Both transferring and transferred parties can document the technology transfer report; however, they should reach an agreement on its contents, since this report means the completion of technology transfer.

5.3.4 Check and Approval by Quality Department

It is desirable that the quality departments of transferring and transferred parties should establish confirmation process for all kinds of technology transfer documentation, and should check and approve the documentation.

5.4 Implementation of Technology Transfer

Avoid as much as possible the technology transfer from transferring to transferred party only by handing over the technology transfer documentation.

It is recommended that the both parties should cooperate to implement technology education, training and validations at facilities where the transferred technology is actually used.

5.5 Manufacturing Related Documents Including Drug Product Standard Code

The transferred party should compile documents such as Drug Product Standard Code necessary for manufacturing, various standards and validation plans/reports after the completion of technology transfer. While the transferred party is responsible for compiling these documents, the transferred party should obtain conformation by the transferring party as appropriate.

5.6 Verification of Results of Technology Transfer

After the completion of technology transfer and before the start of manufacturing of the product, the transferring party should verify with appropriate methods such as product testing and audit that the product manufactured after the technology transfer meets the predetermined quality, and should maintain records of the results.

6. Examples of Technical Information to be Contained in Technology Transfer Documentation

The 1st to 5th chapters indicate basic concept of technology transfer, related items, and transfer procedures. This chapter exemplifies detailed understanding and contents of technical information to be contained in the technology transfer documentation. This chapter is classified into four sections, that is, facilities and equipments, test methods, drug substances, and drug products, for the sake of convenience; however, it is not recommended to use this classification in case of actual technology transfer.

6.1 Technical Information of Facilities and Equipments

For technology transfer, technical information of products as well as those of manufacturing facilities and equipments are important. To establish facilities and equipments conforming to GMP, it is essential to obtain and understand information from R&D process so that quality assurance of subject drugs can be secured and the facilities and equipments can comply with required conditions for manufacturing. For this purpose, the following technical information should be transferred.

- A person in charge of research and development should clarify considerations of GMP compliance specific to manufacturing methods (manufacturing processes) of the drug, and present them to a facility and equipment department.
- A person in charge of facility and equipment should establish facilities and equipments reflecting the above considerations, clarify details of the establishment and operational considerations of those facilities and equipments, and present them to a manufacturing department.
- A manufacturer should fully understand the above information, implement validations, perform appropriate operations and controls in conformity to the established facilities and equipments, and records results of operations and controls.

6.1.1 Technical Information to Establish New Facilities and Equipments

To establish new facilities and equipments in conformity to manufacturing of the drug, the facility and equipment department should set up required specifications (so called objectives) based on considerations presented by the R&D department, and realize functions in view of considerations specific to the facilities and equipments. In this regard, some functions may be combined, and it is required to prepare definite rationale for establishing functions. To comply with GMP, it is prerequisite to prepare documents of processes through specification decision and realization of functions as well as qualification evaluation, which can be explained to the third party (so called design qualification) as technical information.

Information Necessary for the Establishment of Facilities and Equipments

Information necessary for the establishment of facilities and equipments in conformity to GMP are classified into the following three categories.

- 1) Required Functions of facilities and equipments necessary for quality assurance of the drug
- 2) Required functions of facilities and equipments specific to manufacturing methods (manufacturing processes)
- 3) Basic required functions necessary for GMP compliance such as prevention of contamination, and human failures, etc.

Regarding 1) and 2), the person in charge of research and development should extract information affecting facilities and equipments from results of quality design during drug development (information on composition, manufacturing methods and specification), review results of scale-up and quality variability factors during possible pilot research, fully understand them and present documents containing clarified considerations of GMP compliance specific to subject drugs and manufacturing methods (manufacturing processes) to the person in charge of facility and equipment.

The person in charge of facility and equipment should document interpretations of the above information in forms such as “quality requirement specification” and present the documentation to the person in charge of research and development to confirm each other. The both persons should clarify differences of each thought by conforming

documents prepared from their own perspectives, and establish certain input data of facility and equipment establishment by obtaining necessary or insufficient evidence data, extracting insufficient data, and feeding back them to the R&D department.

Concerning 3), information can be collected by sorting out and reviewing GMP requirements for properties of the drug and manufacturing methods and organization of facilities and equipments. Degree of contamination and acceptable contamination level of the subject drugs and acceptable limit of residues are important to determine prevention level of contamination and cleaning methods at the facilities and equipments. Since policies on facilities and equipments such as multi-item production level and automatic production level may have a great impact on granting levels to facilities and equipments regarding prevention for human failures such as cross-contamination or mix-up, measures should be taken in view of properties of drugs and manufacturing methods which are to be used at the facilities and equipments to be established.

Information on the Establishment of Facilities and Equipments

Establishing facilities and equipments includes actions to upgrade facilities and equipments to be functions for achieving established objectives (required specifications), plan and design details while reflecting considerations specific to the facilities and equipments, construct them in time for the start of manufacturing, and perform qualification evaluation upon the trial operation, while it is important to transfer results of the establishment of facilities and equipments to the drug manufacturer so that the manufacturer can implement validations and manufacturing.

It is important for GMP compliance to shape into documents the achievements of series of activities (design, procurement, building, construction, trial operation, etc.) from initial stages of establishment (plan and design), the trial operation through qualification evaluation, and present them to the third party.

6.1.2 Technical Information When Applied to Established Facilities and Equipments

The drug is often manufactured in existing facilities and equipments. Although there are limitations attributable to the characteristics of the existing facilities and equipments, technical documents should be prepared to demonstrate that those facilities and equipments meet required specifications for quality assurance. Basic contents of the technical documents are similar to those of new facilities and equipments, while only difference is documentation method.

Information necessary for the establishment of existing facilities and equipments are classified into the following three categories as in the case of the new facilities and equipments.

- 1) Required functions of facilities and equipments necessary for quality assurance of the drug
- 2) Required functions of facilities and equipments specific to manufacturing methods (manufacturing processes)
- 3) Basic required functions necessary for GMP compliance such as prevention of contamination, and human failures, etc.

Concerning considerations of applications to existing facilities and equipments in 1) and 2), existing functions should be clarified, and it should be verified that the functions are maintained by maintenance and inspection including routine monitoring. Then, activities are required to compare documents such as “quality requirement specification” prepared as in the case of input information of new facilities and equipments with existing functions and maintenance conditions in the existing facilities and equipments, and identify differences between them. If there are any differences, input information should be realigned by feedback of necessary and insufficient evidence data and other required information to the R&D department.

Regarding 3), activities are required to compare properties of facilities and equipments such as multi-item production level and automatic production level of the existing facilities and equipments as well as granting levels to facilities and equipments regarding prevention for human failures such as cross-contamination or mix-up with conditions for quality assurance attributable to properties of subject drugs and manufacturing methods, and to clarify differences between them. If there are any differences, measures should be taken as in the cases of 1) and 2).

6.2 Technology Transfer of Test Methods

This chapter exemplifies items to be included in the development report and the technology transfer plan both of

which are important to technology transfer of test methods, and describe general concepts.

6.2.1 Development Report of Test Methods

The main objective of documenting development report of test methods is to make quality assurance of drugs more secured one by appropriately transferring technical information accumulated at each stage from design of test methods through those implementation between various departments (organizations).

Therefore, it is desirable that the development report should include details of test methods, information related to drug properties such as physicochemical properties, biological properties, and safety information, background of development of the test methods and rationale for the establishment, and validity and rationale for specifications from early research and development phase to manufacturing.

Specifications and Test Methods

Test methods subject to technology transfer include the following.

- Test methods for drug substances
- Test methods for drug products
- Test methods for raw materials and labeling and packaging material
- Test methods for in-process tests
- Test methods for drug residue tests
- Test methods of various tests concerning environmental load (waste and wastewater treatment, etc.)

Rational for Specifications and Background

Especially for historic records of specifications of contents, impurities, and degradation products, rationales for their establishment and changes should be included.

Results of Validations

Results of analytical validations for established test methods should be described.

Development History of Important Test Methods (Development Report on Test Methods)

Concerning test methods necessary for the evaluation of product quality and important attributes, development and change histories including their rationales should be described. The test methods include the followings.

- Test methods to measure contents and organic impurities
- Test methods to measure residual solvents and volatile compounds
- Dissolution tests for oral solid drug products
- Test methods to measure residual and mixed minerals in drug substances such as metals
- Test methods to evaluate physicochemical properties of drug substances and drug products such as polymorphism and hygroscopicity

It is especially useful to describe in detail significant operating conditions considered to affect test results (including items concerning test equipments, reagents and test solutions, and reference standards) in relation to developmental history of tests so that transferred party can effectively understand transferred information and attain its technology as well as the description may contribute to future modification of test methods.

Developmental history of already established test methods specified in pharmacopoeia, etc. need not to be described; however, it is required to indicate rationale for adopting the test methods as well as that the test methods may apply to the samples to be analyzed.

Summary of Test Results (Summary of Batch Analysis)

Summary of test results of batches used to develop test methods described in the development report should be described as chart including references to raw data.

Reference Standards

Reference standards to be used in tests of subject substances (drug substances, chemically related substances, etc.) should be described. The description should include methods of manufacturing, purification, evaluation for the purity and quality, and storage.

Other information

Items other than the above such as information of drug substances and drug products (properties, stability, manufacturing methods, and formula, background of drug development, containers, etc.) should be described if necessary. If those information are described in the Common Technical Document (CTD), references to raw data should be included.

6.2.2 Technology Transfer Plan of Test Methods

For technology transfer of test methods, it is required to clarify validation range and acceptance criteria of conformity of technology transfer regarding individual test methods to be transferred. The validation range (e.g. full validations, reproducibility, etc.) should be judged on the basis of results of evaluation of technologies, facilities and equipments of transferred party, and the range may be influenced by information to be contained in the technology transfer documentation.

For comparative evaluation of test results, samples (including dose range, number of batches, etc.), specific test methods and evaluation methods to be used in the transferring and transferred parties should be specified.

Acceptance criteria should be established for each test method of subject items on the basis of accumulated test results of the past and analytical validation data, and rationales for the acceptance criteria should be clearly described.

Technical information to be described in or attached to the technology transfer plan (including references to the development report) are shown as follows.

Information of Raw Materials

- Summary including physical and chemical properties and stability
 - Name and structural formula
 - Stability data
- Specifications and test methods
 - Specific test methods and specifications
 - Change history of specifications and test methods and its rationale
 - Results of analytical validation
- List of reference standards (Test results should be attached.)
- Information of toxicity and safety for laboratory use
- List of subject samples for comparative evaluation and their test results

Information of Drug Substances

- Summary including physicochemical properties and stability
 - Name and structural formula
 - Elucidation of chemical structure
 - Possible isomers
 - Stability data (including severe test data)
- Batch records
 - Chemical synthesis methods of subject batches
 - Analytical data of batches
 - Impurity profile of representative batch
- Specifications and test methods
 - Specific test methods and specifications (including items related to efficacy such as particle size distribution, polymorphism, crystallinity, and hygroscopicity)
 - Change history of specifications and test methods and their rationales
 - Results of analytical method validation
- List of reference standards (Test results should be attached.)
- Development report on test methods (Interim report is acceptable depending on development phases.)
- Information of toxicity and stability for laboratory use
- List of subject samples for comparative evaluation and their test results

Information of Drug Products

- Summary including formula and stability
 - Active ingredients and contents

- Elucidation of decomposition mechanism and products
- Stability data (including severe test data)
- Storage conditions and expiry date (if established)
- Analytical data of batches
- Specifications and test methods
 - Specific test methods and specifications (including items related to efficacy such as particle size distribution, dissolution)
 - Change history of specifications and test methods and its rationale
 - Results of analytical method validation
- List of reference standards (Test results should be attached.)
- Development report on test methods (Interim report is acceptable depending on development phases.)
- Information of safety for laboratory use
- List of subject samples for comparative evaluation and their test results

Information on Implementation of Technology Transfer

- Persons in charge of planning, checking and settlement of technology transfer
- Test methods
- Objectives
- Persons in charge of transferring and transferred parties
- Training plan (including explanation of test methods and demonstration)
- Plan of comparative evaluation study
 - Samples: Lot No. (including rationale for the number of lots), storage condition during test, and handling after the completion of the test (disposal or return to the transferred party, etc.)
 - Test period
 - Number of repeated tests
 - Handling of data (Handling method)
 - Retest and handling of outlier
 - Acceptance criteria
 - Storage of raw data (storage department, storage place, and duration, etc.)
 - Judge (person in charge of judgment in the transferring party)

6.3 Technology Transfer of Drug Substances

During R&D processes prior to technology transfer of drug substances, information indicated in 6.3.1 to 6.3.3 should be collected, and based on these information, technology transfer documentation including those indicated from 6.3.4 onward should be prepared.

6.3.1 Information to be Collected During Quality Design (Research Phase)

Items Concerning Raw Materials, Intermediates and Drug Substances

Items Concerning Raw Materials, Intermediates and Drug Substances

- Impurity profile and information on residual solvents (structure of impurities and route of synthesis)
- Information on descriptions of crystals of drug substances (crystallization, salt and properties of powders)
- Information on stability and description (raw materials, drug substances (including packaged drug substances), intermediates, solutions, crystallized solution, and humid crystals)
- Information on safety of drug substances, intermediates, and raw materials (Material Safety Data Sheet (MSDS))
- Information on animal origins of raw materials, etc.
- Information on packaging materials and storage methods (quality of packaging materials, storage temperature, and humidity)
- Expiry and retest dating
- Information on reference standards and seed crystals (method of dispensing, specifications and test methods, and storage methods)

Items Concerning Manufacturing Methods

- Information on manufacturing methods (synthetic routes and purification methods)
- Information on operating conditions (control parameters and acceptable range)
- Information on important processes and parameters (identification of processes and parameters which will

- affect quality)
- Information on in-process test
- Information on rework and reprocessing (processes and methods)
- Basic data concerning manufacture (properties, heat release rate, reaction rate, and solubility, etc.)
- Data concerning environment and safety (environmental load and process safety)

Items Concerning Facilities and Equipments

- Information on equipment cleaning (cleaning methods, cleaning solvents, and sampling methods)
- Information on facilities (selection of materials, capacity, and equipment types, and necessity of special equipments)

Items Concerning Test Methods and Specifications

- Information on specifications and test methods of drug substances, intermediates, and raw materials (physicochemical, microbiological, pyrogenic substances and physicochemical properties, etc.)
- Validations for test methods of drug substances and intermediates

6.3.2 Items to be Checked in the Review of Scale-up

Manufacturing processes of drug substances often involve handling of unstable chemical substances, and they have characteristics accompanied with chemical changes. Therefore, scale-up should be considered with much attention to prediction of handling period for each operational unit and stability of subject compounds during operation, and conditions of scale-up should be established.

Also, since factors of equipments may have significant influence on qualities regarding scale dependent parameters of operational parameters, considerations should be given in this regard.

Items to be confirmed in reviewing scale-up of reaction and crystallization processes are shown as follows:

Items to be Confirmed in Reviewing Scale-Up of Reaction Processes

- Reproducibility of temperature changes and its effects (effects of delay in temperature up and down on quality)
- Effects of churning in heterogeneous and semi-batch reactions (formations of concentration distribution and diffusion-controlled zone)
- Prediction and effect of operation period of consecutive reaction or exothermic reaction in semi-batch reactors (extension of operation period due to insufficient capacity of facilities and its effects on quality)
- Balance between heat release rate and heat dissipation capacity (temperature changes of exothermic reaction and its effects)
- Effects of facilities (validity of required capacity of utility, temperature distribution, and effects of overheating of laminar film, etc.)
- Confirmation of fluctuations due to scale-up (phenomenon which did not appear in the laboratory and small-scale manufacturing)

Items to be Confirmed in Reviewing Scale-up of Crystallization Processes

- Effects of churning (effects on particle size and polymorphism, and selection of scale-up factors)
- Reproducibility of temperature changes (reproducibility of established temperature changes and effects on quality)
- Effects on facilities (temperature distribution, changes in flow condition, effects of local concentration distribution and temperature distribution, and supercooling of laminar film)
- Prediction of time for solid-liquid separation and its effects (stability of crystallized solution waiting for filtration)
- Confirmation of operability (problems at actual equipment levels such as crystallized solution emission, transfer, and churn load)

6.3.3 Elucidation of Quality Variability Factors

To elucidate quality variability factors, the following items should be reviewed during quality design through scale-up review.

Processes Affecting Quality

To identify processes which may affect quality of final drug substances, such as processes to generate final substances, structures with pharmacological activities, and processes that can remove residual impurities in drug

substances and processes where impurities unremoval in purification are generated.

Establishment of Important Parameters Affecting Quality

Among parameters controlling the above processes, those which may affect the quality of final drugs such as generation and elimination of impurities, and physiochemical properties of the final drug substances should be investigated as subjects to change control, and control ranges of parameters which affect the quality should be established as important parameters. The important parameters are subject to validation. Parameters not affecting the quality are not subject to validation, but their change histories should be recorded.

6.3.4 Development Report on Drug Substances

The development report should include the followings:

- Development history including different synthetic methods used to manufacture investigational drugs
- Finally determined chemical synthetic route
- Change history of processes
- Quality characteristics of manufactured batches
- Specifications and test methods of intermediates and final drug substances
- Rationale for establishment of important processes
- Important parameters and control range
- References to existing reports and literatures, etc.

6.3.5 Technology Transfer Information of Drug Substances

Technology transfer information which transferring party should compile are shown as follows.

- **Information on Manufacturing Methods**
 - Development report on synthetic drug substances or those corresponding to the report
 - Plan and report of process validations
 - Items of in-process control: in-process test (test methods and specifications)
 - Investigation report on causes of abnormalities (if occurred)
- **Information on Cleaning Procedures**
 - Cleansing instructions
 - Record of cleaning
 - Plan and report of cleaning validation
 - Test methods and specifications
 - Validation report on analytical methods used for cleaning validations
- **Information on Analytical Methods**
 - Development report on analytical methods or those corresponding to the report
 - Test methods and specifications (raw materials, intermediates, final drug substances, and container/closure)
 - Validation report on release test methods
 - Stability test (validation report on analytical method, plan/report of stability test, container form, reference standard, and relevant reports)
 - Investigation report on causes of out-of-specification (OOS) test results (if occurred)
- **Information on Methods of Storage/Transportation**
 - Container/closure system
 - Expiry and retest dating
 - Conditions of transportation
 - Information on sensitivity to temperature, humidity, light, and oxygen
 - Instructions of temperature monitoring for drug substances which need cold storage
- **Information on Facilities**
 - Structural materials

- Category and type of main facility
- Important facilities for final processing that may affect physicochemical properties (particle size and surface conditions, etc.)
- **Information on Environmental Management (Drug Substances for Injection and Highly Active Substances, etc.)**
 - Clean area (temperature, humidity, microorganism monitoring, airborne particles, and control of differential pressure)
 - Information on safety
 - Safety information of raw materials, intermediates, and final drug substances
 - Information on degradability
 - Information on dust explosion
 - Information on deflagration
- **Information on Industrial Hygiene/Occupational Health**
 - Protection for operators
 - Protection for products

6.4 Technology Transfer of Drug Products

During R&D processes prior to technology transfer of drug products, information indicated in 6.4.1 to 6.4.3 should be collected, and based on these information, technology transfer documentation including those indicated from 6.4.4 onward should be prepared.

6.4.1 Information to be Collected During Quality Design (Research Phase) (Oral solid formulation)

Items Concerning Compositions

- Physicochemical properties of drug substances (crystallinity, melting point, dissolution, distribution coefficient, hygroscopicity, degradant, impurities, particle size, wettability, moisture, handling, etc.)
- Biopharmaceutical properties of drug substances (hygroscopicity and dose dependency, etc.)
- Stability of drug substances (temperature, humidity, and light)
- Compatibility of drug substances with inactive ingredients
- Formula design of drug products in clinical phases and its rationale (hygroscopicity, dose dependency, etc.)
- Formula design of final drug products and its rationale (reasons for combining individual inactive ingredients and validities)
- Change histories of formula during development and relations with final drug products
- Packaging design
- Stability of drug products (temperature, humidity, and light)
- Information on drug substances, inactive ingredients, and packaging materials (specifications, manufacturers, Drug Master File, MSDS, etc.)
- Information on origins of drug substances and inactive ingredients (raw materials of animal origins, etc.)

Items Concerning Manufacturing Methods

- Information on selection of dosage forms (direct compressed tablets, dry and wet granulation, agitation fluidized bed granulation, uncoated tablets, coated tablets, properties of inactive ingredients, etc.)
- Information on manufacturing methods of drug products in clinical phases (manufacturing flows, manufacturing conditions, in-process control, etc.)
- Manufacturing methods of final prescribed drug products (manufacturing flows, manufacturing conditions, in-process control, scale-up, validation, etc.)
- Information on other important processes and manufacturing procedures (determination of granulation end-point, determination of mixing time with lubricants, cleaning methods, cleaning validation, etc.)

Items Concerning Facilities and Equipments

- Information on equipment cleaning (cleaning methods, cleaning solvents, sampling methods, etc.)
- Information on equipments (selection of materials, capacity and equipment types, necessity of special equipments, etc.)

Items Concerning Test Methods and Specifications

- Specifications and test methods of drug substances (physicochemical test, microbial test, etc.)
- Specifications and test methods of inactive ingredients (grade, physicochemical test, microbial test, etc.)
- Specifications and test methods of packaging materials (specifications, physicochemical test, microbial test, etc.)
- Acceptance criteria for product assessment (internal control specification based on stability, etc.) and specifications for application (approved specifications to ensure expiry date)
- Validation for test methods of drug substances and products

(Injectable Solutions (sterile drug products))**Items Concerning Compositions**

- Information on formula design (reasons for combining individual inactive ingredients and validities; pH, relations between inactive ingredients and stability, overages, etc.)
- Information on stability of drug substances (heat, light and oxygen)
- Information on safety of drug substances and raw materials (MSDS)
- Information on origins of drug substances and raw materials (raw materials of animal origins, etc.)
- Formula design of drug products in clinical phases and its rationale (dissolution, change histories of dosage forms, etc.)
- Formula design of final drug products and its rationale (reasons for combining individual inactive ingredients and validities)
- Disparities in quality between different lots of drug substances and raw materials, stability of lots of raw materials, and effects on impurities
- Basic documents to ensure sterilization and cleaning in view of composition
- Information on stability of drug products (heat, light, oscillation, and oxygen)
- Change histories of formula in the process of development and rationale to ensure equivalence

Items Concerning Manufacturing Methods

- Information on selection of dosage forms (solution, freeze dry or powder preparations; relations with stability)
- Information concerning rationale for container/closure system and its validity (effects on stability such as eluate from containers or closures, interactions between drug products and containers (absorbability), and sealing performance, etc.)
- Information on initial design of manufacturing methods (aseptic manipulation or final sterilization method; effects of heat sterilization on stability)
- Information on selection of process filters (absorbability, etc.)
- Process design and important processes (test items in important processes and specifications)
- Rationale for design to ensure sterilization and cleaning in view of manufacturing methods

Items Concerning Facilities and Equipments

- Information on equipment cleaning (cleaning methods, cleaning solvents, and sampling methods)
- Information on facilities (selection of materials, capacity, and equipment types, and necessity of special equipments)

Items Concerning Test Methods and Specifications

- Specifications and test methods of drug substances (physicochemical test, microbial test, pyrogenic substances, etc.)
- Specifications and test methods of inactive ingredients (physicochemical test, microbial test, pyrogenic substances, etc.)
- Specifications and test methods of container/closure system (physicochemical test, microbial test, pyrogenic substances, etc.)
- Specifications and test methods of packaging materials (specifications, etc.)
- Specifications and test methods of products (physicochemical test, microbial test, pyrogenic substances,

etc.)

- Specifications of shipment (internal control specifications in view of stability, etc.) and specifications of products (approval specifications to ensure expiry date)
- Validation of test methods of drug substances and products
- Reference standard and reference substance (dispensing methods, specifications and test methods, and storage methods and stability, etc.)

6.4.2 Scale-up Validation and Detection of Quality Variability Factors (Development Phase)

(Oral solid formulation)

- Mixing conditions in mixing process of raw materials (uniformity of contents)
- Granulation conditions in granulation process (determination of granulation end-point, tablet hardness, and dissolution)
- Drying end-point in drying process (tablet hardness, compression problems, and stability)
- Mixing conditions in granulation mixing process (uniformity of contents)
- Mixing conditions in lubricant mixing process (tablet hardness, and dissolution)
- Time series fluctuations in tablet compressing process or filling process (tablet weight, tablet hardness, and uniformity of contents)
- Fluctuations due to raw materials (processes in manufacturers of raw materials and changes in material qualities, etc.)
- Fluctuations due to facilities (exchange of consumable parts, changes of equipments, and changes in manufacturing processes including automated processes, etc.)

(Injectable Solutions (Sterile Drug Products))

- Dispersion of final moisture and contents between different shelves and/or within the same shelf in freeze drying process
- Changes and dispersion in water content in rubber closures of vials
- Dispersion of contents and impurities, etc. after the final sterilization
- Concerning fluctuations of raw materials, dispersion in particle size which may affect solubility, peroxide which affect stability, and viable cell counts which affect abacterial situations should be evaluated.
- Concerning facilities, effects of temperature distribution within facilities and effects of changes in important parameters on product quality should be evaluated. Especially for drugs that are highly sensitive to oxygen, water and light as well as preparations with minute content such as protein, relations between conditions of facility operations and stability should be fully understood.
- Validity of solution preparation process (uniformity of contents of all raw materials and stability in solution conditions, etc.)
- Validity of sterile filtration processes (completeness, conformity of filtration process and drug solution, stability of filtrated drug solution, and initial disposal rate, etc.)
- Microorganism capture efficiency of barrier filter (validation data)
- Rationale for cleaning conditions in the container/closure system (cleaning validation, drying and residual moisture, etc.)
- Rationale for sterilization conditions in the container/closure system (validations of sterilization and pyrogenic substances removal, residual moisture of closures, etc.)
- Validity of filling processes (accuracy of filling, conformity of filling system and drug solution, stability of filled drug solution, and initial disposal rate, etc.)
- Validity of freeze-dry process (freeze-dry conditions, uniformity of inside of freeze-dry equipment, water contents and stability, etc.)
- Validity of capping and metal sealing (replacement rate of inactive gas in a head space and stability of the inactive gas)
- Validity of final sterilization process (validation of sterilization)
- Validity of test process (development of test process, types of foreign substances, and accuracy of test)
- Development of cleaning methods of facilities and validation of cleaning

- Development of sterilization methods of facilities and validation of sterilization
- Validity of in-process control of sterile operation (culture media filling test, etc.)
- Methods of environmental management and monitoring data (methods of sterilization)
- Control parameters of important processes and process test data
- Data of all batches including those used in non-clinical and clinical studies

6.4.3 Development Report

The development report should contain the following elements.

- Rationale for the selection of dosage forms
- Explanation of formula design
- Change histories of compositions and manufacturing methods
- Consideration of scale-up
- Finally determined manufacturing methods
- Change histories of manufacturing processes
- Quality characteristics of manufactured batches
- Specifications and test methods of final drug products
- Identification of important manufacturing processes and rationale for their control parameters (parameters)
- Control parameters (parameters) in each process and their set values
- References to existing reports and literatures, etc.

6.4.4 Information of Technology Transfer of Drug Products

Cases considered as information of technology transfer are shown as follows.

Information on Manufacturing Methods

- Development report on drug products or those corresponding to the report
- Master batch records of manufacturing (format of manufacturing instructions/records)
- Manufacturing records (batches for establishment of specifications for approval and validation batches, etc.)
- Plan and report of process validations
- Items of in-process control: in-process test (test methods and specifications)
- Investigation report on causes of abnormalities (if occurred)

Information on Test and Packaging

- Test procedures (accuracy of test and limit of defects)
- Container/closure system
- Specifications of primary packaging (moisture proof, light blocking, etc.) and conformity to packaging materials

Information on Cleaning Procedures

- Cleaning instructions
- Plan and report of cleaning validations
- Test methods and specifications
- Validation report on analytical methods used for cleaning validations

Information on Analytical Methods

- Development report on analytical methods or those corresponding to the report
- Test methods and specifications (inactive ingredients, drug substances, final drug products, container/closure system, and packaging materials)
- Validation report on release test methods
- Stability tests (validation report on analytical methods, plan and report of stability tests, packaging conditions, reference standards and relevant reports)
- Investigation report on causes of out-of-specification (OOS) test results (if occurred)

Information on Storage and Transportation Methods

- Specifications of secondary packaging
- Expiry date
- Transportation conditions and tests
- Information on sensitivity to temperature, humidity, and light
- Instructions of temperature monitoring for drug products which need cold storage

Information on Facilities

- Structural materials
- Category and type of main facility

Information on Environmental Management

- Clean area (temperature and humidity, microorganism monitoring, airborne particles, and control of differential pressure)
- Information on safety
 - Safety information of hazardous raw materials, drug substances, and final drug products

Information on Industrial Hygiene/Safety

- Protection for operators
- Protection for products

7. Points of Concern For Preparing Technology Transfer Documentation

For smooth technology transfer, information related to the transfer and necessary items should be appropriately documented and recorded. In this regard, summaries are already described in the above; however, it is recommended to prepare the following documents.

- 1) Documents to clarify applicable technologies, burden shares, responsibilities, and approval systems, etc. concerning the technology transfer (written agreements, memorandums, etc.)
- 2) Organizations of technology transfer (at both of transferring and transferred parties)
- 3) Development report
- 4) Product specifications
- 5) Technology transfer plan
- 6) Technology transfer report

Concerning 1), 3) and 4) which need comments on descriptions, this chapter will show details of items to describe, and points of concern for description.

7.1 Documents To Clarify Applicable Technologies, Burden Shares, Responsibility System, etc. Concerning Technology Transfer

The following chart shows details of items to be described in documents clarifying applicable technologies, burden shares, responsibilities, and approval system, etc. concerning technology transfer, and points of concern for description. Any types and forms of the documents are acceptable if they include the items in the following chart, and no duplications of the items stipulated or described in detail in other technology transfer documents are required.

Items	Details	Remarks
1 Organizations	Organizational framework, organization chart, department (person) in charge, and separation between manufacturing and quality departments	
2 Supervisor	Clarify supervisor of technology transfer	

	(manufacturing supervisor is acceptable) and his/her responsibilities.	
3 Responsibility system	Clarify organization and its responsibilities, document control system, persons in charge of manufacturing department and quality department.	
4 Structure and equipments	Maintenance, inspection and calibration of manufacturing facilities and equipments, antipollution measurements, etc.	
5 Documentation and records	Clarify all technology transfer documentations. Describe control methods of documentation and records, and storage period.	SOP list may substitute the documentation and records, if implemented under the control of GMP; however, "cleaning categories" and "cleaning methods of facilities and equipments" should be described in detail.
6 Manufacturing control	Standard manufacturing procedure, and manufacturing instructions and records Industrial hygiene control methods of buildings and facilities Industrial hygiene control methods of operators Report on manufacturing control and quality control Control methods of raw materials, intermediates, products, etc.	For existing products, existing GMP documents can be used.
7 Quality control	Determination of test results and report methods Control method of reference samples Maintenance and inspection of pilot facilities and equipments Control methods of test results Control methods of reference standards, reagents, and test solutions, etc. Handling of retest	
8 Shipment	Control methods of shipment (procedures and judge)	
9 Validation	Organization for validation Describe communication and confirmation methods, discussion, and approval, etc. concerning validations. Conformation of results of installation qualification	
10 Change control	Specify handling of change controls in advance.	
11 Deviations	Clarify handling of abnormalities, deviations, and out-of-specification (OOS) test results.	
12 Other necessary items		
12.1 Persons in charge	Describe persons in charge at both parties.	
12.2 Periodic report	Describe formats of periodic reports, such as annual report.	
12.3 Changes in technology transfer documentation such as required specifications and product specifications	Describe communication and confirmation methods and necessary formats for changes.	
12.4 Storage of technology transfer documentation such as required specifications	Specify storage period and disposal time.	

and product specifications		
12.5 Revision history	Store revision history.	
12.6 Others	Handling of not specified items	

7.2 Technical information to be Described in the Development Report, Product Specification, etc.

The following chart shows technical information and points of concern to be described in documents such as the development report, product specification, etc. of drug substances.

Items	Details	Remarks
Development report of drug substances		
1 Change history of process design and manufacturing methods during development	<ul style="list-style-type: none"> History of manufacturing methods of drug substance used in Phase I, II and III studies, etc., bioequivalence of drug substance quality, and justification for starting materials and manufacturing methods, etc. 	
2 Information on final product		
2.1 Product name	<ul style="list-style-type: none"> Scheduled brand name in the certificate of approval 	<ul style="list-style-type: none"> Not necessary, if not yet determined.
2.2 Specifications and test methods	<ul style="list-style-type: none"> Describe all of specifications and test methods described in the certificate of approval. 	<ul style="list-style-type: none"> Describe agreed specifications as well, if any.
2.2.1 Raw materials	<ul style="list-style-type: none"> Specifications and test methods of raw materials to be used 	<ul style="list-style-type: none"> Clarify suppliers. Test results
2.2.2 Container and closure	<ul style="list-style-type: none"> Specifications and test methods of container and closure to be used 	<ul style="list-style-type: none"> Clarify suppliers. Test results
2.2.3 Packaging and labeling materials	<ul style="list-style-type: none"> Specifications and test methods of packaging and labeling materials to be used 	<ul style="list-style-type: none"> Clarify suppliers. Test results
2.2.4 Intermediates	<ul style="list-style-type: none"> Sampling procedures, specifications and test methods of intermediates 	<ul style="list-style-type: none"> For intermediates not to be isolated, description can be omitted, provided that the rationale should be described in the development report. Describe added specifications for trading (such as acceptance criteria for product assessment), if any.
2.2.5 Drug substance	<ul style="list-style-type: none"> Sampling procedures, specifications and test methods of drug substance 	<ul style="list-style-type: none"> Describe added specifications for trading (such as acceptance criteria for product assessment), if any.
2.2.6 Form of test results	<ul style="list-style-type: none"> Attach sample form of manufacturer. 	
2.3 Manufacturing methods and procedures, etc.	<ul style="list-style-type: none"> Describe manufacturing flows, manufacturing procedures, in-process control, and required facility capacity, etc. as detail as possible. 	<ul style="list-style-type: none"> Describe scientific evidence based data (including stability data to determine unit operating conditions) in the development report. Confirm important parameters at the time of predictive validation and change validation.
2.4 Packaging methods and procedures, etc.	<ul style="list-style-type: none"> Describe packaging methods and procedures. 	
2.5 Storage conditions	<ul style="list-style-type: none"> Describe storage conditions of raw materials, intermediates, and drug substances. 	<ul style="list-style-type: none"> Temperature and humidity ranges, light, and container in use Describe evidence data in the development report.

2.6 Expiry date	<ul style="list-style-type: none"> Expiry dates of raw materials, intermediates, and drug substances 	<ul style="list-style-type: none"> Describe evidence data in the development report. Describe stability data as much as possible.
2.7 Transportation conditions	<ul style="list-style-type: none"> Describe transportation conditions and cautions for transportation of raw materials, intermediates and drug substances. 	
2.8 Information on safety	<ul style="list-style-type: none"> Describe information on safety of raw materials, intermediates, and drug substances. Describe information on safety of each unit operation (reaction and post-treatment, etc.). 	<ul style="list-style-type: none"> Attach MSDS as much as possible. Attach safety data of processes as much as possible.
3 Stability		
3.1 Raw materials		<ul style="list-style-type: none"> Describe physicochemical safety (temperature, humidity, and light). Describe microbiological safety.
3.2 Intermediates		
3.3 Drug substances		
4 Information for environmental assessment	<ul style="list-style-type: none"> Describe influence on environment. Describe necessary data for assessment. 	<ul style="list-style-type: none"> Describe waste disposal methods as well.

The following chart shows technical information and points of concern of drug products to be described in documents such as the development report, and product specification, etc.

Items	Details	Remarks
Development report of drug products		
1 Properties of drug substances	<ul style="list-style-type: none"> Physicochemical and pharmaceutical properties necessary for drug product design (such as dissolution, particle size, hygroscopicity, incompatibility, absorbability and stability, etc.) 	Describe properties concerning formula to be transferred.
2 Change history of formula design and manufacturing methods during development *	<ul style="list-style-type: none"> History of formula and manufacturing methods of drug products used for non-clinical and clinical studies, bioequivalence between different drug products, rational for formula of final drug products and the manufacturing methods, etc. 	Describe properties concerning formula to be transferred.
3 Information on final drug product		
3.1 Product name	<ul style="list-style-type: none"> Scheduled brand name in the certificate of approval 	<ul style="list-style-type: none"> Not necessary, if not yet determined.
3.2 Indications and dosage and administration	<ul style="list-style-type: none"> Indications in the certificate of approval 	<ul style="list-style-type: none"> Not necessary, if not yet determined.
3.3 Ingredients/contents	<ul style="list-style-type: none"> Ingredients/contents in the certificate of approval 	<ul style="list-style-type: none"> In case of revision of contents, its rationale should be included.
3.4 Specifications and test methods	<ul style="list-style-type: none"> Describe all specifications and test methods in the certificate of approval. 	<ul style="list-style-type: none"> Describe agreed specifications, if any.
3.4.1 Drug substances	<ul style="list-style-type: none"> Specifications and test methods of drug substances to be used 	<ul style="list-style-type: none"> Clarify suppliers. Master file registration No., if any. Test report
3.4.2 Inactive ingredients	<ul style="list-style-type: none"> Specifications and test methods of inactive ingredients to be used 	<ul style="list-style-type: none"> Clarify suppliers. Master file registration No., if any. Test report
3.4.3 Primary packaging materials	<ul style="list-style-type: none"> Specifications and test methods of primary packaging materials 	<ul style="list-style-type: none"> Clarify suppliers. Master file registration No., if any. Test report
3.4.4 Secondary packaging materials	<ul style="list-style-type: none"> Specifications and test methods of secondary packaging materials 	
3.4.5 Intermediates	<ul style="list-style-type: none"> Specifications and test methods of intermediates 	
3.4.6 Final products	<ul style="list-style-type: none"> Specifications and test methods of final products 	<ul style="list-style-type: none"> Describe applied specifications for application and/or specifications before shipment, if any.
3.4.7 Forms of test results	<ul style="list-style-type: none"> Attach sample form of an manufacturer. 	
3.5 Manufacturing methods and manufacturing procedures, etc.	<ul style="list-style-type: none"> Describe manufacturing flows, manufacturing procedures, and in-process control as detail as possible. 	
3.6 Packaging methods and packaging procedures, etc.	<ul style="list-style-type: none"> Describe packaging flows, packaging procedures, and in-process control as detail as possible. 	
3.7 Storage conditions	<ul style="list-style-type: none"> Storage conditions of drug substances, inactive ingredients, primary packaging materials, secondary packaging materials, intermediates, and final products 	<ul style="list-style-type: none"> Temperature and humidity ranges, light and container in use

3.8 Expiry and retest dating	<ul style="list-style-type: none"> Expiry date of drug substances, inactive ingredients, primary packaging materials, secondary packaging materials, intermediates, and final products 	<ul style="list-style-type: none"> Describe rationale for expiry and retest dating. Describe stability data as much as possible.
3.9 Transportation conditions	<ul style="list-style-type: none"> Describe transportation conditions of drug substances, inactive ingredients, primary packaging materials, secondary packaging materials, intermediates, and final products, and cautions for their transportation. 	
3.10 Information on safety	<ul style="list-style-type: none"> Describe information on safety of drug substances, inactive ingredients, primary packaging materials, secondary packaging materials, intermediates and final products. 	<ul style="list-style-type: none"> Attach MSDS as much as possible.
4 Stability		
4.1 Drug substance		<ul style="list-style-type: none"> Describe physicochemical safety (temperature, humidity, and light). Describe microbiological safety as well.
4.2 Intermediates		
4.3 Final products		
5 Environmental assessment	<ul style="list-style-type: none"> Clarify information necessary for environmental assessment, and if there is no environmental impact, clarify “no environmental impact.” 	<ul style="list-style-type: none"> Describe waste disposal methods as well.

ISPE Prague Conferences

Marriott Hotel • Prague, Czech Republic
19 > 23 September 2005

Preliminary
Programme

Early bird deadline:
5 August 2005

19-21 September

Global Regulatory GMP Conference – New Regulatory Initiatives
and Achieving International Harmonisation

20-21 September

- Barrier Isolation Technology Forum
- Biopharmaceutical Facilities and Case Studies

22 September

- GAMP® Good Practice Guide for Laboratory Systems Validation

22-23 September

- Planning Strategies for the Effective Management of Global Investigational Medicinal Products (IMP) Supplies in the 21st Century
- The Challenges and Opportunities in Future Science-Based API Manufacture



23 September

- GAMP 4 - Maintaining the Validated State of Computer Systems

The Conference will also include **networking opportunities, social activities** and a **Table Top exhibition**.



Global Regulatory GMP Conference – New Regulatory

19-21 September 2005

Conference Leaders

Charles Hoiberg, Pfizer, USA

Michael Wierer, European Directorate for Quality Medicines Council of Europe

Conference Description

The globalisation of the pharmaceutical industry continues to progress at a rapid pace, adding to the complexity of meeting regulatory requirements and expectations.

This inaugural ISPE Global Regulatory GMP Conference is a key event which will bring together regulators and the pharmaceutical industry from around the world. Leading regulators and senior industry professionals from Europe, USA and Asia will present their insights and address a variety of issues affecting the industry now and in the future.

The Conference will focus on GMPs, manufacturing and inspections, as they pertain to new regulatory initiatives and harmonised international standards. You will have a unique opportunity to gain a competitive edge in your organisation by keeping abreast of the rapidly changing regulatory environment.

On Day Three, delegates will participate in Round Table Discussion Forums on a variety of topics resulting from the previous two days. Here, you will have the opportunity to interact with regulatory and industry speakers and fellow delegates in a relaxed and lively manner, and ask questions which may not have been addressed in the previous two days.

Learning Objectives

At the conclusion of this conference, you will be able to:

- Describe the latest global GMP regulatory initiatives from Europe (EMA), USA (FDA) and Japan (MHLW)
- Understand the challenges of EU enlargement and new legislation
- Apply the strategies of achieving international harmonisation in a multi-national business
- Appreciate the challenges of global GMP inspections from regulatory and industry perspectives
- Understand the roles and activities of the World Health Organisation (WHO), the Pharmaceutical Inspection Cooperation Scheme (PIC/S) and the International Standards Organisation (ISO) in the global environment

- Discuss the impact on the international arena of emerging pharmaceutical manufacture in Asia
- Update colleagues on the ICH process including Q8, Q9 and Q10
- Apply your insight of European industry experiences of Quality Systems implementation
- Describe the regulatory challenges of supplying Investigational Medicinal Products (IMPs) for global clinical trials
- Discuss and share experiences with fellow regulatory and industry speakers and delegates

Who Should Attend

All personnel in Production, QA, QC, Engineering, Validation, IT, Regulatory Affairs and Compliance in Primary, Secondary and Biopharmaceutical operations will find this conference of importance and value in the much changing global regulatory environment.

Individuals from global regulatory agencies will also benefit from attendance.

Initiatives and Achieving International Harmonisation



Tentative Agenda Topics

- European Regulatory GMP Perspective and Update
- Update on FDA GMP Initiatives
- Global GMP Harmonisation - A Japanese Perspective
- Global Challenges of an Expanded Europe
- WHO Initiatives Toward Globalisation
- PIC/S - A Catalyst for Harmonisation
- ICH Developments - Influence on the Global Environment
- Global Interfaces Between Regulators and Industry
- Challenges of Global GMP Inspections
- Quality Systems in Europe - An Industry Perspective
- Q7A and APIs - A Model for International Harmonisation
- Emerging Pharmaceutical Manufacture in Asia
- Regulatory Challenges of Supplying Investigational Medicinal Products for Global Trials - An Industry Perspective
- ISO/CEN Contamination Control Standards - Update and Relationship with GMPs
- A Regulator's Experiences with Global and MRA Inspections



Round Table Discussion Forums

(Wednesday, 21 September)

The Conference will include several opportunities for delegates to raise questions with the speakers after presentations and in the Panel Discussion sessions, and also to network with industry and regulatory delegates/speakers during the breaks and Networking Reception.

There will be three sessions as follows:

- 09.00 – 10.15
- 11.00 – 12.15
- 13.45 – 15.00

Speakers

Linda Broad, Pfizer, UK

Joseph Famulare, FDA, USA

Gordon Farquharson, Bovis LL Pharma, UK

Lothar Hartmann, Hoffman La Roche, Switzerland

Stuart Heir, Novartis, Switzerland

Yukio Hiyama, MHLW, Japan

Sabine Kopp, WHO, Switzerland

Ludevit Martinec, State Institute of Drug Control, Slovakia

Gordon Munro, Watson Pharma, USA

Gopal Nair, Grasp Enterprises, India

Jörg Neuhaus, Germany

Jean Louis Robert, Laboratoire National de Santé, Luxembourg

Kathy Wengel, Johnson and Johnson, Belgium

Representative from the European Medicines Agency (EMA)

Representative from PIC/S



Engineering Pharmaceutical Innovation



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- Affiliates/Chapters
- Committees
- Students
- Media

Certification

- Professional Certification Commission

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Regulatory

ISPE Global Regulatory GMP Conference

New Regulatory Initiatives and Achieving International Harmonization

19-21 September 2005 – Prague, Czech Republic

The inaugural ISPE Global Regulatory GMP Conference provided delegates the opportunity to hear presentations and insights from leading regulators and senior industry professionals from Europe, the USA, and Asia. The following articles address a variety of key issues affecting the industry now and in the future.

Full articles are available to ISPE Members only.

Global GMP Harmonization: A Japanese Perspective

Japan instituted sweeping changes to its Pharmaceutical Affairs Law (PAL) to bring it in line with Good Manufacturing Practices, International Conference on Harmonization (ICH), and quality standards in the western world. The changes include revision of its quality regulations, approval matters as they relate to manufacturing, pharmaceutical development, and GMP standards and related guidelines. "The new system is very similar to the Western system," said Yukio Hiyama, Division of Drugs, National Institute of Health Sciences, and Ministry of Health, Labour and Welfare (MHLW).

[ISPE Members read the full article...](#)

Harmonizing GMP Requirements – PIC/S Benefits the Global Pharmaceutical Industry

The strengths of the Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S) is its large membership, high criteria for joining, focus on training and the development and revision of GMP guides, according to Robert Tribe, a GMP consultant to regulatory authorities. "And the US Food and Drug Administration (FDA) is expected to apply to join PIC/S," he said.

[ISPE Members read the full article...](#)

Globalization and the World Health Organization (WHO)

The World Health Organization's (WHO) strategy over the past decades has been to harmonize pharmaceutical standards to ensure people everywhere have access to the essential medicine they need and that the medicines are safe, effective, and of good quality, said Dr. Sabine Kopp, of WHO's quality assurance and safety team. WHO has 192 Member states and headquarters and WHO's six regional offices work to achieve those goals.

[ISPE Members read the full article...](#)

Quality Systems Need to be Integrated – The FDA's Council on Pharmaceutical Quality has a Mission

When the FDA created the Council on Pharmaceutical Quality two years ago, its mission was to help the Agency modernize its regulations governing pharmaceutical manufacturing and product quality. The Council's report, issued in September 2004, is a starting point, not the end of the process and soon the results of the council's expert working groups would be available making it possible for the FDA to carry out the work it wants to do going forward. One goal identified was to develop a plan to rearrange FDA's drug quality program and expand it internationally.

[ISPE Members read the full article...](#)

The International Conference on Harmonization (ICH) – Progress Forward

Common standards make it easier to understand the assessment process in the three regions governed by the International Conference on Harmonization, which include Europe, the United States, and Japan. "The outcome of the International Conference on Harmonization is a very positive one and based on discussions from the three regions, industry, and regulatory, we managed to make substantial progress toward

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quality of medicinal products," Dr. Jean-Louis Robert, Laboratoire National de Sante', Service du Controle des Medicaments. "Even if at first sight it might look like higher requirements nevertheless they are scientifically sound."

[ISPE Members read the full article...](#)

European Regulatory GMP Perspective and Update

In the EU (European Commission and EMEA), there are basically two different procedures to initiate marketing authorizations, including: Mutual Recognition Agreements and centralized procedures. Both systems maintain the same quality, safety, and efficacy standards. "In the last year, one of the challenges of the enlarged EU was how to meet GMP standards throughout the 25 states," explained Dr. Jean-Louis Robert, Laboratoire National de Sante', Service du Controle des Medicaments.

[ISPE Members read the full article...](#)

A Regulator's Experience with Global and MRA Inspections

When Good Manufacturing Practices are harmonized flimsy excuses like "it used to be like this" will disappear as a defense when pharmaceutical companies learn that some aspect of their operations fall short. Though it will take "some time" to achieve harmonization of Good Manufacturing Practices (GMP), it is not possible to totally harmonize GMPs in every geographic location because local conditions may demand a modified approach according to Dr. Joerg Neuhaus, Bezirksregierung Koeln, Germany.

[ISPE Members read the full article...](#)