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).

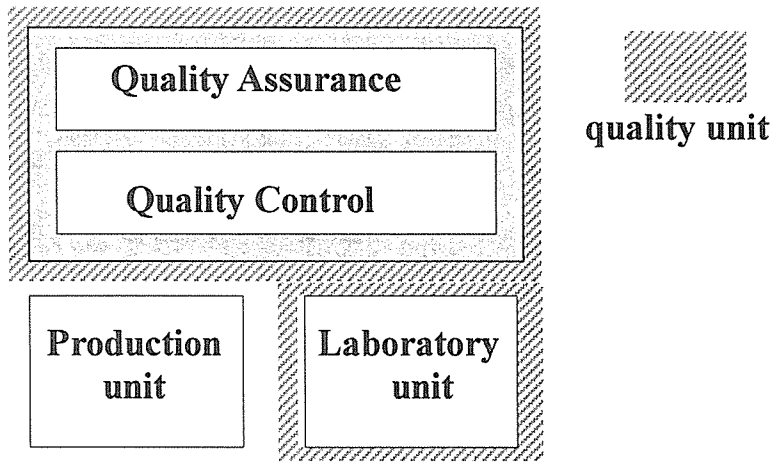
Although the GQP Ministerial Ordinance refers to the quality assurance unit of manufacturing distributors, in this guideline, the target to be considered is the role of quality assurance activities in the quality unit, assuming establishment of self-directed GMP systems of manufacturing sites (manufacturers).

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

2.22 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 predesignated" 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 dissembling 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 resign, 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