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 tabletting, 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, scrach, 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