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 devises/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.