7.51 Manufacturing operations should be conducted in a manner that will prevent contamination by materials other than the product.

7.52 Measures to prevent contamination should be taken for intermediate products being manufactured.

7.53 Methods for preventing contamination should be periodically inspected in accordance with the written procedures, etc.

7.6 Microbiological Contamination Control

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

8. Packaging and Labeling

8.1 General Matters

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

8.2 Control of Packaging Materials

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

8.3 Control of Labeling Materials

8.30 Access to the label storage areas should be limited to authorized personnel, except in the case where an equivalent level of control can be achieved by other methods.

8.31 Labels used on containers of drug products should include the name, the lot number and quantity of the products, as well as shelf life or expiration date, or retest date, and storage conditions where applicable.

8.32 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

8.33 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels which bear neither lot number nor other lot-related information should be retained and stored in a manner that prevents mix-ups and provides proper identification.

8.34 Obsolete and out-of-date labels should be destroyed.

8.35 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

8.36 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

8.37 A printed label, which is representative of those used, should be included in the batch production record.

8.4 Packaging and Labeling Operations

8.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

8.41 Prior to the start of packaging and labeling operations, it should be confirmed whether the building and facilities defined under the provision of Article 10, Item 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs are clean, and whether products, packaging/labeling materials and documents that are not required for the relevant operations do not remain in the work area for the relevant operations. The confirmation results should be documented and retained.

8.42 Packaging operations should be monitored to prevent contamination, cross-contamination, and mix-up, and should be physically and spatially separated from the operations related to other products. Labeling operations should be monitored to prevent mix-up, and should be physically and spatially separated from the operations related to other products.

8.43 Prior to the start of packaging and labeling operations, the production unit should confirm whether the name of products and packaging/labeling materials, the lot

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

8.44 The name and lot number of the product subject to packaging operations should be posted in a visible position in the packaging room and by the packaging process line.

8.45 In the case where samples collected from the packaging and labeling process lines for in-process testing/inspection are returned to the labeling process lines, the operations should follow the predefined procedures. In the case where the packaging and labeling operations are stopped due to the occurrence of an abnormality and then restarted, special investigations should be made, and operations should begin again only after approval by authorized personnel. The investigation results should be documented and retained.

8.46 In where case products became temporarily unidentifiable as a result of packaging operations, the subsequent process should be advanced as rapidly as possible until identifiable conditions are obtained. If prompt transfer of the operation to the next process is difficult, appropriate measures should be taken to prevent mix-up and labeling errors.

8.47 Products containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the packages have been opened during transport.

9. Storage and Release from Manufacturing Site

9.1 Storage Operations

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

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

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

9.2 Operations of Release from Manufacturing Site

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

9.21 It should be ensured that the contract carriers of products understand and comply with appropriate conditions of transport and storage.

9.22 If a potential risk to the quality of the products to be used for manufacturing at other manufacturing site has been found after release from the manufacturing site, immediate contact should be made with the receiving manufacturer.

10 Laboratory Control

10.1 General Control

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

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

10.11 Reagents and reference standards received should be controlled in accordance with written procedures, and should be labeled with the date of purchase, the expiration date, and where applicable, the date of seal opening. Test solutions, etc. that need preparation should be prepared in accordance with the written procedures, which should be documented, and the documents should be retained. Expiration date of the prepared test solutions, etc. should be determined appropriately based on their characteristics. Prepared test solutions, etc. should be labeled with the item name, preparation number, date of preparation, name of the personnel who performed preparation, expiration date, and where applicable, the storage conditions, and conversion coefficient, etc. Containers for subdividing water and solvents to be used for testing should also be labeled with the item name, etc.

10.12 Primary reference standards should be obtained as appropriate for the testing of products. Suppliers of the primary reference standards should be documented, and the documents should be archived. Primary reference standards should be stored and used in accordance with the supplier's recommendations, which should be documented, and the records should be retained. Primary reference standards obtained from an officially qualified supplier can usually be used without testing, provided they are stored under conditions that are consistent with the supplier's recommendations.

10.13 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity[30] and purity of the primary reference standard. Appropriate documentation of this testing should be retained.

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

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

10.14 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each lot of the secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with written procedures.

10.15 Water for test purposes having a quality that does not affect the test results should be available. In the case of in-house preparation of water for tests, the equipment to be used for water purification should be controlled and the water quality should be checked regularly. The process and results should be documented, and the documents should be retained.[31]

10.16 Reference samples should be representative of the product lots from which they are taken. Other samples may also so be taken to monitor the most unstable stage (e.g., at the start and end of production).

10.2 Certificate of Analysis

10.20 Certificate of Analysis should be issued for each lot of product on request.

10.21 The Certificate of Analysis should include the name of the product, the lot number, the specifications, the numerical results obtained, and results of overall assessment.

10.22 The Certificate of Analysis should be dated and signed or sealed by the person at the quality unit who is responsible for the testing with descriptions of the name (the corporate name), address (location of the major office of the corporate) and telephone number of the manufacturer or testing institutions.

10.3 Monitoring of Product Stability

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

10.30 To confirm product stability, stability should be monitored for at least one lot per year (except when no batch is produced in the year), and stability testing should be performed at least once a year. Stability of products to be released to other manufacturers should be monitored in the same manner where applicable.

10.31 Test procedures for stability monitoring should be validated and be appropriate for stability assessment.

10.32 Samples to be used for stability monitoring should be collected from the products, the release of which from the manufacturing site has been approved. If there is no impediment to doing so, samples can be collected from intermediate products under packaging conditions that ensure product stability.

10.33 Storage conditions should be consistent with the stability-related ICH guidelines, where applicable.

10.4 Expiry Date or Expiry for Use

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

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

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

11. Validation

11.1 Validation Policy

11.10 Documents on the validation operating procedure defined under the provision of Article 8, Paragraph 4, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include overall policy and manufacturer's intention, and methods adopted for validation of manufacturing processes, cleaning procedures, analytical methods, in-process test procedures, as well as validation of computerized buildings and facilities and procedures, plan, review, approval and documentation at each stage of validation.

11.11 Critical process parameters and product characteristics (usually, these should be identified during development stages or based on actual production data) should be defined within a range necessary for reproducible operations (these should include the following):[32]

- Identification of process parameters that may affect critical quality characteristics of the relevant products; and
- Determination of ranges for each critical process parameter to be used for routine process control

11.2 Validation Documentation

11.20 The validation protocols and documents related to validation results should be reported by the person responsible for validation to the quality unit in accordance with the procedures defined under the provision of Article 13, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, which should be reviewed and approved by the quality unit and other predesignated personnel.

11.21 The validation protocol should specify the type of validation to be conducted (e.g., retrospective, prospective, or concurrent validation), validation method, number of process runs, and critical processes, in addition to the matters defined under the

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

Enforcement Notification, etc.

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

11.3 Qualification

11.30 Qualification of equipment and their operational performance at the time of installation, reequipping or maintenance, which are defined under the Enforcement Notification, should be carried out, usually, by conducting the following operations, individually or in combination.

1) Design Qualification (DQ): Documented verification to confirm whether the requirements for the manufacturing equipment ascertained in the process development studies performed for the purpose of manufacturing products having an intended quality are scientifically and reliably reflected in the basic design of the equipment used in the actual production. This procedure is usually performed by confirmation, etc. of design specifications and design drawings.

2) Installation Qualification (IQ): Documented verification to confirm whether the installed or modified manufacturing equipment complies with the approved (notified) design and the manufacturer's requirements.

3) Operational Qualification (OQ): Documented verification to confirm whether the installed or modified manufacturing equipment to be used for actual production can be operated in compliance with the intended performance in the range of expected operating conditions after conducting IQ and calibration of the equipment.

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

11.4 Efficiency Study

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

11.5 Approaches to Validation

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

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[33] These include process parameters.

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

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

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

11.51 As an exception, retrospective validation can be performed instead of confirmation by actual manufacturing for some adequately established processes that ensure critical product quality, provided the following conditions are met:

1) Critical quality characteristics and critical process parameters of the relevant processes have been identified;

2) Appropriate acceptance criteria and control methods for in-process testing of the relevant processes have been established;

3) There have been no failures in critical processes or products that can be attributed to causes other than operator errors, or equipment failures unrelated to equipment suitability; and

4) Quality characteristics have been established for existing products manufactured by the relevant processes.

11.52 Lots selected for retrospective validation should be representatives of all lots manufactured during the review period, including any lots that fail to conform to the specifications. They should be sufficient in number to demonstrate the consistency of the relevant processes. Reserve samples may be tested to obtain data for retrospective validation.

11.53 Prior to conducting process validation on an actual production scale, a tentative maintenance program should be established based on the findings of IQ and OQ, and preparations should be made for the measures designed to optimize the maintenance program including the timing and items subject to maintenance after the validation.

11.6 Cleaning Validation

11.60 Cleaning validation should be performed on the processes where contamination or incidental carryover of products has major impacts on product quality.

11.61 Cleaning validation should reflect patterns of actual use of the equipment to be cleaned. In the case where equipment used for manufacturing of various products is cleaned in accordance with the same procedures, a representative product can be selected for the relevant cleaning validation. This selection should be based on the residue limit estimated in consideration of solubility, difficulty in cleaning, as well as potency, toxicity, and stability.

11.62 The cleaning validation protocol should describe the equipment to be cleaned, procedures, packaging/labeling materials, acceptable cleaning level, process parameters for monitoring and controlling, analytical methods, type of samples to be collected, and sampling and labeling methods.

11.63 In order to detect both insoluble and soluble residues, an appropriate sampling method should be selected among the swab method, rinse method, and alternative method (e.g., direct extraction) for cleaning validation. The sampling method should ensure quantitative measurement of the levels of residues remaining on the equipment surfaces after cleaning. The swab method may be impractical when the product contact surface is not easily accessible due to equipment design or process limitations (e.g., inside of pipes and parts of the filling machine in contact with liquids, and small-sized complex instruments, etc.).

11.64 For cleaning validation, validated analytical methods having adequate sensitivity to detect residues and contaminants at the detection limit level should be used. The recovery level attainable by the relevant analytical methods should be established. Residue limits should be practical and achievable, and the method should be capable of verifying the measurement at levels below the relevant limits, and be based on the data of the most highly toxic residues or those with the

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

11.65 Operations of cleaning, sanitation and disinfection of equipment should be appropriate in consideration of contamination by microorganisms and endotoxins in the manufacturing processes where control of the microbial count or endotoxin level in the product is necessary, or their contamination may become problematic.

11.66 Cleaning procedures should be monitored periodically at appropriate intervals even after validation in order to ensure that these procedures are effective in routine production. The hygiene level of the equipment to be cleaned may be monitored by analytical testing, and where applicable, by visual inspection. Visual inspection may allow detection of gross contamination concentrated in small areas that cannot be detected by sampling and analysis.

11.7 Analytical Method Validation

11.70 In the case where the analytical methods to be adopted are not listed in the compendium, such as the Japanese Pharmacopoeia, etc., and other acknowledged references[36], the relevant analytical methods should be validated. All the testing methods should be validated under actual usage conditions, which should be documented, and the documents should be archived.

11.71 Analytical methods should be validated in consideration of the ICH guidelines for analytical method validation. The degree of analytical method validation should reflect the purpose of the targeted analytical method and the step of the manufacturing process to which the relevant analytical method is applied.

11.72 Analytical instruments to be used for testing/inspection of products and

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

packaging/labeling materials should be appropriately qualified.

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

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

12. 10 In addition to changes attributable to complaints and recall, those attributable to regulatory requirements should also be covered by change control.

12.11 The document related to change control procedures prepared in accordance with Article 8, Paragraph 4 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as "change control procedures") should include changes to the quality management system, raw materials and packaging/labeling materials (including changes of suppliers), specifications, manufacturing methods, testing methods, and buildings and facilities (including related software).[37]

12.12 Changes should be drafted and reviewed by an appropriate division, and should be approved by the quality unit.

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

12.13 The change control protocols should include the following matters:

1) The evaluation defined under the provision of Article 14, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include evaluation of the necessity of revalidation, the necessity of additional testing required to justify the changes, and the necessity of partial change application;

2) Prior to the changes, methods for evaluation of product quality (including accelerated stability tests, stability monitoring program, etc.) and evaluation criteria should be determined in advance;

3) Prior to changes, methods for revision of documents related to the changes and methods for education and training of personnel should be determined in advance, and the document revision and the education and training should be conducted in a reliable manner;

4) Prior to the changes, "other necessary actions" defined under the provision of Article 14, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, such as the necessity of changes to specifications, testing methods, expiry dates or expiry for use, and labeling should be determined in advance.

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

13. Non-conforming Products

13.1 Non-conforming

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

quarantined.

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

13.2 Returns

13.20 Returned products should be discarded unless their quality is proven to be acceptable on the basis of the conditions of storage or transport after release from the manufacturing site until return, elapsed time, appearance of the containers, etc., and results of testing conducted after return, etc.

13.21 The following matters related to the returned products should be documented, and the documents should be archived:

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

14. Quality Information

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

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

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

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

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

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

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

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

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

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