4.52　Buildings and facilities that are used for manufacturing of other drugs and quasi-drugs should not be used for the operations (including weighing, milling and packaging) related to manufacturing of highly toxic agrochemicals, such as herbicides and insecticides, etc.　Such highly toxic agrochemicals should be handled and stored separately from drugs and quasi-drugs.

4.6 Design and Set-up of Buildings and Facilities

4.60　Buildings and facilities that may adversely affect product quality due to their surfaces coming into contact with products should be set up so that such contact can be avoided.[13]

4.61　Buildings and facilities should only be used within their qualified operating range.

4.62　Major buildings and facilities used for manufacturing of products (e.g., blender, tabletting machine, etc.) should be appropriately identified by labeling.

4.63　Substances, such as lubricants, heating fluids, and coolants, etc. should not contact products as these substances may adversely affect product quality.　It is desirable to use food grade oils as an alternative.[14]

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[13] Buildings and facilities that may contact products include tanks, pipes, filters, ion-exchange resins, hoses, gaskets, chromatographs, etc.　Specific items to be considered are as follows: (1) chemical resistance (products do not react with or corrode the contact area); (2) extractables (extract from the contact area does not adversely affect product quality; particular attention should be paid to extractables from high-molecular materials (hoses, gaskets, filters, columns, and linings, etc.), and if necessary, data on extractable characteristics should be obtained from suppliers to confirm information on contraindications with products and reactivity with products, etc. based on the chemical characteristics of such extractables　Moreover, safety evaluation data (toxicity studies, etc) related to the surface materials should be obtained from suppliers.　The same is also described in the 21CFR, 211.65(a) and (b)); (3) adsorption (evaluation of adsorption to high-molecular weight materials is important particularly in cases of liquid agents.　Effects of the substances extracted from the surface of high-molecular weight materials on product quality should be assessed.)

[14] Areas where lubricants, heating fluids, and coolants, etc. may contact products include, for example, shaft and pump, etc. for stirring.

4.64　If necessary, closed or contained equipment should be used. Where open equipment is used, or equipment is opened, appropriate preventive measures should be taken to minimize the risk of contamination.

4.65　A set of drawings related to the current construction should be maintained for critical buildings and facilities (e.g., instrumentation, utility-related equipment, etc.).

4.7 Maintenance and Cleaning of Buildings and Facilities

4.70　Procedures for cleaning of the buildings and facilities that are used for manufacturing control and quality control of products (including the detailed procedures necessary for cleaning with an efficient and reproducible method by personnel) and those related to subsequent release for use of the relevant buildings and facilities in the next batch should be included in the hygiene control standard code. These procedures should include:

- A complete description of the methods for cleaning (including the methods for dilution of cleaning agents), as well as the materials and chemicals, etc. to be used for cleaning;
- Instructions for disassembling and reassembling each structural component of buildings and facilities if required to ensure proper cleaning;
- Instructions for removal or obliteration of previous batch identification;
- Instructions for protection of clean buildings and facilities from contamination prior to use
- Testing/inspection of buildings and facilities for cleanliness immediately before use, if feasible; and
- When appropriate, the maximum time that may elapse from completion of the process-related operations to cleaning of buildings and facilities, and the cleaning expiry date after cleaning.[15]

[15] The risk of contamination of the process equipment during the period from cleaning of buildings and facilities to the next batch of production should be considered (e.g. possible risk of negative pressure, contamination from accessory piping, and contamination from drain piping).

4.71　Buildings and facilities should be cleaned to prevent contamination or carry-over of a material that may adversely affect product quality. When appropriate, buildings and facilities should be sanitized, disinfected or sterilized.

4.72　Where buildings and facilities are used for continuous production by successive batches of the same product or production of only the relevant product during a specified period (campaign production), they should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradation products or objectionable level of microorganisms).

4.73　Non-dedicated buildings and facilities should be cleaned in each case of changeover of product items to prevent cross-contamination.

4.74　Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents suitable for the residues should have been defined and justified.

4.75　Buildings and facilities should be labeled by appropriate methods[16] to identify their contents and cleanliness status.

4.76　It should be confirmed that filters to be used at the final stage of the product manufacturing process do not release fibers.[17]

4.8 Calibration

4.80　For calibration of equipment related to the manufacturing control defined under the provision of Article 10, Item 8 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, and that related to the inspection defined under the provision of Article 11, Item 4 of the ministerial ordinance, a list of measuring instruments should be prepared, the risks related to product quality should be assessed, and the necessity of calibration as well as the calibration frequency should have been

[16] For example, "before cleaning," "completion of cleaning," "during production," etc.
[17] With respect to discharge of fibers and other foreign matter from the filter itself, when appropriate, flushing cleaning, etc. should be considered prior to use based on the data provided by the supplier.

specified in advance.

4.81 Calibration of equipment should be performed using methods that are traceable to the certified standards, if national standards are available.

4.82 The current calibration status of critical equipment should have been specified. A calibration seal should be affixed to the calibrated equipment, in which the calibration results, the scheduled date of the next calibration, etc. should be described.

4.83 Measuring equipment that does not meet the calibration criteria should not be used. Any measuring equipment that does not meet the calibration criteria or whose calibration validity has expired should be labeled as "not permitted for use," etc.

4.84 In cases of deviations of critical measuring equipment from approved calibration standards, investigations should be made to assess the impacts of the relevant deviations on the quality of the product that have been manufactured using the relevant equipment after the previous calibration. Investigation methods, for example, may include checking the presence or absence of any problems by testing/inspection with proper measuring equipment based on the quality standard determined by the equipment using the reference product manufactured after the last successful calibration. If any abnormality has been detected as a result of investigation, necessary actions to be taken should be discussed.

4.9 Computerized Buildings and Facilities and Procedures

4.90 Computerized buildings and facilities and procedures related to manufacturing control and quality control of products should be validated. The degree and scope of the validation should be decided considering the diversity, complexity and importance of the computerized buildings and facilities.

4.91 Installation qualification and operational qualification should be appropriately performed for the hardware and software related to the computerized buildings and facilities and procedures.

4.92 Commercially available software that has been qualified does not require the same level of testing as that required for a computer system designed originally for the relevant manufacturing process. If existing computerized buildings and facilities and procedures have not been validated at the time of installation, a retrospective validation may be conducted using appropriate records.

4.93 Data of computerized buildings and facilities and procedures should be sufficiently controlled to prevent unauthorized access to or change in data. The data should be controlled to prevent their omission. In the event data are changed, previous data, name of person who made the change, and the date of change should be documented, and the documents should be archived.

4.94 A procedural manual should be prepared for implementation and maintenance of the computerized buildings and facilities and procedures.

4.95 In the case of the manual entry of critical data, such data need to be reviewed by a second party to confirm whether or not accurate entry has been made. This reconfirmation review can be conducted by a second operator or by the computer system related to the relevant computerized buildings and facilities and procedures.

4.96 Any failure in computerized buildings and facilities and procedures that may affect the reliability of product quality, should be investigated and documented, and the documents should be archived.

4.97 Changes in the computerized buildings and facilities and procedures should be made in accordance with the manual for change control. All changes, including modifications and extensions, which have been made for the critical parts of the

hardware and software of the computer system related to the computerized buildings and facilities and procedures should be documented, and the documents should be archived. These documents should demonstrate that the relevant computerized buildings and facilities and procedures are ultimately maintained in a validated state.

4.98 If breakdowns or failures of the computer system related to the computerized buildings and facilities and procedures may result in the permanent loss of records, a back-up system should be provided. A measure of ensuring data protection should be established for the manufacturing control and quality control-related computer system.

5. Documentation Control and Records

5.1 Documentation Control

5.10 The documentation and record control manual, defined under the provision of Article 8, Paragraph 4, Item 9 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should specify the preparation, defined under the provision of Article 20, Items 1 and 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, abolition and recovery procedures.

5.11 The documents should be prepared in a language and context that are understandable to the personnel who are engaged in activities related to the manufacturing control and quality control of products at manufacturing sites.

5.12 The documents should be prepared so as to demonstrate clearly how they are related to other documents.

5.13 When preparing records, the name of the person who made entries should be inscribed using an indelible means in a predefined space directly after operations. Any correction to entries should be dated and signed or sealed, and the original

entry should be kept in a legible state. In the case of correction of records that may affect product quality (yield, analytical values related to process control, etc.), the reason for the corrections should be provided.

5.14 The original records or their copies should be readily available during their archiving period at the manufacturing site where the relevant operations have been performed. Records that can be promptly retrieved from an archiving site other than the relevant manufacturing site by electronic or other means are acceptable.

5.15 Where reduction techniques such as microfilming or electronic records are used for archiving of product master formulae, instructions, manuals and copies of original records (photocopies, microfilm, microfiche, and other accurate copies of the original records), suitable retrieval equipment and a means to produce a hard copy should be readily available.

5.2 Manufacturing Instructions and Batch Records

5.20 Manufacturing instructions should mention the criteria used when deciding release to the subsequent processes.[18] When master manufacturing instructions are prepared, a person at the production unit who is responsible for preparation of the master manufacturing instructions should enter the date and affix his/her signature or seal. The relevant quality unit should confirm the content of the master manufacturing instructions, which should be dated and signed or sealed by a person in the relevant unit, who is responsible for the confirmation.

5.21 The batch record should be confirmed by a person at the production unit who is responsible for preparation of the batch record to assure that the batch record is a

[18] Concrete matters to be described in manufacturing instructions include product name, list of raw materials and packaging/labeling materials, accurate description of the quantity or ratio of the raw materials and packaging/labeling materials (including measuring units), working spaces and critical buildings and facilities, order of operations, related process parameters, instructions for sampling, judging standards for laboratory testing/inspection related to in-process control, limit times of individual processes or the overall process, range of anticipated yield, and storage conditions of products, as well as conditions for storage of packaging/labeling materials.

correct version and has been prepared legibly in accordance with the appropriate manufacturing instructions.

5.22 In the case of continuous production, the lot number to be described in the manufacturing instructions and batch records can be replaced by the date of manufacturing and manufacturing code for identification until the final lot number is assigned.

5.23 The items related to major processes, which should be documented in the batch records, include the following (in addition to items defined by other regulations, such as Enforcement Notification, etc.):

1) Date and, where applicable, time;

2) Amount, lot number or control number of the raw materials and packaging/labeling materials used in the manufacturing process;

3) Major buildings and facilities used;

4) Records of sampling;

5) Records of packaging and labeling;

6) Records of critical process parameters;

7) Any deviation noted, its evaluation, and results of investigation conducted as appropriate (or reference to the investigation results when the relevant results have been separately archived);

8) Results of decision for release to the subsequent processes; and

9) Signatures or seals of the persons who have performed and directly supervised

the operations in each critical process.

5.3 Buildings and Facilities Cleaning and Use Records

5.30 The buildings and facilities cleaning (including sanitation, disinfection and sterilization) and periodic maintenance and etc. records, which are defined under the provisions of Article 9, Item 1, and Article 10, Items 6 and 8 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, date, time (only when applicable), name and lot number of the products manufactured using the relevant buildings and facilities, and name of the persons who have been engaged in the operations of cleaning and maintenance should be provided in use record.

5.31 If buildings and facilities are dedicated to the manufacture of only one product, preparation of individual use records is not necessary provided that the lot number of the product follows a traceable sequence. In cases where dedicated buildings and facilities are used, the records of cleaning, periodic maintenance and use can be part of the batch record.

5.4 Packaging and Labeling Materials Records

5.40 The records related to storage and inventory of the materials, defined under the provision of Article 10, Item 5 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should provide the name and identification number of the supplier (if available) and any matters defined under the Enforcement Notification. The records related to conformity judgment on the materials, defined under the provision of Article 10, Item 4 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should provide the contents of the final handling of the packaging and labeling materials that have been judged to be non-conforming.

5.41 Approved original labeling materials (master labels) should be archived for comparison with the labeling materials that have been used for each lot of products (those used for the representative lot should be attached to batch

records).

5.5 Testing/Inspection Records

5.50 The testing/inspection records, defined under the provision of Article 11, Paragraph 1, Items 1 and 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs and the Enforcement, should provide the following contents and any matters:

1) Descriptions of the name of the suppliers, and where applicable, the quantity of the samples collected for testing/inspection;

2) Comments and other references related to the testing/inspection method used;

3) Descriptions of the quantity of samples used for each testing/inspection, reference standards, reagents, preparation of standard solutions, and other cross-references;

4) Complete records of all raw data obtained by each testing/inspection, graphs, charts and spectra, etc. obtained from analytical instruments (these should be properly identified to show the specific materials, etc., and their lot or control number);

5) Records of all calculations performed in connection with the testing/inspection, including units of measure, conversion coefficient, and equivalence coefficient, etc.; and

6) The signature or seal of a responsible person at the quality unit and the date to show that the original records have been reviewed for accuracy, completeness, and compliance with established specifications.

5.51 Complete records should be archived for the following matters:

1) Contents of any modifications of established analytical methods;

2) Results obtained by all stability tests performed on products; and

3) Results of investigations made on the causes of deviations from specifications

6. Control of Raw materials and Packaging/Labeling Materials

6.1 General Control

6.10 Suppliers of critical raw materials and packaging/labeling materials should be jointly evaluated with Licensed Marketing Approval Holders.[19]

6.11 Raw materials and packaging/labeling materials should be purchased from suppliers approved by the quality unit in conjunction with Licensed Marketing Approval Holders.

6.12 If a supplier of critical raw materials and packaging/labeling materials is not itself the manufacturer of the materials, the name (corporate name) and address (address of the main body of the corporate) of the supplier should be provided.

6.13 Change in suppliers of critical raw materials and packaging/labeling materials should be handled in accordance with the procedures for change control.

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

6.20 Upon confirmation of receipt of packaging/labeling materials defined under the provision of Article 10, Item 4 of the GMP Ministerial Ordinance for Drugs and

[19] In addition to onsite audit, methods for evaluation of suppliers include the following: (1) receipt of a GMP Certificate issued by the relevant regulatory authority in the case of overseas manufacturers; (2) confirmation of past record of ISO accreditation (however, GMP Certificate is prioritized for GMP-applied sites), etc.

Quasi-drugs, as well as raw materials, a visual inspection should be performed to check the labeling of each container of the raw materials and packaging/labeling materials (and make sure that the descriptions are different but the information is essentially the same), and to check for container damage, broken seals, evidence of tampering, and contamination, etc. Raw materials and packaging/labeling materials should be held under quarantine separately from other products and materials until approval for use after the testing/inspection defined under the provision of Article 11, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.

6.21 In the case where newly received raw materials and packaging/labeling materials are mixed with existing stocks (including solvents, etc., in a large-volume storage tank), the incoming material should be tested in advance to confirm their appropriateness. The necessary procedures should be established to ensure that any mix-up of incoming raw materials and packaging/labeling materials with existing stocks is prevented.

6.22 In the case where raw materials and packaging/labeling materials are transported by non-dedicated tankers, etc., it should be confirmed that there is no cross-contamination mediated by the relevant tankers, etc. Thereby, confirmation may be made by application of the following methods:

1) Receipt of a certificate of cleaning;

2) Testing for trace impurities; and

3) Onsite audit of the supplier

6.23 Large-volume storage containers, their installed piping, filling and discharge lines for raw materials and packaging/labeling materials should be appropriately identified.

6.24 Containers for raw materials and packaging/labeling materials should be labeled

appropriately. The labeling should provide at least the following information. The status of each lot should be identified by labeling in the event the lot is relocated or if the control unit of the lot is changed. When completely and appropriately computerized buildings and facilities and procedures[20] are employed, it is not necessary to make all of the labeling contents visually readable.

1) Product name;

2) Lot number or control number;

3) Control condition of the contents (e.g., "under isolation," "under testing," "accepted," "rejected," "returned material," "recalled material," etc.); and

4) Where applicable, expiry date or expiry for use, or the date of retest.

6.25 For a lot number or control number to be assigned to the received raw materials and packaging/labeling materials, attention should be paid to the following matters:

1) Even in the case of an identical lot at the supplier, an independent lot number or control number should be assigned at the time of receipt, when the lot is received in installments.

2) Even in the case where the lot number or control number is the same, when the lot is placed in two or more containers, a control method should be adopted so that each container can be identified, if necessary.[21]

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[20] This corresponds to the case in which non-visual information has been controlled by a computer system using barcode labeling and RFID tags, etc.

[21] Irrespective of the lot and control unit at receipt of raw materials and packaging/labeling materials, the possibility that storage status may be different in each container should be considered; for example, the number of package openings may be different. Therefore, this was stipulated, considering the necessity to specify containers for sampling. However, it is not necessarily required to assign a lot number or control number to each container, provided that another control method to identify each container is adopted.

6.3 Sampling and Testing/inspection of Packaging/Labeling Materials at Receipt

6.30 In the case where some of the items for testing are omitted at receipt of raw materials and packaging/labeling materials defined under the provision of Article 11, Paragraph 11, Items 1 and 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, such materials should be assessed based on sufficient evidence (e.g., quality history of the raw materials and packaging/labeling materials supplied in the past) that suppliers have a system to supply raw materials and packaging/labeling materials conforming to the specifications, and it should be confirmed whether their test data of the relevant items are stable and that the items do not have the potential to become non-conforming considering the range of the specifications. Thereby, at least 3 lots or 3 control units should be tested in advance based on full analyses to ascertain the validity of the test data by confirming the continuous consistency of the test data obtained by both parties. Even when several of the acceptance tests have been omitted, full analyses should be performed at appropriate intervals to ascertain the reliability of the Certificate of Analysis issued by the supplier.

6.31 In the case where special equipment or techniques are necessary due to the explosiveness, harmfulness, etc. of the raw materials used for manufacturing of the drug substance, the test results described in the appropriate Certificate of Analysis issued by the supplier can be utilized as part of the acceptance test data of the relevant raw materials. In the case where the acceptance test is omitted, the reason for the omission should be clearly documented in the product master formula after prior approval by the quality unit.[22]

6.32 Collected samples should be representative of the lot or control unit. Sampling procedures including the number of containers to be sampled, as well as sampling points in the containers and sampling amount, should be predefined in

[22] Such a case is also predicated on evaluations of suppliers and transportation conditions. If the evaluation results are undesirable, measures, such as confirmation using the samples for testing/inspection, etc. should be taken.

consideration of the importance of the relevant raw materials or packaging/labeling materials, quality variability, quality history of the materials supplied from the relevant suppliers in the past, and the quantity needed for proper testing.

6.33 Sampling of the materials defined under the provision of Article 11, Paragraph 1, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should be conducted at predefined locations in accordance with the procedures designated to prevent contamination of the sampled raw materials and packaging/labeling materials, as well as other products and materials.

6.34 Samples defined under the provision of Article 11, Paragraph 1, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should be collected in accordance with the following procedures[23]:

1) The containers of components selected shall be cleaned where necessary, by appropriate means;

2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures;

3) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing;

4) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample; and

5) Containers from which samples have been taken shall be marked to show that samples have been removed from them. (attachment of a label describing "sampled," etc.).

[23] The same have been stipulated also in the 21CFR 211.84(c).

6.4 Storage

6.40 Raw materials and packaging/labeling materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

6.41 Containers for storage of raw materials and packaging/labeling materials should be stored off the floor and suitably spaced to permit cleaning and testing.

6.42 Raw materials and packaging/labeling materials should be stored in a proper manner so that the oldest stock is used first, except for particular cases.

6.5 Re-evaluation

6.50 In the case where received raw materials and packaging/labeling materials have been stored for a period that exceeds the expiry date, or they have been exposed to heat or humidity, re-evaluation should be performed to determine their suitability for use. However, indefinite storage based on repeated re-evaluations should be avoided.

7. Production and In-Process Control

7.1 Manufacturing Operations

7.10 Prior to start of the manufacturing operations, cleaning of the buildings and facility, defined under the provision of Article, 10, Item 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, should be confirmed, and whether products, packaging/labeling materials, and documents that are not required for the relevant operations do not remain in the working spaces for the operations.

7.11 Raw materials should be weighed or measured under appropriate conditions that do not affect product quality, etc. Weighing and measuring devices should be of

suitable accuracy for the intended use.

7.12 If raw materials are subdivided for manufacturing processes to be performed later, appropriate containers should be used, and the following information should be placed on the labels of the relevant containers:

- Name, lot number or control number of the raw material;
- Subdividing number, when necessary;
- Weight or volume of the raw material in the relevant container; and
- Where applicable, expiry date or expiry for use, or date of retest

7.13 Critical weighing, measuring, or subdividing operations should be witnessed by personnel other than those who perform the operations (this does not apply to the case where the operations can be controlled under equivalent conditions by other methods). Prior to use, the personnel who perform the operations should make sure that products and packaging/labeling materials are those specified in the manufacturing instructions.

7.14 Other critical operations should be witnessed by personnel other than those who perform the operations (this does not apply to the case where the operations can be controlled under equivalent conditions by other methods).

7.15 Actual yields (net yields) should be compared with theoretical yields at the predefined steps in the manufacturing processes. A theoretical yield with appropriate ranges should be established based on laboratory testing data, pilot-scale data or the data obtained in the actual production scale. Deviations in yields in critical processes should be investigated to determine their impacts on the resulting quality of affected lots, and the results confirmed.

7.16 The operation status of equipment should be indicated on their main part (this does not apply to the case when the operations can be controlled under equivalent conditions by a computerized control system).

7.17　Any products excluded from the manufacturing process (e.g., products excluded from the manufacturing process by reason of filling failure, tabletting failure, etc.) should be stored in places differentiated from those for storage of other products. This should be documented and archived.

7.2　Time Limits

7.20　If time limits for process completion are to be specified in the manufacturing instructions, they should ensure the manufacturing control and quality control of products.[24] Deviations in time limits should be assessed and documented, and the documents should be archived. However, in the case where processes with specific target values are running, such as pH adjustment or drying to predetermined specifications, setting of time limits is inappropriate. The time of completion of such processes should be determined by in-process sampling and testing/inspection.

7.3　In-Process Control

7.30　Written procedures should be established to monitor the progress and control the status of processes that affect the quality characteristics of products (content, titer, dissolution profile, etc.). In-process control and the acceptance criteria should be determined based on the information obtained during development stages or actual production data.

7.31　Acceptance criteria, and type and scope of testing related to in-process control should be established depending on the quality characteristics of products, content of the process and impacts of the relevant process on product quality.

7.32　Critical in-process control (and monitoring of critical processes) should be documented, and then approved by the quality unit.

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[24] Particularly, in the case of storage of intermediate products for a long term, storage conditions (storage place (temperature and humidity, etc.), storage container, storage period, etc.) that have been confirmed in advance should be documented so that product quality does not deteriorate during the storage period.

7.33 When process adjustments are made by personnel at the production unit without prior approval by the quality unit, the adjustments should be made within the limits predefined and approved by the quality unit. All tests and results related to in-process control should be documented as a part of manufacturing records.

7.34 Samples to be used for process controls should be representative of the lot. Sampling procedures (including sampling points and sampling amount) should be based on scientifically valid methods.[25]

7.35 Investigations on the cause of out-of specification (OOS) results are not usually needed for in-process testing/inspection that is performed for the purpose of monitoring or process adjustment.

7.36 In-process sampling should be conducted in accordance with the procedures for preventing contamination of products and ensuring the integrity of the samples after sampling.

7.4 Lot-Blending Process

7.40 Any lot that has been judged to be out-of specification from test results should not be blended with other lots for the purpose of meeting specifications.

7.41 The lot-blending process (this refers to the process of blending products within the same specifications[26] to produce a homogenous lot[27]) should be appropriately controlled and documented in accordance with the manufacturing instructions, and the documents should be archived. A new lot produced in the lot blending

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25 "Samples to be used for process controls" are different from those to be used for "in-process testing/inspection that is performed for the purpose of monitoring or process adjustment" described in Chapter 7. 35. They are used for confirmation related to on-process control that is particularly necessary for manufacturing of a final product of consistent quality.

26 In the case where processes before and after the lot-blending process are performed consecutively, or that the quality of individual (small) lots has been confirmed to be equivalent, it is not mandatory to perform testing/inspection of individual (small) lots; therefore, it is not required to confirm the specification conformity of individual (small) lots.

27 Manufacturing of products by blending of residual materials formed in the manufacturing process of a previous lot with a new lot (namely, rescue), and blending with other lots for the purpose of meeting specifications of a non-conforming lot do not apply to the "lot-blending process" defined here.

process (hereinafter referred to as "blended lot") should be tested as appropriate to ascertain whether it meets the predefined specifications.

7.42 The record of the lot-blending process should be prepared to allow traceability back to the original individual lots used for the blending process.

7.43 Procedures for the lot-blending process should be based on scientifically valid methods.

7.44 In the case where the physicochemical homogeneity of blended lots critically affects product characteristics (e.g., drug products of oral solid preparation), 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, etc.) that may be affected by the lot-blending process.

7.45 If the lot-blending process may have adverse impacts on the stability of blended lots, stability testing should be performed to decide whether the blended lots are suitable for release.

7.46 The shelf life or expiry for use of blended lots should be based on the manufacturing date of the oldest lot or leftover lots among the lots used for blending.

7.5 Contamination Control

7.50 Residual materials that are carried over into successive lots (e.g., residues adhering to the wall of the milling machine or granulator, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the materials to the next process) should be controlled so that they do not adversely affect product quality.