

**JAPAN PHARMACEUTICAL EXCIPIENTS  
COUNCIL (JPEC)**

**SELF-IMPOSED STANDARDS OF GOOD MANUFACTURING PRACTICES  
FOR PHARMACEUTICAL EXCIPIENTS**

**1. SELF-IMPOSED STANDARDS FOR MANUFACTURING CONTROL AND  
QUALITY CONTROL OF PHARMACEUTICAL EXCIPIENTS  
(GMP SOFTWARE)**

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**2. SELF-IMPOSED STANDARDS FOR BUILDINGS AND FACILITIES FOR  
MANUFACTURING PLANTS OF PHARMACEUTICAL EXCIPIENTS  
(GMP HARDWARE)**

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**3. SELF-IMPOSED STANDARDS FOR MANUFACTURING CONTROL AND  
QUALITY CONTROL OF PHARMACEUTICAL EXCIPIENTS  
(VALIDATION STANDARDS)**

<b>Established</b>	<b>October 1, 2006</b>
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## **1. SELF-IMPOSED STANDARDS FOR MANUFACTURING CONTROL AND QUALITY CONTROL OF PHARMACEUTICAL EXCIPIENTS (GMP SOFTWARE)**

### **(Purpose)**

**Article 1** The purpose of this Standards is to provide guidance on self-imposed controls required for assuring the quality of pharmaceutical excipients, and to enable pharmaceutical excipients to match with requirements raised through the development of pharmaceutical drug products of a higher quality, both with a final intent to promote and level up the public health care.

### **(Definitions)**

**Article 2** In this Standard the term “pharmaceutical excipient” means any substance to be added during the course of formulating a pharmaceutical drug product for ensuring the stability, safety or homogeneity, and for promoting the dissolution or controlling the release, depending on characteristic features of the dosage form.

2. In this Standard the term “manufacturer” includes anyone who practices all or partial manufacturing processes of pharmaceutical excipients (including operations of storage) as a profession.

3. In this Standard the term “product” means a material which is undergone manufacturing processes of the manufacturing plant [including a material manufactured in the manufacturing process which must undergo further manufacture before the formation of a product (hereinafter referred to as an “intermediate product”) manufactured in the manufacturing process; the same hereinafter].

4. In this Standard the term “labeling and packaging materials” means containers, wrappers and package inserts of a product, and labels to be attached onto the containers and wrappers.

5. In this Standard the term “lot” means a batch of product manufactured so as to have a uniform quality in a series of manufacturing processes in a unit of manufacturing period and raw materials (hereinafter referred to as “the products etc.”).

6. In this Standard the term “control unit” means a batch of labeling and packaging materials which are confirmed to have a uniform quality.

7. In this Standard the term “validation” means to validate and document that anticipated results yield from buildings and facilities for the manufacturing plant and operating procedures, processes and other methods of manufacturing control and quality control (hereinafter referred to as “the operating procedures”).

8. In this Standard the term “calibration of meters” means clarification of a

relationship of the values obtained by the measuring instrument and the true values, using appropriate standard measuring instruments and standard substances in consideration of required accuracy.

9. In this Standard the term “manufacturing plant” means any place of business or industrial plant where the pharmaceutical excipient concerned is manufactured, and what is called whole of the functions of a plant (including business premises, warehouses and welfare facilities and the like).

10. In this Standard the term “work area” means the area where the pharmaceutical excipient concerned is manufactured, except for incidental facilities, that are disposed apart from the main work area, such as business premises, resting rooms, outfit room, lavatories, testing and inspecting offices, electric machine rooms, power distribution rooms, fittings warehouses and the like.

11. In this Standard the term “work room” means the enclosed space, in a work area, to be used for weighing and charging of raw materials, formulating, repackaging, filling or sealing of product (including intermediate products undergoing the final purification), inclusive of changing room, air shower room, lobby, carrying-in room for raw materials, washing room for implements and washing recesses that are annexed to them, if any.

12. In this Standard the term “partial processing plant for packaging etc.” means the plant for carrying out the manufacturing processes after filling primary packages or film-bag liners with product and including putting in outer containers or wrapper.

### **(Scope of application)**

**Article 3** The manufacturer shall perform manufacturing control and quality control of products at the manufacturing plant.

2. The manufacturer shall provide buildings and facilities that are capable of performing manufacturing control and quality control of products at the manufacturing plant.

### **(Manufacturing unit and quality unit)**

**Article 4** Each manufacturer shall designate, at each manufacturing plant, a product security pharmacist for pharmaceutical excipients (hereinafter referred to as “the product security pharmacist”) and place an unit involved in the manufacturing control (hereinafter referred to as “manufacturing unit”) and an unit involved in quality control (hereinafter referred to as “quality unit”) respectively under the supervision of the product security pharmacist concerned.

(1) The quality unit shall be independent of the manufacturing unit.

- (2) The person responsible for the manufacturing unit shall not hold the position of a person responsible for the quality unit.

**(Product security pharmacist)**

**Article 5** The product security pharmacist shall perform the following duties:

- (1) To supervise the operations of the manufacturing control and of the quality control, and to control and superintend so that the operations of the manufacturing control and of the quality control are performed appropriately.
- (2) When there is a possibility of resulting in quality problem or of significant effect on the quality of the products, to ensure that the necessary actions are speedily taken, to confirm how the matter is in progress, and to give instructions, according to demand, to take action necessary for improving etc.

2. The manufacturer shall make efforts for the effective performance of the duties assigned to the product security pharmacist.

3. The manufacturer shall designate the product security pharmacist who meets any of the following requirements:

- (1) Pharmacist
- (2) A person who has completed an advanced course majoring in pharmacy or chemistry at a university and has engaged in the duty of manufacturing or quality control of pharmaceutical excipients for more than two years.
- (3) A person who has learned a course of study on the subject of pharmacy or chemistry at a senior high school or any higher rank school and has engaged in the duty of manufacturing or quality control of pharmaceutical excipients for more than five years.
- (4) A person who is admitted by the manufacturer to have knowledge and experience equal to or more than the person referred to in item (3).

**(Personnel)**

**Article 6.** The manufacturer shall designate responsible persons (hereinafter referred to as “responsible persons”), properly depending on organization and scale of the plant, and kind of duty, who have abilities to perform manufacturing control and quality control appropriately.

2. The manufacturer shall post appropriate number of responsible persons depending on organization and scale of the plant, and kind of duty.

3. The manufacturer shall secure the number of persons satisfactorily to be able to perform manufacturing control and quality control properly.

4. The manufacturer shall lay down the duty and management system properly in written form for the persons (including product security pharmacist and responsible persons) who are engaged in the duties of manufacturing control and quality control.

**(Product master formula)**

**Article 7.** The manufacturer shall prepare, at each manufacturing plant, the product master formula for each product (excluding intermediate product; the same in this article), describing the following matters, retain it and furthermore obtain the consent of the quality unit.

- (1) Manufacturing procedure
- (2) Other necessary matters.

**(Operating procedures etc.)**

**Article 8.** The manufacturer shall prepare, at each manufacturing plant, a hygienic control standard code describing the sanitation and hygiene of the buildings and facilities and of personnel, and other necessary matters, and retain it.

2. The manufacturer shall prepare, at each manufacturing plant, a manufacturing control standard code describing the storage of product etc., the control of manufacturing process and other necessary matters, and retain it.

3. The manufacturer shall prepare, at each manufacturing plant, a quality control standard code describing methods of collecting samples and of evaluating the analysis and testing results, and other necessary matters, and retain it.

4. For the proper and smooth conduct of the manufacturing control and quality control, the manufacturer, in addition to the duties specified in the preceding three paragraphs, shall prepare, at each manufacturing plant, documents of the operating procedures shown in the following (hereinafter referred to as “operating procedures”), and retain it.

- (1) The operating procedures for the control of release out of the manufacturing plant.
- (2) The operating procedures for validation.
- (3) The operating procedures for the control of change.
- (4) The operating procedures for the control of departure.
- (5) The operating procedures for the managements toward information about quality etc. and quality inferiority.
- (6) The operating procedures for recall.
- (7) The operation procedures for self-inspection

- (8) The operation procedures for training.
  - (9) Operation procedures for control of documents and records.
  - (10) Operation procedures for other items required for the proper and smooth conduct of the manufacturing control and quality control.
5. The manufacturer shall provide the manufacturing plant with the product master formula, hygienic control standard code, manufacturing control standard code, quality control standard code and documents of the operating procedures (hereinafter referred to as “the operating procedures etc.” as a general term).

**(Manufacturing control)**

**Article 9.** The manufacturer shall have the manufacturing unit perform the following duties related to manufacturing control in accordance with the operating procedures etc.

- (1) To prepare the manufacturing directions describing instructions, precautions and other necessary matters during the manufacturing process and to retain them.
- (2) To manufacture the products in accordance with the manufacturing directions.
- (3) To make the manufacturing records of products by lot and to retain them.
- (4) To confirm the adequacy of labeling and packaging materials for the products by lot, to prepare the records of the results and to retain them.
- (5) To store, under appropriate conditions, products etc. by lot, and labeling and packaging materials by control unit, to manage receipt and distribution of these products etc., and labeling and packaging materials, to prepare the records of the results and to retain them.
- (6) To confirm cleanliness of the buildings and facilities, to prepare the records of the results and to retain them.
- (7) To perform the sanitation and hygiene of personnel, to prepare the records of the results and to retain them.
- (8) To perform regular inspection and maintenance of the buildings and facilities, to prepare the records of the results and to keep them. Further to perform calibration of meters adequately, to prepare the records of the results and to retain them.
- (9) To confirm that the manufacturing control is appropriately performed from the records of manufacture, storage, receipt and distribution, and sanitation and hygiene, and to report the confirmation in writing to the quality unit.
- (10) Other duties necessary for the manufacturing control.



**(Quality control)**

**Article 10.** The manufacturer shall have the quality unit perform systematically and appropriately the following duties related to quality control of pharmaceutical excipients in accordance with the operating procedures etc.

- (1) To collect samples of product etc. by lot, and those of labeling and packaging materials by control unit, for the conduct of analysis and testing, to prepare their records and to retain them.
- (2) When water is used in the manufacturing process, to collect samples of water periodically for the conduct of analysis and testing, to prepare their records and to retain them.
- (3) When organic solvents are used in the manufacturing process, to collect samples periodically for the conduct of analysis and testing of residual solvents in the products, to prepare their records and to retain them.
- (4) To perform the analysis and testing of the collected samples by lot or by control unit (including the cases where the analysis and testing are performed on the manufacturer's own responsibility using other testing facilities of the manufacturer concerned or other institutions and without causing hindrance to the proper analysis and testing; the same hereinafter), to prepare records thereof and to retain them.
- (5) To retain a reserve sample, under appropriate storage conditions, from each lot of product (excluding intermediate products), consisting of at least twice the quantity necessary for all the required tests, for a period of time corresponding to the term of quality assurance plus one year from the date of manufacturing. The term of quality assurance referred here means the time during which the quality is assured.
- (6) In the case of the product for which a retesting date [prescribed date when it is required to perform the analysis and testing again for the confirmation such as whether the product (excluding intermediate product), for which a specific time has passed after the date of manufacturing, still conforms to the prescribed specifications or not] is prescribed instead of the term of quality assurance, to retain a reserve sample, under appropriate storage conditions, from each lot of product, for 3 years after the date when the distribution of the concerned lot of product has been completed.
- (7) To perform regular inspections and maintenance of analysis and testing facilities and equipments, to prepare their records and to retain them. Further to perform calibration of meters used for analysis and testing properly, to prepare their

records, and to retain them.

(8) To evaluate results of analysis and testing referred in Item 4 of this Paragraph 1, and to report the results in writing to the manufacturing unit.

(9) Other necessary duties.

2. The manufacturer shall have the quality unit confirm, under the provision in Item 9 of the preceding Article and in accordance with the operating procedures etc., the results of confirmation by lot regarding manufacturing control reported from the manufacturing unit.

#### **(Control of release of products from the manufacturing plant)**

**Article 11.** The manufacturer shall have the quality unit perform the duties, in accordance with the operating procedures etc., to decide through appropriate evaluation of the results of manufacturing control and quality control, whether or not it is proper to release the product (excluding intermediate products; the same under this article) from the manufacturing plant.

2. The person in charge of the duties of the preceding paragraph shall be competent for performing the duties concerned appropriately and smoothly.

3. The manufacturer shall make efforts for the effective performance of the duties assigned to the person in charge of the duties of paragraph 1.

4. The manufacturer shall not release the product from the manufacturing plant until a decision on paragraph 1 is made appropriately.

#### **(Validation)**

**Article 12.** The manufacturer shall have a person, designated beforehand, perform the following duties in accordance with the operating procedures etc.

(1) To perform validation in the following cases:

A. Cases where manufacturing of pharmaceutical excipients is newly started at the manufacturing plant.

B. Cases where a change which might cause a serious effect on the quality of the pharmaceutical excipient is made.

C. Other cases required for the proper conduct of manufacturing control and quality control of pharmaceutical excipients.

(2) To report in writing to the quality unit the protocol and the results of validation.

2. The manufacturer shall take all the required action, if improvements are found necessary for the manufacturing control and quality control based on the results of validation in Item 1 of the preceding paragraph, prepare records of the action taken,

and to retain the records.

**(Control of changes)**

**Article 13** In cases where a change in the operating procedures etc., which might cause an effect on the quality of the product, is to be made, the manufacturer shall have a person, designated beforehand, perform the following duties in accordance the operating procedures:

- (1) To evaluate the effect of the change concerned on the quality of the product, to obtain approval from the quality control unit on the change to be made based on the result of evaluation, to prepare the records of the results, and to retain the records.
- (2) When changes are to be made based on the approval of the quality control unit in accordance with the preceding item, to revise the operating procedures concerned, to conduct training of personnel, and to take other actions necessary.

**(Control of deviation)**

**Article 14** When there is a deviation from the manufacturing procedures etc. (hereinafter referred to as “deviation”), the manufacturer shall have a person, designated beforehand, perform the following duties in accordance the operating procedures etc.:

- (1) To record the contents of the deviation.
- (2) When there is a critical deviation, to perform the following duties:
  - A. To evaluate the effect of the deviation on the quality of the product and to take appropriate actions.
  - B. To prepare records of the results of evaluation and the actions taken as stipulated in the preceding A, to retain the records, and to report in writing to the quality control unit.
  - C. To obtain confirmation from the quality control unit on the results of evaluation the actions taken as stipulated in the preceding B.
2. The manufacturer shall have the quality control unit prepare records of the results of confirmation pursuant to Item (2) C. of the preceding paragraph in accordance with the operating procedures etc., retain the records, and to report the results along with the records in Item (2) B. of the preceding paragraph properly in writing to the product security pharmacist.

**(Information about quality etc. and management of defective products)**

**Article 15** When information about quality etc. (hereinafter referred to as an “quality information”) of the product (excluding intermediate products; the same under this article) is received, the manufacturer, unless it is evident that the manufacturing plant is not responsible for the matters relevant to the quality information, shall have a person, designated beforehand, perform the following duties in accordance with the operation procedures etc.:

- (1) To investigate the cause of the quality information, and to take all the required actions if improvements are found necessary for the manufacturing control and quality control.
  - (2) To prepare records describing the contents of the quality information concerned, clarified causes, as well as corrective actions taken, to retain the records, and to report in writing to the quality control unit without delay.
  - (3) To obtain confirmation from the quality control unit on the record of the preceding Item (2).
2. If actual or potential defects in quality of a product are confirmed based on the confirmation as stipulated in Item (3) of the preceding paragraph, the manufacturer shall have the quality control unit report the fact concerned in writing to the product security pharmacist in accordance with the operating procedures etc.

**(Recall action)**

**Article 16** When recall action is taken for the reason connected with the quality etc. of the product (excluding intermediate products; the same under this article), the manufacturer shall have a person, designated beforehand, perform the following duties in accordance with the operation procedures etc.:

- (1) When the recalled products are to be stored, to store the recalled products by separation for a fixed time, and to properly dispose the recalled products.
- (2) To prepare recall action records describing the contents of the recall, to retain the records, and to report in writing to the quality control unit and product security pharmacist.

**(Self-inspection)**

**Article 17** The manufacturer shall have a person, designated beforehand, perform the following duties in accordance with the operating procedures etc.:

- (1) To perform the regular self-inspection of manufacturing control and quality control of products at the manufacturing plant.
- (2) To report the results of self-inspection in writing to the product security

pharmacist.

(3) To prepare records of the self-inspection results, and to retain the records.

2. The manufacturer shall take all the required actions if improvements are found necessary for the manufacturing control and quality control based on the results of self-inspection as stipulated in Item 1 of the preceding paragraph, and prepare records of the action taken, and to retain the records.

#### **(Training)**

**Article 18** The manufacturer shall have a person, designated beforehand, perform the following duties in accordance with the operating procedures etc.:

(1) To conduct systematically training of personnel engaged in manufacturing control and quality control regarding the manufacturing control and quality control.

(2) To report the status of training in writing to the product security pharmacist.

(3) To prepare records of the conduct of training, and to retain the records.

#### **(Document and record control)**

**Article 19** The manufacturer shall have a person, designated beforehand, perform the following duties to control the documents and records that relate to the requirements of this Standard in accordance with the operating procedures etc.:

(1) In the preparations or revisions of the documents, to approve, distribute and retain in accordance with the operating procedures etc.

(2) In the preparations or revisions of the operating procedures etc., to put a date to the operating procedures etc. concerned and to retain the records containing the progress of the revisions concerned made so far.

(3) To retain the documents and records that relate to the requirements of this Standards for 5 years after the date of recording (in the case of the operating procedures etc., after the date of stopping to use) [in the case of the products (excluding intermediate products; the same in this article) concerned with the records etc., for which the term of quality assurance plus one year exceed 5 years, the term of quality assurance plus one year, excluding the records for the training].

(4) In the case of the products for which a retesting date is prescribed instead of the term of quality assurance, to retain the documents and records concerned for 3 years after the date when the distribution of the concerned lot of product from the manufacturing plant has been completed.

## **2. SELF-IMPOSED STANDARDS FOR BUILDINGS AND FACILITIES FOR MANUFACTURING PLANTS OF PHARMACEUTICAL EXCIPIENTS (GMP HARDWARE)**

### **(Purpose)**

**Article 1** The purpose of this Standards is to provide guidance on self-imposed controls required for assuring the adequacy of buildings and facilities for manufacturing plants of pharmaceutical excipients, and to enable pharmaceutical excipients to match with requirements raised through the development of pharmaceutical drug products of higher quality, both with a final intent to promote and level up the public health care.

### **(Buildings and facilities of manufacturing plants for the manufacturer of pharmaceutical excipients)**

**Article 2** The buildings and facilities of manufacturing plants for products concerned with pharmaceutical excipients shall meet the following requirements:

#### **(Manufacturing plant)**

- (1) To have adequate facilities and equipment for the manufacture of the products at the manufacturing plant.
- (2) To appropriately lay out the facilities and equipment so that contaminations and confusions of product etc., labeling materials and packaging materials are prevented; smooth and proper operations are not interfered; and cleanings and maintenances are easily operated.
- (3) To have facilities for supplying water etc. of the quality or quantity needed to manufacture the product (including cleaning water for facilities, equipment and containers).
- (4) To have washing and toilet facilities and dressing rooms.
- (5) Facilities and equipment (including facilities etc. where air and water are participated and come in contact with products) used in common with manufacturing of different products (including intermediate products) shall be appropriately laid out so as to facilitate the smooth and proper conversion operation and structured for easy cleaning and maintenance and for preventing cross-contamination.
- (6) When manufacturing facilities (including facilities etc. where air and water are participated and come in contact with products) for different products (including intermediate products) are built together in the same work area or work room, action shall be taken to prevent cross-contamination.

- (7) Following operating procedures etc., cleaning and maintenance of facilities and equipment shall be appropriately performed in accordance with the purposes for which they are used, sterilization shall be performed according to need, these shall be put on records, and the records shall be retained.
- (8) To have facilities for the disposal of poisonous gases if generated in manufacturing any particular item.

**(Work area)**

- (9) Work areas shall meet the following requirements:
  - A. To be adequately lighted, illuminated, ventilated and cleaned.
  - B. To be distinctly separated from living quarters and other unsanitary areas.
  - C. To have an adequate area for the operations to be performed.
  - D. To have facilities for the control of dust, insects and rodents. Proviso: This provision shall not apply to the work area where the manufacturing process is carried out prior to the final purification insofar as the manufacturing facilities for such process have a well-closed structure.
  - E. To have facilities or equipment for the disposal of sewage and waste.
  - F. To have facilities for the disposal of poisonous gases if generated in manufacturing any particular item.

**(Work room)**

- (10) Among the work areas, the work room shall be provided with facilities and equipment for the prevention of contamination by dust and microorganism, based on the kind of product and manufacturing process of intended product. Proviso: This provision shall not apply when the same effects are obtained from the functions of the manufacturing facilities, etc.
- (11) Among the work areas, the work room for weighing raw materials, formulating, filling or sealing products shall be constructed so as not to allow passage for personnel other than those working in the room. Proviso: This provision shall not apply when there is no risk of contamination by personnel other than those working in the room.
- (12) Among the work areas, the work room for filling to sealing intermediate products which have undergone the final purification shall meet the following requirements:
  - A. To have no entrances and exits opening directly to the exterior, except for an emergency exit. Proviso: This provision shall not apply to work rooms provided with facilities and equipment for prevention of contamination from exterior.
  - B. To have entrances, exits and windows of the room that can be locked.

- C. The sewage disposal facilities in the room shall be constructed so as to prevent contamination of the room.
- D. The ceiling of the room shall be constructed so as to prevent dust and dirt from falling.
- E. To have pipes and ducts in the room constructed so as to prevent accumulation of dust and dirt on their surface. Proviso: This provision shall not apply when the pipes and ducts can facilitate the easy cleaning.

**(Storage of raw materials, labeling and packaging materials and products)**

- (13) To have adequate facilities for the sanitary and safe storage of raw materials, labeling and packaging materials and products which are separated.

**(Facilities and equipment for the analysis and testing)**

- (14) To have facilities and equipment for the analysis and testing of products etc., labeling and packaging materials. Proviso: This provision shall not apply when the analysis and testing are performed on the manufacturer's own responsibility using other testing facilities of the manufacturer or other testing institutions without causing hindrance to the proper analysis and testing.

**(Buildings and facilities of partial processing plants for packaging etc.)**

**Article 3** The buildings and facilities of partial processing plants for packaging etc. shall meet the following requirements:

- (1) To have adequate facilities and equipment for the sanitary and safe storage of products (excluding intermediate products; the same in this article), and labeling and packaging materials.
- (2) To have an adequate area for the operations to be performed.
- (3) To have adequate facilities and equipment for the analysis and testing of products, and labeling and packaging materials. Proviso: This provision shall not apply when the analysis and testing are performed on the manufacturer's own responsibility using other testing facilities of the manufacturer or other testing institutions without causing hindrance to the proper analysis and testing.



### **3. SELF-IMPOSED STANDARDS FOR MANUFACTURING CONTROL AND QUALITY CONTROL OF PHARMACEUTICAL EXCIPIENTS (VALIDATION STANDARDS)**

#### **1. On Validation Standards**

It is stipulated that the validation mentioned in “SELF-IMPOSED STANDARDS FOR MANUFACTURING CONTROL AND QUALITY CONTROL OF PHARMACEUTICAL EXCIPIENTS (GMP SOFTWARE)” be performed according to the following “Validation Standards” and “Enforcement Requirements for the Validation Standards”.

#### **2. Validation Standards**

##### **(1) Purpose**

The purpose of validation is to validate that buildings and facilities of a manufacturing plant, and manufacturing procedures, process and other methods of manufacturing control and quality control (hereinafter referred to as “the operating procedures etc.”) yield anticipated results, and to ensure the constant manufacture of products of intended quality by documenting such procedures.

##### **(2) Definitions**

- A.** “Anticipated results” means concrete and verifiable specifications or standards to be met each facility, process and product for the manufacture of products of intended quality.
- B.** “Manufacturing support system” means a manufacturing water supply system and air-condition system.
- C.** “Facility qualification” mean confirmation of appropriate selection and proper installation of manufacturing facilities, measuring instruments, manufacturing environment control facilities, etc., and appropriate operation thereof in conformity with the assigned specifications at the time of installation and maintenance thereof.
- D.** “Calibration” means clarification of a relationship of the values obtained by measuring instruments used in the manufacturing operations and the true value, using appropriate standard measuring instruments and standard substances in consideration of required accuracy.
- E.** “Performance qualification” means confirmation, by means of a challenge test etc., of appropriate operation of the manufacturing procedures as originally intended (producing expected results) in the whole range of expected operating conditions.

- F.** “Challenge test” means a test to confirm that the expected results are obtained in the worst case.
- G.** “Worst case” means an upper or lower limit of the permissible manufacturing conditions within the range of the operating procedures.
- H.** “Confirmation at an actual production scale” means confirmation, that each facility, process, quality of products yield anticipated results by manufacturing a product (three lots in principle) at an actual manufacturing scale, using buildings and facilities at the manufacturing plant concerned.
- I.** “Prospective validation” means identification, based on the results of study for industrialization and past production records of similar products, of variation factors (e.g., physical properties of raw materials, and labeling and packaging materials, operating conditions, and hereinafter referred to as “variation factors”) which may give effect on the quality of the specified products, for each of the subjects to be validated specified in Section (3) of this Standards, and validation of the appropriateness of permissible conditions of the variation factors for constant manufacture of products of intended quality.
- J.** “Regular verification of process control” means evaluation and confirmation to be made after starting manufacturing of a pharmaceutical excipient that the variation factors are within the scope of permissible conditions by means of collecting the results of process control and testing and analysis routinely performed.
- K.** “Revalidation on change” means a validation to be conducted when a change made in raw materials, labeling and packaging materials, manufacturing process and buildings and facilities is deemed to cause a serious effect on the quality of products. As in the case of the prospective validation, revalidation for change shall be conducted to identify variation factors and to validate the appropriateness of permissible conditions of the variation factors for constant manufacture of products of intended quality.
- L.** “Regular revalidation” means a validation to be conducted for regular confirmation of a change with time in the process specificity and the product quality. The timing and the details of the regular revalidation shall be determined in consideration of production frequency and results of the regular verification of process control. This revalidation verifies that the variation factors and corresponding permissible conditions remain appropriate for constant manufacture of products of intended quality.
- M.** “Retrospective revalidation” means statistical analysis of test data and

production records collected for the well-established manufacturing process. This validation is conducted exceptionally in place of confirmation at an actual production scale.

N. “Concurrent validation” means a validation conducted in step with an actual manufacturing. This validation is conducted when data on manufacturing operation cannot be used for prospective validation or revalidation on change for the reasons that the number of manufacturing lots is limited, manufacturing of the product concerned is rare, or a product is manufactured using a validated process while making improvements.

**(3) Subjects to Be Validated**

The manufacturer shall perform validation of operation procedures etc. for the product validated, in principle, regarding the following items. Proviso: Regarding items A and C, it shall be satisfactory to conduct the validation for each facility or equipment respectively, and regarding C, it shall be satisfactory to evaluate depending on the indicator components alone on the basis of rational grounds.

- A. Manufacturing process
- B. Manufacturing support system
- C. Cleanliness and other operations

**(4) The Operating Procedures for Validation**

- A. The operating procedures for validation pursuant to the provisions of Article 8, Paragraph 4, Item 2 of the Self-imposed Standards of Good Manufacturing Practices for Pharmaceutical Excipients shall contain the following.
  - (A) Matters concerning the responsibility etc. of a person previously designated by the manufacturer specified under Article 12, Paragraph 1 of the Self-imposed Standards of Good Manufacturing Practices for Pharmaceutical Excipients (hereinafter referred to as “validation manager”).
  - (B) Matters concerning timing of validation specified in Section (5) B of this Standards.
  - (C) Matters concerning preparation, amendment and approval of the protocol specified in Section (5) A of this Standards.
  - (D) Matters concerning reports, evaluation and approval (including recording method) of the validation results.
  - (E) Matters concerning keeping the validation documents.
  - (F) Other necessary matters.
- B. The operating procedures for validation shall be prepared for the subjects validated specified in Section (3) of this Standards as specified in Section (5) of

this Standards.

- C. In the operating procedures for validation, the name of the enactor of the procedure, the date of enactment and, in case of an amendment, the name of the person responsible for the amendment, the date, contents and reason for the amendment shall be recorded.
- D. The manufacturer shall appropriately maintain the operating procedures for validation after clearly establishing the process of revision and the abolition of details of the operating procedure for validation.

**(5) Duties of Validation Manager**

The validation manager shall fulfill the duties as specified in the following Items in accordance with the operating procedures for validation.

- A. To prepare a validation protocol (hereinafter referred to as “protocol”) for manufacturing processes of products to be manufactured in accordance with the operating procedures for validation. The following matters shall be mentioned in the protocol in consideration of the content of validation.
  - (A) Items of validation
  - (B) Purpose of respective validation items (including the purpose of validation itself).
  - (C) Expected results of a manufacturing process etc.
  - (D) Method of validation (including method of evaluation of the validation results).
  - (E) Duration of validation
  - (F) Name of the person responsible for validation
  - (G) Name of the preparer of the protocol and the date of preparing the protocol and, in case of amendment, the name of the person responsible for the amendment, date, contents and reason for the amendment.
  - (H) Other necessary matters.
- B. To conduct the following validations in accordance with the protocol provided under the section (5) A of this Standards.
  - (A) Prospective validation items conducted in case for new manufacturing of pharmaceutical excipient:
    - 1. Installation qualification of facilities
    - 2. Calibration
    - 3. Performance qualification
    - 4. Confirmation at an actual production scale
  - (B) Validation conducted periodically except for prospective validation after

starting manufacturing of pharmaceutical excipient:

1. Revalidation on change

- ① Facility qualification on change
- ② Calibration of measuring instruments on change
- ③ Performance qualification on change
- ④ Confirmation at actual production scale on change (In principle, three lots of a product are manufactured as the revalidation on change. Otherwise at least one lot of a product is manufactured as the concurrent validation.)

2. Regular revalidation

- ① Facility qualification when checked for maintenance.
- ② Calibration on the meter inspection
- ③ Performance qualification (item conducted according to need)

3. Regular verification of process control

Results of process control, and testing and analysis routinely performed are collected and evaluation and confirmation are made that the variation factors are within the scope of permissible conditions.

C. To confirm on evaluation that the expected validation results are achieved.

D. Other duties prescribed in Article 12 of the Self-imposed Standards of Good Manufacturing Practices for Pharmaceutical Excipients.

**3. Enforcement Requirements for the Validation Standards**

**(1) Status of Existing Manufacturing Products**

Products which have been manufactured shall be subject to in compliance with the following requirements so far as they are intended for continued manufacture.

**A. Confirmation at an actual production scale**

If prospective validation has not been conducted, confirmation shall be made of the product (three lots in principle) at an actual production scale in step with the manufacturing of the product concerned. In case of a product which has no planned manufacturing, validation items shall be established and entered in the operating procedures for validation. Proviso: This provision may not apply to the product of which case is judged as that applying of retrospective validation or concurrent validation is appropriate.

**B. Revalidation**

**(A) Revalidation on Change**

The revalidation on change shall be conducted in accordance with (5) B (B) 1

of this Standards in the case where the change in raw materials, labeling and packaging materials, procedures, manufacturing process and building and facilities are made in accordance with the Self-imposed Standards of Good Manufacturing Practices for Pharmaceutical Excipients, so long as the change may affect the quality of the product.

**(B) Regular Revalidation**

If a trend analysis is impossible due to inadequate data from the regular verification of process control, hence the timing and items of validation are not established, the timing, items and procedures to select items for validation shall be mentioned in the operating procedures for validation.

**(C) Retrospective validation**

If data are inadequate for statistical analysis, the procedures to collect data shall be described in the operating procedures for validation so that the validation is conducted on collection of adequate data.

**(D) Subjects to Be Validated**

Validation shall be conducted of a product as to the subjects specified in this Validation Standard 2 (3). Proviso: If it is possible that there is no presence of change (changes in raw materials, labeling and packaging materials, manufacturing process, building and facilities etc.) which have an effect on the quality of products, application may be limited, for the time being, to manufacturing processes that may give a serious effect on the quality of products (hereinafter referred to as “critical processes), in consideration of product characteristics.

**(2) Products Manufactured for Confirmation at an Actual Production Scale**

When validation is conducted as to the subjects specified in this Validation Standards 2 (5) B, the product thus manufactured (excluding intermediate product; the same hereinafter) may be shipped as the product after confirmation that the product has been manufactured in accordance with the Self-imposed Standards of Good Manufacturing Practices for Pharmaceutical Excipients, and passed the specifications for pharmaceutical excipients.

Concluded

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