Chapter 5 Manufacture at Two or More Than Two Manufacturing Plants

(Manufacture at two or more than two manufacturing plants)

Article 16 Each manufacturer who entrusts the partial performance of manufacturing process of a pharmaceutical excipient (hereinafter referred to as "entruster") to a manufacturing plant of another manufacturer (hereinafter referred to as "entrustee") shall make an agreement with the said entrustee for the following Items, in order to assure a proper implementation of manufacturing control and quality control of the said manufacturing process.

(1) The scope of the said contract.

(2) Technical conditions concerning the manufacture to be conducted on the basis of the said contract (hereinafter referred to as "contract manufacturing").

(3) Confirming by the entruster at regular intervals that the said contract manufacturing is properly performed at the manufacturing plant of the entrustee.

(4) Providing the entrustee with instructions as to the said contract manufacturing .

(5) Confirming the completion of any corrective actions, when the entruster has recognized the need of making any improvement on manufacturing control or quality control of the said contract manufacturing and has provided with instructions to take actions required in accordance with the above Item.

(6) Quality control procedures for goods transport and delivery.

(7) Miscellaneous particulars required for ensuring a proper implementation of manufacturing control and quality control of the contract manufacturing.

2. The entruster and the entrustee shall describe the above agreement in Product Standard Code, Manufacturing Control Standard Code, Manufacturing Hygiene Control Standard Code, and Quality Control Standard Code In this case, however, it may be sufficient for these documents to contain only particulars relevant to portions of manufacturing process to be carried out by either the entruster or the entrustee on their own, irrespective of the requirements of Article 5, Article 6, Article 8, and Article 10.

3. Instructions by the entruster in accordance with requirements of Item 4 in Paragraph 1 shall be established in written form.

4. The entrustee shall report in written form to the entruster that the product security pharmacist of the entrustee has evaluated properly the result of manufacturing control and quality control concerning the said contract manufacturing before shipment.

5. The entruster shall charge an individual having prior destination with duties given in the

following Items.

(1) Confirming in accordance with requirements in Items 3 and 5 of Paragraph 1.

(2) Reporting in written form the result of confirmation according to the previous Item to the product security pharmacist of the manufacturing plant of the entruster.

(3) Establishing the record of confirmation according to Item 1 and maintaining it for 3 years from the date of establishment.

[Commentary]

15. Points Related to Article 16

A. In Paragraph 1 "manufacturing process of pharmaceutical excipients" means the process of from the supply of raw materials to the judgment for shipping approval.

B. In Item 2 of the same Paragraph "technical conditions" mean those that follow.

(a) Matters pertaining to Product Standard Code.

(b) Matters pertaining to Manufacturing Control Standard Code, Manufacturing Hygiene Control Standard Code.

(c) Matters pertaining to Quality Control Standard Code.

C. In Item 3 of the same Paragraph "confirming by the entruster at regular intervals that the said contract manufacturing is properly performed at the manufacturing plant of the entrustee" means that the entruster evaluates at regular intervals in a proper manner that the said contract manufacturing is performed according to an appropriate manufacturing control and quality control. Particularly when it corresponds to a contract on partial processing license of manufacture specified as "special case of manufacturing at two or more than two manufacturing plants" in 3 of Article 1 of the Ordinance for the Enforcement of the Pharmaceutical Affairs Law, the entruster should make an on-the-spot evaluation at the manufacturing plant of the entrustee. In addition, "at regular intervals" means that the confirmation should be commenced before start of manufacturing the first lot to be released.

D. In Item 4 of the same Paragraph "providing the entrustee with instructions" means that the instructions should include those for any actions required for a case when the entrustee recognizes the need of making improvement on manufacturing control and quality control for conducting the said contract manufacturing.

E. In Item 6 of the same Paragraph "quality control procedures" are those that include the

following matters.

(a) Matters pertaining to transporting intermediate products between the entruster and the entrustee.

(b) Matters pertaining to testing intermediate products in shipping and receiving.

(c) Matters pertaining to handling intermediate products that are non-conformable to specifications in the case of (b).

F. In Item 7 of the same Paragraph "particulars required" are those that include the following matters.

(a) Matters related to liaison individual(s) designated to each other.

(b) Matters related to making communication as to any change in manufacturing methods, conditions, and the like.

(c) Matters related to establishing and holding a record required for manufacturing control, quality control, and the like.

(d) Matters related to reporting any issue occurred in the said contract manufacturing process.

(e) Matters related to handling any complaint.

G. In the provisory clause of Paragraph 2 "it may be sufficient for these documents to contain only particulars relevant to portions of manufacturing process to be carried out by either the entruster or the entrustee on their own" means that it is sufficient for the entruster and the entrustee to describe matters pertaining to the manufacturing process they conduct on their own; however, the entruster should possesses copies of documents relevant to validation carried out by the entrustee.

H. In Paragraph 4 "that the product security pharmacist of the entrustee has evaluated properly the result of manufacturing control and quality control concerning the said contract manufacturing before shipment" means that the product security pharmacist should evaluate the contract manufacturing of the said pharmaceutical excipient to have been performed properly according to appropriate procedures for manufacturing control and quality control, including the result of such performance, for making judgment of shipping approval.

I. In Paragraph 5 "an individual having prior destination" purports the same as are given in the above A of '10'.

Article 17 Each manufacturer shall establish procedures of quality control for transport, receipt, and delivery, as well as the other miscellaneous particulars required, in order to assure the proper performance of manufacturing control and quality control at the said manufacturing process, in a case when the manufacture of a pharmaceutical excipient is to be conducted at two or

more than two manufacturing plants of the manufacturer.

2. Each manufacturer shall describe in Product Standard Code, Manufacturing Control Standard Code, Manufacturing Hygiene Control Standard Code, Quality Control Standard Code, or written procedures those particulars established in accordance with the above Item in this case, however, it may be sufficient for these documents to contain only particulars concerning the partial manufacturing process to be carried out in each relevant manufacturing plant, irrespective of the requirements of Article 5, Article 6, Article 8, and Article 10.

[Commentary]

16. Points Related to Article 17

A. In Paragraph 1 "the manufacture of a pharmaceutical excipient is to be conducted at two or more than two manufacturing plants of the manufacturer" means that in-house contract manufacturing and in-house subdividing for the manufacture of a pharmaceutical excipient are conducted by the same manufacturer at two or more than two manufacturing plants of their own.

B. In Paragraph 1 "procedures of quality control for transport, receipt, and delivery, as well as the other miscellaneous particulars required" purports the same as in (e) of the above '15'; also included are those particulars that are considered necessary to be established and consequently self-established with reference to Article 16 of this self-imposed Standard.

C. In the provisory clause of Paragraph 2 "it may be sufficient for these documents to contain only the particulars concerning the partial manufacturing process to be carried out at each relevant manufacturing plant" means that the description may contain only the particulars relevant to the manufacturing process to be carried out at each relevant manufacturing plant.

Self-Imposed Standards for Buildings and Facilities of Manufacturing Plants For Pharmaceutical Excipients ("GMP Hardware": Draft) And Its Commentary

(Purpose)
Article 1

The purpose of the present self-imposed Standards is to provide guidance on self-imposed controls required for buildings and facilities of manufacturing plants for 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

1. In the present Standards the term "pharmaceutical excipient" means any substance to be added during the course of formulating a pharmaceutical drug product for ensuring the stability, safety and homogeneity, as well as for promoting the dissolution or for controlling the release in accordance with characteristic features of the dosage form.

2. In the present Standards "product" means a finished product of a pharmaceutical excipient obtained after all the manufacturing processes are completed.

3. In the present Standards "raw materials" means substances to be used for manufacturing pharmaceutical excipients (including substances not contained in the product), excluding packaging materials and intermediate products.

4. In the present Standards "packaging materials" means packages, containers, liners for the product, and labels to be attached onto the package and/or the container.

5. In the present Standards "intermediate product" means a material prepared in the intermediate process of manufacturing a pharmaceutical excipient product, which will undergo further processing to become a pharmaceutical excipient product.

[Commentary]

1. In Relation to Articles 1 and 2

(1) For pharmaceutical drug products and pharmaceutical active ingredients as bulk drug substances, compliance to relevant regulations has been regarded as application approval criteria, for the purpose of assuring a high level of quality of the drug product and the pharmaceutical active ingredient through the manufacturing process. For pharmaceutical excipients, the quality has been assured up to the present through various firm-claimed control standards. Such a situation as above has resulted in establishing the present self-imposed Standards to harmonize well with the existing regulations for pharmaceutical drug products and pharmaceutical active ingredients.

(2) It should be remembered that the purpose of this GMP (The Standards of Manufacturing and the Quality Controls for Pharmaceutical Excipients) can be achieved through compliance to the control-related Standard (GMP software) coupled with the equipment-related Standard (GMP hardware).

(3) A pharmaceutical excipient, which is described in the Pharmacopoeia of Japan and to which Paragraph 1 of Article 5, Chapter 2 (Buildings and Facilities for Drug Manufacturing Plants to Which the Standards for Manufacturing Control and Quality Control Shall Not Apply) in "Regulations for Buildings and Facilities for Pharmacies etc. (the Ministry of Health and Welfare Ordinance No. 2, dated February 1, 1961)" is applied, should meet all requirements in the said "Paragraph 1 of Article 2, Chapter 2 of the Regulations for Buildings and Facilities for Pharmacies etc.", as well as requirements of the present self-imposed Standards.

(4) Typically, the process for manufacturing a pharmaceutical excipient is composed of various stages (for example, reaction, extraction, distillation, crystallization, filtration/washing, and sieving) through which the purity is increased stepwise. Accordingly, the self-imposed Standards should be applied to every stage in and after charge-in of raw materials, and concentrated control in accordance with the self-imposed Standards should be maintained in and after the stage that may have a critical effect on the product quality (stages in which intermediate products capable of decisively governing the quality of the pharmaceutical excipient are produced).

(5) Pharmaceutical excipients are so many in kind and so different in manufacturing process from one another, depending on their starting materials, method of manufacture, facilities for the manufacture, or the like, that "any step that may give a serious effect on the product quality" of a pharmaceutical excipient should be determined by the manufacturer, and the rationale should be documented in Product Standard or relevant documents.

(General Provisions)
Article 3

1. The plant shall have facilities and equipment necessary for and adequate to the manufacture of the product (including its intermediate products).

2. Any facilities and equipment (including those related to the handling of air and water

that come in contact with the product and their intermediate products), which are used in common for manufacturing different products (including their intermediate products), shall be placed to facilitate smooth and proper change-over operations without difficulty and to have such structures with such considerations given to the prevention of cross contamination as those capable of smooth cleaning and maintenance.

3. Appropriate actions shall be taken against cross contamination, when buildings and facilities for manufacturing different product items (including facilities and the like for the air and water that come in contact with the product and their intermediate products) are juxtaposed in the same work area or the same work room.

[Commentary]

2. In Relation to Articles 3

(1) The categories of "manufacturing plant" in Paragraph 1, "work area" and "work room" in Paragraph 3 should be specified as follows:

A. "Manufacturing plant" means an operation plant or a factory for manufacturing the pharmaceutical excipient.

B. "Work area" means an area in which work for manufacturing the pharmaceutical excipient is performed, with the proviso that appurtenant facilities, such as offices, resting rooms, gowning rooms, toilets, testing rooms, power houses, power distribution stations, stocks depositories, etc. are excluded, insofar as these are segregated from the work area.

C. "Work room" means a separated area in the work area for performing the operations of weighing and charging raw materials, as well as of formulating, filling or sealing products (including intermediate products undergoing the final purification), with the proviso that gowning rooms, air-shower rooms, anterooms, materials receiving rooms, equipment washing rooms, toilets, etc. are included, insofar as they are adjoined to the work room.

(2) "Facilities and equipment necessary for and adequate to the manufacture" in Paragraph 1 means those that follow:

A. "Facilities and equipment necessary for" means facilities and equipment necessary on the occasion of manufacture of a product at the manufacturing plant, and those necessary for manufacturing an intermediate product.

B. "Facilities and equipment adequate to manufacture" means the facilities and equipment provided with materials, structures, and placement, each adequate for the manufacture of the intended quality of product.

(3) "Placed to facilitate smooth and proper change-over operations without difficulty" in Paragraph 2 means the following:

A. The facilities and equipment should be placed and constructed with considerations given to minimizing residuals of components of the preceding product item.

B. The facilities and equipment should be provided with materials, structure, and placement, with considerations given to smooth performance of cleaning operations in product change-over (including operations of cleaning and rinsing with the succeeding product after the change-over), as well as smooth performance of maintenance work.

C. In addition to the above, the facilities and equipment should be designed with considerations on the possibility of contamination from exterior sources during change-over operations.

D. In the above actions of A, B, and C, the extent of cross contamination associated with the product change-over should be permissible, if it falls within a range that the contamination has no impact on the function and the safety of each pharmaceutical excipient concerned.

(4) "Different product items" in Paragraphs 2 and 3 means other product items of different chemical structure or composition from the pharmaceutical excipient concerned. Any product item identical to the pharmaceutical excipient concerned in chemical structure or in composition, but different in product name because of its intended use, is not called a different product item.

(5) "Facilities and equipment used in common for manufacturing different products" in Paragraph 2 means to involve a case where parts of the facilities and equipment (including facilities etc. of the air and the water that come in contact with the product or its intermediate products) are in common use for manufacturing different products. Provided that, in a case where different two or more product items are manufactured concurrently through processing, such as distillation and sieving, in a series of manufacturing process, those facilities and equipment in the ante-processes including distillation, sieving, etc., are not called as facilities and equipment in common use.

(6) "Facilities and equipment in juxtaposition" in Paragraph 3 means to include a case where parts of facilities and equipment for manufacture of different product items (including facilities etc. of the air and the water that come in contact with the product or its intermediate products) are juxtaposed in the same work area.

(7) "Actions shall be taken against cross contamination" means either one of the following actions:

A. The manufacturing facilities concerned have a tightly-sealed structure or a structure capable of isolating or segregating the exposed portion.

B. Operations for the manufacture of different product items are controlled so as not to conduct concurrently.

C. Using the other methods, control is carried out so that the extent of cross contamination may fall within a range that the contamination has no impact on the function and the safety of each pharmaceutical excipient concerned.

(Work Area)

Article 4

Work areas shall meet the following requirements. Proviso: This provision shall not apply to a case where manufacturing facilities in the manufacturing process concerned are well-closed structure.

A. To be adequately lighted, illuminated, ventilated, and cleaned.

B. To be distinctly separated from living areas and other unsanitary areas.

C. To have an adequate area for the operations to be conducted.

D. To have facilities for the control of dust, insects, and rodents.

E. To have floors made of wood, concrete or equivalent materials.

F. To have draining and ventilation facilities and equipment provided with structures needed to prevent contamination of the work area.

G. To have facilities needed for the disposal of sewage and waste.

H. To have disinfection facilities for operating personnel.

I. To have facilities for the treatment of hazardous gases if generated in manufacturing any particular item.

[Commentary]

3. In Relation to Articles 4

(1) "Living areas and other unsanitary areas" in B means the field for daily life that might produce dust or microbial contamination, such as living rooms, resting rooms, kitchens, toilets, garbage pits, or ditches.

(2) "Adequate area for the operations to be conducted" in C means to include the space for easily conducting maintenance, inspection, and cleaning, as well as clear the passage.

(3) "Equivalent materials" in E means any material that is incapable of dust generation and has a smooth surface and easily cleanable structure.

(4) "To have facilities needed for the disposal of sewage and waste" in G means to have facilities or equipment for removing and disposing sewage and waste that have generated during processing, so that the sewage and waste cannot affect the succeeding process or deteriorate the product. The final methods and procedures should be enough to comply with legal regulations concerned, as well as the policy of the manufacturer.

(5) "Disinfection facilities" in H means hand-washing facilities provided with cationic

detergents, disinfecting agents, sterilizing lamps, or the like.

(Work Room)
Article 5

Work rooms shall meet the following requirements.

A. Work tables in the work room shall be constructed so as not to hinder the smooth, proper operations.

B. Work rooms shall be constructed so as not to allow passage for personnel other than those working in the work room. Proviso: This provision shall not apply to a case where there is no risk of contamination of pharmaceutical excipients caused by personnel other than those working in the room.

C. The entrances, exits, and windows shall be capable of locking.

D. The ceilings shall be made of wood, concrete or equivalent materials, and be boarded so as to prevent dust and dirt from falling.

E. The floors shall be made of concrete, tile, mortar, wood with a smooth surface free of crevices, or those of equally cleanable materials.

F. Pipes and ducts in the room shall be 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.

G. When facilities for performing such operations as subdividing, filling, or packaging of different products (including intermediate products) are juxtaposed, measures shall be taken to prevent cross contamination.

H. The draining and ventilation facilities and equipment in the work room shall be provided with structures needed to prevent contamination of the work area.

I. To have gowning rooms. Proviso: This provision shall not apply to the case where there is no risk of contamination of the product.

[Commentary]

4. In Relation to Articles 5

(1) "Work tables in the work room shall be constructed so as not to hinder the smooth, proper operations" in A means the following:

A. To be constructed with materials capable of not generating contamination with dust or

microorganisms, as well as of easy cleaning.

B. To have adequate space with consideration for the prevention of mixup and mistakes that might occur during operations.

(2) "To be constructed so as not to allow passage for personnel other than those working in the work room" in B means that the work room concerned should be placed so as not to be used as passage to other work areas or work rooms.

(3) "A case where there is no risk of contamination of pharmaceutical excipients caused by personnel other than those working in the room" in B means either one of the following:

A. A case where the operation of subdividing, filling, packaging, or the like are conducted in a facilities of a closed system.

B. A case where there are facilities juxtaposed for sanitation prior to entering the work room, such as air-shower rooms, gowning rooms, or the like.

C. A case where controls are conducted using the other methods, so as to prevent any risk of contamination.

(4) "Be capable of locking" in C means lockable doors or any other measures to keep out unauthorized personnel, insects, birds, dust, or the like coming from the exterior.

(5) "Actions shall be taken to prevent cross contamination" in F means either one of the following:

A. The operations of subdividing, filling, or packaging of different product items are controlled so as not to conduct concurrently.

B. At least the facilities for subdividing, filling, or packaging of either one of different products are of a closed system.

C. Using the other methods, controls are carried out so that the extent of cross contamination may fall within a range that the contamination has no impact on the function and the safety of each pharmaceutical excipient concerned.

(Storage of Raw Materials, Packaging Materials, and Products) Article 6

There shall be adequate facilities for sanitary and safe storage in separated area of each raw materials, packaging materials, intermediate products, and products.

[Commentary]

5. In Relation to Articles 6

"There shall be adequate facilities for sanitary and safe storage" means the facilities needed for preventing contamination, deterioration and damage which might be caused by direct sunlight, soak in water, as well as by dust, insects, rodents, birds, etc. from the exterior.

(Facilities for Analysis and Testing)
Article 7

There shall be provided with facilities and equipment necessary for the analysis and testing of raw materials, packaging materials, intermediate products, and products. Proviso: This provision shall not apply to the case when the analysis and testing are performed on the manufacturer's own responsibility using other testing facilities of the manufacturer, the testing institutions designated by the Minister of Health and Welfare, or official testing institutions, from necessity under circumstances judged as unavoidable, without causing hindrance to the proper analysis and testing.

[Commentary]

6. In Relation to Articles 7

(1) "There shall be provided with facilities and equipment necessary for the analysis and testing of raw materials, packaging materials, intermediate products, and products" means to have facilities and equipment needed for conducting analysis and testing in accordance with the method and procedures specified in Product Standards for raw materials, packaging materials, intermediate products, and products.

(2) "When the analysis and testing are performed on the manufacturer's own responsibility using other analysis and testing facilities of the manufacturer, the analysis and testing institutions designated by the Minister of Health and Welfare, or official analysis and testing institutions" in the Proviso means to ask employees of the manufacturer to perform the analysis and testing using other analysis and testing facilities of the manufacturer etc., or to request other analysis and testing institution etc. for performing the analysis and testing on the manufacturer's own responsibility.

(3) "From necessity under circumstances judged as unavoidable, without causing hindrance to the proper analysis and testing" in the Proviso should be interpreted on the manufacturer's own responsibility, with reference to Matters in Notice 1 and 2 of Notification No. 410 from Pharmaceuticals and Cosmetic Division of Pharmaceutical Affairs Bureau, MHW, dated June 29, 1992 (On the Use of Other Analysis and Testing Facilities of the Manufacturer at the Manufacturing Plant of Pharmaceutical Products).