pharmacist.

**[Commentary]**

**3. Points Related to Article 4**

A. In Item 1 of Paragraph 1 "supervising both the manufacturing control manager and the quality control manager" means that, in the organized system of a manufacturing plant for pharmaceutical excipients, the product security pharmacist is senior in post to each of the manufacturing control manager and the quality control manager, and has yet a final authority and responsibility for manufacturing control and quality control.

B. In Item 2 of the same Paragraph "appropriately evaluating results from manufacturing control and quality control to make decision of approval for product release from the manufacturing plant" means that release approval of any excipient product manufactured should be decided only after grasping correctly each implemented status of manufacturing control and quality control; accordingly, each manufacturer should not release any excipient product without this decision.

C. In Item 3 of the same Paragraph "to confirm" means such confirmations that validation, internal audit, education/training, as well as those confirmations specified in Item 1 of Paragraph 5 in Article 16, have been all appropriately conducted; furthermore, in making confirmation on validation, internal audit, education/training and those confirmations specified in Item 1 of Paragraph 5 in Article 16, any finding of inappropriate performance of assigned duties should be reported to the manufacturer (or to the entrusting manufacturer in the case relevant to confirmations specified in Item 1 of Paragraph 5 in Article 16).

D. In Paragraph 2 "should avoid any hindrance" means that each manufacturer should never disturb the task performance of the product security pharmacist, and with no end to this, purporting that each manufacturer should support positively performing the duties of the product security pharmacist.

(Product Standard Code)

**Article 5** Each manufacturer shall establish Product Standard Code for each pharmaceutical excipient and for each manufacturing plant relevant to the manufacture of the said pharmaceutical excipient to describe the manufacturing procedures and miscellaneous particulars needed.

**[Commentary]**

**4. Points Related to Article 5**

A. "Manufacturing procedures and miscellaneous particulars needed" mean those that follow:

(a) General nomenclature and brand name of the pharmaceutical excipient to be manufactured.

(b) Date of approval (required only for an excipient product with approval for manufacture).

(c) Components (or characters, if the components are unclear).

(d) Specifications and test methods of raw materials, intermediates, and the excipient product.

(e) Specifications and test methods for liners.

(f) Specifications and test methods for containers.

(g) Specifications of indication materials and packaging materials.

(h) Manufacturing methods and manufacturing procedures (including in-process testing procedures).

(i) Standard quantity for charge-in of components and supporting evidences thereof.

(j) Storage conditions for intermediate products.

(k) Storage conditions for products.

(l) Precautions for use or handling.

As to the specifications and test methods, the following should be included in Product Standard Code:

(i) When more strict specifications and more accurate test methods than those specified in compendia are used, such specifications and test methods with supporting evidences.

(ii) Those firm-claimed specifications and test methods to be applied to raw materials and products which are established on the needs from quality control, together with supporting evidences thereof, when such specifications and test methods are not described in any compendia,

(iii) Those firm-claimed specifications and test methods to be applied to intermediates and containers and those firm-claimed specifications to be applied to indication materials and packaging materials, when such specifications and test methods are not described or insufficiently specified in any compendia and have accordingly been established on the needs from quality control.

(iv) As to (d), (e) and (f) in the above A, particulars for tests and examinations, together with specifications and test methods to be applied, when tests are performed at facilities different from those of the said manufacturer or by employing any institution specified by the Minister of Health

and Welfare or other official testing institutions.

As to the storage conditions, Product Standard Code should contain the description of those stability test results on which the conditions have been determined.

B. Product Standard Code should include the name of an individual in charge of establishment and the date of establishment; the name of an individual in charge of revision and the date of revision should be included, when revised.

## Chapter 2 Manufacturing Control

(Manufacturing Control Standard Code and Manufacturing Hygiene Control Standard Code)

**Article 6** Each manufacture shall establish for each manufacturing plant Manufacturing Control Standard Code that describes particulars relevant to the storage of raw materials, control of the manufacturing process, and the others needed. Concomitantly, Manufacturing Hygiene Control Standard Code shall be established for each manufacturing plant to describe particulars concerning hygiene control of the buildings and facilities (except those for testing and examination; the same shall apply hereinafter), hygiene control of operators, and the others needed.

**[Commentary]**

**5. Points Related to Article 6**

A. "Particulars relevant to the storage of raw materials, control of the manufacturing process, and the others needed" means those that follow:

(a) Precautions for receiving, storing, and releasing raw materials and packaging materials.

(b) Precautions for storing intermediates.

(c) Precautions for storing and releasing products.

(d) Access limitations to the manufacturing site for manufacturing process control; any particulars for process inspection.

(e) Check-up points in controlling manufacturing equipment and devices (including those for instrument calibration), as well as cautions against any occurrence of trouble.

(f) Particulars pertaining to operation controls for operators.

(g) Miscellaneous particulars relevant to manufacturing control.

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B. "Hygiene control for operators" purports preventing an excipient product from being contaminated with operator-carried pathogenic bacteria and the like.

C. "Hygiene control of the buildings and facilities (except those for testing; the same shall apply hereinafter), hygiene control for operators, and the others needed" means those that follow:

(a) The following particulars relevant to hygiene control for operation rooms, equipment, devices, and the like.

(i) Assignment of places, equipment and devices to be sanitized, and establishment of sanitation frequency.

(ii) Sanitation procedures; maintenance and control of chemical agents and tools to be used.

(iii) Procedures of post-sanitation inspection.

(b) The following particulars relevant to hygiene control for operators.

(i) Establishment of criteria for working uniforms.

(ii) Procedures for grasping the health state of operators.

(iii) Procedures for hand wash.

(iv) Precautions pertaining to manufacturing hygiene.

(c) Miscellaneous particulars needed for manufacturing hygiene control

D. Descriptions in Manufacturing Control Standard Code and in Manufacturing Hygiene Control Standard Code should include the name of an individual in charge of establishment and the date of establishment; the name of an individual in charge of revision and the date of revision should be included, when revised.

(Responsibility of Manufacturing Control Manager)

**Article 7** Each manufacturer shall direct the manufacturing control manager to conduct properly those duties pertaining to manufacturing control for pharmaceutical excipients which are specified in the following, in accordance with Product Standard Code, with Manufacturing Control Standard Code or with Manufacturing Hygiene Control Standard Code.

**(1)** Establishing a manufacturing order that describes directions, precautions, miscellaneous particulars needed, for operating with the manufacturing process.

**(2)** Conducting the following duties in person, or according to the contents of the duties, charging with those tasks another individual who has been designated in advance.

A. Manufacturing the specified pharmaceutical excipient in accordance with the manufacturing order.

B. Establishing for each lot a record on manufacturing the pharmaceutical excipient.

C. Confirming for each lot that indications and packages are appropriate, and establishing the record of confirmation.

D. Appropriately storing, receiving, shipping, and establishing their records for each lot of raw materials and products and for each control unit of packaging materials.

E. Confirming and establishing the record that the buildings and equipment have been washed and sanitized.

F. Performing and establishing the record of hygiene control for operators.

G. Conducting and establishing the record of periodical examination and maintenance of the buildings and facilities (including instrument calibration).

H. Miscellaneous tasks required.

(3) Reviewing the records on the manufacture, storage, receipt, shipment, and manufacturing hygiene control to confirm that the manufacturing control has been carried out appropriately, and subsequently reporting in written form the result to the product security pharmacist.

(4) Maintaining records on the manufacture, storage, receipt, shipment, and manufacturing hygiene control, for 3 years from the date of establishment.

**[Commentary]**

**6. Points Related to Article 7**

A. In Item 1 "directions, precautions, miscellaneous suggestions, and the like, for operating with the manufacturing process" means those that follow.

(a) The name of an individual in charge of making the order and the date of making the order.

(b) Name, appearance, lot number or manufacturing number of the pharmaceutical excipient

(c) Name and the charge-in quantity of raw materials.

(d) Theoretical yields of intermediate products in each step of the manufacturing process or of the excipient product ( or standard yield in a case of obtaining the theoretical yield with difficulty).

(e) Directions to or precautions for operations at each step of the manufacturing process.

(f) Directions to or precautions concerning the packaging materials.

B. "Manufacturing order" in Item 1 should in general be issued for each lot.

C. The implication of "charging with the tasks another individual who has been designated in advance" is that an individual with a sufficient knowledge of the task has been designated in advance to have the responsibility of the said task, for the purpose of making clear the system of

task assignment.

D. The implication of A in Item 2 is that operations at each manufacturing process within the manufacturing control unit should be performed in accordance with the manufacturing order.

E. The "record on the manufacture of the pharmaceutical excipient" in B of Item 2 means what is called a manufacturing record; the following particulars should be described in the record.

(a) Name and lot number or manufacturing number of the pharmaceutical excipient.

(b) Name of the manufacturing process and the date of operation.

(c) Name, lot number or manufacturing number and the charge-in quantity of raw materials.

(d) Name and control number of packaging materials and the quantity used.

(e) Yield at each manufacturing step and percent of yield against the theoretical yield.

(f) Results from in-process testing by the manufacturing control unit and actions against any failure.

(g) Actions against any failure upon testing by the quality control unit.

(h) Evidences for confirming that each manufacturing process has been operated in accordance with the manufacturing order.

(i) In addition to the above, any actions taken during the manufacturing operation.

(j) Name of an individual in charge of recording and the date of recording.

(k) Evidences for confirming by the manufacturing control manager that manufacturing control has been conducted appropriately.

(l) Evidences for decision made by the product security pharmacist for product release.

F. As to raw materials, excipient products (including intermediate products), and packaging materials, "appropriately storing, receiving, shipping, and establishing the record" in D of Item 2 means those that follow.

(a) Raw materials, intermediate products, excipient products, and packaging materials should be stored each in a clearly divided site.

(b) Raw materials, intermediate products, excipient products, and the containers (of which specifications and test methods are described in compendia) are categorized and stored with a proper indication or with partitions as to the status of testing. Those that have been judged as unacceptable should be stored at a site clearly divided from the others.

(c) Indication materials should be inspected upon receipt prior to storage. Any immediate actions including disposal should be taken for those judged as unacceptable.

(d) Indication materials should be categorized for storage, each at a site indicated with the name of

material to be stored.

(e) When there makes a modification in description on indication materials, any immediate actions including disposal should be taken for the old version.

(f) To the packages and containers on which indications are given in accordance with Paragraph 7 of Article 2, the above (c) through (e) should be applied.

(g) Raw materials, intermediate products, and excipient products should be stored according to such storage conditions as specified for each, so as not to affect the quality. Furthermore, storage conditions specified by relevant laws, regulations, and ordinances should be followed for storing those pertinent materials.

(h) Record should be established for storage, receipt and delivery of each item and lot of raw materials.

(i) Record should be established for quality, receipt and delivery of each item and lot of excipient products, whereby the date of receipt, quantity received, actions taken during storage, date of shipment, quantity of shipment, and destination should be all described.

(j) Record should be established for storage, receipt and delivery of packaging materials should be recorded for each product item and for individual control units.

G. In H of Item 2 "miscellaneous tasks required" means those related to access limitation to operation areas except for personnel engaged in manufacturing operations.

## Chapter 3 Quality Control

(Quality Control Standard Code)

**Article 8** Each manufacturer shall establish Quality Contol Standard Code at each manufacturing plant to describe procedures of sampling, procedures of evaluating test results, and the other particulars needed.

**[Commentary]**

**7. Points Related to Article 8**

A. "procedures of sampling, procedures of evaluating test results, and the other particulars needed" means those that follow.

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(a) Particulars related to procedures of sampling for testing raw materials, intermediate products, excipient products, and packaging materials.

(b) Particulars related to sampling spot assignment.

(c) Particulars related to test result evaluation.

(d) Particulars related to reporting test results to the product security pharmacist and to the manufacturing control manager.

(e) Particulars related to sampling and control of reserve samples.

(f) Particulars related to inspection and maintenance of equipment and devices (including instrument calibration) to be used for testing.

(g) Particulars related to conducting procedures of aging test for quality.

(h) Particulars related to ensuring the quality of reference standards, reagents, and test solutions to be used for testing.

(i) Particulars related to re-testing procedures required.

(j) Those particulars other than the above pertaining to testing.

When raw materials, packaging materials, or excipient products are tested using facilities different from those of the said manufacturer or by employing institutions specified by the Minister of Health and Welfare, or using other official testing institution, procedures of sample shipment and of evaluating the test result should be described in the document.

B. Quality Control Standard Code should have the description of the name of an individual in charge of establishment and the date of establishment; the name of an individual in charge of revision and the date of revision should be included, when the document is revised.

(Responsibility of Quality Control Manager)

**Article 9** Each manufacturer shall direct the quality control manager to conduct properly and systematically the duties on the quality control of pharmaceutical excipient that are specified in the following, in accordance with Product Standard Code or Quality Control Standard Code.

(1) Conducting the following tasks in person, or according to the contents of the tasks, charging an individual having prior designation with the tasks.

A. Sampling from each lot of raw materials and excipient products and from each control unit of packaging materials to perform tests required and to establish records thereof.

B. When water is used in the manufacturing process, sampling at regular intervals a sufficient amount of samples required for testing, and establishing the record thereof.

C. When an organic solvent is used in the manufacturing process, sampling at regular

intervals a sufficient amount of samples required for testing for residual solvent in the excipient product, and establishing the record thereof.

D. Performing tests with those samples for each lot or for each control unit, otherwise at regular intervals, and establishing records thereof; however, this is not always required for those tests included in any of the following 1) through 4), provided it is conducted on the firms own responsibility by use of testing facilities or testing institutions that are mentioned in the following 1) through 4) and yet when it can be carried out without difficulty and is regarded as unavoidable.

1) For testing on those pharmaceutical excipients that are only subdivided: Other official testing institutions.

2) For testing raw materials and packaging materials: Testing facilities different from those of the manufacturer or the testing institutions specified by the Minister of Health and Welfare or other official testing institutions.

3) For advanced physical, chemical, and biochemical tests pertaining to excipient products and for testing by use of animals: Testing facilities different from those of the manufacturer or the testing institutions specified by the Minister of Health and Welfare or other official testing institutions.

4) For testing pertaining to excipient products (except for the tests mentioned in (3)): Testing facilities different from those of the manufacturer.

E. Storing not less than a double of the quantity required for performing specified tests as reserve sample from each lot of excipient products, at appropriate storage conditions for 3 years from the date of manufacture.

F. Checking and maintaining (including instrument calibration) equipment and devices pertaining to testing at regular intervals and establishing records thereof.

G. Other necessary tasks.

(2) Evaluating the test result and reporting in written form to the product security pharmacist and to the manufacturing control manager.

(3) Maintaining records concerning the testing for 3 years from the date of establishment.

**[Commentary]**

**8. Points Related to Article 9**

A. The sampling mentioned in A of Item 1 means that it should generally be conducted by

personnel of quality control unit.

B. The record of sampling (sampling record) should involve the following.

In this case, however;

(1) When they are described in the test record specified in the following C, it is not necessary to establish a sampling record separately. When the manufacturing process water to be used is the same as or equivalent to city water and sampling is made at regular intervals by an official institution, sampling is not required to perform, but

evidences for sampling should be recorded.

(a) Name of sample and lot number or manufacturing number otherwise control number.

(b) Date of sampling and the name of sampling personnel.

C. The record of testing (test record) specified in D of Item 2 should include the following.

(a) Name of sample and its lot number or its manufacturing number or its control number.

(b) Test items, test date, the name(s) of testing personnel(s), and the result of testing.

(c) Evaluation of the test result, date of evaluation, and the name of personnel in charge of making the evaluation: whereby;

(1) When the manufacturing process water is the same as or equivalent to city water and sampling is made at regular intervals by an official institution, the test result may be used instead, but description should be made according to the above particulars. As to "residual solvent", determination should be made for all solvents used, and the result should be expressed in the unit of "part per million".

(2) For testing the raw materials mentioned in (2) of D in Item 1, when a stable state of quality of a specified raw material and the reliability of the test have been both verified through statistical analysis of previous test data and through performance of regular quality reviews and of cross-check, test data obtained by the supplier may be applied to tests except for identification test, on the firm's own responsibility; however, description should be made in accordance with the above.

D. The test record mentioned in the above C should be established at the manufacturing plant for manufacturing the said pharmaceutical excipient, even in the case when tests are conducted using testing facilities other than those of the manufacturer, or those institutions specified by the Minister of Health and Welfare, otherwise other official testing

institutions, each being exceptionally authorized in the provisory clause. In this case, the following should be described, where 'the name of testing personnel' should read as follows for description. In the case of using the test result on city water reported by the official institution concerned, the name of the official institution should be described.

i) The name of particular testing facilities other than those of the manufacturer or the name of the testing institution specified by the Minister of Health and Welfare, otherwise the name of other official testing institution used.

ii) Date of requesting the testing.

iii) Date of receipt of the test result.

E. Implication of "for a case when the said test is conducted on the firm's own responsibility by use of the testing facilities or testing institutions" in the provisory clause in D of Item 1 is that the firm directs their personnel of the firm to perform the test using other testing facilities or requests testing to the testing institution on the firm's own responsibility; the firm should also evaluate the result obtained. In this case, the following should be entered into an agreement.

(a) Technical conditions necessary for entrusting with the test and the method of quality control for sample transfer.

(b) The method of communication.

F. Judgment on "when it can be carried out without difficulty and yet is regarded as unavoidable" in the provisory clause in D of Item 1 is made in accordance with the Official Notice No. 410, dated June 29, 1992, from Pharmaceuticals and Cosmetic Division, Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare (on the utilization of facilities different from those in the plant of the said manufacturer for manufacturing a pharmaceutical product).

G. Implication of "testing on the pharmaceutical excipients only subdivided" in the provisory clause of (1) in D of Item 1 is that other official testing institutions (body corporate defined in Article 34 of the Civil Law Act), as well as the testing institutions specified by the Minister of Health and Welfare, may be available.

H. "Testing facilities other than those of the manufacturer" of (2), (3), and (4) in D of Item 1 means testing facilities located at different plants of the said manufacturer for manufacturing pharmaceutical excipients or equivalents thereto.

I. "The testing facilities specified by the Minister of Health and Welfare" of (2) and (3) in D of Item 1 means those specified by the Official Notice No. 652, dated March 30, 1995, issued by the Director-General, Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare.

J. Those that are acceptable as "advanced physical and chemical testing" in (3) of Item 1 generally fall in the category of such a more advanced tests than general tests of the Japanese Pharmacopoeia as are given in the following (tests listed in "Attachment 2" given in the official Notice No. 333, dated March 31, 1994, issued by the Director-General,

Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare; with (o) through (s) supplemented.)

(a) tests using an automatic polarimeter.

(b) tests using a thin-layer chromatograph equipped with densitometer.

(c) tests using a gas-chromatograph equipped with a detector of electron-capture type.

(d) tests using a ultracentrifuge.

(e) tests using a Fourier-Transform Infrared Spectrometer.

(f) test using an atomic adsorption spectrometer.

(g) tests using a Raman spectrometer.

(h) tests using a mass spectrometer.

(i) tests using a gas-chromatographic mass spectrometer.

(j) tests using a automatic amino acid analyzer.

(k) tests using a nuclear magnetic resonance spectrometer.

(l) tests using an x-ray microanalyzer.

(m) tests using an instrument for enzyme immunoassay.

(n) tests using an instrument for radioimmunoassay.

(o) tests using a gas-chromatograph.

(p) tests using a high-performance liquid chromatograph.

(q) tests using an infrared spectrometer.

(r) tests using a spectrofluorophotometer.

(s) tests using a potentiometer.

(t) other tests which correspond to (a) through (n) and are approved by the Minister of Health and Welfare.

K. When there are used "other official testing institutions specified by the Minister of Health and Welfare, otherwise official testing institutions" of (2) and (3) in D of Item 1, the under-mentioned should be followed for.

(a) The quality control manager should prepare and maintain an Itemized list of tests to be requested (Format (1)-1 and Format (1)-2 (given in the Official Notice No. 333, dated March 31, 1994, issued by the Director-General, Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare), each for raw materials and packaging materials.
Amendment should be made for any change in the contents of the list.

(b) In requesting the test, a written request (Format 2) should be forwarded, together with specifications of the sample and test procedures, as well as samples of sufficient quantity enough to

perform the test. The samples to be forwarded should be indicated with the following particulars.

i) Name of the sample.

ii) Lot number or manufacturing number or reference number.

iii) Name of the manufacturing plant.

iv) Precautions for sample storage.

(c) Immediate reporting should be made, when the Minister of Health and Welfare or Prefectural Governor issues warning to matters related to the request for testing.

L. When there are used "testing facilities different from those of the said manufacture" in (2), (3), and (4) of D in Item 2, (a), (b), and (c) of the above K should be applied.

M. In (e) of Item 1 "specified tests" means those described in Product Standard Code. In the same paragraph "appropriate storage conditions" means generally the same storage conditions as are applied to samples in the form of finished product (in such an unavoidable case as is found with a large volume or the like, samples in a form capable of exhibiting functions equivalent to its finished product) under a normal distribution.

N. In (g) of Item 1 "other necessary tasks" means those that include "when there is a need of performing aging test, sufficient amount of samples should be taken from a particular lot".

O. In (d) of Item 1 and Item 2 "record" means that which includes the original test record.

## Chapter 4 Other Duties Pertaining to Manufacturing Control and Quality Control

(Written Procedures of Validation and the Like)

**Article 10** Each manufacturer shall establish written procedures for validation, handling of complaints, handling of recalls, internal auditing, and education and training (hereinafter referred to as "written procedures" for brevity) for each manufacturing plant, in order to properly conduct the duties specified in the next Article through Article 15, inclusive.

**[Commentary]**

**9. Points Related to Article 10**

A. "Written procedures for validation, handling of complaints, handling of recalls, internal

auditing, and education and training" means the documents that clearly describe such procedures capable of conducting smoothly and appropriately the duties related to validation, handling of complaints, handling of recalls, internal auditing, and education and training; the following particulars should be included therein.

(a) Written procedures for validation:

Particulars relevant to procedures capable of performing appropriately the duties specified in Article 11 of the Self-Imposed Standard.

(b) Written procedures for handling of complaints:

Particulars relevant to procedures capable of performing appropriately the duties specified in Article 12 of the Self-Imposed Standard.

(c) Written procedures for handling of recalls:

Particulars relevant to procedures capable of performing appropriately the duties specified in Article 13 of the Self-Imposed Standard.

(d) Written procedures for internal auditing:

Particulars relevant to procedures capable of performing appropriately the duties specified in Article 14 of the Self-Imposed Standard.

(e) Written procedures for education and training:

Particulars relevant to procedures capable of performing appropriately the duties specified in Article 15 of the Self-Imposed Standard.

(Validation)

**Article 11** Each manufacturer shall charge another individual designated in advance with the tasks indicated in the following Items, in accordance each with the written procedures.

**(1)** Validating in the following cases:

A. A case when the manufacture of a pharmaceutical excipient will newly start at the said manufacturing plant.

B. A case when there is any change in manufacturing procedures that will affect significantly the quality of pharmaceutical excipients.

C. Another case to be considered necessary for a proper performance of the manufacturing control and quality control for pharmaceutical excipients.

**(2)** Reporting in written form the result from validation to the product security pharmacist.

**(3)** Maintaining the documents prepared during the validation for 3 years from the date of preparation.

2. Each manufacturer shall implement actions needed for improvement pertaining to the manufacturing control or quality control on the basis of results from the validation activities according to Item 1 of the previous Paragraph; the actions shall be documented and maintained for 3 years from the date of preparation.

**[Commentary]**

**10. Points Related to Article 11**

A. In Item 1 "another individual having prior designation" means an individual who has a sufficient knowledge of the task and received prior designation to hold the responsible post for the task.

B. The validation specified in Item 1 should be implemented in accordance with standards specified separately.

C. In A of the same Item "a case when the manufacture of a pharmaceutical excipient will newly start" means a case when a pharmaceutical excipient will be manufactured first at the manufacturing plant.

D. In B of the same Item "a case when there is any change in manufacturing procedures that will affect significantly the quality of pharmaceutical excipients" means a case when there is any change in raw materials, packaging materials, procedures, manufacturing process, buildings or equipment, and yet the change is supposed to affect significantly the quality of pharmaceutical excipients to be manufactured.

E. In C of the same Item "another case to be considered necessary for a proper performance of the manufacturing control and quality control for pharmaceutical excipients" means that follows, in addition to the case indicated in the criteria of the above B.

(a) A case when past operation records of equipment, as well as test data obtained during the intermediate and final processing, are to be analyzed for evaluation, on conditions that the composition, procedures, and instruments are identical.

(b) A case when any possible influences on process characteristics and the quality of excipient products are systematically re-evaluated.

(Handling of Complaints)

**Article 12** Each manufacturer shall charge the product security pharmacist of the said

manufacturing plant with the duties indicated in the following Items in accordance with written procedures, upon receipt of a complaint on the quality and relevant particulars of a pharmaceutical excipient, with the exception that matters pertaining to the complaint are clearly found not attributable to the said manufacturing plant.

**(1)** Investigating the cause of all matters pertaining to the complaint, and implementing necessary actions when any improvement in manufacturing control or quality control is required.

**(2)** Establishing a complaint record that includes details of the complaint, results from the cause investigation, and corrective actions taken, to maintain for 3 years from the date of establishment.

**[Commentary]**

**11. Points Related to Article 12**

A. "The quality and relevant particulars of a pharmaceutical excipient" means the quality of a pharmaceutical excipient, direct package and container, external package, labels on the containers, and the like.

B. In Item 2 "details of the complaint, results from investigation on the cause, and corrective actions taken" mean those that follow:

(a) Details of complaint

(i) Name of the pharmaceutical excipient complained, the package form, and lot number or manufacturing number.

(ii) The date and location of the complaint occurred, the name and address of the complainant.

(iii) The nature, details of the complaint and of how the complaint was made.

(b) Results from investigating the cause.

(i) Results from investigating the pharmaceutical excipient pertaining to the complaint (name of the market investigated , the status of delivery and use, and the like).

(ii) Results from investigating reserve samples.

(iii) Results from investigating test data.

(iv) Results from investigating manufacturing records, storage records, and results from investigating manufacturing hygiene control records.

(c) Judgment on the basis of results from investigating the cause.

(d) The status of any corrective actions taken.

(Handling of Recall)

**Article 13** Each manufacturer shall charge the product security pharmacist of the said manufacturing plant with the duties indicated in the following Items in accordance with written procedures, in a case when a recall is made by reasons of the quality of a pharmaceutical excipient and relevant particulars, with the exception that the reasons resulting in the recall are clearly found not attributable to the said manufacturing plant.

**(1)** Investigating the cause that has ended in the recall, and implementing necessary corrective actions when any improvement in manufacturing control or quality control is required.

**(2)** Holding the recalled pharmaceutical excipient in a separate site for a specified period of time, and subsequently conducting a proper disposition.

**(3)** Establishing a complaint record that includes details of the recall, results of investigating the cause, and corrective actions taken, to maintain for 3 years from the date of establishment.

**[Commentary]**

**12. Points Related to Article 13**

A. Implication of "the quality of a pharmaceutical excipient and relevant particulars" is the same as is described in the above A of '11'.

B. In Item 2 "for a specified period of time" means the period of time until the disposition of the pharmaceutical excipients recalled is determined.

C. In Item 3 "details of the recall, results of investigating the cause, and corrective actions taken" means those that follow.

(a) Details of the recall.

(i) Reason of the recall

(ii) Name, packaged form, and lot number or manufacturing number of the pharmaceutical excipient recalled.

(iii) Results of the recall.

(b) Results from the cause investigation.

(i) Results from investigating the recalled pharmaceutical excipient (the status of delivery,

use, and the like).

(ii) Results from investigating reserve samples.

(iii) Results from investigating test data.

(iv) Results from investigating manufacturing records, storage records, and results from investigating manufacturing hygiene control records.

(c) Conclusion of the cause investigation.

(d) The status of any corrective actions taken.

(Internal Audit)

**Article 14** Each manufacturer shall charge an individual having prior destination with the duties indicated in the following Items in accordance with written procedures.

**(1)** Internal auditing at regular intervals on manufacturing control and quality control for the manufacture of pharmaceutical excipients at the said manufacturing plant.

**(2)** Reporting in written form the result of internal auditing to the product security pharmacist.

**(3)** Establishing the record of internal audit for maintaining for 3 years from the date of establishment.

2. Each manufacturer shall implement actions needed for improvement concerning the manufacturing control or quality control on the basis of results from the internal auditing in accordance with Item 1 of the previous Paragraph; the actions shall be documented to maintain for 3 years from the date of establishment.

**[Commentary]**

**13. Points Related to Article 14**

A. Implication of "an individual having prior destination" in Paragraph 1 is the same as in the above A of '10'.

B. In Item 1 "internal auditing at regular intervals on manufacturing control and quality control for the manufacture of pharmaceutical excipients" means that internal auditing at regular intervals should be made for the following particulars, including their actual status, for the purpose

of evaluating an appropriate performance of manufacturing control and quality control for pharmaceutical excipients at the said manufacturing plant.

(a) GMP organization chart.

(b) Duties of the product security pharmacist.

(c) Product Standard Code.

(d) Manufacturing Control Standard Code.

(e) Manufacturing Hygiene Control Standard Code.

(f) Duties of the manufacturing control manager.

(g) Quality Control Standard Code.

(h) Duties of the quality control manager.

(i) Written procedures related to validation, handling of complaints, handling or recalls, internal auditing, as well as education and training.

(j) Tasks related to validation.

(k) Tasks related to handling of complaints.

(l) Tasks related to handling of recalls.

(m) Results of the above internal auditing and of confirming any of corrective actions taken.

(n) Tasks related to education and training.

(o) Tasks related to the manufacture at two or more than two manufacturing plants.

C. Results of the internal auditing specified in Item 2 of Paragraph 1 should include those that follow:

(a) Date of implementation.

(b) Judgment based on the result of internal auditing.

(c) Recommendation for improvement, if needed.

(Education and Training)

**Article 15** Each manufacturer shall charge an individual having prior destination with the duties indicated in the following Items in accordance with written procedures.

(1) Providing the operators systematically with education and training on manufacturing control and quality control.

(2) Reporting in written form the result of education and training to the product security pharmacist.

(3) Establishing the record of education and training to maintain for 3 years from the date of establishment.

**[Commentary]**

**14. Points Related to Article 15**

A. Implication of "an individual having prior destination" in Paragraph 1 is the same as in the above A of '10'.

B. In Item 1 "the operators" means those who are engaged in manufacturing operations and quality control operations and also those who have any possibility of affecting the quality and related features of an excipient product (including operators of maintenance and cleaning operations).

C. In Item 1 "education and training" means those consisting of the education of theories and practical training.

D. In Item 1 "education and training on manufacturing control and quality control" should include those that follow, each depending on the nature of operations.

(a) Outlines of GMP (including the relevant laws and regulations).

(b) Outlines of manufacturing hygiene control.

(c) Outlines of the actual state of compliance with GMP within the said manufacturer (or at the manufacturing plant).

(d) Particulars relevant to the performance of operations (including on-the-job training).

E. The intent of "providing the operators systematically" in Item 1 is to implement the education and training followed by an efficiency evaluation at regular intervals.

F. In Item 2 "report" means to include the following.

(a) Date of Implementation

(b) Each name of individuals receiving education and training.

(c) Each name of individual(s) providing education and training.