Tentative translation (as of March 16, 2007)
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Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

To: Directors-General
Department of Health
Prefectural Governments

Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law

Pursuant to the provisions of Article 2, Paragraph 12 of the Pharmaceutical Affairs Law (Law No. 145, 1960, hereinafter referred to as "Revised Pharmaceutical Affairs Law") as amended by the enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and the Blood Collection and Donation Services Control Law (Law No. 96, 2002), drugs as drug substances shall not require marketing approvals. In addition, the obligation of obtaining licenses for manufacturing, etc. on a product-by-product basis (including the license for manufacturing under Articles 12 and 13, the license for the drug importer under Article 22, and the case applied *mutatis mutandis* to Article 23, all as prescribed in the pre-revised Pharmaceutical Affairs Law [hereinafter referred to as the "previous law"]), has also been abolished. Furthermore, under Article 14, Paragraph 6 of the Revised Pharmaceutical Affairs Law, for drugs, quasi-drugs, cosmetics, and medical devices that are specified by cabinet orders, the conformity with the standards regarding the methods of manufacturing control and quality control of such products shall be checked at the time of approval and before expiration of the period specified by the cabinet order.

Along with this revision, pursuant to the PFSB Notification No. 0709004 issued by the Director-General of Pharmaceutical and Food Safety Bureau, dated July 9, 2004, "the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Control Law," the application for marketing approval of drugs (excluding *in vitro* diagnostic drugs; the same applies hereinafter), quasi-drugs, and cosmetics (hereinafter referred to as "drugs, etc.") shall newly include the following in the approval application form: information on the manufacturing site, and quality-related matters such as the description, manufacturing methods, specifications and test methods, storage methods, expiration dates (retest periods), etc., of drug substances, which have been considered as approval items for drug substances up until now. However, for drugs registered in the Drug Master File, the description in the Drug Master File shall be included in the approval application form.

The guideline for describing the manufacturing method and other items on the marketing approval application form and the procedures, etc. for approval review are handled as follows. Accordingly, you are requested to inform relevant businesses and organizations under your jurisdiction of this guideline and to provide adequate guidance.

Section 1 Describing Manufacturing Methods on Marketing Approval Application Forms to Be Submitted on and after April 1, 2005

1. Prescription drugs and OTC drugs containing a new active ingredient (including drugs for which an application is submitted during the re-examination period)

   (1) To complete the approval application form for drug products, in addition to the matters related to the drug substance, including the ingredients, quantity, identity, storage method, expiration date, as well as specifications and test methods, etc., the manufacturing method and matters related to the manufacturing sites of the drug substance and the drug product shall be entered in the Manufacturing Method column on the approval application form in accordance with the description guidelines in Attachments 1 and 2. However, if the drug falls under the category of biological products (such as vaccines and blood products) as listed in the Minimum Requirements for Biological Products, recombinant DNA technology-applied drugs, cell culture derived drugs, or other biotechnological/biological products, such descriptions shall be made by referring to Attachment 3, in principle, and by referring to Attachments 1 and 2 as necessary.

   (2) In describing the manufacturing site and manufacturing method in the Manufacturing Method column on the approval application form, the applicant shall refer to the description examples in Attachments 1 and 2, and personally distinguish and establish in advance the matters to be addressed in a partial change approval application, and the matters to be addressed in the notification of minor changes for the approval requirements specified under the provisions of Article 14, Paragraph 10 of the Revised Pharmaceutical Affairs Law (hereinafter referred to as "minor change notification"), at the time when the manufacturing method is changed.

   (3) As necessary, data that shows the flow of the manufacturing process shall be prepared and attached as reference data to the approval application form, by referring to the flow charts of the manufacturing processes as illustrated in Attachments 4, 5, 6, and 7.

   (4) In cases where food/industrial products manufactured at manufacturing sites that have not obtained a license for manufacturing or accreditation of foreign manufacturer (hereinafter referred to as "license for manufacturing, etc.") was used as drug substances out of necessity, it is sufficient to describe only matters relating to the manufacturing site for the drug substances concerned, regardless of the provisions in (1) above. The marketing authorization holder shall use such food/industrial products as drug substances under their responsibility, establish specifications and test methods for the relevant ingredient, and shall make the manufacturer that uses the relevant ingredient as raw materials conduct an acceptance test.

   (5) Item (4) above shall be handled as an interim measure during the transitional period to the Revised Pharmaceutical Affairs Law.

2. OTC drugs [except for OTC drugs containing a new active ingredient (including drugs for which an approval application was submitted during its re-examination period); the same applies hereinafter], quasi-drugs, and cosmetics

   (1) To complete the approval application form for drug products as OTC drugs,

quasi-drugs that are subject to GMP compliance, quasi-drugs that are insecticides or rodenticides (hereinafter referred as to "OTC drugs, etc."), in addition to matters relating to the ingredient, quantity, identity, storage method, expiration date, and specifications and test methods, the manufacturing site and the scope of the manufacturing process shall be described in the Manufacturing Method column, in accordance with Section 1 in Attachment 1 for drug substances, and Section 1 in Attachment 2 for drug products.

(2) To complete the approval application form for quasi-drugs (excluding quasi-drugs that are subject to GMP compliance and quasi-drugs that are insecticides or rodenticides) and cosmetics, in addition to matters relating to the ingredients, quantity, identity, storage method, expiration date, and specifications and test methods, the manufacturing site and the scope of the manufacturing process shall be entered in the Manufacturing Method column in accordance with Section 1 of Attachment 2.

(3) Descriptions other than those for which the description method is provided in (1) and (2) above can be made according to existing examples. However, in the range of existing descriptions in the Manufacturing Method column, the applicant shall personally distinguish and establish in advance the matters to be addressed in a partial change approval application or a minor change notification for the approved matters at the time when the manufacturing method is changed.

(4) Notwithstanding the provisions in (1) to (3) above, descriptions regarding the country of origin, body part, and processing method, etc. such as inactivation, of raw materials derived from animals based on the Standard on Biologically-derived Raw Material and the Notification issued by the Director of Evaluation and Licensing Division; Director of Safety Division; Director of Compliance and Narcotics Division; and Director of Blood and Blood Products Division, Pharmaceutical and Medical Safety Bureau in their joint names, "Administrative Procedures, etc. after Partial Revision of the Enforcement Regulations of the Pharmaceutical Affairs Law" (PMSB/ELD Notification No. 0520001, PMSB/SD Notification No. 0520001, PMSB/CND No. 0520001, PMSB/BBPD No. 0520001, dated May 20, 2003) shall be based on existing examples. Changes in the relevant descriptions in the Manufacturing Method column shall follow the procedures in items 2.2 and 2.3 of Attachments 1 and 2, respectively.

(5) As necessary, data that explains the flow of the manufacturing process shall be prepared, and shall be attached as reference data when submitting an approval application.

(6) In cases where food/industrial products manufactured at a manufacturing site that has not obtained a license for manufacturing, etc. were used as drug substances of OTC drugs, etc. out of necessity, it is sufficient to describe only matters relating to the manufacturing site for the drug substances concerned, notwithstanding the provisions in (1) and (3) above. The marketing authorization holder shall use such food/industrial products as drug substances under their responsibility, establish specifications and test methods for the relevant ingredient, and make the manufacturer that uses the relevant ingredient as raw materials conduct an acceptance test.

(7) Items (1) to (3) and (6) above shall be handled as an interim measure during the

transitional period to the Revised Pharmaceutical Affairs Law.

3. Crude drugs
The Manufacturing Method column on the approval application form for crude drugs shall be written down based on the example for that of OTC drugs.

4. Subdividing manufacture
The approval application form for subdividing manufacturing under the previous law had allowed for simplified descriptions in the Manufacturing Method column, etc. in the past. However, taking into consideration that the marketing authorization holder with marketing approval shall be responsible for the quality and market for the product under the Revised Pharmaceutical Affairs Law, the Manufacturing Method column on the approval application form shall, in principle, be written down in accordance with items 1 to 3 above in the future. Other columns shall be written down adequately, rather than with simplified descriptions.

Section 2 Handling of Procedures, etc. for Approval Reviews

1. Handling of changes during approval reviews
During approval reviews for drugs, etc. the matters addressed in a partial change approval application as well as the matters addressed in a minor change notification, both of which were established by the applicant themselves and entered in the Manufacturing Method column on the approval application form, shall be taken into consideration.

2. Handling of changes in manufacturing method, etc.

(1) For changes in the manufacturing method of drugs, etc., adequate validation and change control, etc. shall be conducted as a prerequisite for changes in either a partial change approval application or a minor change notification, regardless of the magnitude of the impact on quality. That is, a change shall be made based on the judgment that the change imposes no obvious impact on the quality through change control as performed under GMP.

(2) Suitability to a minor change notification shall be judged individually based on items 1.2, 2.2, and 2.3 in Attachment 1 for drug substances, items 1.2, 2.2, and 2.3 in Attachment 2 for drug products, and items 1.2 and 2.3 in Attachment 3 for drug substances and drug products related to biological products, etc. However, changes to the manufacturing site and manufacturing method of drug substances for OTC drugs, etc. (excluding drug substances for biological products, etc. and designated pharmaceutical active ingredients) may, in principle, be addressed in a minor change notification.

(3) The applicant shall personally judge whether or not the change falls under the matters to be addressed in a partial change approval application by referring to the matters already established based on the description guidelines in Attachments 1 to 3. In the following cases, however, the applicant may consult with the regulatory authority that is to review the applicable product.
① Validity of the evaluation protocol to be implemented at the time of change
② Appropriateness of the judgment that the change imposes no obvious impact on the quality (of the product) from the results of tests implemented in accordance

with the protocol

③ Other matters that require a consultation at the time of change in the Manufacturing Method column

In addition, with regard to the process specified as a matter to be addressed in a minor change notification, in the event that the impact on the quality is judged to be different from that estimated previously, such as a case where the change control procedure produced results such that impact on the quality cannot be denied, the change shall be suspended or re-examined, or an application for a partial change approval or for approval of a new product shall be submitted. The applicant shall consult with the regulatory authority that is to review the relevant product as necessary.

(4) As with the partial change approval application, when submitting the minor change notification, a table comparing the old and new contents shall be attached as reference data in order to clarify the contents of the changes. The contents of minor change notifications shall be restricted only to the matters to be changed, and the applicant shall submit a statement to the effect that they have implemented adequate validation and change control.

(5) The point in time for a change to be addressed in a minor change notification shall be interpreted as the time when the said change has been made, or the time when the product manufactured based on the said change is released. The marketing authorization holder shall determine which time point should be chosen depending on the details of the change, provided, however, that appropriate follow-up shall be made so that products that are different from the description on the approval certificate may not be released after the change.

(6) When the matter to be addressed in a minor change notification is changed to one that is to be addressed in a partial change approval application, the minor change notification shall be submitted.

(7) In the event that it is discovered in the GMP inspection that a minor change notification had been submitted concerning changes in manufacturing process that should not have originally been addressed in the minor change notification, the minor change notification becomes invalid, and there may be the possibility that the manufacturer may be accused of violating the Pharmaceutical Affairs Law. In this case, products that have already been manufactured using the method after the change and products that have already been marketed shall be subject to necessary administrative actions, such as a suspension of the release or recall of the product, in the light of risks, etc., associated with the change. In addition, when the GMP inspecting authorities have any doubts as to whether the change should be addressed in a partial change approval application at the time of the GMP inspection, the GMP inspecting authorities shall liaison with the regulatory authority that is to review the relevant product.

(8) For OTC drugs, quasi-drugs, and cosmetics, when the matters to be addressed in a partial change application specified in Attachments 1 and 2 are changed, it is necessary to submit a partial change approval application. However, for matters to be addressed in a minor change notification, the minor change notification is not required, provided that the relevant matter has not been described on the approval certificate.

(9) With the exception of biological products, etc., extension of the expiration period is possible if stability tests are continued after approval, by submitting a minor change notification in accordance with the commitments relating to the implementation of stability tests that were submitted at the time of the approval review.

(10) It is possible to submit a minor change notification while a partial change approval application is being submitted. However, in this case, all of the matters related to the minor change notification shall be addressed in the partial change approval application by switching the partial change approval application forms.

3. Handling of Drug Master Files
Even when submitting an application to register a Drug Master File as specified in Article 14, Paragraph 11 of the Revised Pharmaceutical Affairs Law, the matters to be addressed in the registration application shall be handled in the same way as in 1. above.

Section 3 Others

1. Handling of the manufacturing scale in technical documents attached at the first submission of marketing approval application

(1) The data that is submitted with an approval application for establishing and describing the manufacturing method and specifications and test methods in their respective columns shall be collected from the manufacturing facilities with a scale that reflects actual production; this does not necessarily have to be data obtained at manufacturing facilities with an actual production scale at the time when submitting the application.

(2) Before the GMP compliance inspection that is implemented prior to the approval of drugs, etc., the manufacturing methods for final actual production shall be established, including its control standards/control values, etc. for the process parameters, critical process steps, and key intermediates, and shall be submitted together with manufacturing-related data to the regulatory authorities. Furthermore, the timing for applying for a GMP compliance inspection shall be taken into consideration, since it is necessary to obtain data from the manufacturing facilities where the actual production takes place.

Section 4 Notification of Modifications to Descriptions on Approval Certificate for Products for Which Approval Was Granted or Filed under the Previous Law up to March 31, 2005

1. Under the provisions of Article 3 of Supplementary Provision, Enforcement Regulations of the Revised Pharmaceutical Affairs Law, those who has license for manufacturing or importing/marketing drugs (hereinafter referred to as “manufacturers, etc.”) approved under the previous law shall submit a notification of modifications to the descriptions on the approval certificate” (hereinafter referred to as “notification of modifications to the descriptions on the approval certificate”) for each approved product by the expiration date of the license. In such a case, the notification shall be prepared in accordance with Section 1 above.

2. With regard to approval applications based on the previous law, if the license period under the previous law expires between April 1, 2005 and the point in time when the approval is obtained, a notification of modifications to the descriptions on the approval certificate shall be submitted promptly after approval of the application is obtained.

3. Before submitting the notification of modifications to the descriptions on the approval certificate following a renewal of the license for manufacturing under the previous law, when a partial change approval application or a minor change notification is submitted, modifications to descriptions shall be made so that the contents of the changed portion may be consistent with the matters entered on the marketing approval application form.

4. Even in cases where modifications to descriptions has been completed as in the case of the 3 above, a notification of the modifications to descriptions shall be also submitted when renewing the license for manufacturing. In this case, it is not necessary to enter the contents of the modifications that were made to descriptions again, and it is acceptable to enter only the time at which the modifications to descriptions were completed in the Remarks column.

5. The notification of modifications to the descriptions on the approval certificate shall be submitted by an electronic method, such as the FD, specified separately.

6. When making modifications to the descriptions on the approval certificate, the manufacturing process and the specifications and test methods that are actually conducted shall be entered and the descriptions that deviate from the contents specified on the previous approval certificate and the product master formula shall not be made.

7. For products that have been approved previously through a written application, in addition to the Manufacturing Method column, the descriptions on the approval certificate such as for the ingredients, composition, identity, dosage and administration, indications, storage method, expiration date, specifications and test methods, and the therapeutic classification that is described in the Remarks column shall be electronically modified before a notification of modifications to the descriptions on the approval certificate is submitted. In doing so, a copy of the approval certificate shall be also attached.

8. With regard to the form used for modifying the descriptions on the approval certificate, Form No. 24 (1) of the Enforcement Regulations for the Revised Pharmaceutical Affairs Law shall be used. However, in the case of 7 above, a notification using the separate form shall also be submitted.

9. Based on Article 8 of the Supplementary Provisions of the Law and the Supplementary Provisions of Cabinet Order for Modification, approvals made under the previous law shall be regarded as approvals under the Revised Pharmaceutical Affairs Law from April 1, 2005 onwards. However, drug substances used exclusively for the manufacture of drug products shall not be subject to marketing approval pursuant to Article 2, Paragraph 12 of the Revised Pharmaceutical Affairs Law. Therefore, when the notification of modifications to the descriptions on the approval certificate is submitted as stated in 1 above, approval for drug substances used exclusively for the manufacture of drug products shall be excluded.

Attachment 1

1. Guideline for Descriptions on Approval Application Forms for the Manufacturing Method of Chemical Drug Substances

A. General Notices

With regard to descriptions in the Manufacturing Method column:
In the "Manufacturing Method column," the manufacturing site and the manufacturing method shall be written down according to the following.

1. Manufacturing Site

1.1 Description of the manufacturing site

- For each manufacturing site (including the manufacturing sites of entrusted manufacturers and testing facilities), the name and address of each site, as well as the scope of the manufacturing process covered, shall be entered in the column.
- The license or accreditation number for each manufacturing site shall be entered in the column.
- However, if the manufacturing site has already been entered in the Manufacturing Site column on the marketing approval application, it is not necessary to write down the address and the license or accreditation number.

1.2 Matters relating to the manufacturing site to be addressed in a partial change approval application

- Since changes in manufacturing sites require adequate change control, they shall be, in principle, addressed in partial change approval applications for matters that have been approved. However, if a change falls under one of the following and its change control has been carried out properly, it shall be addressed in a minor change notification.
  ① A change to a manufacturing site that exists in Japan, of which the change in the manufacturing method falls within the scope of a minor change notification, is classified in the same license or accreditation category, and complies with GMP (refers to cases where the same status is expected to be maintained thereafter, such as there not being any GMP non-compliances found; the same applies hereinafter) in GMP inspections (i.e., on-site inspection only; the same applies hereinafter) conducted within the last 2 years for a product of a similar class that shares related processes.
  ② A change in the facilities related to testing
  ③ A change in the facilities related only to packaging, labeling, and storage.

- Changes from a domestic manufacturing site to a foreign manufacturing site, and changes in manufacturing sites within foreign countries shall also be addressed in a minor change notification if they meet the above conditions.

2. Manufacturing Method

2.1 Description of manufacturing method

- All of the processes, from the starting materials to the primary packaging process of the drug substance, shall be described according to the process sequence. However, if there is a secondary packaging process, this secondary packaging process shall also be

included if it has the function of ensuring stability of the drug substance.

- The applicant shall start by describing the process necessary for quality assurance of the drug substance. The starting materials shall be determined according to the concept indicated in the Notification issued by the Director-General of the Pharmaceutical and Food Safety Bureau, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" (PFSB No. 1200, dated November 2, 2001). However, since describing a manufacturing process that consists of only one process as a reaction process has the risk of the starting materials directly affecting the quality of the drug substance, such descriptions should be avoided in principle.

- The manufacturing method shall be described according to its flow. The description shall include the following items.
  ① The names and molecular formulas (chemical structures shall be shown in a separate sheet, as necessary; the same applies hereinafter) of the starting materials and intermediates
  ② The names and molecular formulas of the reagents used in the reaction and purification, as well as the names of solvents
  ③ The name of the drug substance
  ④ Critical processes or the processes after the final intermediate shall be specified, if any such processes exist, and an outline on the in-process operations shall be explained*.

- From among the series of operating procedures in the manufacturing process, the matters needed for ensuring the constancy of quality shall be appropriately selected and described.
  ① Quantities of raw materials, solvents, catalysts and reagents, as well as equipment, operating conditions (e.g., temperature, pressure, pH, time), percentage yield (actual yield), critical process steps, key intermediates, process parameters (e.g., temperature, pH, time), etc. shall be appropriately described. Details on equipment with special functions shall be described.
  ② Target values/set values may be included in operating conditions, etc. If a target value/set value is set, the reference value shall be enclosed in 『 』or 《 》(refer to "2.2 Distinction between a partial change approval application and a minor change notification for the manufacturing method," for information on how to use symbols), and at the same time, an allowable range for the target value/set value must be established in the product master formula or standard operating procedures (SOPs). However, if these parameters are set for parametric release (limited to cases where release determination is conducted by a sterilization parameter instead of the sterility test defined in ICH-Q6A), or if the parameters can affect the quality significantly, it is necessary to specify an allowable range on the approval application form, and they must not be made a target value/set value. In this case, deviations from the range of parameters written on the approval application form will not be acknowledged. In addition, the batch size may be handled according to the target value/set value, and in such a case, the standard batch size shall be written down on the approval application form.
  ③ In cases where a test has been performed to ensure that the critical process from among the manufacturing process, as indicated in ①, is controlled, the name of the test method, its principle, key points, and control values/acceptance criteria shall be described.
  ④ Control criteria for starting material(s), and the name, principle, and key points of

the test method, shall be described.

⑤ For raw materials derived from cows, etc., matters on the country of origin, body part , processing method, and, as needed, other matters that are necessary as from the perspective of quality/safety assurance, such as information on TSE data, shall be described. For raw material derived from humans and animals, the matters that are considered critical from the perspective of quality/safety assurance, such as its origin, donor screening contents, inactivation/elimination processing methods for bacteria, fungi, viruses, etc., during the manufacturing process shall be described.

⑥ Among the raw materials used in the critical process, the control criteria for the raw material(s) that affect the quality significantly, as well as the name, principle, and key points of the testing method shall be described.

⑦ The control criteria for raw material(s), and the names, principles, and key points of the testing methods that are used after the final intermediate shall be described.

⑧ The control criteria and the control method (including the name, principle, and key points of the test method) of the key intermediate and final intermediate shall be described.

⑨ Other matters necessary for quality assurance shall be also described.

2.2 Distinction between a partial change approval application and a minor change notification for the manufacturing method

- Any Changes in the description in the Manufacturing Method column require appropriate change control, and shall be addressed in a partial change approval application or minor change notification.
- A change other than those in manufacturing processes that fall within the scope of a partial change approval application shall be addressed in a minor change notification if it does not affect the quality of final product.
- For changes that are reasonably judged to have no impact on the quality of products, such as changes in the country of origin in relation to bovine spongiform encephalopathy (BSE), changes in the compendia, other changes based on the administrative procedures, and changes to narrow specification values/acceptance criteria, it is acceptable to submit a minor change notification.
- For raw material derived from humans and animals, if changes are made to the country of origin, etc. to cope with new risks such as infectious factors, or other changes have been made based on the administrative procedures, it is acceptable to submit a minor change notification when indicating that such a change has been made.
- Among the standard batch sizes or the process parameters that serve as target values/set values, the matters to be addressed in a minor change notification shall be enclosed in 『 』, and those to be addressed in a partial change approval application shall be enclosed in 《 》. Furthermore, the matters to be addressed in a minor change notification other than target values/set values shall be enclosed in " ", and other matters shall be addressed in a partial change approval application.

2.3 Matters to be addressed in a partial change approval application for the manufacturing method

- Changes in reaction processes (starting materials and intermediates)
- Outline of in-process operations* following the final intermediate, and changes in the raw materials used
- In the case of a critical process, outline of in-process operations and changes in the raw materials used

- Changes in information relating to the test method and acceptance criteria, if tests on the key intermediate or on the critical processes as part of release tests for the drug substance are to be performed
- Changes in matters that require special control, from among the control criteria and control methods for starting materials, key intermediates, and raw materials (for example, changes in matters relating to the manufacture of an aseptic drug substance)
- Changes in matters that require special control, from among the parameters for the final process and critical process, as well as from among test methods and acceptance criteria that ensure that these processes are controlled (for example, changes in matters relating to the manufacture of an aseptic drug substance)
- Changes in equipment that require special control
- Changes in control criteria for solvents used in the final purification process, in cases where the solvent has a large possibility of affecting the drug substance in particular
- Addition and deletion of methods relating to inactivation and elimination of pathogens such as bacteria and viruses, and changes in inactivation and elimination conditions (however, if improvements in the pore size of the removal membrane, etc., are sufficiently validated, such changes may be addressed in a minor change notification)
- Other changes in matters that require special control

3. Reference Data

In order to facilitate understanding on the manufacturing method, the following reference data shall be attached as necessary.

- Annotations explaining the reasons, etc., for the distinction between the matters to be addressed in a partial change approval application and matters to be addressed in a minor change notification (Refer to "Reference.")
- A flow chart of the manufacturing method describing the following matters:
  ① Names and chemical structures (or molecular formulas) of the starting material(s) and intermediates
  ② Names and chemical structures (or molecular formulas) of the reagents used in the reaction and purification, as well as the names of the solvents
  ③ Names and chemical structures of the drug substance (including the stereochemistry of the drug substance)
  ④ With regard to the critical process or processes after the final intermediate, specify which processes they are, and also describe the outlines of in-process operations *

* Outline of in-process operation: Write down a name that makes it possible to identify the nature of the process operation, such as re-crystallization operation, filtration operation, extraction operation, and column chromatography.

Terminology

Critical process:
Refers to a process that includes process conditions, tests, and other related parameters that need to be controlled within predetermined control values to ensure that the drug substance meets specifications.
The following are examples of critical processes.

- Blending of multiple ingredients
- Phase transformation and separation processes (concentration, filtration)
- Processes where temperature control and pH control are important
- Processes where a substantial component element of the molecular structure is formed, and interim processes where a major chemical transformation is generated

- Processes where an important impurity is generated or where such impurity is removed from the drug substance
- Processes where optical purity is determined during the manufacture of an optically active drug
- Final purification process.

Intermediates:
For chemically synthesized drug substances, intermediates are materials produced during the synthetic process of a drug substance that undergoes further molecular changes before it becomes a drug substance. Intermediates may or may not be isolated.

Final intermediate:
A final intermediate is the compound from which the drug substance is produced by performing the next reaction. The reaction process involves the formation or cleavage of covalent bonds, but does not include a salt-exchange reaction.

Target value/set value:
A target value is a value, such as a measured value, obtained from the result of implementing a particular manufacturing process, whereas a set value is a value that is set as a condition in order to implement a particular manufacturing process. Whether either or both target and set values should be established, and whether such values should fall within the scope of a partial change approval application or a minor change notification depend on each manufacturing process.

B. Examples of Descriptions on Approval Application Forms (Drug Substances)

Examples of descriptions are shown for the approval application form for a drug substance. In order to grasp the flow of overall operations, examples are described according to the flow of the manufacturing process, without separating the matters that should be changed by a partial change approval application (hereinafter referred to as "partial change matters") from the matters that can be changed by a minor change notification (hereinafter referred to as "notification matters"). However, as shown in the examples of descriptions below, in addition to describing notification matters on the approval application form so that they can be distinguished easily, parameters, etc., that are handled as target values/set values are also to be described distinctively. This also applies to cases where a notification is submitted to be consistent with descriptions on the approval application forms that are required for marketing approval under the Revised Pharmaceutical Affairs Law. "Reference" consists of explanations with annotations that clarify the reasons, etc., relating to the distinction between partial change matters and notification matters, and shall be attached to the application form as reference data, as necessary.

The descriptions on approval application forms shown here are only provided as examples. When completing an actual approval application, the contents of descriptions on the approval application form should follow section 2.1, and judgments on the distinction between partial change matters and notification matters should be made in accordance with sections 2.2 and 2.3. Descriptions should be made based on case-by-case judgment depending on the characteristics of each drug.

Examples of Descriptions for Drug Substances

Step 1 (Critical process)

Mix 2-(1-triphenylmethyl-1*H*-tetrazole-5-yl)-4'-bromomethylbiphenyl [1]『(21.6 kg)』, 2-formyl-5-[(1*E*,3*E*)-1,3-pentadienyl]-1*H*-imidazole [2]『(6.9 kg)』, potassium carbonate 『(11.8 kg)』, and dimethylformaldehyde『(60 L)』at『25℃ for 24 hours』. Add sodium borohydride 『(3.2 kg)』, and mix further at『25℃ for 24 hours』. Filter the reaction mixture, and remove the insoluble matter. Concentrate the filtrate under vacuum. Add water『(50 L)』to the residue, and extract it with ethyl acetate『(50 L)』. Wash the organic layer with water 『(50 L)』and "10%" saline solution『(30 L)』. Concentrate the organic layer under vacuum until it is reduced by approximately one-half. Stir the residue at『5℃ for 3 hours』. Centrifuge the precipitated crystals, and wash them with ethyl acetate『(10 L)』. Dry the crystals under vacuum at《40℃》for 8 to 10 hours, and obtain 1-[2'-(1-trityl-1*H*-tetrazole-5-yl)-4-biphenylmethyl]- 5-[(1*E*,3*E*)-1,3-pentadienyl]-2-hydroxymethylimidazole [3].

Step 2

Mix the [3]『(approximately 22 kg)』obtained in Step 1, "10%" hydrochloric acid『(200 L)』, and tetrahydrofuran『(400 L)』at『25℃ for 4 hours』. Add "10%" sodium hydroxide aqueous solution『(200 L)』to the reaction mixture. Concentrate the mixed liquid under vacuum. Add water『(100 L)』to the residue. Filter it and remove insoluble matter. Adjust the pH of the filtrate to pH 3±0.5 with "35%" hydrochloric acid. Centrifuge the precipitated crystals, and wash them with water. Dry the crystals under vacuum at《40℃》, and obtain crude crystals of 1-[2'-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl)-5-[(1*E*,3*E*)-1,3-pentadienyl]-2-hydroxymethyl-1*H*-imidazole [4].

Step 3

Add the crude crystals from [4] with "90%" methanol『(80 L)』, and dissolve the crystals by heating to『60℃』and stirring. Add active carbon, and stir at『60℃ for 30 minutes』. Remove solid matter through pressurized filtration, and wash with the heated "90%" methanol『(5 L)』. Blend the filtrate and wash liquid, cool them down to《30℃》gradually, and allow precipitation to occur. After crystallization, cool them down further, and stir at《5℃》for 1 hour or more. Centrifuge the precipitated crystals, and wash them with "90%" methanol『(10 L)』that has been cooled to below《10℃》. After vacuum drying the crystals at《40℃》, pulverize the crystals to 10 μm or less in median diameter, and obtain 1-[2'-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl)-5-[(1*E*,3*E*)-1,3-pentadienyl]-2-hydroxymethyl-1*H*-imidazole [4].

Step 4 (Packaging process)

Put [4] in polyethylene bags, and pack the bags in fiber drums.

Control items and control values for the intermediate [3] in Step 1 (Key intermediate)

Item	Control values
Appearance	Pale yellowish-white crystalline powder (macroscopic observation)
Identification	Conform to the specification (IR)
Related substances	Not more than 4% (HPLC, area percent)

Dimethylformamide	Not more than 1000 ppm (GC)
Content	Not less than 93% (HPLC, absolute calibration curve method)

Control items and control values for the crude crystals [4] in Step 2 (Key intermediate)

Items	Control values
Appearance	White to pale yellowish-white crystals or crystalline powder (macroscopic observation)
Total related substances	Not more than 0.4% (HPLC, absolute calibration curve method)
Related substance I	Not more than 0.3% (HPLC, absolute calibration curve method)
Other related substances	Not more than 0.1% (HPLC, absolute calibration curve method)

Control items and control values for the dried crystals [4] in Step 3 (Key intermediate)

Items	Control values
Appearance	White to pale yellowish-white crystals or crystalline powder (macroscopic observation)
Tetrahydrofuran	Not more than 100 ppm
Methanol	Not more than 300 ppm

Note: From among the standard batch sizes or the process parameters that serve as target values/set values, notification matters are enclosed in 『 』, while partial change matters are enclosed in《 》. Notification matters other than target values/set values are enclosed in " ", while other matters are partial change matters.

"Reference"

Step 1

Mix 2-(1-triphenylmethyl-1*H*-tetrazole-5-yl)-4'-bromomethylbiphenyl [1] 『(21.6 kg)』 *1), 2-formyl-5-[(1*E*,3*E*)-1,3-pentadienyl]-1*H*-imidazole [2] 『(6.9 kg)』 *1), potassium carbonate 『(11.8 kg)』 *1), and dimethylformaldehyde 『(60 L)』 *1) at 『25℃ for 24 hours』 *2). Add sodium borohydride 『(3.2 kg)』 *1), and mix further at 『25℃ for 24 hours』 *2). Filter the reaction mixture, and remove the insoluble materials. Concentrate the filtrate under vacuum*4). Add water 『(50 L)』 *1) to the residue, and extract it with ethyl acetate 『(50 L)』 *1). Wash the organic layer with water 『(30 L)』 *1) and "10%"*3) saline solution 『(30 L)』 *1). Concentrate the organic layer under vacuum*4) until it is reduced by approximately one-half. Stir the residue at 『5℃ for 3 hours』 *2). Centrifuge*4) the precipitated crystals, and wash them with ethyl acetate 『(10 L)』 *1). Dry*4) the crystals under vacuum at 《40℃》 for 8 to 10 hours*5), and obtain 1-[2'-(1-trityl-1*H*-tetrazole-5-yl)-4-biphenylmethyl]-5-[(1*E*,3*E*)-1,3-pentadienyl]-2-hydroxylmethylimidazole [3]. (Percentage yield or actual yield)*6)

Step 2

Mix the [3] 『(approximately 22 kg)』 *1) obtained in Step 1, "10%" hydrochloric acid 『(200 L)』 *1), and tetrahydrofuran 『(400 L)』 *1) at 『25℃ for 4 hours』 *2). Add "10%"*3) sodium hydroxide aqueous solution 『(200 L)』 *1) to the reaction mixture. Concentrate the mixture under vacuum*4). Add water 『(100 L)』 *1) to the residue. Filter it and remove insoluble matter. Adjust the pH of the filtrate to pH 3±0.5*7) with "35%"*3) hydrochloric acid. Centrifuge*4) the precipitated crystals, and wash them with water. Dry*4) the crystals under vacuum at 《40℃》 *5), and obtain crude crystals of 1-[2'-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl)-5-[(1*E*,3*E*)-1,3-pentadienyl]-2-hydroxymethyl-1*H*-imidazole [4].

Step 3

Add the crude crystals from [4] with "90%"*3) methanol 『(80 L)』 *1), and dissolve the crystals by heating to 『60℃』 *2) and stirring. Add active carbon, and stir at 『60℃ for 30 minutes』 *2). Remove solid matter through pressurized filtration*4), and wash with the heated "90%"*3) methanol 『(5 L)』 *1). Blend the filtrate and wash liquid, cool them down to 《30℃》 *5) gradually, and allow precipitation to occur. After crystallization, cool them down further, and stir at《5℃》for 1 hour or more*5). Centrifuge*4) the precipitated crystals, and wash them with "90%" *3) methanol 『(10 L)』 *1) that has been cooled to below 10℃. After vacuum drying*4) the crystals at 《40℃》 *5), pulverize the crystals to 10μm or less in median diameter*8), and obtain 1-[2'-(1*H*-tetrazole-5-yl)biphenyl-4-yl] methyl)-5-[(1*E*,3*E*)-pentadienyl]-2-hydroxymethyl-1*H*-imidazole [4].

Step 4 (Packaging process)

Put [4] in polyethylene bags*9), and pack the bags in fiber drums*10).

Note:

*1) This indicates variable figures that depend on scale, and is a matter to be notified

*2) This temperature and time are target values/set values (width or range is entered in and controlled by the product master formula and SOPs)

*3) Minor change is possible for the concentration

*4) Vacuum concentration, centrifugation, and vacuum drying are operating principles
*5) This temperature (range is entered in the product master formula) and time are critical matters
*6) Include actual yield or percentage yield, if it is an essential condition in ensuring the quality
*7) The pH in this case is critical, and the range must be specified
*8) Particle size is controlled as a partial change matter
*9) Write down the name of the material for the primary container
*10) Describe the secondary container, if it functions to secure stability

2. Guideline for Descriptions on the Approval Application Form for the Manufacturing Method of Chemical Drug Products

A. General Notices

With regard to descriptions in the Manufacturing Method column:
In the "Manufacturing Method" column, the manufacturing site and the manufacturing method shall be written down according to the following.

1. Manufacturing Site

1.1 Description of the manufacturing site

- For each manufacturing site (including the manufacturing sites of contract manufacturers and testing facilities), the name and address of each site, as well as the scope of the manufacturing process covered, shall be entered in the column.
- The license or accreditation number for each manufacturing site shall be entered in the column.
- However, if the manufacturing site has already been entered in the Manufacturing Site column on the marketing authorization application, it is not necessary to write down the address and the license or accreditation number.

1.2 Matters relating to the manufacturing site to be addressed in a partial change approval application

- Since changes in manufacturing sites require adequate change control, they shall be, in principle, addressed in partial change approval applications for matters that have been approved. However, if a change falls under one of the following and its change control has been carried out properly, it shall be addressed in a minor change notification:
  ① A change to a manufacturing site that exists in Japan, of which the change in the manufacturing method falls within the scope of a minor change notification, is classified in the same license or accreditation category, and complies with GMP (refers to cases where the same status is expected to maintained thereafter, such as there not being any GMP non-compliances found; the same applies hereinafter) in GMP inspections (i.e., on-site inspection only; the same applies hereinafter) conducted within the last 2 years for a product of a similar category that shares related processes
  ② A change in the facilities related to testing
  ③ A change in the facilities related only to packaging, labeling, and storing

- Changes from a domestic manufacturing site to a foreign manufacturing site, and changes in manufacturing sites within foreign countries shall also be addressed in a minor change notification if they meet the above conditions.

2. Manufacturing Method

2.1 Description of manufacturing method

- All of the processes, from the raw materials to the packaging/labeling processes of the drug product, shall be described according to the process sequence.
- In accordance with the flow of the manufacturing process, raw materials, batch size,

preparation fluid/solvents, yields, intermediate products, primary packaging materials, etc. shall be specified, together with the operating conditions.

- From among the series of operating procedures in the manufacturing process, the matters needed for ensuring the constancy of quality shall be appropriately selected and described.
  ① Quantities of raw materials, critical processes, process parameters, equipment, operating conditions (e.g., speed, temperature, pressure, pH, time) shall be adequately described. Details on equipment with special functions shall be described.
  ② Target values/set values may be included in operating conditions, etc. If a target value/set value is set, the reference value shall be enclosed in 『 』or《 》(refer to "2.2 Distinction between a partial change approval application and a minor change notification for the manufacturing method," for information on how to use symbols), and at the same time, an allowable range for the target value/set value must be established in the product master formula or standard operating procedures (SOPs). However, if these parameters are set for parametric release (limited to cases where release determination is conducted by a sterilization parameter instead of the sterility test defined in ICH-Q6A), or if the parameters can affect the quality significantly, it is necessary to specify an allowable range on the approval application form, and they must not be made a target value/set value. In this case, deviations from the range of parameters written on the approval application form will not be acknowledged. In addition, the batch size may be handled according to the target value/set value, and in such a case, the standard batch size shall be written down on the approval application form.
  ③ Control procedures (e.g., process control value, acceptance criteria, outline of test method) performed to guarantee that the processes indicated in ① from among the manufacturing processes are controlled shall be described.
  ④ Specifications and test methods for raw materials that have a significant impact on quality shall be described (excluding those entered in the Specification and Test Methods column).
  ⑤ For raw materials derived from cows, etc., matters on the country of origin, body part, processing method, and, as needed, other matters that are necessary from the perspective of quality/safety assurance, such as information on TSE data, shall be described. For raw material derived from humans and animals, the matters that are considered critical from the perspective of quality/safety assurance, such as its origin, donor screening contents, inactivation/elimination processing methods for bacteria, fungi, viruses, etc., during the manufacturing process shall be described.
  ⑥ Specifications and an outline of test methods for intermediate products. However, if testing is to be implemented where the specifications for the intermediate products serve as part of the release tests for the product, the details of test methods shall be described.
  ⑦ Names of raw materials and packaging materials that affect the quality of the product shall be written down.
  ⑧ The manufacturer and model number or specifications for packaging materials that affect the quality of the product shall be written down as necessary.

2.2 Distinction between a partial change approval application and a minor change notification for the manufacturing method

- Any changes to the description in the Manufacturing Method column require

appropriate change control and shall be addressed in a partial change approval application or a minor change notification.

- A change other than those in manufacturing processes that fall within the scope of a partial change approval application shall be addressed in a minor change notification if it does not affect the quality of the final products.
- For changes that are reasonably judged to have no impact on the quality of products, such as changes in the country of origin in relation to bovine spongiform encephalopathy (BSE), changes in the compendia, other changes based on administrative procedures, and changes to narrow the range of specification values/acceptance criteria, it is acceptable to submit a minor change notification.
- For raw material derived from humans and animals, if changes are made to the country of origin, etc., to cope with the new risks such as infectious factors, or other changes have been made based on the administrative procedures, it is acceptable to submit a minor change notification when indicating that such a change has been made.
- Among the standard batch sizes or the process parameters that serve as target values/set values, the matters to be addressed in a minor change notification shall be enclosed in 『 』, and those to be addressed in a partial change approval application shall be enclosed in 《 》. Furthermore, the matters to be addressed in a minor change notification other than target values/set values shall be enclosed in " ", and other matters shall be addressed in a partial change approval application.

2.3 Matters to be addressed in a partial change approval application for the manufacturing method*

- Changes in the operating principle for critical processes, and changes in the process control criteria as the endpoint criteria for quality of the process
- Changes in the names of materials used for packaging materials that affect the quality of the product (however, for solid oral preparations, a minor change notification is acceptable for changes in the name of a material, if polyethylene, polyethylene terephthalate, polyvinyl chloride, polyvinylindene chloride, polypropylene, cyclic polyolefin, aluminum foil, cellophane, multi-film that combines these materials, or glass is used as the name of material for immediate containers and the like)
- Changes in information relating to the test method and acceptance criteria, if tests on an intermediate product or on the critical processes as a part of release tests for the drug product are to be performed
- Changes in matters relating to aseptic manufacturing and in matters that require special control, such as functional excipients for prolonged release forms, from among the quality and control methods for raw materials
- Changes in matters relating to aseptic manufacturing, matters that require special control and so forth, from among the test methods and acceptance criteria that ensure that the critical process parameters and their processes are controlled.
- Additions and deletions relating to inactivation and elimination methods of pathogens such as bacteria and viruses, and changes in inactivation and elimination conditions (however, if improvements in the pore size of the removal membrane, etc., are sufficiently validated, such changes may be addressed in a minor change notification)
- Changes in matters related to equipment that requires special control.
- Changes in other matters that require special control.

* A process that directly affects the quality standard items as represented by approved specification items is defined as a critical process, and should be described on the approval certificate, including the "endpoint criteria for quality" for the process and the control method (operating parameter) for fulfilling the endpoint criteria for quality.

Changes in the principle of unit operation for critical processes and in the process control criteria as endpoint criteria for quality shall be addressed in a partial change approval application. On the other hand, operating conditions, etc., for controlling the endpoint criteria for quality shall be addressed in a minor change notification.

3. Reference Data

In order to facilitate understanding on the manufacturing method, the following reference data shall be attached as necessary.

- Annotations explaining the reasons, etc., for the distinction between the matters to be addressed in a partial change approval application and matters to be addressed in a minor change notification (Refer to "Reference.")
- A flow chart of the manufacturing method

Terminology

Critical process:

Refers to a process that includes process conditions, tests, and other related parameters that need to be controlled within predetermined control values to ensure that the product meets specifications.

The following are examples of critical processes.

- Blending process, granulation process, particle size refining process, transport process, and tableting process for low amount solid dosage forms
- Process for determining dissolution profiles for solid dosage forms
- Processes in which the manufacturing scale affects product specifications, such as the blending process, granulation process, solution preparation process, filtration process, freeze drying process, and terminal sterilization process
- Processes for material control, process filter control, etc., to determine bioburdens in manufacturing methods using aseptic operation
- Processes that may generate degradants, such as the granulation process and drying process for solid dosage forms, and the solution preparation process and terminal sterilization process for injectable drug products
- Processes that affect the stability of the product, including the primary packaging process and the manufacturing process, such as the drying process

Endpoint criteria for quality:

Characteristics of an intermediate product that have a significant effect on quality standards as represented by the specifications and test methods of the final product.

- Example 1: Particle size distribution of granules (an intermediate product), for which the distribution in the strength for different particle sizes varies greatly. The criteria can be met if the homogeneity itself is measured, but this particle size has a significant effect on the homogeneity of the final product, by which segregation might occur in the next process. (Particle size distribution)
- Example 2: Water content in cases where the water content in granules has a significant impact on the time-course change of dissolution. (Water content)

Target value/set value:

A target value is a value, such as a measured value, obtained from the result of implementing a particular manufacturing process, whereas a set value is a value that is set as a condition in order to implement a particular manufacturing process. Whether either or both target and set values should be established, and whether such values should fall under matters to be addressed in a partial change approval application or a minor change notification depend on each manufacturing process.

B. Examples of Descriptions on Approval Application Forms (Drug Products)

Examples of descriptions are shown for the approval application form for a drug product. In order to grasp the flow of overall operations, examples are described according to the flow of the manufacturing process, without separating the matters that should be changed by a partial change approval application (hereinafter referred to as "partial change matters") from the matters that can be changed by a minor change notification (hereinafter referred to as "notification matters"). However, as shown in the examples of descriptions below, in addition to describing notification matters on the approval application form so that they can be distinguished easily, parameters, etc., that are handled as target values/set values are also to be described distinctively. This also applies to cases where a notification is submitted to be consistent with descriptions on the approval application forms that are required for marketing approval under the Revised Pharmaceutical Affairs Law. "Reference" consists of explanations with annotations that clarify the reasons, etc., relating to the distinction between partial change matters and notification matters, and shall be attached to the application form as reference data, as necessary.

The examples of descriptions here were prepared for 3 types of dosage forms: tablets, injectable liquid, and freeze-dried injectable drugs. The descriptions on approval application forms shown here are only provided as examples. When completing an actual approval application, the contents of descriptions on the approval application form should follow section 2.1, and judgments on the distinction between partial change matters and notification matters should be made in accordance with sections 2.2 and 2.3. Descriptions should be made based on case-by-case judgment depending on the characteristics of each drug.

Examples of Descriptions for Tablets

Critical processes:
<First step> Blending/granulation/drying processes
<Fourth step> Tableting process
<Fifth step> Sugar coating process
<Sixth step> Packaging process

<First step> Blending/granulation/drying processes

Put『x kg』of XYZ, 『x kg』of calcium carmellose, and『x kg』of lactose in a fluidized bed granulator "(250 L)," and mix well. Then, spray hydroxypropylcellulose solution and granulate the mixture. The granulation endpoint is determined by [Process control 1]. Next, dry the granules. The drying endpoint is when the exhaust air temperature is 『50℃』(standard drying time: 『90 minutes』). After allowing the granules to cool naturally, measure the water activity in the dried granules [Process control 2]. If the measured value exceeds the control value, add a drying operation for a maximum of『60 minutes』.

<Second step>Particle size refining process

Place the dried granules manufactured in the first step in a sieving machine, and refine the granules with a "screen of 1 mm in diameter (φ)."

<Third step> Granule blending process

Place『n batches』of the refined granules (x kg/batch) manufactured in the second step and magnesium stearate (x kg/batch) in a V- blender "(1000 L)," and blend them for "10 to 20 minutes."

<Fourth step> Tableting process

Example 1: Put『x kg』of the granules manufactured in the third step in a rotary tableting machine, and compress them into tablets so that the tablets are "x to x N/m in hardness," "xx to xx mg in tablet weight," and "○ to ○ mm in thickness." [Process control 3]

Example 2: Put『x kg』of the granules manufactured in the third step in a rotary tableting machine, and compress them into tablets under a "preliminary pressure of x t/pestle (x to x t/pestle)" and a "main pressure of x t/pestle (x to x t/pestle)" at a speed of『xx rpm』. [Process control 3]

<Fifth step> Sugar coating process

Place the uncoated tablets manufactured in the fourth step into a coating machine (High Coater: "HC-150"), and spray them with a mixture of『11.5 L』of primary coating solution and『11.5 L』of syrup solution, by dividing the mixture over the course of several sprays. After each spray and before drying, spray the tablets with a primary coating spray powder. The total amount of the primary coating spray powder to be used is『60 kg』. After primary coating is complete, dry the coated tablets at an air flow temperature of 48℃ (45℃ to 50℃) (standard drying time:《60 minutes》).

Next, spray『275 L』of kneading-in solution, and dry the tablets.

After allowing the tablets to cool down naturally to around room temperature, spray 『225 L』of syrup solution. After spraying is complete, dry the tablets.

Add『150 g』of Macrogol 6000 and dry the tablets. [Process control 4]

<Sixth step> Packaging process

Example 1: Using a PTP packaging machine, fill tablets into "polypropylene film," set them in "aluminum foil," and heat seal them. Cut the sealed product to make PTP sheets.
"Seal the PTP sheets with aluminum/polyethylene laminated film to make them into products packed in aluminum bags, and then put them into paper boxes." [Process control 5]

Example 2: Using a PTP packaging machine, fill tablets into "polypropylene film," set them in "aluminum foil," and heat seal them at 190℃ to 210℃ (control range of 175℃ to 230℃). Cut the sealed product to make PTP sheets.
"Seal the PTP sheets with aluminum/polyethylene laminated film to make them into products packed in aluminum bags, and then put them into paper boxes."

[Process control 1]: When x g of the process sample is weighed and its particle size is measured with a sieve with an eee mesh, the remaining amount on the sieve is x to x w/w% of the total amount.

[Process control 2]: When x g of the process sample is weighed and water activity is measured using a water activity measuring device, the value obtained is 2% to 4%.

[Process control 3]: When the content uniformity test is performed with the process sample, the sample conforms to the test.

[Process control 4]: When weight and thickness are measured with the process sample, the weight is 220 mg (218 to 223 mg), and the thickness is 4.6 ± 0.3 mm.

[Process control 5]: When the process sample is immersed into water and vacuumed below x kPa, there are no air bubbles generated.

Terminology

Hydroxypropylcellulose solution: Pour『x kg』of hydroxypropylcellulose into『xx L』of purified water, and stir the mixture.

Primary coating solution: Dissolve『1.3 kg』of sucrose and『0.6 kg』of powdered acacia in purified water to make『3L』.

Syrup solution: Dissolve『44.4 kg』of sucrose in purified water to make『50 L』.

Primary coating spray powder: Mix『6.0 kg』of precipitated calcium carbonate and 『6.0 kg』of talc.

Kneading-in solution: Add purified water to『43.6 kg』of sucrose,『13.9 kg』of precipitated calcium carbonate, 『8.6 kg』of talc, and『2.0 kg』of powdered acacia, and mix them to make『60 L』.

Note: From among the standard batch sizes or the process parameters that serve as target values/set values, notification matters are enclosed in 『 』, while partial change matters are enclosed in《 》. Notification matters other than target values/set values are enclosed in " ", while other matters are partial change matters.

"Reference"

<First step> Blending/granulation/drying processes

Put 『x kg』 *1) of XYZ, 『x kg』 *1) of calcium carmellose, and 『x kg』 of lactose*1) in a fluidized bed granulator*2) "(250 L)"*1) and mix well. Then, spray hydroxypropylcellulose solution and granulate the mixture. The granulation endpoint is determined by [Process control 1]. Next, dry the granules. The drying endpoint is when the exhaust air temperature is 『50℃』 *1) (standard drying time: 『90 minutes』 *1)). After allowing the granules to cool naturally, measure the water activity in the dried granules [Process control 2]. If the measured value exceeds the control value, add a drying operation for a maximum of 『60 minutes』 *1).

<Second step>Particle size refining process

Place the dried granules manufactured in the first step in a sieving machine, and refine the granules with a "screen of 1 mm in diameter (φ)." *3)

<Third step> Granule blending process

Place 『n batches』 *1) of the refined granules (x kg/batch) manufactured in the second step and magnesium stearate (x kg/batch) in a V-blender*2) "(1000 L)" *1), and blend them for "10 to 20 minutes" *4).

<Fourth step> Tableting process

Example 1: Put 『x kg』 *1) of the granules manufactured in the third step in a rotary tableting machine*2), and compress them into tablets so that the tablets are "x to x N/m in hardness" *5), "xx to xx mg in tablet weight" *5), and "○ to ○ mm in thickness" *5). [Process control 3]

Example 2: Put 『x kg』 *1) of the granules manufactured in the third step in a rotary tableting machine*2), and compress into tablets under a "preliminary pressure of x t/pestle (x to x t/pestle)" *6), "main pressure of x t/pestle (x to x t/pestle)" *6) at the speed of 『xx rpm』 *6). [Process control 3]

* Example 1 is a quality standard, while Example 2 is an operating parameter control.

<Fifth step> Sugar coating process

Place the uncoated tablets manufactured in the fourth step into a coating machine (High Coater*7): "HC-150" *8)), and spray them with a mixture of 『11.5 L』 *1) of primary coating solution and 『11.5 L』 *1) of syrup solution, by dividing the mixture over the course of several sprays. After each spray and before drying, spray the tablets with a primary coating spray powder. The total amount of the primary coating spray powder to be used is 『60 kg』 *1). After primary coating is complete, dry the coated tablets at an air flow temperature of 48℃ (45℃ to 50℃)*9) (standard drying time: 《60 minutes》)*9).

Next, spray 『275 L』 *1) of kneading-in solution, and dry the tablets.

After allowing the tablets to cool down naturally to around room temperature, spray 『225 L』 *1) of syrup solution. After spraying is complete, dry the tablets.

Add 『150 g』 *1) of Macrogol 6000 and dry the tablets. [Process control 4]

<Sixth step> Packaging process

Example 1: Using a PTP packaging machine, fill tablets into "polypropylene film"*10), set them in "aluminum foil," and heat seal them. Cut the sealed product to make PTP sheets.

"Seal the PTP sheets with aluminum/polyethylene laminated film to make them into products packed in aluminum bags, and then put them into paper boxes" *11). [Process control 5]*12)

Example 2: Using a PTP packaging machine, fill tablets into "polypropylene film"*10) , set them in "aluminum foil," and heat seal them at 190℃ to 210℃ (control range of 175℃ to 230℃)*13). Cut the sealed product to make PTP sheets.
"Seal the PTP sheets with aluminum/polyethylene laminated film to make them into products packed in aluminum bags, and then put them into paper boxes"*11).

[Process control 3]: When the content uniformity test is performed with the process sample, the sample conforms to the test*14)

Terminology

Hydroxypropylcellulose solution: Pour 『x kg』 *1) of hydroxypropylcellulose into 『xx L』 *1) of purified water, and stir the mixture.

Primary coating solution: Dissolve 『1.3 kg』 *1) of sucrose and 『0.6 kg』 *1) of powdered acacia in purified water to make 『3L』 *1).

Syrup solution: Dissolve 『44.4 kg』 *1) of sucrose in purified water to make 『50 L』 *1).

Primary coating spray powder: Mix 『6.0 kg』 *1) of precipitated calcium carbonate and 『6.0 kg』 *1) of talc.

Kneading-in solution: Add purified water to 『43.6 kg』 *1) of sucrose, 『13.9 kg』 *1) of precipitated calcium carbonate, 『8.6 kg』 *1) of talc, and 『2.0 kg』 *1) of powdered acacia, and mix them to make 『60 L』 *1).

Note:

*1) This indicates variable figures that depend on scale, and is a matter to be notified
*2) The type of equipment represents an operating principle
*3) In this case, the diameter of the screen is not a critical control value
*4) The time in this step is a rough target
*5) Set as quality standard values, and vary according to differences in equipment and the lots of raw materials, etc.; the process is ultimately controlled by the process control value 3
*6) Set as parameter controls (quality assurance based on validation), and vary according to the differences in equipment and the lots of raw materials; the process is ultimately controlled by the process control value 3
*7) Equipment name represents operating principle, and is a partial change matter
*8) Model number differs according to scale
*9) In this case the process is assured by temperature and time, and therefore the temperature and the time are critical matters
*10) Write down the name of materials used for the primary container
*11) Descriptions relating to the secondary container and onwards are notification matters
*12) In Example 1, sealing performance is guaranteed by process control 5
*13) In Example 2, sealing performance is guaranteed by validation
*14) This test can be conducted as a substitution for the content uniformity test and assay for specifications and test methods

Examples of Descriptions for Injectable Liquids

Critical processes:
<Second step>pH adjustment/volumetric adjustment processes
<Third step> Filtration/filling process
<Fourth step> Sterilization process

<First step> Dissolution process
Dissolve『x kg』of sodium hydroxide in『xx L』of Water for Injection. Transfer this solution to a mixing tank. Add『xx L』of Water for Injection heated to『80℃』to the solution, and allow it to cool down naturally to 65℃ to 75℃ while stirring it. Add 『xx kg』of '△△ (drug substance)' while keeping the temperature at 65℃ to 75℃, and stir until the drug substance is dissolved. [Process control 1]

<Second step>pH adjustment/volumetric adjustment processes
Adjust the pH of the drug substance preparation to『x.x』using "1 mol/L" hydrochloric acid solution prepared with Water for Injection. In addition, use "1 mol/L" sodium hydroxide solution prepared with Water for Injection as necessary.
Add an adequate volume of Water for Injection to make the total volume『xxx L』, and stir it for『at least 15 minutes』. As necessary, adjust the pH by using "1 mol/L" hydrochloric acid solution or "1 mol/L" sodium hydroxide solution. [Process control 2]

<Third step> Filtration/filling processes
Filter the drug preparation solution through a "cartridge filter made of cellulose" (pore size: 0.2μm).
Fill x.x ± x.x mL of the solution into each of the colorless x mL glass ampoules that were washed and depyrogenated (at xx℃ for at least x minute(s)), and then seal the ampoules. [Process control 3]

<Fourth step> Sterilization process
Perform terminal sterilization for a maximum of 『XX thousand』filled ampoules in an autoclave at the settings of "xx℃ to xx℃ for x to x minutes," making sure that the product temperature remains at 121℃ for 20 minutes. [Process control 4]

<Fifth step> Packaging process
Affix the label to each ampoule.

[Process control 1] Confirm that dissolution occurs by visual inspection.
[Process control 2]
Description: Colorless, clear solution
pH: x.x to x.x
Related substances: When the test is conducted based on liquid chromatography, the related substance I should be not more than x%.
Microbial limit: Not more than xx cfu/mL
[Process control 3] The weight of a filled and sealed ampoule should be x.x ± x.x g.
[Process control 4] Test the seal performance of the ampoules by using an automatic leak detector.

Note: From among the standard batch sizes or the process parameters that serve as target

values/set values, notification matters are enclosed in 『 』, while partial change matters are enclosed in《 》. Notification matters other than the target values/set values are enclosed in " ", while others matters are partial change matters.

"Reference"

<First step> Dissolution process

Dissolve『x kg』[*1)] of sodium hydroxide in『xx L』[*1)] of Water for Injection. Transfer this solution to a mixing tank. Add『xx L』[*1)] of Water for Injection heated to『80℃』[*2)] to the solution, and allow it to cool down naturally to 65℃ to 75℃[*1)] while stirring it. Add 『xx kg』[*1)] of '△△ (drug substance)' while keeping the temperature at 65℃ to 75℃[*3)], and stir until the drug substance is dissolved. [Process control 1]

<Second step>pH adjustment/volumetric adjustment processes

Adjust the pH of the drug substance preparation to『x.x』[*5)] using "1 mol/L"[*4)] hydrochloric acid solution prepared with Water for Injection. In addition, use "1 mol/L"[*4)] sodium hydroxide solution prepared with Water for Injection as necessary.

Add an adequate volume of Water for Injection to make the total volume『xxx L』[*1)], and stir it for『at least 15 minutes』[*6)]. As necessary, adjust the pH by using "1 mol/L"[*4)] hydrochloric acid solution or "1 mol/L"[*4)] sodium hydroxide solution. [Process control 2]

<Third step> Filtration/filling process

Filter the drug preparation solution through a "cartridge filter made of cellulose"[*7)] (pore size: 0.2μm)[*8)].

Fill x.x ± x.x mL[*11)] of the solution into each of the colorless x mL glass ampoules[*10)] that were washed and depyrogenated (at xx℃ for at least x minute(s))[*9)], and then seal the ampoules. [Process control 3]

<Fourth step> Sterilization process

Perform terminal sterilization for a maximum of『XX thousand』[*1)] filled ampoules in an autoclave at the settings of "xx℃ to xx℃ for x to x minutes"[*13)], making sure that the product temperature remains at 121℃ for 20 minutes[*12)]. [Process control 4]

<Fifth step> Packaging process

Affix the label to each ampoule.

Note:

*1) This indicates variable figures that depend on scale, and is a matter to be notified
*2) The temperature is a rough target
*3) When dissolution temperature is critical, the temperature is a critical matter
*4) Concentration can be changed
*5) The pH in this process is rough target
*6) Time is a target value
*7) As the filtration in this case is performed simply by way of precaution, it thus has a low criticality
*8) Pore size indicates function
*9) In this case, the quality is assured by the operating parameters such as temperature and time
*10) Material and volume are specified
*11) Fill volume is a critical matter
*12) Essential condition for sterilization
*13) Operational parameter to fulfill the sterilization condition

Examples of Descriptions for Freeze-Dried Injectable Drugs

Critical processes:
<Second step>Aseptic filtration/filling processes
<Third step> Freeze-drying process

<First Step> Drug solution preparation process
(1) Dissolution
Under a nitrogen stream, fill『xx L』of Water for Injection in a "△△L" capacity dissolution tank. Pour『xx kg』of active ingredient A, 『x kg』of raw material B, and 『x kg』of raw material C, and dissolve them. [Process control 1]
(2) Filtration
Filter the prepared solution through a "hydrophilic membrane filter with a pore size of 0.45μm."
(3) pH adjustment
Adjust the pH to『approximately x.x』with "5%" sodium hydroxide solution (prepared using Water for Injection).
(4) Volumetric adjustment of preparation
Add Water for Injection to make the total amount『xx kg』. [Process control 2]
Store the drug solution in a closed tank filled with nitrogen gas at a temperature of ○℃ or lower, and proceed to the next process within △ hours.

<Second step>Aseptic filtration/filling process
(1) Aseptic filtration
Aseptically filter the drug solution prepared in the first step through a cartridge filter made of cellulose acetate with a pore size of 0.22μm. [Process control 3]
(2) Filling
In a clean booth and under a nitrogen stream, fill a liquid volume of 2,000 mg ±3% of the drug solution into each colorless glass vial (capacity: ○○ mL) cleaned and dry-sterilized beforehand.
(3) Partial stoppering
Using a partial stoppering machine for rubber stoppers, partially stopper the drug solution-filled vials with rubber stoppers that have been washed and steam-sterilized beforehand. Use the rubber stoppers within 2 days after sterilization.

<Third step> Freeze-drying process
(1) Loading/freezing
After setting the shelf temperature of a freeze-drier at『–40℃』, load the partially stoppered vials that have been collected into the freeze-drier, and freeze-dry them at a shelf temperature of『–40℃』for『3 hours』(maximum batch size: 『36,000 vials』).
(2) Primary drying
After raising the temperature from『–40℃』to『20℃』under a vacuum of『x Pa』over a period of『x minutes』, carry out primary drying of the vials at『20℃』for『△ hours』.
(3) Secondary drying
After primary drying is complete, raise the temperature to『40℃』over a period of『x minutes』. Then, carry out secondary drying under a vacuum of『x Pa』for『△ hours』. [Process control 4]
(4) Unloading

Using nitrogen, return the pressure to 『–20 kPa』, and fully stopper the vials. After full stoppering, return the pressure to normal atmosphere with compressed air of a humidity of x% or lower.

<Fourth step> Clamping process
Clamp the freeze-dried vials using a press-type cap-clamping machine. [Process control 5]

<Fifth Step> Packaging process
Affix a label to each vial, and package them.

[Process control 1] Confirm that dissolution occurs by visual inspection.

[Process control 2] Appearance: Colorless, clear solution. No foreign matters are observed macroscopically;
pH: x.x to x.x; Absorbance (UV xxx nm): △.△△ ± △.△△

[Process control 3] Filter integrity: When a forward flow test is conducted using a filter integrity test machine "(type △△ manufactured by XX company)," the pressure is "25 kPa or less."

[Process control 4] After completion of drying, maintain a vacuum of 5 Pa for 5 minutes, and make sure that pressure does not increase to above 10 Pa.

[Process control 5] Test vials using a visual inspection machine for vials under a light of more than 1,500 lx.
Appearance: No stains or scratches on the vials. The clamping condition is favorable. The freeze-dried cake is in the form of white powder or lumps. This test can be treated as a substitute for the release test.
Solution clarity: When the vial content is dissolved in xx mL of Water for Injection, the solution is colorless or transparent pale yellow, without any (visual) foreign insoluble matters.
Airtightness: No leaks occurred at 0.25 Mpa.

Note: From among the standard batch sizes or the process parameters that serve as target values/set values, notification matters are enclosed in 『 』, while partial change matters are enclosed in 《 》. Notification matters other than the target values/set values are enclosed in " ", while other matters are partial change matters.

"Reference"

<First step> Drug solution preparation process

(1) Dissolution

Under a nitrogen stream, fill 『xx L』 *1) of water for injection in a "△△ L"*1) capacity dissolution tank. Pour 『xx kg』 *1) of active ingredient A, 『x kg』 *1) of raw material B, and 『x kg』 *1) of raw material C, and dissolve them. [Process control 1]

(2) Filtration

Filter the prepared solution through a "hydrophilic membrane filter with a pore size of 0.45μm"*2).

(3) pH adjustment

Adjust the pH to 『approximately x.x』 *4) with "5%"*3) sodium hydroxide solution (prepared using Water for Injection).

(4) Volumetric adjustment of preparation

Add Water for Injection to make the total amount 『xx kg』 *1). [Process control 2]

Store the drug solution in a closed tank filled with nitrogen gas at a temperature of ○℃ or lower, and proceed to next process within △ hours*5).

<Second step>Aseptic filtration/filling process

(1) Aseptic filtration

Aseptically filter the drug solution prepared in the first step through a cartridge filter*5) made of cellulose acetate with a pore size of 0.22μm*6). [Process control 3]

(2) Filling

In a clean booth under a nitrogen stream*7), fill a liquid volume of 2,000 mg ±3%*10) of the drug solution into each colorless glass vial (capacity: ○○ mL)*9) cleaned and dry-sterilized*8) beforehand.

(3) Partial stoppering

Using a partial stoppering machine for rubber stoppers, partially stopper the drug solution-filled vials with rubber stoppers that have been washed and steam-sterilized beforehand*8). Use the rubber stoppers within 2 days after sterilization*11).

<Third step> Freeze-drying process

(1) Loading/freezing

After setting the shelf temperature of a freeze-drier at 『–40℃』 *12), load the partially stoppered vials that have been collected into the freeze-drier, and freeze-dry them at a shelf temperature of『–40℃』 *12) for『3 hours』 *12) (maximum batch size: 『36,000 vials』 *1)).

(2) Primary drying

After raising the temperature from 『–40℃』 *12) to 『20℃』 *12) under a vacuum of 『x Pa』 *12) over a period of『x minutes』 *12), carry out primary drying of the vials at 『20℃』 *12) for 『△ hours』 *12).

(3) Secondary drying

After primary drying is complete, raise the temperature up to 『40℃』 *12) over a period of 『x minutes』 *12). Then, carry out secondary drying under a vacuum of 『x Pa} *12) for 『△ hours』 *12). [Process control 4]

(4) Unloading

Using nitrogen, return the pressure to 『–20 kPa』 *12) , and fully stopper the vials. After full stoppering, return the pressure to normal atmosphere with compressed

air[*13)] of a humidity of x% or lower.

<Fourth step> Clamping process
Clamp the freeze-dried vials using a press-type[*14)] cap-clamping machine. [Process control 5]

<Fifth step> Packaging process
Affix a label to each vial, and package them.

[Process control 3] Filter integrity: When a forward flow test is conducted using a filter integrity test machine "(type △ △ manufactured by XX company)"[*15)], the pressure is "25 kPa or less"[*15)].

[Process control 5] Test vials using a visual inspection machine for vials under a light of more than 1,500 lx.
Appearance: No stains or scratches on the vials. The clamping condition is favorable. The freeze-dried cake is in the form of white powder or lumps. This test can be treated as a substitute for the release test.
Solution clarity: When the vial content is dissolved in xx mL of Water for Injection, the solution is colorless or transparent pale yellow, without any (visual) foreign insoluble matters.
Airtightness: No leaks occurred at 0.25 Mpa.
* Appearance and solution clarity (foreign insoluble matter test) can be substituted for the drug product specification tests (release tests).

Note:
*1) This indicates variable figures that depend on scale, and is a matter to be notified
*2) This process is for eliminating insoluble materials, etc., and is less critical
*3) Concentration can be changed; if the solution temperature is critical, temperature is a critical matter
*4) The pH of this process is a rough target
*5) If the drug is unstable, necessary time shall be specified based on validation to assure the quality
*6) In order to guarantee this process, it is important to specify the filter
*7) Describe the environmental equipment and conditions necessary to assure the quality
*8) Conditions required for quality (e.g., cleaned and sterilized) are specified
*9) Specify the material and capacity
*10) Specify the manufacturer's product number of the product actually used (specified based on validation)
*11) Necessary control items
*12) Operational parameter is set based on the validation of equipment actually used
*13) Specify the critical condition for quality assurance
*14) Specify the function of the equipment
*15) If another machine can perform the same test, restrictions are not made to a specific machine. Specifications depend on the machine/apparatus

3. Guideline for Descriptions on Approval Application Forms for the Manufacturing Method of Biological Products, etc. [Biological Drugs (Biotechnological/Biological Products) and Specific Biological Products]

This guideline intends to address biological products (such as vaccines and blood products) as listed in the Minimum Requirements for Biological Products, as well as recombinant DNA technology-applied drugs, cell culture drugs and other biotechnological products/specified biological products. However, since it is difficult to show a description example representing all products due to the diversity of biological drugs, this guideline indicates general principles for describing biological drugs that are targeted in the PMSB/ELD Notification No. 571 issued by the Director of Evaluation and License Division, Pharmaceutical and Medical Safety Bureau, dated May 1, 2001, "Establishing Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products." Other related drugs shall also be described by referring to this guideline.
The approval application form for drug products shall be completed by referring to A. General Notices in Attachment 2.

A. General Notices

With regard to descriptions in the Manufacturing Method column:
In the "Manufacturing Method column," the manufacturing site and the manufacturing method shall be written down according to the following.

1. Manufacturing Site

1.1 Description of the manufacturing site

- For each manufacturing site (including the manufacturing sites of contract manufacturers and testing facilities), the name and address of each site, as well as the scope of the manufacturing process covered, shall be entered in the column.
- The license or accreditation number for each manufacturing site shall be entered in the column.
- However, if the manufacturing site has already been entered in the Manufacturing Site column on the marketing approval application, it is not necessary to write down the address and the license or accreditation number.

1.2 Matters relating to the manufacturing site to be addressed in a partial change approval application

- Since changes in manufacturing sites require adequate change control, they shall be, in principle, addressed in partial change approval applications for matters that have been approved. However, for changes that are related to facilities for inspection and testing, if the change falls under 2.1 below, and control for the change has properly been carried out, it shall be addressed in a minor change notification.

2. Manufacturing Method and Related Matters

2.1 Preparation methods and control methods for cell substrates (tables and figures shall be used as necessary)

① Preparation methods

1) Preparation of gene expression constructs

For genetic recombinant technology-applied drugs, describe information on how to obtain the gene, the background to preparation, and the structure, etc. with regard to the gene expression constructs.

2) Preparation of master cell bank
Describe the background to the preparation of the master cell bank that was implemented using the host and the gene expression construct.

3) Preparation of working cell bank
Describe the background to the preparation of the working cell bank from the master cell bank.

② Control methods
With regard to the master cell bank and the working cell bank, describe (1) testing items for characterization tests and purity tests, as well as analytical methods and the criteria, (2) information relating to stability during storage, and (3) the propagation procedure, etc.

2.2 Manufacturing Method

- The processes from cell culture and purification to storage shall be described.
  ① The process required to ensure the quality of the drug shall be described.
  ② Raw materials, reagents that may affect the quality of the product, critical processes, key intermediates, major equipment, critical process parameters (e.g., temperature, pH, time), etc., shall be described adequately. From among equipment with special functions, details (e.g., function, capacity) on those that affect the quality of the product shall be described.
  ③ With regard to critical processes for which in-process control tests have been established, the testing items, analytical methods, and acceptance criteria for approval or rejection shall be described.
  ④ In cases where a key intermediate that is isolated/stored is established, the storing conditions and duration shall be described. In addition, when an in-process control test is set for the key intermediate, the testing item, analytical method, and acceptance criteria for approval or rejection shall be specified.

- For the process parameters, target values/set values may be included in operating conditions, etc. If a target value/set value is set, the reference value shall be enclosed in 『 』 or 《 》(refer to "2.3 Distinction between a partial change approval application and a minor change notification for the manufacturing method," for information on how to use symbols), and at the same time, an allowable range for the target value/set value must be established in the product master formula or standard operating procedures (SOPs). However, if these parameters are set for parametric release (limited to cases where release determination is conducted by a sterilization parameter instead of a sterility test), or if the parameters can affect the quality significantly, it is necessary to specify an allowable range on the approval application form. In addition, the batch size shall also be able to be handled according to the target value/set value, and in such a case, the standard batch size shall be described on the approval application form. (Note)

- Raw materials
  ① Raw materials used for cell culture such as components of culture media, monoclonal antibodies used for purification, biologically-derived raw materials such as enzymes, and raw materials used in the preparation of drug substances shall be described.

② For raw materials derived from cows, etc., matters on the country of origin, body part, processing method, and the other matters that are from the viewpoint of quality/safety assurance, and as necessary, such as information on TSE data, shall be described.
③ For raw material derived from humans and animals, matters that are considered critical from the viewpoint of quality/safety assurance such as its origin, donor screening content, inactivation/elimination processing methods, for bacteria, fungi, viruses, etc., in the manufacturing process, shall be described.

- The following shall be described as a flow chart of the manufacturing method.
  ① Processes, from cell culture though storage, that are necessary for quality assurance (including all the different process units), as well as key intermediates, if established
  ② Critical process parameters and related matters for each process (doubling level of cell numbers, cell concentration, pH, time, temperature, etc.)
  ③ In-process control tests
  ④ Capacity of equipment with special functions that affect the quality of the product

- Other matters necessary for quality assurance

2.3 Distinction between a partial change approval application and a minor change notification for the manufacturing method

- As changes in the matters entered in the Manufacturing Method column require adequate change control, they shall therefore be addressed in a partial change approval application, in principle. (Note)
  However, in the event that it is evident that there is an extremely low possibility of the change having an adverse impact on the quality/safety of the final product, and in the following confirmed cases, a minor change notification may be applicable.

  ① Based on the type of drug and the type of change in the manufacturing method, a minor change notification may be applicable. For the applicable cases, the applicant may make such a proposal when submitting an approval application; the proposal will be judged during the review as to whether it can be accepted. As an example of applicable case, the allowable range for process parameters, etc. that is proposed at the time of application may be changed during the review for approval or on the occasion of the actual production results thereafter.
  ② In cases where in-house in-process control tests and similar target values are described and the change is made.
  ③ Changes in the scope of the manufacturing process at the same manufacturing site, in principle, shall be addressed in a minor change notification.
  ④ For changes that are reasonably judged to have no adverse effects on the quality of the product, such as changes to the country of origin of bovine spongiform encephalopathy (BSE), changes in the compendia, other changes based on administrative procedures, and changes to narrow specification value/acceptance criteria, it is acceptable to submit a minor change notification.
  ⑤ For raw material derived from humans and animals, if changes are made to the country of origin, etc., to cope with new risks against such as infectious factors, or changes have been made based on the administrative procedures, it is acceptable to submit a minor change notification when indicating that such a change has been made.

- Among the standard batch sizes or the process parameters that serve as target values/set values, the matters to be addressed in a minor change notification shall be enclosed in 『 』, and those to be addressed in a partial change approval application shall be enclosed in 《 》. Furthermore, the matters to be addressed in a minor change notification other than target values/set values shall be enclosed in " ".

Terminology

Critical process:
Refers to a process that affects quality (of the product), and includes process conditions, tests, and other related parameters that need to be controlled within predetermined control values to ensure that the drug substance meets specifications.

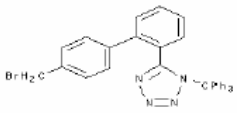
Target value/set value:
A target value is a value, such as a measured value, obtained from the result of implementing a particular manufacturing process, whereas a set value is a value that is set as a condition in order to implement a particular manufacturing process. Whether either or both target and set values should be established, and whether such values should fall under matters to be addressed in a partial change approval application or a minor change notification depend upon each manufacturing process.

Note: Because biological drugs are produced by utilizing biosynthesis processes in biological bodies, it may be possible that materials that are inhomogeneous in molecular structure are produced. Furthermore, as some changes in the higher structure of the molecule that are difficult to be determined by physicochemical analyses can affect biological activity, evaluation of the impact by changes in the manufacturing method on the quality, safety, and efficacy of the product is considered as being different from that of ordinary chemical drugs. Since biological drugs consist of various kinds of materials such as proteins, glycoproteins, polypeptides, and their derivatives, and their controls also vary, it is difficult to uniformly specify the matters to be addressed in a minor change notification for biological drugs.
Accordingly, in the case of biological drugs, changes in the matters described on an approval application form shall, in principle, be addressed in a partial change approval application.
However, in cases where it is judged that the quality of the product is ensured by the operating control items or in-process control tests, etc., described on the application form, changes in the process parameters that serve as target values/set values or in the reference values relating to standard batch size may be addressed in a minor change notification.
There may be cases where in-house in-process control tests and similar target values/set values are included in the approval application form; these shall be addressed in a minor change notification.

Attachment 4

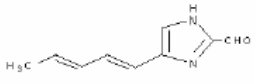
Flow Chart of the Manufacturing Process (Drug Substances)

Step 1



2-(1-triphenylmethyl-1*H*-tetrazole-5-yl)-4'-bromomethylbiphenyl

$C_{33}H_{25}BrN_4$



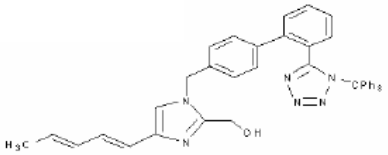
2-formyl-5-[(1*E*,3*E*)-pentadienyl]-1*H*-imidazole

$C_9H_{10}N_2O$

Reaction — 1) K_2CO_3, DMF — Potassium carbonate, Dimethylformaldehyde

Reaction — 2) NaBH4 — Sodium borohydride

Extraction/filtration/drying — 3) H_2O, $CH_3COOC_2H_5$ — Water, ethyl acetate, 10% saline solution



1-[2'-(1-trityl-1*H*-tetrazole-5-yl)-4-biphenylmethyl]-5-[(1*E*,3*E*)-1,3-pentadienyl]-2-hydroxylmethylimidazole

Step 2

Reaction — 1) 10%HCl, THF — 10% hydrochloric acid, Tetrahydrofuran

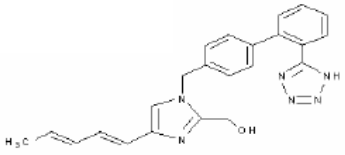
Purification/filtration/drying — 2) 10%NaOH, 35%HCl, H_2O — 10% sodium hydroxide, 35% hydrochloric acid, Water

Crude

Step 3

Purification — 1) 90%MeOH, Activate Carbon — 90% methanol, Activate carbon

Filtration/drying/micronization — 2) 90%MeOH — 90% methanol



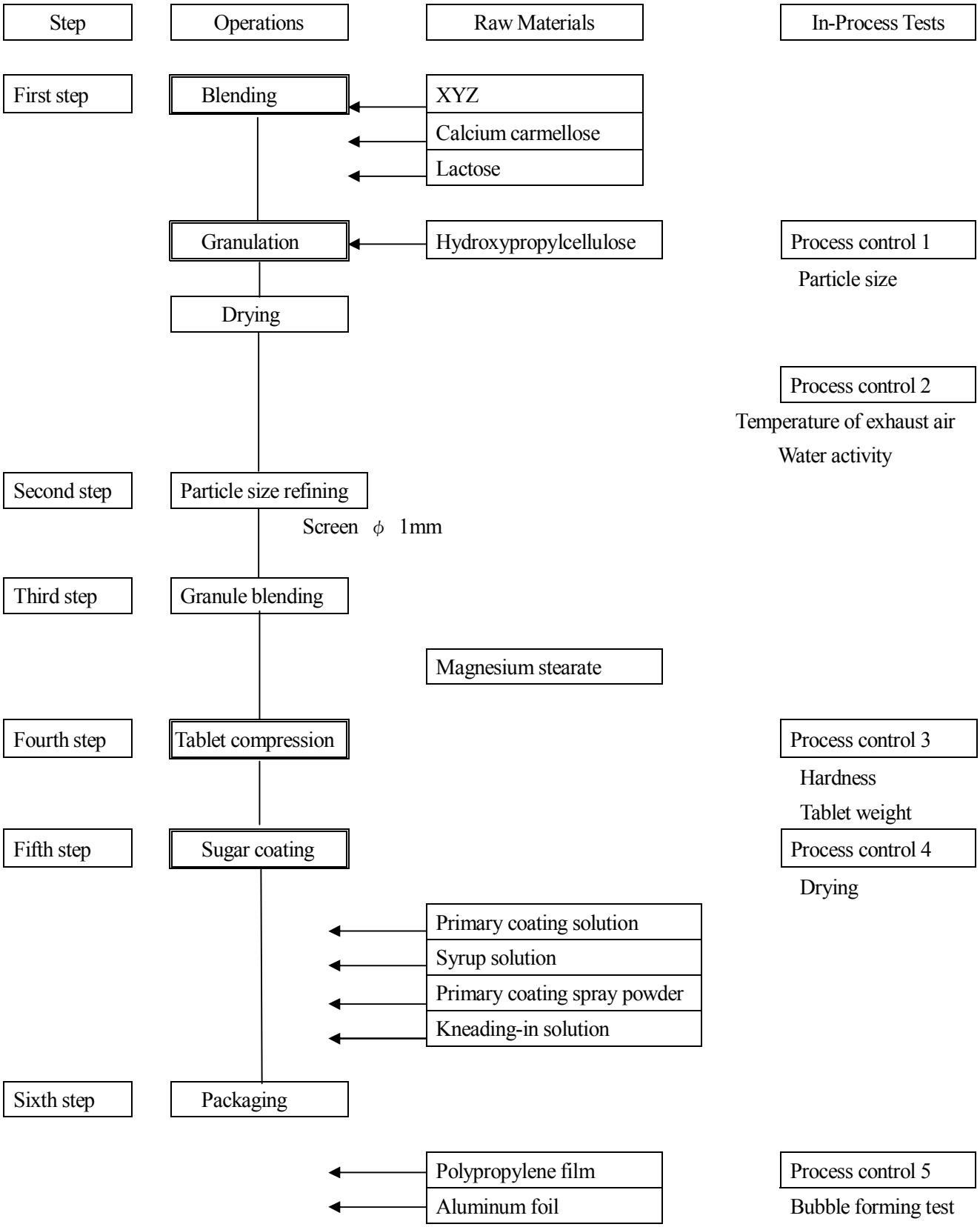
1-[2'-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl)-5-[(1*E*,3*E*)-1,3-pentadienyl]-2-hydroxymethyl-1*H*-imidazole

Step 4 [Packaging process]

Fill the final purified crystals into polyethylene bags and pack the bags in fiber drums.

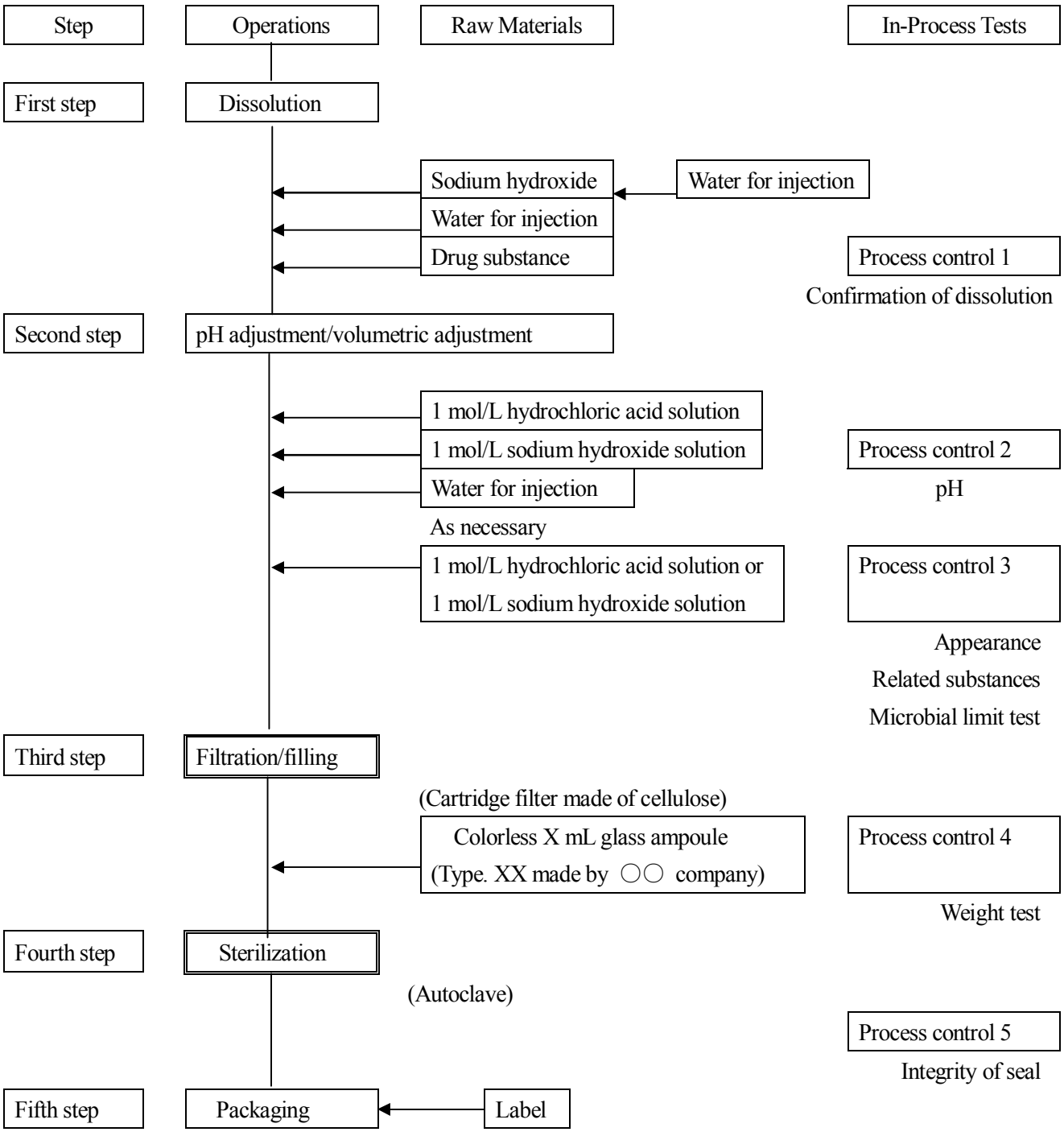
Attachment 5

Flow Chart of the Manufacturing Process (Tablets)



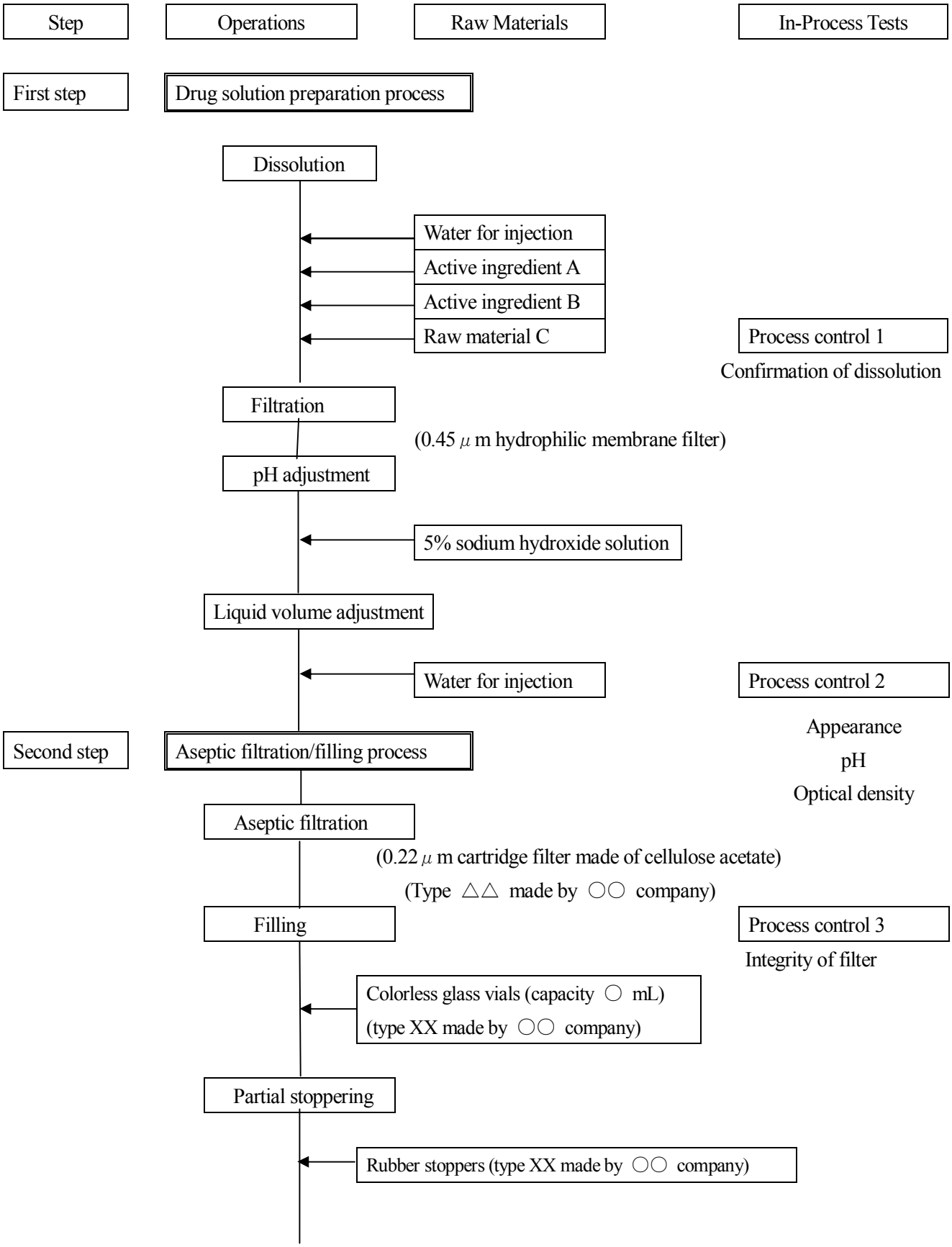
Attachment 6

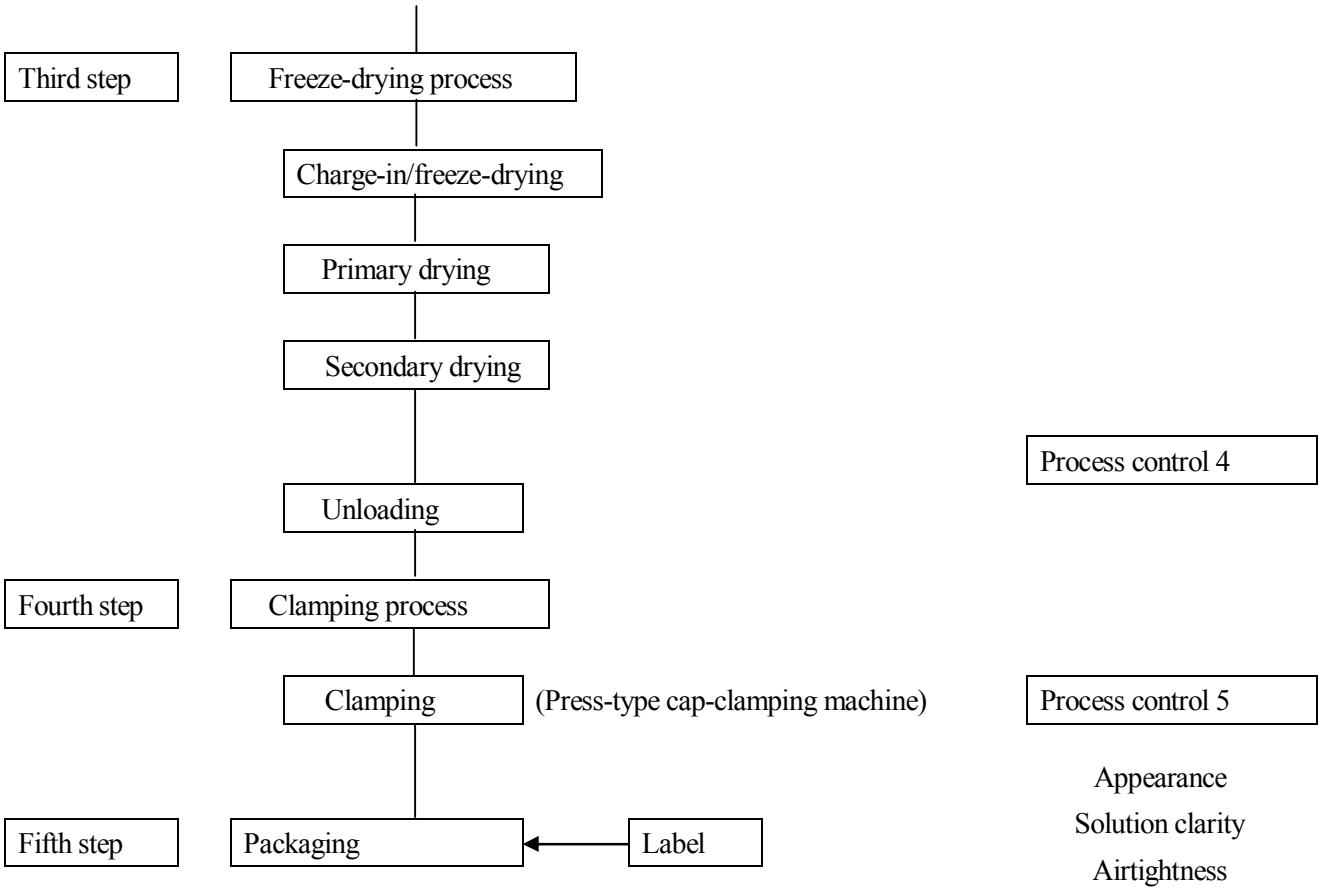
Flow Chart of the Manufacturing Process (Injectable Liquids)



Attachment 7

Flow Chart of the Manufacturing Process (Freeze-dried Injectable Drugs)




Third step
Freeze-drying process
Charge-in/freeze-drying
Primary drying
Secondary drying
Process control 4
Unloading
Fourth step
Clamping process
Clamping
(Press-type cap-clamping machine)
Process control 5
Appearance
Solution clarity
Airtightness
Fifth step
Packaging
Label

Attached Form*

Notification of Modifications to Description on Approval Certificate
for Marketing of Drug/Quasi-drug

<table>
<tr><td colspan="2">Approval No.</td><td></td><td>Date of approval</td><td></td></tr>
<tr><td rowspan="2">Name</td><td>Non-proprietary name</td><td colspan="3"></td></tr>
<tr><td>Brand name</td><td colspan="3"></td></tr>
<tr><td colspan="2">Ingredients and quantity or identity</td><td colspan="3"></td></tr>
<tr><td colspan="2">Manufacturing method</td><td colspan="3"></td></tr>
<tr><td colspan="2">Dosage and administration</td><td colspan="3"></td></tr>
<tr><td colspan="2">Indications</td><td colspan="3"></td></tr>
<tr><td colspan="2">Storage method and expiration date</td><td colspan="3"></td></tr>
<tr><td colspan="2">Specifications and test methods</td><td colspan="3"></td></tr>
<tr><td rowspan="2">Manufacturing site for the product to be marketed</td><td>Name</td><td>Address</td><td>License or approval category</td><td>License or approval No.</td></tr>
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<tr><td rowspan="2">Manufacturing site for the drug substance</td><td>Name</td><td>Address</td><td>License or approval category</td><td>License or approval No.</td></tr>
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<tr><td colspan="2">Remarks</td><td colspan="3">Therapeutic category No.</td></tr>
</table>

The undersigned hereby notifies modifications to the description on the approval certificate for marketing of the indicated drug/quasi-drug.

Date:

Address (address of the main office in the case of a corporation)
Name (names of the corporation and its representative in the case of a corporation)

(Seal)

To: Chief Executive of the Pharmaceuticals and Medical Devices Agency or Prefectural Governor

Notes

1. Use A4 format (JIS)
2. Submit one original copy and one duplicate copy.
3. Print legibly using back ink.

** This English version is only provided for reference. A notification must be submitted in Japanese.*