○GQP省令、医薬品・医薬部外品GMP省令、機器・体外診QMS省令及び構造設備規則の仮英訳について

（平成17年9月9日）
（事務連絡）

（各都道府県衛生主管部(局)あて厚生労働省医薬食品局監視指導・麻薬対策課通知）

下記の資料について、業務上の参考資料としてご活用されるよう別添のとおり配布いたします。

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別紙4　構造設備規則の仮英訳

担当：品質指導係

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（平成17年9月9日）
（事務連絡）

（(別記)あて厚生労働省医薬食品局監視指導・麻薬対策課通知）

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〔別記〕
日本製薬団体連合会
日本製薬工業協会
日本医薬品原薬工業会
日本大衆薬工業協会
社団法人日本薬業貿易協会

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日本大衆薬工業協会長
1030001　東京都中央区日本橋小伝馬町13―4　共同ビル3階
(社)日本薬業貿易協会理事長
1010054　東京都千代田区神田錦町1―23　日薬貿ビル
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［別紙1］

Tentative translation VER. 1[1]

MHLW Ministerial Ordinance No.136, 2004

In accordance with the provision of Item (1) of Article 12-2 of Pharmaceutical Affairs Law(Law No.145, 1960), MHLW Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices is established as follows.

22 September 2004
Chikara SAKAGUCHI
Minister of Health, Labour and Welfare

Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices

CONTENTS

17 to 20)
Chapter 4 Standards for Quality Assurance for Medical Devices(Articles 21 to 25)
Supplementary Provision
――――――――――――

[1]Note/This is a tentative translation of afore-mentioned Ordinance in English which is not an authentic and not formally autholised by Ministry of Health, Labour and Welfare of japan.

Chapter 1 General Provisions

(Purpose)

Article 1 This Ministerial Ordinance shall provide the standards in accordance with Item (1) of Article 12-2 of the Pharmaceutical Affairs Law(Law No.145, 1960)(hereinafter referred to as “Law”)which provides that such standards shall be provided by the MHLW Ministerial Ordinance.

(Definitions)

Article 2 “Quality assurance duty” throughout this Ministerial Ordinance means the duty necessary, in case where the drugs(excluding active pharmaceutical ingredients, and hereinafter referred to as such), quasi-drugs, cosmetics or medical devices(hereinafterreferred to as “drugs, etc.”)are marketed, for ensuring quality of the products(including the intermediate products that have undergone the intermediate process and need to undergo subsequent process to be the(final)products, and hereinafter referred to as such)including: controlling market release of the drugs, etc.; supervising the manufacturers, foreign manufacturers specified in Paragraph 1 of Article 13-3 of Law(hereinafter referred to as “foreign manufacturers”)and other organisations who conduct the duties concerned with the manufacturing(including testing, etc.)(hereinafter referred to as “manufacturers, etc.”); handling the information on the quality, etc. and the quality defects, etc. ;handling recall; and other duties necessary for controlling the quality of the products.

2. “Market release” throughout this Ministerial Ordinance means releasing the drugs, etc. that are manufactured(including the case where the manufacturing of own products is outsourced to an external organisation, but excluding the case where the contracted Products are manufactured by the marketing authorisation holder under a contract with an external organisation, and hereinafter referred to as such)or imported for the purpose of marketing.

3. “Lot” throughout this Ministerial Ordinance means a grouping of the products that are manufactured so as to have a uniform quality in a series of the manufacturing process for a certain manufacturing period.

4. “Cell/tissue-based drug” throughout this Ministerial Ordinance means the drug composed of human or animal cells or tissue(excluding human blood and the drugs which compose of the components manufactured using human blood).

5. “Cell/tissue-based medical device” throughout thls Ministerial Ordinance means the medlcal device composed of human or animal cells or tissue.

Chapter 2 Standards for Quality Assurance for Drugs

(Duties of General Marketing Manager)

Article 3 The marketing authorisation holder of drugs shall have the general marketing manager specified in Paragraph 2 of Article 17 of Law(hereinafter referred to as “general marketing manager”)conduct the following duties.

(1) To supervise the quality assurance manager specified in Paragraph 3 of next Article,

(2) To determine necessary measures, in addition to those specified in Item (2) of Paragraph 2 of Article 11, based on the reports from the quality assurance manager specified in preceding Item (1), and to instruct the quality assurance department specified in Paragraph 2 of next Article and other departments or responsible persons concerned with the quality assurance duties to take such measures,

(3) To respect the opinions of the quality assurance manager specified in preceding Item (1), and

(4) To have the quality assurance department specified in preceding Item (2) closely collaborate with the safety control management department specified in Paragraph 1 of Article 4 of the Ministerial Ordinance on Standards for Post-marketing Safety Management for Drugs, Quasi-drugs, Cosmetics and

Medical Devices(MHLW Ministerial Ordinance No.135, 2004, and hereinafter referred to as “Standards for Post-marketing Safety Management”), (for the marketing authorisation holder of drugs other than those specified in Paragraph 1 of Article 49 of Law, with the safety control manager specified in Paragraph 2 of Article 13 of Standards for Post-marketing Safety Management(hereinafter referred to as “safety control management department” in this Chapter)), and with other departments concerned with the quality assurance duties.

(Organisation and Personnel for Quality Assurance Duties)

Article 4 The marketing authorisation holder of drugs shall have a sufficient number of personnel who have competence for conducting the quality assurance duties properly and efficiently.

2. The marketing authorisation holder of drugs shall establish a quality assurance department that supervises the quality assurance duties and meets the following requirements(hereinafter referred to as the “quality assurance department” in this Chapter).

(1) To be supervised by the general marketing manager,

(2) To have a sufficient number of personnel who have competence for conducting the duties assigned to the quality assurance department properly and efficiently, and

(3) To be independent of any department engaged in the sales of the drugs, etc. and any other department that affects proper and efficient conduct of the quality assurance duties.

3. The marketing authorisation holder of drugs shall assign a responsible person in charge of the quality assurance duties who meets the following requirements (hereinafter referred to as “quality assurance manager” in this Chapter).

(1) To be the responsible person in charge of the quality assurance department,

(2) To be the person who has engaged in the quality assurance duties or other similar duties for at least three years,

(3) To be the person who has competence for conducting the quality assurance duties properly and efficiently, and

(4) Not to be the person who belongs to the department engaged in the sales of the drugs, etc. nor who could hinder the proper and efficient conduct of the quality assurance duties.

4. The marketing authorisation holder of drugs shall define and document properly the scope of responsibilities of the personnel engaged in the quality assurance duties(including the general marketing manager and the quality assurance manager, and hereinafter referred to as such), and the system for supervising them.

(Quality Standard Code)

Article 5 The marketing authorisation holder of drugs shall establish, for each of the drugs, documents which describe the items of the marketing approval of the drugs and other necessary items concerned with the quality of the drugs (hereinafter referred to as “quality standard code”).

(Quality Assurance Duty Procedure Documents)

Article 6 The marketing authorisation holder of drugs shall establish documents for the following procedures for proper and efficient conduct of the quality assurance duties(hereinafter referred to as “quality assurance duty procedure documents” in this Chapter).

(1) The procedure for controlling market release,

(2) The procedure for ensuring the proper manufacturing control and quality control,

(3) The procedure for handling the information on quality, etc. and quality defects, etc.,

(4) The procedure for handling recall,

(5) The procedure for the self-inspections,

(6) The procedure for the training,

(7) The procedure for controlling the storage, etc. of the drugs,

(8) The procedure for controlling the documents and records,

(9) The procedure for the mutual collaboration among the departments or

responsible persons concerned with the quality assurance duties including the safety control management department, and

(10) Other necessary procedures for proper and efficient conduct of the quality assurance duties.

2. The marketing authorisation holder of drugs shall place the quality standard code specified in preceding Article and the quality assurance duty procedure documents specified in preceding Paragraph 1(hereinafter referred to as “quality assurance duty procedure documents, etc.” in this Chapter)in the office where the general marketing manager conducts his/her duties, and also place copies thereof in other offices where the quality assurance duties are conducted,

(Contract with Manufacturers, etc.)

Article 7 The marketing authorisation holder of drugs shall conclude a contract for the following items with the manufacturers, etc. of the products and descrlbe the details of the agreement in the quality assurance duty procedure documents, etc. to ensure that the manufacturing control and quality control are conducted properly and efficiently by the manufacturers, etc.

(1) The scope of the manufacturing and other duties concerned with the manufacturing conducted by the manufacturers, etc. (hereinafter referred to as “manufacturing duties” in this Chapter), and the procedure for the manufacturing control, quality control and shipment concerned with the manufacturing duties,

(2) The technical requirements for the manufacturing procedure, testing procedure, etc.,

(3) The nature and extent of the periodical verification, by the marketing authorisation holder, of the manufacturing duties that they are conducted under the proper and efficient manufacturing control and quality control,

(4) The procedures of the quality control during the transportation and delivery of the products,

(5) The procedures and the responsible persons to communicate, in advance, any change in the manufacturing procedure, testing procedure, etc. to the marketing authorisation holder, in case where such a change could affect the quality of the products,

(6) The procedures and the responsible persons to promptly communicate the following information on the products obtained by each of the manufacturers, etc. to the marketing authorisation holder, and

a. Information on the discontinuance of the manufacturing, import or distribution of the products, or the recall, disposal or other actions taken for the products to prevent jeopardising the public health and hygiene, and

b. Other information on the quality, etc. of the products.

(7) Other necessary items.

(Duties of Quality Assurance Manager)

Article 8 The marketing authorisation holder of drugs shall have the quality assurance manager conduct the following duties in accordance with the quality assurance duty procedure documents, etc.

(1) To supervise the quality assurance duties,

(2) To verify that the quality assurance duties are conducted properly and efficiently,

(3) To report in writing whatever necessary for conducting the quality assurance duties to the general marketing manager, in addition to those reported to him/her in accordance with the provisions of Item (3)c, of Paragraph 5 of Article 9, Item (3) of Paragraph 2 of Article 10, Item (4) of Paragraph 1 of Article 11, Items (1) and (5) of Paragraph 2 of Article 11, Item (2) of Article 12, and Paragraph 2 of Article 13, and

(4) To communicate with or instruct in writing, where necessary, the manufacturers, etc., distributors, pharmacy proprietors, hospital proprietors, clinic proprietors and other parties concerned, when conducting the quality assurance duties.

(Control of Market Release)

Article 9 The marketing authorisation holder of drugs shall, in accordance with

the quality assurance duty procedure documents, etc., ensure that the results of the manufacturing control and quality control are properly evaluated and that the decisions on market release are made properly and efficiently, and shall not allow the shipment of the drugs until the decisions are properly made.

2. The marketing authorisation holder of drugs shall, in accordance with the quality assurance duty procedure documents, etc., have the person designated beforehand in the quality assurance department or the manufacturers of the products properly evaluate the results of the manufacturing control and quality control, make decisions on market release for each lot(for each manufacturing number, in case where the drugs do not constitute a lot, and hereinafter referred to as such)and establish records of the results of the evaluation and decisions and records concemed with the market release including the shipping consignees.

3. The person who conducts the duties of making decisions on market release specified in preceding Paragraph 2 shall have competence for conducting the duties properly and efficiently.

4. The marketing authorisation holder of drugs shall, in case where any person other than the quality assurance manager makes decisions on market release, have the person report properly in writing the results of the decisions, to the quality assurance manager.

5. In case where the marketing authorisation holder of drugs has the manufacturers conduct the duties specified in Paragraph 2 of this Article, the following duties shall be fulfilled.

(1) To conclude a contract, in advance, with the manufacturers for the following items,

a. Establishing the procedure for controlling market release conducted by the manufacturers,

b. Designating a person beforehand in the manufacturing site of the products who conducts the duties specified in Paragraph 2 of this Article,

c. Reporting promptly in writing, in case where any deviation from the procedure specified In preceding a. has occurred, the deviation to the quality assurance manager, and making decisions on market release and shipping the drugs to the market in accordance with the instructions of the quality assurance manager, by the manufacturers, and

d. Allowing the marketing authorisation holder to periodically verify that the manufacturers conduct the market release duties properly and efficiently.

(2) To have the person designated beforehand in the quality assurance department conduct the verification specified in preceding Item (1) d. and establish records concerned with the results of the verification properly,

(3) To have the quality assurance manager conduct the following duties in case where improvements are necessary for the market release duties conducted by the manufacturers, and

a. Instructing in writing the manufacturers to take necessary actions,

b. Requesting the manufacturers to report the results of the actions taken, evaluating the results properly, conducting, where necessary, on-site verification of the manufacturing site and establishing records concerned with the results of the evaluation and verlfication, and

c. Reporting in writing the results of the evaluation and verification specified in preceding b. to the general marketing manager.

(4) To have the person other than the quality assurance manager, in case where he/she conducts the verification and establishment of records specified in preceding Item (2), report in writing the results of the verification and establishment of records to the quality assurance manager.

6. The marketing authorisation holder of drugs shall properly provide the person who makes decisions on market release in accordance with the quality assurance duty procedure documents, etc. with the information on the quality, efficacy and safety of the drugs necessary for making the decisions properly and efficiently.

(Ensuring Proper Manufacturing Control and Quality Control)

Article 10 The marketing authorisation holder of drugs shall have the person

designated beforehand in the quality assurance department conduct the following duties in accordance with the quality assurance duty procedure documents, etc.

(1) To periodically verify that the manufacturing control and quality control by the manufacturers, etc. is conducted properly and efficiently in accordance with the standards and items specified in MHLW Ministerial Ordinances that are provided to be established under the provisions of Item (4) of Paragraph 2 of Article 14 and Paragraph 2 of Article 18 of Law and in accordance with the contract specified in Article 7 of this Ministerial Ordinance, and to establish records regarding the results of the verification, and

(2) To have the person other than the quality assurance manager, in case where he/she conducts the verification and establishment of records specified in preceding Item (1), report in writing the results of the verification and establishment of records to the quality assurance manager.

2. The marketing authorisation holder of drugs, in case where improvements are necessary for the manufacturing control and quality control conducted by the manufacturers, etc., shall have the quality assurance manager conduct the following duties in accordance with the quality assurance duty procedure documents, etc.

(1) To instruct in writing the manufacturers, etc. to take necessary actions,

(2) To request the manufacturers, etc. to report the results of the actions taken, to evaluate the results properly, to conduct, where necessary, on-site verification of the manufacturing site, etc. and to establish records concerned with the results of the evaluation and verification, and

(3) To report in writing the results of the evaluation and verification specified in preceding Item (2) to the general marketing manager.

3. The marketing authorisation holder of drugs, in case where he/she has been communicated by the manufacturers, etc. with any change in the manufacturing procedure, the testing procedure, etc. which could affect the quality of the products, shall have the person designated beforehand in the quality assurance department conduct the following duties in accordance with the quality assurance duty procedure documents, etc.

(1) To evaluate the details of the communication from the manufacturers, etc., to verify that the change does not seriously affect the quality of the products, to conduct, where necessary, on-site verification of the manufacturing site, etc. that the manufacturing control and quality control are conducted properly and efficiently, and to establish records concerned with the results of the evaluation, verification and establishment of records, and

(2) To have the person other than the quality assurance manager, in case where he/she conducts the evaluation, verification and establishment of records specified in preceding Item (1), report in writing the results of the evaluation, verification and establishment of records to the quality assurance manager.

4. The marketing authorisation holder of drugs, in case where he/she identifies that the change could seriously affect the quality of the products as the result of the evaluation specified in Item (1) of preceding Paragraph 3, shall have, in accordance with the quality assurance duty procedure documents, etc., the quality assurance manager instruct promptly in writing the manufacturers, etc. to take necessary actions including improvements, etc.

5. The marketing authorisation holder of drugs shall provide the manufacturers, etc. with the information on the quality of the drugs necessary for conducting the manufacturing control and quality control properly and efficiently.

(Handling Information on Quality, etc. and Quality Defects, etc.)

Article 11 The marketing authorisation holder of drugs shall, in case where he/she has received the information on the quality, etc. of the drugs (hereinafter referred to as “quality information” in this Chapter), have the quality assurance manager conduct the following duties in accordance with the quality assurance duty procedure documents, etc.

(1) To examine the quality information and to evaluate properly the effects of the matters concerned with the quality information on the quality, efficacy

and safety of the drugs and on the human health,

(2) To investigate the cause of the matters concerned with the quality information,

(3) To take necessary corrective actions in case where they are necessary for improving the quality assurance duties or the manufacturing control and quality control by the manufacturers etc. based on the results of the evaluation or investigation specified in preceding two Items (1) and (2),

(4) To establish records describing the details of the quality information, the results of the evaluation, the results of the investigation and the improvements specified in preceding three Items (1) to (3), and to promptly report in writing the records to the general marketing manager,

(5) To give instructions in writing to the manufacturers, etc., in case where they are necessary for the investigation specified in preceding Item (2) or the improvements specified in preceding Item (3), as well as to request the manufacturers, etc. to report in writing the results of the actions taken based on the instructions, to evaluate the results properly and to conduct, where necessary, on-site verification of the progress of the improvements made in the manufacturing sites, etc., and to establish records concerned with the results, and

(6) To provide promptly in writing the safety control management department with the quality information which is concerned with the measures to ensure safety specified in Paragraph 2 of Article 2 of Standards for Post-marketing Safety Management(hereinafter referred to as “measures to ensure safety”).

2. The marketing authorisation holder of drugs shall, in case where he/she has identified quality defects or their possibility as a result of the duties specified in preceding Paragraph 1, in accordance with the quality assurance duty procedure documents, etc., have the general marketing manager and the quality assurance manager conduct the following duties.

(1) To have the quality assurance manager report promptly the quality defects or their possibility to the general marketing manager and to establish records thereof,

(2) To have the general marketing manager, in case where he/she has received the report specified in preceding Item (1), promptly make decisions on necessary actions including recall to prevent jeopardy, etc., and give instructions to the quality assurance manager and to other departments concerned,

(3) To have the quality assurance manager, in case where he/she has received the instructions from the general marketing manager in accordance with the provision of preceding Item (2), promptly take the necessary actions,

(4) To have the quality assurance manager closely collaborate with the safety control management department and other departments concerned to ensure that the actions specified in preceding Item (3) are taken properly and efficiently, and

(5) To have the quality assurance manager report in writing the progress and the results of the actions taken specified in preceding Item (3) to the general marketing manager.

(Handling Recall)

Article 12 The marketing authorisation holder of drugs shall, in case where he/she conducts recall of the drugs, have, in accordance with the quality assurance duty procedure documents, etc., the quality assurance manager conduct the following duties.

(1) To segregate the drugs recalled, and to dispose of them properly after storing for a certain period, and

(2) To establish records describing the details of the recall, and to report in writing them to the general marketing manager.

(Self-inspections)

Article 13 The marketing authorisation holder of drugs shall, in accordance with the quality assurance duty procedure documents, etc., have the person designated beforehand conduct the following duties.

(1) To conduct the self-inspections periodically on the quality assurance duties and to establish records of the results, and

(2) To have the person other than the quality assurance manager, in case where he/she conducts the duties specified in preceding Item (1), report in writing the results of the self-inspections to the quality assurance manager.

2. The marketing authorisation holder of drugs, in case where improvements are necessary based on the results of the self-inspections, shall have the quality assurance manager take necessary actions, establish records of the actions and report in writing the results of the actions to the general marketing manager.

(Training)

Article 14 The marketing authorisation holder of drugs shall have the person designated beforehand establish a plan of training for the personnel engaged in the quality assurance duties.

2. The marketing authorisation holder of drugs shall have, in accordance with the quality assurance duty procedure documents and the plan of training specified in preceding Paragraph 1, the person designated beforehand conduct the following duties.

(1) To implement as planned the training concerned with the quality assurance duties for the personnel engaged in the quality assurance duties, and to establish records of the implementation of the training, and

(2) To have the person other than the quality assurance manager, in case where he/she conducts the duties specified in preceding Item (1), report in writing the progress of the training to the quality assurance manager.

(Control of Drug Storage, etc.)

Article 15 The marketing authorisation holder of drugs, in case where he/she stores or displays the drugs he/she manufactured, etc. or imported for the purpose of marketing, shall meet the following requirements.

(1) To assign responsible persons in charge of the duties of storing or displaying the drugs, or

(2) To ensure that the personnel engaged in the duties of storing or displaying the drugs, Including the responsible persons, meet the following requirements,

a. Not belonging to the quality assurance department, and

b. Having competence necessary for conducting the duties, and having completed necessary training.

(3) To be provided with the buildings and facilities that meet the following requirements in the office where the general marketing manager conducts his/her duties, and to maintain them properly, and

a. Being provided with the facilities necessary for storing the drugs sanitarily and safely,

b. Being ensured sufficient area necessary for conducting the operations properly and efficiently, and

c. Conforming to the provisions specified in Paragraphs 2, 3, and 4 of Article 1 of the Regulations for Buildings and Facilities of Pharmacies, etc. (MHW Ministerial Ordinance No.2, 1961) in case where he/she handles the radiopharmaceuticals. In this case, “dispensing rooms” in the provisions of Paragraphs 3 and 4 of Article 1 of the Regulations shall read “work rooms”.

(4) To establish records concerned with the duties of storing or displaying the drugs including control of the receipt and delivery of the drugs.

(Control of Documents and Records)

Article 16 The marketing authorisation holder of drugs shall control the documents and records specified in this Chapter in accordance with the following requirements.

(1) To approve, distribute, maintain, etc. the documents in case where they are established or revised in accordance with the quality assurance duty procedure documents,

(2) To put the date of the establishment or the revision of the quality assurance duty procedure documents, etc. on them, and to maintain records of the history of previous revisions in case where they are established or revised, and

(3) To maintain the documents and records specified in this Chapter for the following period from the date of the establishment(from the date when they

fell into disuse, for the quality assurance duty procedure documents, etc.).

a. 30 years plus the shelf life or the period until the expiry date (hereinafter referred to as “shelf life”)for the specified biological-origin products specified in Paragraph 10 of Article 2 of Law(hereinafter referred to as “specified biological-origin products”) or for the biological-origin products specified in Paragraph 9 of Article 2 of Law manufactured using human blood as the origins of the raw materials (including those used in the manufacturing process, and hereinafter referred to as such)(hereinafter referred to as “human-blood-origin products”),

b. 10 years plus the shelf life for the biological-origin products specified in Paragraph 9 of Article 2 of Law(hereinafter referred to as “biological-origin products”), or for cell/tissue-based drugs(except for those listed in preceding a.),

c. 5 years for the drugs other than the biological-origin products or the cell/tissue-based drugs(1 year plus the shelf life for the drugs concerned with the documents and records of which shelf life plus 1 year exceeds 5 years), or

d. 5 years for the documents and records concerned with the training, notwithstanding the period specified in the provisions of preceding a., b. and c.

Chapter 3 Standards for Quality Assurance for Quasi-Drugs and Cosmetics

(Assignment of Quality Assurance Manager)

Article 17 The marketing authorisation holder of quasi-drugs and cosmetics (hereinafter referred to as “quasi-drugs, etc.” in this Chapter) shall assign a responsible person in charge of the quality assurance duties beforehand who meets the following requirements(hereinafter referred to as “quality assurance manager” in this Chapter).

(1) To be the person who has competence for conducting the quality assurance duties properly and efficiently, and

(2) Not to be the person who belongs to the department engaged in the sales of the drugs, etc. nor who could hinder the proper and efficient conduct of the quality assurance duties.

(Documents and Duties, etc. concerned with Quality Assurance Duty Procedure)

Article 18 The marketing authorisation holder of quasi-drugs, etc. shall establish documents for the following procedures for proper and efficient conduct of the quality assurance duties(hereinafter referred to as “quality assurance duty procedure documents” in this Chapter).

(1) The procedure for establishing records concerned with market release,

(2) The procedure for ensuring the proper manufacturing control and quality control,

(3) The procedure for handling the information on quality, etc. and quality defects, etc.,

(4) The procedure for handling recall,

(5) The procedure for controlling the documents and records, and

(6) Other necessary procedures for proper and efficient conduct of the quality assurance duties.

2. The marketing authorisation holder of quasi-drugs, etc. shall conduct the following duties in accordance with the quality assurance duty procedure documents.

(1) To establish records concerned with market release,

(2) To verify that the quasi-drugs, etc. for marketing are manufactured properly and efficiently by the manufacturers, etc., and to establish records of the verification,

(3) To evaluate the effects of, and to investigate the cause of the matters concerned with the quality information on the human health in case where the marketing authorisation holder has received the information on the quality, etc. concerned with the products, and to make necessary improvements in case where they are necessary and to establish records thereof,

(4) To provide promptly in writing the safety control manager specified in Paragraph 2 of Article 13 applied mutatis mutandis under Article 14 of

Standards for Post-marketing Safety Management(hereinafter referred to as “safety control manager”)with the information specified in preceding Item (3) which is concerned with the measures to ensure safety,

(5) To promptly take necessary actions including recall in case where the marketing authorisation holder has identified quality defects or their possibility of the quasi-drugs, etc. for marketing, and to establish records thereof, and

(6) To conduct other necessary duties concerned with the quality assurance duties.

3. The marketing authorisation holder of quasi-drugs, etc. shall place the quality assurance duty procedure documents in the office where the general marketing manager conducts his/her duties, and also place copies thereof in other offices where the quality assurance duties are conducted.

(Provision to be Applied Mutatis Mutandis)

Article 19 The provisions of Article 3, Paragraph 1 of Article 4, Article 8 and Article 16 shall be applied mutatis mutandis to the standards for quality assurance for quasi-drugs, etc. In this case, “the quality assurance manager specified in Paragraph 3 of next Article” in Item (1) of Article 3 shall read “the quality assurance manager”, “, in addition to those specified in Item (2) of Paragraph 2 of Article 11, based on the reports from the quality assurance manager specified in preceding Item (1)” in Item (2) of Article 3 shall read “based on the reports from the quality assurance manager”, “the quality assurance department specified in Paragraph 2 of next Article” in same Item shall read “the quality assurance manager”, “other departments or responsible persons” in same Item shall read “the responsible persons in charge of the duties”, “the quality assurance manager specified in preceding Item (1)” in Item (3) of Article 3 shall read “the quality assurance manager”, “the quality assurance department specified in preceding Item (2)” in Item (4) of Article 3 shall read “the quallty assurance manager”, “the safety control management department specified in Paragraph 1 of Article 4 of the Ministerial Ordinance on Standards for Post-marketing Safety Management for Drugs, Quasi-drugs, Cosmetics and Medical Devices(MHLW Ministerial Ordinance No.135, 2004, and hereinafter referred to as “Standards for Post-marketing Safety Management”)or, for the marketing authorisation holder of drugs other than those specified in Paragraph 1 of Article 49 of Law, with the safety control manager specified in Paragraph 2 of Article 13 of Standards for Post-marketing Safety Management(hereinafter referred to as “safety control management department” in this Chapter)” in same Item shall read “the safety control manager”, “other departments concerned with” in same Item shall read “the responsible persons in charge of the duties concerned”, “the quality assurance duty procedure documents, etc.” in Article 8 shall read “the quality assurance duty procedure documents”, “the quality assurance duties to the general marketing manager, in addition to those reported to him/her in accordance with the provisions of Item(3)c. of Paragraph 5 of Article 9, Item (3) of Paragraph 2 of Article 10, Item (4) of Paragraph 1 of Article 11, Items (1) and (5) of Paragraph 2 of Article 11, Item (2) of Article 12, and Paragraph 2 of Article 13” in same Article shall read “the quality assurance duties to the general marketing manager”, “, distributors, pharmacy proprietors, hospital proprietors, clinic proprietors and other” in same Article shall read “other”, the quality assurance duty procedure documents, etc.” in Article 16 shall read the quality assurance duty procedure documents”, and “the following period” in Item (3) of same Article shall read “5 years”.

(Exceptions to Standards for Quality Assurance for Quasi-drugs Designated by Minister of Health, Labour and Welfare)

Article 20 The provision of preceding Chapter 2 shall be applied to the marketing of the quasi-drugs designated by the Minister of Health, Labour and Welfare as those that require special attention to their manufacturing control or quality control in accordance with the provision of Paragraph 2 of Article 20 of Enforcement Order of Pharmaceutical Affairs Law(Cabinet Order No.11, 1961), notwithstanding the provisions of preceding three Articles 17, 18 and 19.

Chapter 4 Standards for Quality Assurance for Medical Devices

(Handling of Notifications on Repairs)

Article 21 The marketing authorisation holder of medical devices shall, in case where he/she has received the notification specified in Paragraph 6 of Article 191 of the Enforcement Regulations of the Pharmaceutical Affairs Law(including the case where it is applied mutatis mutandis under Article 192), have the person designated beforehand in the quality assurance department specified in Paragraph 2 of Article 4 applied mutatis mutandis under Article 25 give in writing the repairers the instructions for the proper repairing procedures and other matters necessary for maintaining the quality, efficacy and safety of the medical devices, in accordance with the quality standard code specified in Article 5 applied mutatis mutandis under Article 25 and the quality assurance duty procedure documents specified in Paragraph 1 of Article 6 applied, mutatis mutandis under Article 25(hereinafter referred to as “quality assurance duty procedure documents, etc.” in this Chapter).

(Quality Assurance by Distributors or Leasers)

Article 22 The marketing authorisation holder of medical devices, in accordance with the quality assurance duty procedure documents, etc., shall give in writing the distributors and leasers(hereinafter referred to as the “distributors, etc.” in this Chapter)the instructions for the procedures established beforehand for ensuring the quality of the medical devices for marketing in their offices.

(Handling of Notifications Concerned with Distributing or Leasing Used Devices)

Article 23 The marketing authorisation holder of medical devices shall, in case where he/she has received the notification specified in Paragraph 1 of Article 170(including the case where it is applied mutatis mutandis under Paragraphs 2 and 3 of Article 178)of the Enforcement Regulations of the Pharmaceutical Affairs Law, have the person designated beforehand in the quality assurance department specified in Paragraph 2 of Article 4 applied mutatis mutandis under Article 25, in accordance with the quality assurance duty procedure documents, etc., give in writing the distributors, etc. the instructions for the actions necessary for maintaining the quality, efficacy and safety of the medical devices.

(Control of Documents and Records Concerned with Medical Devices)

Article 24 The marketing authorisation holder of medical devices shall maintain the documents and records concerned with the specially designated maintenance-control-required medical devices, or the installation-control-required medical devices(excluding the specified biological-origin products and the human-blood-origin products)for 15 years(5 years for those concerned with the training)from the date of the establishment(from the date when they fell into disuse for the quality assurance duty procedure documents, etc.), notwithstanding the provision of Item (3) of Article 16 applied mutatis mutandis under next Article.

(Provisions to be Applied Mutatis Mutandis)

Article 25 The provisions of Article 3 to Article 16(excluding Item (3) c, of Paragraph 1 of Article 15)shall be applied mutatis mutandis to the standards for quality assurance for medical devices. In this case, “drugs other than those specified in Paragraph 1 of Article 49 of Law” in Item (4) of Article 3 shall read “the controlled medical devices and the general medical devices”, and “pharmacy proprietors” in Article 8 shall read “repairers, leasers”.

2. The quality assurance duty procedure document specified in Paragraph 1 of Article 6 applied mutatis mutandis under preceding Paragraph 1, shall describe the following matters.

(1) The procedure for handling the notifications from the repairers,

(2) The procedure for ensuring the quality of the medical devices by the distributors and leasers, and

(3) The procedure for handling the notifications from the distributors or leasers of the used medical devices.

Supplementary Provision

This Ministerial Ordinance shall come into effect on 1 April 2005.

［別紙2］

Tentative translation VER. 1[1]

MHLW Ministerial Ordinance No.179, 2004

In accordance with the provisions of Item (4) of Paragraph 2 of Article 14 and Item (4) of Paragraph 2 of Article 14 applied mutatis mutandis under Paragraph 5 of Article 19-2 of Pharmaceutical Affairs Law(Law No.145, 1960), MHLW Ministerial Ordinance to revise the whole of Drugs and Quasi-drugs Manufacturing Control and Quality Control Regulations(MHLW Ministerial Ordinance No.16, 1999)is established as follows.

24 December 2004

Hidehisa OTSUJI

Minister of Health, Labour and Welfare

Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs

CONTENTS

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[1]Note/This is a tentative translation of afore-mentioned Ordinance in English which is not an authentic and not formally autholised by Ministry of Health, Labour and Welfare of Japan.

Chapter 1 General Provisions

(Purpose)

Article 1 This Ministerial Ordinance shall provide the standards in accordance with the provision of Item (4) of Paragraph 2 of Article 14(including the case where it is applied mutatis mutandis under Paragraph 5 of Article 19-2, and hereinafter referred to as such)of Pharmaceutical Affairs Law(Law No.145, 1960) (hereinafter referred to as “Law”)which provides that such standards shall be provided by MHLW Ministerial Ordinances.

(Definitions)

Article 2 “Product” throughout this Ministerial Ordinance means the object (including those which have undergone the intermediate process and need to undergo subsequent process to be the(final)products(hereinafter referred to as “intermediate product”))that has undergone the manufacturing process in the manufacturing site.

2. “Packaging and labelling material” throughout this Ministerial Ordinance means the container, wrapper and labelling(including the package insert, and hereinafter referred to as such)for the products.
3. “Lot” throughout this Ministerial Ordinance means a grouping of the products or raw materials(hereinafter referred to as “products, etc.”)that are manufactured so as to have a uniform quality in a series of the manufacturing process for a certain manufacturing period.
4. “Controlled unit” throughout this Ministerial Ordinance means a grouping of the packaging and labelling materials that have been verified to be same.
5. “Validation” throughout this Ministerial Ordinance means to verify and document that the buildings and facilities of the manufacturing site, procedures, processes and other procedures of the manufacturing control and quality control(hereinafter referred to as “manufacturing procedure, etc.”) provide the anticipated results.

6. “Clean area” throughout this Ministerial Ordinance means the place, among those areas where the manufacturing operations are conducted(hereinafter referred to as “work areas”), where the weighing operations for the raw materials or the formulating operations for the drug substances are conducted or where the cleaned containers are exposed to the air in the work areas.
7. “Aseptic area” throughout this Ministerial Ordinance means the place, among the work areas, where the aseptic drug substances or sterilised containers are exposed to the air in the work areas, where the filling operations for the drug substances are conducted, where the sealing operations for the containers are conducted, or where the aseptic operations including sterility tests are conducted.
8. “Cell/tissue-based drug” throughout this Ministerial Ordinance means the drug composed of human or animal cells or tissue(excluding human blood and the drugs which compose of the components manufactured using human blood).
9. “Donor” throughout this Ministerial Ordinance means the person who donates the cells or tissue that serves as the raw materials for the cell/tissue-based drugs(excluding those concerned with the body of a brain-dead person specified in Paragraph 2 of Article 6 of Law on Organ Transplantation(Law No.104, 1997)).
10. “Donor animal” throughout this Ministerial Ordinance means the animal which provides the cells or tissue that serves as the raw materials for the cell/tissue-based drugs.

(Scope)

Article 3 The marketing authorisation holder of the drugs specified in Paragraph 1 of Article 14 of Law(excluding in-vitro diagnostic reagents, and hereinafter referred to as such)or quasi-drugs, or the appointed marketing authorisation holder of drugs or quasi-drugs specified in Paragraph 4 of Article 19-2 of Law shall, in accordance with the provision of Chapter 2 or the provision of Chapter 2 applied mutatis mutandis under Chapter 3, have the manufacturer and the foreign manufacturer specified in Paragraph 1 of Article 13-3 of Law (hereinafter simply referred to as “foreign manufacturer”)(hereinafter collectively referred to as “manufacturer, etc.”)conduct the manufacturing control and quality control of the products in the manufacturing site.

2. The manufacturer, etc. of the products concerned with drugs or quasi-drugs shall, in accordance with the provision of Chapter 2 or the provision of Chapter 2 applied mutatis mutandis under Chapter 3, conduct the manufacturing control and quality control of the products in the manufacturing site specified in Article 96 of Enforcement Regulations of Pharmaceutical Affairs Law(MHW Ministerial Ordinance No.1, 1961, and hereinafter referred to as “Enforcement Regulations”).

3. The manufacturer, etc. of the products concerned with drugs or quasi-drugs for export specified in Paragraph 1 of Article 80 of Law shall, in accordance with the provision of Chapter 2 or the provision of Chapter 2 applied mutatis mutandis under Chapter 3, conduct the manufacturing control and quality control of the products.

Chapter 2 Manufacturing Control and Quality Control in Manufacturing Sites of Drug Manufacturers, etc.

Section 1 General Rules

(Manufacturing Department and Quality Department)

Article 4 The manufacturer, etc. shall, for each of the manufacturing sites, establish a department concerned with manufacturing control(hereinafter referred to as “manufacturing department”)and a department concerned with quality control(hereinafter referred to as “quality department”)under the supervision of the drug manufacturing manager specified in Paragraph 3 of Article 17 of Law and the manager controlling the manufacturing of the biological-origin products specifred in Paragraph 1 of Article 68-2 of Law(the biological-origin products specified in Paragraph 9 of Article 2 of Law, and hereinafter referred to as such)(in case of a foreign manufacturer, the person responsible for the manufacturing site which has been recognised in accordance with the provision of Paragraph 1 of Article 13-3 of Law or the person designated beforehand by such a foreign manufacturer)(hereinafter collectively

referred to as “manufacturing manager”).
2. The quality department shall be independent of the manufacturing department.
(Manufacturing Manager)
Article 5 The manufacturing manager shall conduct the following duties.
(1) To supervise the duties of the manufacturing control and quality control (hereinafter referred to as “manufacturing and quality control duties”), and to manage the manufacturing and quality control duties so that they are conducted properly and efficiently, and
(2) To verify that necessary actions have been promptly taken to verify the progress of such actions, and to give instructions, where necessary, to take necessary actions such as improvements, in case where quality defects or a potential risk which could affect the quality of the products exists.
2. The manufacturer, etc. shall ensure that the manufacturing manager can conduct his/her duties without hindrance.
(Personnel)
Article 6 The manufacturer, etc. shall appropriately assign responsible persons who have competence for conducting the manufacturing and quality control duties properly and efficiently(hereinafter simply referred to as “responsible persons”)according to the organisation, size, type of the duties, etc. of the manufacturing site.
2. The manufacturer, etc. shall assign an appropriate number of responsible persons according to the organisation, size, type of the duties, etc. of the manufacturing site.
3. The manufacturer, etc. shall ensure sufficiently the personnel who have competence for appropriately conducting the manufacturing and quality control duties.
4. The manufacturer, etc. shall define and document appropriately the scope of the responsibilities of the personnel(including the manufacturing manager and the responsible persons)engaged in the manufacturing and quality control duties, and the system for supervising the personnel.
(Seihin Hyojun Sho)
Article 7 The manufacturer, etc. shall, for each of the products(excluding the intermediate products, and hereinafter referred to as such in this Article), establish and maintain Seihin Hyojun Sho describing the following items in each of the manufacturing sites concerned with the manufacturing of such products, and have Seihin Hyojun Sho approved by the quality department.
(1) The items of the marketing approval of the drugs concerned with the products,
(2) The items of the standards established in accordance with the provision of Paragraph 1 of Article 42 of Law and other laws, orders and ordinances related to pharmaceutical affairs or the orders or official actions based on the laws and ordinances which are relevant to the quality of the drugs,
(3) The manufacturing procedure(excluding the items indicated in preceding Item (1)),
(4) The following items in case where the products the manufacturer, etc. intend to manufacture are those concerned with the drugs that correspond to the biological-origin products(hereinafter referred to as “biological-origin drugs”), the biological preparations specified in Item (3) a. of Paragraph 2 of Article 80 of Enforcement Order of Pharmaceutical Affairs Law(Cabinet Order No.11, 1961), the drugs designated by Minister of Health, Labour and Welfare in accordance with the provision of Paragraph 1 of Article 43 of Law, the drugs manufactured by application of gene recombination technology, the drugs manufactured using as the raw materials the drugs manufactured by application of gene recombination technology, the drugs manufactured by application of incubation technology of human or animal cells, the drugs using as the raw materials the drugs manufactured by application of incubation technology of human or animal cells or the cell/tissue-based drugs (hereinafter collectively referred to as “biological-origin drugs, etc.”), and
a. The name, essence and property of the objects obtained from humans, animals, plants or microorganisms using as the raw materials or ingredients

and their quantities therein, and other specifications, and
b. The specifications(including the keeping control methods)of the animals utilised in the manufacturing or testing(including the donor animals, and hereinafter referred to as “utilised animals”).

(5) Other necessary items.

(Documented Procedure, etc.)

Article 8 The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain a sanitation control standard code describing sanitation control of the buildings and facilities and the personnel and other necessary matters.

2. The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain a manufacturing control standard code describing the storage of the products, etc., control of the manufacturing process and other necessary matters.

3. The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain a quality control standard code describing the methods of collecting samples, methods of judging the testing results and other necessary matters.

4. The manufacturer, etc. shall, for each of the manufacturing sites, establish and maintain documented procedure for the following items(hereinafter referred to as “documented procedure”)for proper and efficient conduct of the manufacturing control and quality control, in addition to the documents specified in preceding three Paragraphs 1, 2 and 3.

(1) The procedure for controlling the shipment from the manufacturing site,
(2) The procedure for conducting the validation,
(3) The procedure for controlling changes specified in Article 14,
(4) The procedure for controlling deviation specified in Article 15,
(5) The procedure for handling the information on quality, etc. and quality defects, etc.,
(6) The procedure for handling recall,
(7) The procedure for the self-inspection,
(8) The procedure for the training,
(9) The procedure for controlling the documents and records, and
(10) Other necessary procedures for proper and efficient conduct of the manufacturing control and quality control.

5. The manufacturer, etc. shall place the Seihin Hyojun Sho, sanitation control standard code, manufacturing control standard code, quality control standard code, and documented procedure(hereinafter collectively referred to as “documented procedure, etc.”)in the manufacturing site.

(Buildings and Facilities)

Article 9 The buildings and facilities of the manufacturing site of the products shall comply with the following requirements.

(1) To be appropriately cleaned and maintained according to the use, to be sterilised where necessary, and to be ensured that records thereof are established and maintained, in accordance with the documented procedure, etc.,
(2) To be provided with the facilities necessary for disposing of the poisonous gases, in case where they are handled according to the products, etc.,
(3) To be ensured that the work rooms, among the work areas, are provided with the buildings and facilities necessary for preventing contamination with dust or microorganisms, according to the type, dosage form and manufacturing process of the products, with the proviso that this provision shall not apply in case where the manufacturing facilities, etc. provide equivalent functions,
(4) To be ensured that the work rooms, among the work areas, where the weighing operations for the raw materials or the formulating operations, filling operations or sealing operations for the products are conducted are the buildings which do not allow passage of the personnel other than those conducting operations in such work rooms, with the proviso that this provision shall not apply in case where the products could not be

contaminated by the personnel other than those conducting operations in such work rooms,

(5) In case where the products, etc. are easily dispersed and cause hypersensitive reactions in a minute amount or could cross-contaminate and seriously affect other products, to be ensured that the work rooms are exclusively used for such products, etc. and their air-handling system is separated from those used for other products, and

(6) To be provided with the facilities for supplying water(including those for cleaning the facilities and equipment and for washing the containers)of the quality and quantity necessary for the manufacturing.

(Manufacturing Control)

Article 10 The manufacturer, etc. shall have the manufacturing department appropriately conduct the following duties concerned with manufacturing control in accordance with the documented procedure, etc.

(1) To establish and maintain documented manufacturing orders describing the instructions, precautions and other matters necessary for the manufacturing process,

(2) To manufacture the products in accordance with the documented manufacturing orders,

(3) To establish and maintain records concerned with the manufacturing of the products for each lot(for each manufacturing number in case where the products do not constitute a lot, and hereinafter referred to as sueh),

(4) To verify, for each lot, that the packaging and labelling materials of the products are proper, and to establish and maintain records concerned with the results of the verification,

(5) To properly store the products, etc. for each lot and the packaging and labelling materials for each controlled unit to control their receipt and delivery, and to establish and maintain records thereof,

(6) To verify that the buildings and facilities are cleaned, and to establish and maintain records concerned with the results of the verification,

(7) To conduct sanitation control of the personnel, and to establish and maintain records thereof,

(8) To conduct periodical maintenance of the buildings and facilities and to establish and maintain records of the maintenance, and to calibrate, appropriately the measuring equipment and to establish and maintain records of the calibration,

(9) To verify that the manufacturing control is appropriately conducted as evidenced by the records of the manufacturing, storage and receiving and delivering as well as the records of the sanitation control, and to report in writing the results of the verification to the quality department, and

(10) To conduct other duties necessary for manufacturing control.

(Quality Control)

Article 11 The manufacturer, etc. shall have the quality department conduct appropriately as planned the following duties concerned with quality control of the products in accordance with the documented procedure, etc.

(1) To collect samples necessary for testing from each lot of the products, etc. and from each controlled unit of the packaging and labelling materials, and to establish and maintain records of the collection,

(2) To conduct the testing(including those conducted on the manufacturer's, etc. own responsibilities using their testing facilities or other testing institutions and such conduct is verified to present no hindrance to the proper testing, and hereinafter referred to as such)of the collected samples for each lot or for each controlled unit, and to establish and maintain records of the testing,

(3) To store a reserve sample in an amount of at least twice of the quantity necessary for the required testing from the products(limited to those for which decisions on market release are made specified in Paragraph 2 of Article 9 of Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices(MHLW Ministerial Ordinance No.136, 2004), and hereinafter referred to as such in Paragraph 1 of Article 28)for each lot, under appropriate conditions for the shelf life or the

period until the expiry date(hereinafter simply referred to as “shelf life”)of such products plus 1 year(plus 1 month, in case where the products are those concerned with the radiopharmaceuticals)from the date of the manufacturing, with the proviso that this provision shall not apply to those products which do not constitute a lot,

(4) To conduct periodical maintenance of the facilities and equipment for the testing and to establish and maintain records of the maintenance, and to calibrate appropriately the measuring equipment and to establish and maintain records of the calibration,

(5) To judge the results of the testing specified in preceding Item (2), and to report in writing the results of the judgement to the manufacturing department, and

(6) To conduct other duties necessary for quality control.

2. In case where it is deemed that the standards for the manufacturing control and quality control in the exporting country and the procedures for verifying conformity to those standards are equivalent to those in Japan, the testing specified in Item (2) of preceding Paragraph 1(excluding the testing of appearance)may be replaced by verification of the records of the testing for the imported objects which has been conducted by the foreign manufacturer of the exporting country. In this case, the manufacturer shall have the quality department conduct appropriately the following duties.

(1) To conduct periodical verification that the products, etc. are manufactured in accordance with appropriate manufacturing procedure, etc.,

(2) To conduct periodical verification that the manufacturing sites of such foreign manufacturer conform to the standards for the manufacturing control and quality control established in the exporting country,

(3) To establish and maintain records of the verification specified in preceding two Items (1) and (2), and

(4) To verify records of the testing of such products conducted by such foreign manufacturer, and to establish and maintain records of the verification.

3. The manufacturer, etc. shall have the quality department verify, in accordance with the documented procedure, etc., for each lot of the products, the results of the verification concerned with manufacturing control which have been reported by the manufacturing department specified in the provision of Item (9) of preceding Article.

(Control of Shipment from Manufacturing Sites)

Article 12 The manufacturer, etc. shall have the quality department evaluate appropriately the results of the manufacturing control and quality control in accordance with the documented procedure, etc., and conduct the duties to make decisions of whether or not to release the products from the manufacturing site.

2. The personnel who conduct the duties specified in preceding Paragraph 1 shall have competence for conducting such duties properly and efficiently.

3. The manufacturer, etc. shall ensure that the personnel who conduct the duties specified in preceding Paragraph 1 can conduct such duties without hindrance.

4. The manufacturer, etc. shall not ship the products from the manufacturing site before the decisions specified in preceding Paragraph 1 are made properly.

(Validation)

Article 13 The manufacturer, etc. shall have the personnel designated beforehand conduct the following duties in accordance with the documented procedure, etc.

(1) To conduct the validation in the following cases, and

a. The case where the manufacturing of the drugs will newly start at such manufacturing site,

b. The case where any change will be made in the manufacturing procedure, etc. which seriously affect the quality of the products, or

c. Other cases where it is deemed to be necessary to conduct the validation for appropriate conduct of the manufacturing control and quality control of the products.

(2) To report the planning and results of the validation in writing to the quality department.

2. The manufacturer, etc. shall, in case where improvements are necessary for the manufacturing control and quality control based on the results of the validation specified in Item (1) of preceding Paragraph 1, take necessary actions, and establish and maintain records of such actions.

(Change Control)

Article 14 The manufacturer, etc. shall, in case where any change will be made in the manufacturing procedure, etc. which could affect the quality of the products, have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

(1) To evaluate effects on the quality of the products due to such change, to be approved by the quality department with respect to the change being made based on the results of the evaluation, and to establish and maintain records of the evaluation and approval, and

(2) To revise relevant documents, to train the personnel and to take other necessary actions in case where any change is made upon approval of the quality department specified in the provision of preceding Item (1).

(Deviation Control)

Article 15 The manufacturer, etc. shall, in case where any deviation from the manufacturing procedure, etc. (hereinafter simply referred to as “deviation”) has occurred, have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.

(1) To record the details of the deviation, and

(2) To conduct the following duties in case where any serious deviation has occurred.

a. Evaluating effects on the quality of the products due to the deviation, and taking necessary actions,

b. Establishing and maintaining records of the results of the evaluation and the actions specified in preceding a., and reporting them in writing to the quality department, and

c. Being verified by the quality department of the results of the evaluation and the actions which have been reported in accordance with the provision of preceding b.

2. The manufacturer, etc. shall have the quality department establish and maintain records of the verification specified in the provision of Item (2) c. of preceding Paragraph 1 in accordance with the documented procedure, etc., and report appropriately in writing the records together with those specified in Item (2) b. of preceding Paragraph 1 to the manufacturing manager.

(Handling of Information on Quality, etc. and Quality Defects, etc.)

Article 16 The manufacturer, etc. shall, in case where they have received the information on the quality, etc. of the products(hereinafter referred to as “quality information”), have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc., with the proviso that this provision shall not apply in case where the matters concerned with the quality Information are not obviously attributable to their manufacturing site.

(1) To investigate the cause of the matters concerned with such quality information, and to take necessary actions in case where improvements are necessary for correcting the manufacturing control and quality control,

(2) To establish and maintain records describing the details of such quality information, the results of the investigation and the improvements, and to promptly report in writing the records to the quality department, and

(3) To be verified by the quality department of the reports specified in preceding Item (2).

2. The manufacturer, etc. shall, in case where they have identified quality defects or their possibility as a result of the verification specified in Item (3) of preceding Paragraph 1, have the quality department report in writing such matters to the manufacturing manager in accordance with the documented procedure, etc.

(Handling of Recall)

Article 17 The manufacturer, etc. shall, in case where recall of the products has been conducted due to their quality, etc., have the person designated

beforehand conduct the following duties in accordance with the documented procedure, etc.
(1) To segregate the products recalled, and to dispose of them appropriately after storing for a certain period, and
(2) To establish and maintain records of handling of recall describing the details of the recall, and to report in writing them to the quality department and the manufacturing manager, with the proviso that this provision shall not apply in case where the reason for such recall is not obviously attributable to their manufacturing site.

(Self-inspections)

Article 18 The manufacturer, etc. shall have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.
(1) To conduct the self-inspections periodically on the manufacturing control and quality control of the products in their manufacturing site,
(2) To report in writing the results of the self-inspections to the manufactuing manager, and
(3) To establish and maintain records of results of the self-inspections.

2. The manufacturer, etc. shall take necessary actions in case where improvements are necessary for correcting the manufacturing control and quality control based on the results of the self-inspections specified in Item (1) of preceding Paragraph 1, and to establish and maintain records of such actions.

(Training)

Article 19 The manufacturer, etc. shall have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.
(1) To implement as planned the training necessary for conducting the manufacturing control and quality control for the personnel engaged in the manufacturing and quality control duties of the products,
(2) To report in writing the progress of the training to the manufacturing manager, and
(3) To establish and maintain records of the implementation of the training.

(Control of Documents and Records)

Article 20 The manufacturer, etc. shall, for the documents and records specified in this Ministerial Ordinance, have the person designated beforehand conduct the following duties in accordance with the documented procedure, etc.
(1) To approve, distribute, maintain, etc. the documents in case where they are established or revised in accordance with the documented procedure, etc.,
(2) To put the date of the establishment or the revision of the documented procedures, etc. on them, and to maintain records of the history of previous revisions in case where they are established or revised, and
(3) To maintain the documents and records specified in this Ministerial Ordinance for 5 years(1 year plus the shelf life, for the products concerned with such records, etc. (excluding those of the training) of which shelf life plus 1 year exceeds 5 years) from the date of the establishment(from the date when they fell into disuse, for the documented procedure, etc.).

Section 2 Manufacturing Control and Quality Control of APIs

(Quality Control)

Article 21 The manufacturer, etc. (limited to those of the products concerned with active pharmaceutical ingredients (APIs), and hereinafter referred to as such in next Article)shall, notwithstanding the provision of Item (3) of Paragraph 1 of Article 11, store a reserve sample in an amount of at least twice of the quantity necessary for the required testing from the products concerned with APIs for each lot, under appropriate conditions for the period specified in each of the following Items from the date of the manufacturing.
(1) 3 years from the date of completion of the shipment of such a lot from their manufacturing site, for the products for which retest date(the date when the products, etc., after a period has passed from the date of the manufacturing, should be retested to ensure that they are still comply with the certain specifications, etc.) has been assigned and replaced the shelf life, or
(2) 1 year plus the shelf life of the products, for such products other than

those specified in preceding Item (1).

(Control of Documents and Records)

Article 22 The manufacturer, etc. shall, notwithstanding the provision of Item (3) of Article 20, maintain the documents and records specified in this Ministerial Ordinance regarding the products concerned with APIs for 1 year plus the shelf life of such products from the date of the establishment(for the documented procedure, etc., the date when they fell into disuse)(for the products for which retest date has been assigned and replaced the shelf life, for 3 years from the date of completion of the shipment of the lot concerned with such documents and records from their manufacturing site).

Section 3 Manufacturing Control and Quality Control of Sterile Drugs

(Buildings and Facilities of Manufacturing Sites of Sterile Drugs)

Article 23 The buildings and facilities of the manufacturing site of the manufacturer in the category specified in Item (3) of Paragraph 1 of Article 26 of Enforcement Regulations and the foreign manufacturer in the category specified in Item (3) of Paragraph 1 of Article 36 of Enforcement Regulations shall comply with the following requirements, in addition to those specified in Article 9.

(1) To be ensured that the work rooms or controlled work areas (the areas consisting of the work rooms, corridors, etc. that are controlled so as to maintain a uniform quality of cleanliness, and hereinafter referred to as such)among the work areas are provided with the buildings and facilities for maintaining the degree of cleanliness according to the type, dosage form and manufacturing process of the products concerned with sterile drugs,

(2) To be ensured that the work rooms for the drying operations or sterilising operations for the cleaned containers are exclusively used for such operations, with the proviso that this provision shall not apply in case where the cleaned containers could not be contaminated,

(3) To be ensured that the work rooms meet the following requirements,

a. Being provided with the facilities necessary for conducting appropriately the drying and storing operations for the cleaned containers,

b. Being provided with the sterilisation apparatuses necessary for the manufacturing according to the type of the products concerned with the sterile drugs,

c. Being provided with the clean air treated with filters and the buildings and facilities for controlling appropriately the pressure differential in the areas for conducting the aseptic operations, and

d. Being ensured that the facilities of which liquid-contacting piping, etc. affecting the sterility assurance level are easily cleanable and sterilisable in case of manufacturing the products concerned with injectable drugs.

(4) To be ensured that the work rooms or controlled work areas for the formulating operations or filling operations for the drug substances, or for the sterilising operations for the products subsequent to the formulating operations (excluding the labelling and packaging operations) meet the following requirements, and

a. Being segregated from the work areas for non-sterile drugs,

b. Being ensured that the work rooms for the formulating operations and the work rooms for the filling operations or sealing operations are exclusively used for such purposes, and

c. Being provided with the gowning rooms exclusively used for the personnel who conduct the operations specified in preceding b.

(5) To be ensured that the facilities for supplying distilled water, etc. necessary for manufacturing the products concerned with sterile drugs are provided with the structure necessary for preventing contamination of the distilled water, etc. with foreign particulate matter or microorganisms.

(Manufacturing Control)

Article 24 The manufacturer, etc. shall, in case where they manufacture the products concerned with sterile drugs, have the manufacturing department conduct appropriately the following duties concerned with manufacturing control in accordance with the documented procedure, etc., in addition to the duties

specified in Article 10.

(1) To appropriately establish and control a degree of control of the work environment in the work areas such as a degree of cleanliness according to the type, dosage form, property and manufacturing process of the products concerned with sterile drugs to manufacture and the details of the operations in such work areas,

(2) To appropriately establish and control necessary control items for the products, etc. and packaging and labelling materials, such as number of microorganisms, etc. according to the type, dosage form, property, manufacturing process, etc. of the products concerned with sterile drugs to manufacture,

(3) To take actions necessary for preventing contamination, etc. of the products, etc. and packaging and labelling materials with microorganisms, etc. in the manufacturing process,

(4) To appropriately establish and control the control values necessary for process control of the process, etc. which are essential to assure sterility level of the products according to the type, dosage form, property, manufacturing process, etc. of the products concerned with sterile drugs to manufacture,

(5) To appropriately establish and control the control values concerned with microorganic and physicochemical items for the manufacturing water according to that purpose,

(6) To conduct sanitation control of the personnel in accordance with the following requirements, and

a. Placing as much restriction as possible on the personnel other than those engaged in the manufacturing operations entering the work areas,

b. Establishing strict procedures for preventing contamination by the personnel engaged in the operations concerned with the processing of the animal-tissue-origin raw materials, cultivation of the microorganisms, etc. (excluding those actually used as the raw materials, etc. in the manufacturing process of the work areas), and not allowing the personnel, excluding the case where they strictly adhere to the procedure, to enter the work areas for the products concerned with sterile drugs, and

c. Placing as much restriction as possible on the personnel entering the clean areas or aseptic areas under operation.

(7) To conduct sanitation control of the personnel conducting operations in the clean areas or aseptic areas in accordance with the following requirements.

a. Having the personnel engaged in the manufacturing operations, when they enter the clean areas or aseptic areas, appropriately be gowned, etc. according to the extent of the control of such areas, and

b. Having the personnel declare of any health condition that could contaminate the products, etc. with microorganisms, etc. (including when suffering from a skin or hair infectious disease or a cold, when injured, when showing such symptoms as fever or diarrhoea of unknown cause, and hereinafter referred to as such).

(Training)

Article 25 The manufacturer, etc. shall, in case where they manufacture the products concerned with sterile drugs, have the person designated beforehand the following duties in accordance with the documented procedure, etc. in addition to the duties specified in Article 19.

(1) To provide the personnel engaged in the manufacturing or testing operations with the training necessary for manufacturing the products concerned with sterile drugs such as those on sanitation control, microbiology, etc., and

(2) To provide the personnel engaged in the operations in the clean areas, aseptic areas, etc. with the training for taking actions necessary for preventing contamination with microorganisms, etc.

Section 4 Manufacturing Control and Quality Control of Biological-origin Drugs, etc.

(Buildings and Facilities of Manufacturing Sites of Biological-origin Drugs,

etc.)
Article 26 The buildings and facilities of the manufacturing site of the manufacturers, etc. of the products concerned with the biological-origin drugs, etc. shall meet the following requirements, in addition to those specified in Article 9 and Article 23.
(1) To be ensured that the buildings and facilities of the manufacturing site of the products concerned with the biological preparations(excluding the blood preparations which do not constitute a lot)meet the following requirements,
a. Being ensured that the work areas are provided with the following facilities in the rooms distinctly segregated from other rooms, with the proviso that this provision shall not apply in case where such facilities are verified not to be necessary for the manufacturing of the products according to the type, manufacturing procedure, etc. of such products,
(i) The facilities for storing the microorganisms,
(ii) The facilities for keeping the animals for utilising in the manufacturing or testing after inoculation with the microorganisms,
(iii) The facilities for treating the animals for utilising in the manufacturing or testing,
(iv) The facilities for inoculating the microorganisms into the culture media, etc.,
(v) The facilities for cultivating the microorganisms,
(vi) The facilities for collecting, inactivating, sterilising, etc., the cultured microorganisms,
(vii) The facilities for preparing the solution for diluting the undiluted solution,
(viii) The facilities for diluting and subdividing the undiluted solution as well as for sealing the containers,
(ix) The facilities for disinfecting the equipment and instruments used in the manufacturing or testing.
b. Being ensured that the rooms provided with the facilities specified in preceding a. (iv) and (vi) to (viii) as well as the rooms provided with facilities, among the facilities necessary for conducting the testing of the products, etc. and packaging and labelling materials, for conducting the sterility tests meet the following requirements,
(i) Being aseptic rooms, with the proviso that this provision shall not apply in case where such work rooms are provided with the facilities which have functions to allow that the aseptic operations are conducted without hindrance according to the type, manufacturing procedure, etc. of the products, and
(ii) Being provided, in the aseptic rooms specified in preceding (i), with the adjourning anterooms exclusively used for such rooms so that the rooms are routinely accessible only through such anterooms, and not being placed the entrances of the anterooms directly leading to the outside.
c. Being provided with the following facilities in addition to the those specified in preceding a.
(i) The facilities necessary for keeping control for the animals utilised in the manufacturing or testing,
(ii) The facilities for formulating the culture media and their diluted solution,
(iii) The facilities for prior washing and sterilising the equipment and instruments, containers, etc.for use in the manufacturing or testing, and
(iv) The facilities for appropriately disposing of the animal carcasses and other wastes as well as for decontaminating the sewage.
(2) To be ensured that the buildings and facilities of the manufacturing site of the products concerned with the blood preparations which do not constitute a lot meet the following requirements, and
a. Being ensured that the work rooms, among the work areas, for separating and mixing the blood components, injecting and discharging the drug substance solutions as well as conducting the sealing operations for the containers are segregated from the work rooms for the products other than

the blood preparations.
b. Being ensured that the work rooms, among the work areas, for conducting the operations specified in preceding a. in an open-system operation meet the following requirements, and
(i) Being exclusively used for the operations, and
(ii) Being aseptic or being provided with the facilities which have functions to allow that aseptic operations are conducted appropriately.
c. Being ensured that the work areas are provided with the gowning facilities exclusively used for the personnel conducting operations in the aseptic room.

(3) To be ensured that the areas for manufacturing the products using human blood or plasma as the raw materials are distinctly segregated from other areas and provided with the facilities and equipment exclusively used for such manufacturing, with the proviso that this provision shall not apply to the manufacturing process subsequent to the process of inactivating or removing viruses.

(Manufacturing Control)

Article 27 The manufacturer, etc. shall, in case where they manufacture the products concerned with the biological-origin drugs, etc., have the manufacturing department conduct appropriately the following duties concerned with manufacturing control in accordance with the documented procedure, etc. in addition to the duties specified in Article 10 and Article 24.

(1) To take necessary actions, in case where the products, etc. are inactivated or where microorganisms, etc. contained in the products, etc. are inactivated or eliminated, for preventing contamination by the products, etc. which have not undergone such inactivation or elimination,

(2) To conduct continuous measurement of the items necessary for controlling the manufacturing process such as temperature, hydrogen ion index, etc., in case where biochemical technology such as fermentation, etc. is applied in the manufacturing Process,

(3) To take necessary actions, in case where the column chromatography apparatuses, etc. are used in the manufacturing process, for preventing contamination of such apparatuses with microorganisms, and to measure endotoxins, where necessary,

(4) To take necessary actions, in case where the culture media are continuously supplied to and the cultured broth is continuously discharged from the tanks, for maintaining the incubation conditions in such incubation tanks during the incubating,

(5) To conduct sanitation control of the personnel in accordance with the following requirements,
a. Placing as much restriction as possible on the personnel other than those engaged in the manufacturing operations entering the work areas,
b. Placing as much restriction as possible on the personnel entering the clean areas or aseptic areas under operation, and
c. Not allowing the personnel engaged in the manufacturing operations to conduct the duties concerned with the control of the utilised animals (excluding those actually utilised in the manufacturing process of the work areas).

(6) To conduct sanitation control of the personnel conducting the duties in the clean areas or aseptic areas in accordance with the following requirements,
a. Having the personnel engaged in the manufacturing operations wear the clothes, work shoes, caps and masks, which have been disinfected,
b. Having the personnel undergo medical checkups at intervals not exceeding 6 months in order to verify that they do not suffer from the diseases which could contaminate, with microorganisms, etc., the products, etc., and