Ministerial Order on the Standard of Quality Management for Pharmaceuticals, Quasi-Pharmaceuticals, Cosmetics, and Regenerative Medicine Products
(Order of the Ministry of Health, Labour and Welfare No. 136 of 2004) *(Excerpt)*

Chapter 2 The Standard of Quality Management for Pharmaceuticals

(Agreements with Manufacturers, etc.)
Article 7 Marketing license holders of pharmaceuticals must, in order to ensure suitable and timely implementation of manufacturing control and quality control by relevant manufacturers, etc., conclude agreements of the following matters with such manufacturers, etc. for their products, and prescribe such agreements within the written operational procedures for quality management.:

(i) scope of manufacture and other activities by the manufacturer, etc. (hereinafter referred to as "manufacturing activities"), manufacturing control and quality control for such manufacturing activities, and procedures for product release from the manufacturing sites,
(ii) technical requirements regarding production processes, testing/analytical methods, etc.,
(iii) periodic audits by the marketing license holder, whether such manufacturing activities are conducted under suitable and timely manufacturing control and quality control,
(iv) methods for quality control during transport and handing-over of the products,
(v) in the case where the manufacturer, etc. intends to introduce any change of production processes, testing/analytical methods, etc. which may impact on quality of the products, procedures for beforehand notifying to the marketing license holder, and responsible personnel for such notification,
(vi) in the case where the manufacturer, etc. has acquired the following information regarding the products, procedures for prompt notifying to the marketing license holder, and responsible personnel for such notification;
  (a) information regarding discontinuation of manufacture, import or marketing, recalls or dispose of the products, or other measures implemented to prevent occurrence or spread of public health hazards, and
  (b) other information on quality, etc. regarding the products, and
(vii) other necessary matters.

(Control of Product Release to the Market)
Article 9 (1) Marketing license holders of pharmaceuticals must, in accordance with the written operational procedures for quality management, ensure that

certification for their finished products to release to the market or reject has been conducted suitably and timely, and must not release their pharmaceuticals to the market before such release certification suitably conducted.

(2) Marketing license holders of pharmaceuticals must, in accordance with the written operational procedures for quality management, have appointed personnel of their quality assurance department, or manufacturers of the finished products, suitably evaluate their production control and quality control, and have such personnel in charge certify each product batch (each production number, in the case of products that do not consist of batches; the same applies hereinafter) to release to the market or reject, and have such personnel in charge document records on such certification and market release, including shipping destinations.

(3) Personnel engaged in tasks certifying finished products to release to the market or reject pursuant to the provisions of the preceding paragraph must be personnel who have been qualified to conduct such tasks suitably and timely.

(4) Where having other personnel than the quality assurance manager conduct certification of finished products to release to the market or reject, such marketing license holder of pharmaceuticals must have such personnel in charge suitably report in writing the progress and outcome of such certification for its finished products to release to the market or reject, to the quality assurance manager.

(5) Where having a manufacturer of the finished products conduct the tasks as provided in paragraph (2), such marketing license holder must take the following procedures.:

(i) to conclude an agreement with the manufacturer regarding the following matters;

(a) procedures for the control of product release to the market, conducted by the manufacturer;

(b) appointment of personnel engaged in the tasks as provided in paragraph (2) at manufacturing site of the finished products;

(c) in the case where any deviations from the procedures pursuant to the provisions of (a) occurred, prompt notifying such deviation in writing to the quality assurance manager, and certification for the finished products to release to the market or reject under directions of the quality assurance manager; and

(d) periodic audit by the market license holder to ensure that the manufacturer suitably and timely conducts the tasks of product release to the market;

(ii) to have appointed personnel in the quality assurance department suitably conduct audit as provided in (d) of the preceding paragraph, and have such

personnel in charge document records on outcome of such audit;

(iii) in the case where any rectification is needed regarding tasks of product release to the market conducted by the manufacturer, to have the quality assurance manager conduct the following tasks;

(a) to instruct in writing for the manufacturer to implement necessary measures,

(b) to request the manufacturer to report outcome of such measures, and to suitably review such report, conduct on-site audit at the manufacturing site as necessary, and document records on outcome of such review and on-site audit, and

(c) to report in writing outcome of the assessment and audit pursuant to the provisions of (b), to the pharmaceutical marketing general manager, and

(iv) where having personnel other than the quality assurance manager conduct confirmation and record documentation as provided in item (ii), to have such personnel in charge report in writing their outcome to the quality assurance manager.

(6) Marketing license holders of pharmaceuticals must, in accordance with the written operational procedures for quality management, provide the personnel engaged in certification of finished products to release to the market or reject, with information on quality, safety and efficacy concerning their pharmaceuticals, which is necessary for such certification to be suitably and timely conducted.

(Ensuring suitable manufacturing control and quality control by manufacturers, etc.)

Article 10 (1) *(Omitted)*

(2) In the case where any rectification is needed regarding manufacturing control and quality control by relevant manufacturers, etc., the marketing license holder of pharmaceuticals must, in accordance with its written operational procedures for quality management, have its quality assurance manager conduct the following tasks.;

(i) to direct in writing such manufacturer, etc. to implement necessary measures,

(ii) to request such manufacturer, etc. to report on implementation outcome of such measures, to suitably review such report, to conduct on-site audits at its manufacturing site or others as necessary, and to document records on outcome such review and on-site audit, and

(iii) to report in writing outcome of evaluation and audits as provided in the preceding item, to the pharmaceutical marketing general manager.

(3) and (4) *(Omitted)*

(5) Marketing license holders of pharmaceuticals must transfer quality information necessary for suitable and timely implementation of manufacturing control and quality control, for relevant manufacturers, etc.

(Management of Quality Information and Quality Defects, etc.)

Article 11 (1) Where having received information on quality, etc. (hereinafter referred to as "quality information" in this chapter) regarding a pharmaceutical, the marketing license holder of such pharmaceutical must, in accordance with its written operational procedures for quality management, have its quality assurance manager conduct the following tasks.;

(i) to examine such quality information, and to suitably assess the impact on quality, efficacy and safety of the pharmaceutical,

(ii) to investigate matter of causes regarding such quality information,

(iii) in the case where any rectification on quality management operations of the marketing license holder is needed, or manufacturing control and quality control of the manufacturers, etc. concerned, based upon outcome of the assessment or investigation as provided in the preceding two items, to implement necessary measures,

(iv) to document records on details of the quality information, outcome of the assessment, outcome of the investigation, and the measures for rectification as provided in the preceding three items, and to promptly report them in writing to the general pharmaceutical marketing manager,

(v) in the case where any instructions to the manufacturers, etc. is needed for the investigation as provided in the item (ii) or to implement rectification measures as provided in item (iii), to issue written instructions to such manufacturers, etc., and to request such manufacturers, etc. for report in writing on outcome thereof, to suitably evaluate such outcome, to conduct on-site visit for verifying the rectification at the manufacturing sites as necessary, and to document records on outcome thereof, and

(vi) among the quality information, information on the safety measures as provided in Article 2, paragraph (2) of the Standard of Post-marketing Safety Management must be provided in writing to the safety management department without delay.

(2) In the case where any actual or possible quality defect has been identified during the operations as provided in the preceding paragraph, such marketing license holder of pharmaceuticals must, in accordance with its written operational procedures for quality management, have its general pharmaceutical marketing manager and quality assurance manager conduct the following tasks;

(i) the quality assurance manager shall report such actual or possible quality defect to the general pharmaceutical marketing manager, and to document records thereof,

(ii) the general pharmaceutical marketing manager shall, upon receiving a report as provided in the preceding item, promptly determine actions necessary to prevent occurrence of health hazards, such as product recalls, and to instruct the quality assurance manager and other concerned departments regarding those actions,

(iii) the quality assurance manager shall, upon receiving an instruction by the general pharmaceutical marketing manager as provided in the preceding item, promptly take necessary actions,

(iv) the quality assurance manager shall coordinate close cooperation with the safety management department and other concerned departments, and

(v) the quality assurance manager shall report in writing on progress and outcome of implementation of the actions as provided in item (iii), to the general pharmaceutical marketing manager.

(Product Recalls)

Article 12 Where conducting product recalls, such marketing license holder of pharmaceuticals must, in accordance with its written operational procedures for quality management, have its quality assurance managers conduct following tasks.;

(i) after separate storage for a certain period, to suitably dispose the recalled products, and

(ii) to document and retain records detailed on the product recall, and to report in writing to the general pharmaceutical marketing manager.

(Management of Documents/Records)

Article 16 Marketing license holders of pharmaceuticals must implement management of documents/records as provided in this Chapter, in complying with the following requirements:

(i) upon establishing or revising a document, to endorse, distribute, archive, etc. of such document, in accordance with the written operational procedures for quality management;

(ii) upon having established or revised the written operational procedures for quality management, to record dates of the establishment/revision on such written procedures, and to retain records of the history of previous revisions;

(iii) to retain documents/records as provided in this Chapter for the following

period, from the date of documentation (in the case of written operational procedures for quality management, from the date of discontinuance thereof);

(a) where marketing specified biological origin products as provided in Article 2, paragraph (11) of the PMD Act (hereinafter simply referred to as "specified biological origin products") or the biological origin products as provided in Article 2, paragraph (10) of the PMD Act which are produced using human blood as origin materials ("origin materials" refers to objects from which starting materials or other materials (including materials used during the production process) used for production are derived) (hereinafter such biological origin products simply referred to as "human blood origin products"), for a period calculated by adding thirty years to the shelf-life or expiry for use (hereinafter collectively referred to as "shelf-life") of the biological origin product;

(b) where marketing biological origin products as provided in Article 2, paragraph (10) of the PMD Act (hereinafter simply referred to as "biological origin products") or cell/tissue-based pharmaceuticals other than those listed in (a), for a period calculated by adding ten years to the shelf-life of such pharmaceutical;

(c) where marketing other pharmaceuticals than biological origin products or cell/tissue-based pharmaceuticals, for five years; provided, however, where a period calculated by adding one year to shelf-life of such pharmaceutical is longer than five years, for a period calculated by adding one year to the shelf-life of such pharmaceutical;

(d) in the case of documents/records of education/training, five years notwithstanding the periods listed in (a), (b) and (c).